Proazaphosphatranes: versatile molecules with applications in fuel cell technology, biodiesel production and important organic transformations

Kuldeep Wadhwa
Iowa State University

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Proazaphosphatranes: versatile molecules with applications in fuel cell technology, biodiesel production and important organic transformations

by

Kuldeep Wadhwa

A dissertation submitted to the graduate faculty
in partial fulfilment of the requirement of the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
John G. Verkade, Major Professor
George A. Kraus
Richard C. Larock
Victor S. Lin
Klaus Schmidt-Rohr

Iowa State University

Ames, Iowa

2009

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DEDICATION

In memory of my mother the late Mrs. Geeta Wadhwa
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<tr>
<td>aq</td>
<td>aqueous</td>
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<tr>
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<td>tertiary</td>
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<td>Tetrahydrofuran</td>
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<td>Thin layer chromatography</td>
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<td>TMS</td>
<td>Trimethylsilyl</td>
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CHAPTER 1. GENERAL INTRODUCTION

Thesis Organization

This thesis is composed of ten chapters including the present chapter. The $^1$H, $^{13}$C, and $^{31}$P NMR spectra for the reaction products have been compiled in the appendices, which appear at the end of the thesis.

The present chapter contains an introduction and a brief description of each of the remaining chapters. Then follows a general introduction to phosphatranes and phosphatranium ions and their uses as efficient catalysts for various transformations and also as cations for anionic conductors.

The second chapter entitled “$P(i$-$Pr$N$CH_2$CH$_2$)$_3$N: Efficient Catalyst for Synthesizing $\beta$–Hydroxyesters and $\alpha,\beta$–Unsaturated Esters using $\alpha$-Trimethylsilylacetate (TMSEA)” consists of a paper published in the Journal of Organic Chemistry, which describes the use of the commercially available proazaphosphatrane $P(i$-$Pr$N$CH_2$CH$_2$)$_3$N as an efficient catalyst for the synthesis of $\beta$–hydroxyesters and $\alpha,\beta$–unsaturated esters via activation of the silicon-carbon bond of $\alpha$-trimethylsilylacetate. Selectivity for either of these two products was achieved simply by altering the catalyst loading and reaction temperature to afford the addition or stereoselective condensation product.

The third chapter entitled “$P(i$-$Pr$N$CH_2$CH$_2$)$_3$N: An Efficient Catalyst for TMS-1,3-Dithiane Addition to Aldehydes” consists of a communication published in Tetrahedron Letters describing an efficient methodology for the addition of 2-trimethylsilyl-1,3-dithiane (TMS-dithiane) to aldehydes at room temperature using the proazaphosphatrane $P(i$-
PrNCH$_2$CH$_2$)$_3$N. The catalyst loading required for these reactions (5 mol %) is the lowest recorded in the literature, and the majority of the reaction times for this transformation were the shortest thus far reported.

The fourth chapter entitled “$P(i$-$PrNCH$_2$CH$_2$)$_3$N as a Lewis-Base Catalyst for the Synthesis of $\beta$-Hydroxynitriles Using TMSAN” consists of a paper published in the Journal of Organic Chemistry describing an efficient method of synthesizing $\beta$-hydroxynitriles in good to excellent yields using a wide variety of aldehydes (possessing various functional groups), enolizable aliphatic aldehydes, and a wide array of heterocyclic aldehydes. These reactions are facilitated using only 2 mol % catalyst, which, to the best of our knowledge, is the lowest catalyst loading thus far reported for this methodology.

The fifth chapter entitled “$P(PhCH$_2$NCH$_2$CH$_2$)$_3$N: An Efficient Lewis-base Catalyst for the Synthesis of Propargylic Alcohols and Morita-Baylis-Hillman adducts via Aldehyde Alkynylation” reports the contents of a paper submitted for publication on the use of P(PhCH$_2$NCH$_2$CH$_2$)$_3$N as an efficient catalyst for the addition of aryl trimethylsilyl alkynes to various aromatic, aliphatic and heterocyclic aldehydes in THF at room temperature. Only propargylic alcohols were isolated in good to excellent isolated yields in the cases of electron-rich, electron-neutral, heterocyclic and aliphatic aldehydes, whereas $\beta$-branched Morita-Baylis-Hillman-type adducts were isolated with electron-deficient aromatic aldehydes after conventional acid hydrolysis of the TMS ethers.

The sixth chapter entitled “$P(PhCH$_2$NCH$_2$CH$_2$)$_3$N Catalysis of Mukaiyama Aldol Reactions of Aliphatic, Aromatic, Heterocyclic Aldehydes and Trifluoromethyl Ketone” describes a paper in preparation reporting Mukaiyama reactions catalyzed by the title
proazaphosphatrane, which activates the silicon of the Si-O bond of trimethylsilyl enolates for reaction with aldehydes to yield the corresponding aldol products in good to excellent isolated yields. Among ketones, only the activated ketone 2,2,2-trifluoroacetophenone underwent clean aldol product formation with a variety of trimethylsilyl enolates. The reaction conditions were mild; operationally simple; and a variety of functional groups, such as nitro, amino, ester, chloro, trifluoromethyl, bromo, iodo, cyano and fluoro groups were tolerated. Product yields were generally better than or comparable to those recorded in the literature. With bulky (2,2-dimethyl-1-methylenepropoxy)trimethylsilane, only $\alpha,\beta$-unsaturated esters were isolated. Several heterocyclic aldehydes examined gave good product yields.

The seventh chapter entitled “Determination of the Structure of a Novel Anion Exchange Fuel Cell Membrane by Solid-State Nuclear Magnetic Resonance Spectroscopy” consists of a paper published in *Macromolecules* in collaboration with Prof. Klaus Schmidt-Rohr’s group, which reports the synthesis of a novel anion exchange fuel cell membrane by chemically attaching proazaphosphatranium and phosphatranium cations under microwave conditions to the sulfonic groups of Nafion-F®. Solid-state NMR techniques were employed to determine the structure and composition of this anion exchange membrane. The $^{31}$P NMR spectrum showed two main signals with a 2:1 intensity ratio and chemical shift changes of +89 ppm and +46 ppm, respectively, from the main peak of phosphatranium chloride. $^{1}$H–$^{31}$P heteronuclear correlation NMR spectroscopy and $^{1}$H–$^{31}$P recoupling experiments indicated that the proton originally bonded to phosphorus in phosphatranium chloride is replaced in the major component of the Nafion®–proazaphosphatranium/phosphatranium composite. $^{19}$F
NMR experiments showed that the fluorine in the –SO₂F group of the Nafion-F® precursor is completely replaced. $^{31}$P{$^{19}$F} rotational-echo double resonance (REDOR) experiments measured a P–F internuclear distance of ~0.4 nm, which showed that the proazaphosphatranium is covalently attached to Nafion® through an S–P bond. $^{13}$C NMR and $^1$H–$^{13}$C HetCor spectra indicated that the proazaphosphatranium structure is maintained even after the microwave treatment at 180 °C, and also showed the presence of entrapped dimethylformamide solvent.

The eighth chapter entitled “Synthesis of Linear or Branched Polymers Possessing Chemically Bonded Phosphatranium Nitrate as Efficient Nitrate Conducting Membranes” describes the synthesis of polymers containing phosphatranium nitrate bound to polymer backbones. These polymers are designed to function as efficient nitrate ion conductors for carbamide-fueled electrochemical cells.

The ninth chapter entitled “Proazaphosphatran Catalysts Mounted on Perhalogenated Polymers” describes the synthesis of a novel Teflon®-bound azidoproazaphosphatran catalyst for improving the recyclability of a heterogeneous catalyst for biodiesel synthesis by transesterification of soybean oil with methanol.

The thesis ends with the tenth chapter entitled “General Conclusions and Future Work,” which summarizes the findings in chapters 2-9 and provides a prospective outlook for the chemistry of proazaphosphatranes. Included in this chapter are a proposed synthesis of perhalogenated polymer-bound proazaphosphatranes and their application in Lewis-base catalyzed reactions and as a recyclable ligand for palladium-catalyzed cross-couplings. Also
included in this chapter is a proposed new strategy for the room temperature synthesis of polydifluoroacetylene (PDFA) facilitated by a proazaphosphatran. PDFA is a potentially important polymer because of its unusual chemical, electronic and optical properties. The only synthetic route known in the literature involves prior synthesis of the monomer, which is notoriously explosive and pyrophoric.

General Introduction

Proazaphosphatranes (1) are an important class of compounds that find advantageous uses as base catalysts and as ligands for palladium-catalyzed cross-couplings. The first synthesis of a proazaphosphatran, namely, P(MeNCH₂CH₂)₃N, was carried out in our laboratory by Lensink et al. in 1989. Several such compounds soon became commercially available from Aldrich, Fluka and Strem and they are still available today. The unusual basicity of these compounds is evident from their facile P- (rather than N-) protonation to form Nbasal→P transannulated phosphatranium ions of type 2 shown in Figure 1. We have found that proazaphosphatranes, such as those in (Figure 1), are strongly basic as seen from their pKₐ values in this figure.
With the discovery of these novel molecules, a consistently growing array of reactions, catalyzed by strong Lewis bases emerged from our group. For example, Wroblewski and D’Sa synthesized the very strongly basic 1a, which D’Sa et al. then used for the silylation of alcohols. Subsequently, reports from our group appeared in which the use of proazaphosphatranes for the activation of the silicon, e.g., is reported. Thus D’Sa et al. reported the silylation of alcohols using tert-butyldimethylsilyl chloride and Wang and Fetterly reported evidence for the activation of the silyl group of TMSCN and TBDMSCN for the synthesis of cyanohydrins using the reaction between trialkylsilyl nitrile and carbonyl compounds. Proazaphosphatrane 1d was found to be an efficient catalyst for the desilylation of TBDMS ethers. In 2005, Uurgaonkar et al. reported the nucleophilic aromatic substitution of aryl fluorides with aryl silyl ethers using 1c. Recently, the same reaction was reported by Raders using proazaphosphatrane 1c under microwave conditions with a lower catalyst loading. Wang et al. described the allylation of aromatic aldehydes with allyltr trimethylsilanes and the reduction of aldehydes and ketones using poly(methylhydrosiloxane) in the presence of proazaphosphatrane 1d.

Wang et al. also described a mechanistic investigation of the activation of crotvltrimethylsilane using 1a for the catalytic crotylation of aromatic aldehydes. The formation of both α- and γ-addition products in 1:1 ratio in this reaction was observed. The authors proposed the formation of an intermediate of type B depicted in Figure 2, which was later substantiated experimentally by Wang et al. via 29Si and 31P NMR spectroscopic studies. The peak shown at 29Si δ = 7 ppm was attributed to the formation of intermediate B wherein the anion was displaced.
Figure 2

The above results showed that proazaphosphatrane was an excellent catalyst for silyl activation to synthesize useful organic intermediates. Part of the goal of this thesis was to develop the use of proazaphosphatrane to synthesize various useful small organic molecules by the activation of Si-O and Si-C bonds, along with efforts to gain further evidence for silicon group activation (Chapters 2-6).

Previously, Fetterly et al. in our group demonstrated that a phosphatranium cation of type 2 in Figure 1 for which the counter anion is nitrate, is an excellent catalyst for aza- and thia-Michael reactions.\(^{15}\) Evidence was presented that such a nitrate salt in which the cation was bound to a solid support was superior to a commercially available nitrate anion exchange resin. This improved action was attributed to the poor anion-cation attractive interaction in our phosphatranium salts, which was rationalized on the basis of: (i) resonance stabilization of the phosphatranium cation (discussed further in Chapter 7 and 8), and (ii) the bulky size of the cation. Both factors render the nitrate ion “naked”. These results prompted us to chemically bind phosphatranium salts to polymeric membrane supports to function as nitrate ion conducting membranes for fuel cell applications (discussed in Chapter 8). Subsequently
this technique was utilized to develop a novel Nafion®-phosphatrane composite membrane, which showed excellent hydroxide ion conductivity (Chapter 7).

A thermally and air stable derivative of a proazaphosphatrane discovered in our laboratory is shown in Figure 3.\textsuperscript{16} This compound was initially believed to be 3a, but later it was determined to be 3b, using X-ray crystallographic analysis of a homogeneous analog.\textsuperscript{17} Merrifield resin is a polystyrene-based resin cross-linked by divinylbenzene. Heterogeneous catalysts of type 3c have been shown by us to be useful in the acetylation of alcohols with vinyl acetate\textsuperscript{16} and in 1,4 addition reactions.\textsuperscript{18} Reddy \textit{et al.} reported the use of catalyst 3c for the synthesis of biodiesel, but found it to be deactivated after 11 cycles.\textsuperscript{17} It was then discovered via solid state \textsuperscript{13}C NMR techniques (in collaboration with Professor Schmidt-Rohr of this Department) that the catalyst was plugged with organic impurities accumulated during the catalyst cycles, thereby deactivating the catalyst by blocking the active sites.

![Figure 3](image-url)
These observations prompted us to attempt the synthesis of a Teflon®- or Nafion®-bound azidoproazaphosphatrane (Figure 4), which is discussed in Chapter 9. Such a solid support would enable our catalyst system to be stable to elevated temperatures and hydrolytic conditions. Moreover, high recyclability and resistance to plugging of the polymer pores by organic impurities would also be a very beneficial potential outcome.

References


Abstract: In this report we present an efficient synthesis for β-hydroxyesters and α,β-unsaturated esters via activation of the silicon-carbon bond of α-trimethylsilylethylacetate using catalytic amounts of commercially available proazaphosphatrane, P(i-PrNCH₂CH₂)₃N 1a (see above scheme). Selectivity for either of these two products can be achieved simply by altering the catalyst loading and reaction temperature to afford addition or stereoselective condensation. This method is mild and tolerates a wide array of functional groups.
Introduction

β-Hydroxyesters are one of the most important classes of intermediates in the synthesis of natural products. The most common method for the synthesis of such intermediates is the use of the carbon-carbon bond-forming Reformatsky reaction first discovered in 1887 which has been extensively studied since then. The classical Reformatsky reaction utilizes elevated reaction temperatures and is typically carried out in aromatic solvents such as benzene, which are generally not environmentally friendly. An improvement of the Reformatsky reaction involves the use of activated zinc reagents, although the main drawback of this approach is the necessity for preparing fresh metal catalyst in advance, owing to instability of these reagents. As an alternative to the conventional Zn-based Reformatsky methodology, other metals such as iron, nickel, magnesium, manganese and indium can be employed. However, such metals are required in stoichiometric amounts and some of them must be reduced by the addition of a reducing metal. The formation of side products is also an issue in the case of magnesium.

A later development involved the use of the reaction between an α-silylester and a carbonyl (i.e., the silyl-Reformatsky reaction) to yield the corresponding β-hydroxyster. TBAF (6 mol %) has been employed as a source of fluoride ion for activating the α-silyl group to generate a naked carbanion which then adds to the electrophilic carbonyl. However, product yield was only moderate and the substrate scope was limited. Use of an α-dimethylsilylester in DMF solvent at 50 °C for 48 h, gave a 39-93% yield of the corresponding β-hydroxyster. The very strong Schwesinger base P4–tBu (pKₐ 40 in
CH$_3$CN,$^{9a}$ 10 mol %) at –78 °C gave the corresponding β-hydroxyester of the substrate acetophenone in poor yield (29%).$^{8a}$

TBAF (3 mol %) is an effective catalyst for silicon activation in the reaction of TMSEA with aldehydes and ketones at low temperature (–20 °C) affording 24–88% yields of corresponding aldol products.$^{7c}$ Activation of the Si–C bond of TMSEA in a reaction with benzaldehyde using 20 mol % of tris(2,4,6-trimethoxyphenyl)phosphine at 100 °C in DMF was reported by Imamoto et al.$^{7d}$ to give a moderate yield (60%) of corresponding product, but no scope for aldehyde substrates was reported. Hamelin et al. reported silyl-Reformatsky reactions of TMSEA with three aromatic aldehydes using 8 equivalents of CsF as catalyst, which gave 62–75% yields of product at ambient temperature, and 62–84% yields using 440 W microwave radiation.$^{7c}$ Wieden et al. reported the use of K[Al(OCH$_3$)$_4$] (1 mol %) in refluxing pyridine as solvent in silyl-Reformatsky reactions between TMSEA and three aromatic aldehydes, but only moderate yields (39 and 46%) and a good yield of 81% was observed for the aldol products.$^{7f}$

**FIGURE 1.** Proazaphosphatranes

![Proazaphosphatranes](image)

Because of their significant Lewis basicities, proazaphosphatranes 1 in CH$_3$CN$^{9b}$ have been of interest to us as catalysts and reagents ever since their first synthesis in our laboratories. A key structural feature of 1 is the potential for N$_{\text{basal}}$$\rightarrow$P transannulation that
would enhance the nucleophilicity of the phosphorus. We have reported several instances in which 1 is apparently capable of activating a silicon center, e.g., in the silylation of alcohols using a silyl chloride, the synthesis of cyanohydrins from the addition of trimethylsilyl nitrile to carbonyl compounds, the desilylation of TBDMS ethers, and in the nucleophilic aromatic substitution of aryl fluorides with aryl silyl ethers.

Results and Discussion

In the present work, we report the use of 1a as a catalyst for the efficient synthesis of β-hydroxyesters via a silyl-Reformatsky reaction, and α,β-unsaturated esters via Peterson olefination from aldehydes with TMSEA as shown in the scheme in the Abstract. For optimization of the conditions, the reaction between p-tolualdehyde and TMSEA was selected. Excellent catalytic efficiency of 1a and its commercial availability favored its selection for the aforementioned syntheses. Using 5 mol % 1a, this reaction at room temperature underwent mainly condensation to give the corresponding α,β-unsaturated ester B in 75% yield and the desired aldol product A in 19% isolated yield, which is in accord with the B/A ratio of 8:2 observed by proton NMR spectroscopy in the crude reaction mixture (Table 1, entry 1). Increasing the catalyst loading to 10 mol % under the same reaction conditions increased the yield of the condensation product to 77% while decreasing the yield of aldol product (Table 1, entry 2). Raising the temperature to 80 °C, while keeping the loading of 1a at 10 mol %, had no significant effect on the yield of condensation product (Table 1, entry 3). A further increase in loading of 1a to 15 mol % at 25 °C led to a rise in yield of condensation product B (83%, Table 1, entry 4). However, reducing the reaction time gave only a 56% yield (Table 1, entry 4).
Gratifyingly, reducing the loading of 1a to 5 mol % and lowering the temperature to 0 °C resulted in an 82% yield of aldol product A (Table 1, entry 5). Further lowering the loading of 1a to 4 and 2 mol % at 0 °C increased the yield of A to 83 and 86% (Table 1, entries 6 and 7, respectively). When the reaction was carried out for 12 h, incomplete conversion and a lower yield was observed (62%, Table 1, entry 7). Lowering the temperature to –20 °C did not increase the yield of aldol product at 2 mol % loading of 1a (87%, Table 1, entry 8) compared with that attained at 0 °C (86%, Table 1, entry 7). The yields of A obtained with 1a–d screened under the optimized conditions given in Table 1, entry 7 for 1a were good (Table 1, entries 5-7 and 9-12). The yield did not appear to correlate with steric or basicity trends of the proazaphosphatranes, however.

**TABLE 1:** Survey of Proazaphosphatranes as Catalysts for the Synthesis of β-Hydroxyesters and α,β-Unsaturated Esters^a^

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<th>Entry</th>
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<th>Yield of B (%)^b^</th>
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<td>7</td>
<td>78</td>
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<tr>
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To explore the scope of our methodology for the synthesis of β–hydroxyesters, a variety of aromatic, aliphatic and heterocyclic aldehydes were tested with 1a under the optimized conditions given in Table 1, entry 7. Both electron donating and withdrawing groups were well tolerated, affording excellent yields of corresponding aldol product with only traces of dehydrated product detectable by $^1$H NMR spectroscopy in the crude reaction mixtures (Table 2). Electron donating groups such as methyl (Table 1, entry 7), methoxy at both the $p$- and $o$- position (entries 2 and 3, respectively) and halogen groups (entries 4, 5 and 6); and electron withdrawing groups such as nitro (entry 7), cyano (entry 8) and ester (entry 9) afforded good yields of corresponding aldol products. The enolizable aliphatic aldehydes in entry 10 and 11 also underwent the silyl Reformatsky transformation, providing good yields of products. Interestingly, $\alpha,\beta$-unsaturated trans-cinnamaldehyde gave the desired aldol product in excellent isolated yield without significant contamination by 1,4 addition product (entry 12). Sterically hindered aldehydes such as 2,6-dimethylbenzaldehyde (entry 13) and biphenyl-2-carboxaldehyde (entry 14) gave good isolated yields of their corresponding aldol
products. Heterocyclic aldehydes also tolerated our reaction conditions. Both 5- and 6-membered ring aldehydes bearing N-, O- and S- heteroatoms gave excellent yields of their corresponding aldols (entries 15-17).

We then investigated the synthesis of \( \alpha,\beta \)-unsaturated esters, which are useful synthons in natural product synthesis. Prime methodologies for the synthesis of \( \alpha,\beta \)-unsaturated esters are the Wittig and Horner-Wadsworth-Emmons reactions. The most important disadvantage of both these approaches is the necessity to employ an equivalent amount of strong base. The decarboxylation of malonic acid half-esters is also an important route to the synthesis of \( \alpha,\beta \)-unsaturated esters. Advantages of the Knoevenagel reaction are the inexpensive nature of the starting materials, and the easy removal of by-products (CO\(_2\) and H\(_2\)O) to provide pure compounds. However, disadvantages of this method include the use of strongly basic conditions (e.g., the use of pyridine as solvent), excess malonic acid esters, and elevated temperatures. Moreover, the Knoevenagel reaction is not stereoselective, and enolizable aldehydes do not yield the desired products.

Another common approach to the synthesis of \( \alpha,\beta \)-unsaturated esters is the Peterson olefination reaction which has advantages over the Wittig and Horner-Wadsworth-Emmons reactions, including easy reaction work up and product purification. Moreover, isolated-product yields are high. Disadvantageously, however, conventional Peterson olefination reactions consume an equivalent amount of a lithium base. Recently Kondo et al. reported the use of a catalytic amount of P4-\( \tau \)Bu as an efficient base for the condensation reaction of TMSEA with aldehydes, ketones or formanilides to yield the corresponding \( \alpha,\beta \)-unsaturated
esters.\textsuperscript{8a} Ozanne \textit{et al.} have reported the use of catalytic cesium fluoride (12 mol \%) in DMSO as solvent for Peterson olefination of $\alpha$-silylesters with aldehydes or imines.\textsuperscript{8b}

As we show in the present work, the conditions in Table 1, entry 4 are suitable for the condensation of TMSEA with aryl and heterocyclic aldehydes to yield the corresponding $\alpha,\beta$-unsaturated esters (Table 3). Aliphatic aldehydes, on the other hand, did not give the corresponding $\alpha,\beta$-unsaturated ester under our reaction conditions. Along with good tolerance of various functional groups and good to excellent isolated product yields, the reactions in Table 3 were also stereoselective, yielding only trans- products as determined by $^1$H NMR spectroscopy. Electron donating groups such as methyl (entry 1) and methoxy (entry 2) provided the corresponding trans condensation products in excellent yields. The electron withdrawing cyano group allowed complete conversion to the desired product in excellent yield (entry 4). The reaction of trans-cinnamaldehyde with TMSEA also showed stereoselectivity, affording the corresponding condensation product as a mixture of two stereoisomers in a 9:1 ratio as determined by $^1$H NMR spectroscopy (entry 5). Sterically hindered 2,6-dimethylbenzaldehyde gave the desired product in excellent yield (entry 6). Screening of heterocyclic aldehydes for the condensation reaction gave both good stereoselectivity and very good isolated product yield as was shown for 2-thiophenecarboxaldehyde and 2-benzofurancarboxaldehyde (entries 7 and 8, respectively).

\textbf{TABLE 2:} Scope of the Addition Reaction of Aldehydes with TMSEA Catalyzed by 1a\textsuperscript{a}

\begin{tabular}{cccc}
\hline
Entry & Aldehyde & Product & yield (\%)\textsuperscript{b} & lit. yield (\%) \\
\hline
1 & \begin{tikzpicture}
\draw (0,0) rectangle (1,1);
\draw (0.5,0.5) -- (0,1) -- (1,1) -- (1,0) -- cycle;
\draw (0,0) -- (0.5,0.5);
\draw (1,0) -- (0.5,0.5);
\end{tikzpicture} & \begin{tikzpicture}
\draw (0,0) rectangle (1,1);
\draw (0.5,0.5) -- (0,1) -- (1,1) -- (1,0) -- cycle;
\draw (0,0) -- (0.5,0.5);
\draw (1,0) -- (0.5,0.5);
\draw (0.5,-0.5) -- (0.5,0.5);
\draw (0.5,-0.5) -- (1,-0.5);
\draw (0.5,0.5) -- (0.5,1);
\end{tikzpicture} & 71 & 76,\textsuperscript{c} 60,\textsuperscript{d} 70,\textsuperscript{e} 46,\textsuperscript{f} 91\textsuperscript{g} \\
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\end{tabular}
Table 2 continued

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</table>

*Reaction conditions: (a) aldehyde (2 mmol), TMSEA (2.4 mmol), 1a (2 mol%), THF (2 mL), 0 °C, 24 h, 1N HCl (3 mL). bIsolated yield after column chromatography. cSee ref 7c. dSee ref 7d. eSee ref 7e. fSee ref 8b. gSee ref 7f.*

**Conclusion**

In conclusion, we have described a very mild and effective method for the synthesis of aldol products and α,β-unsaturated esters by a simple change in 1a loading and temperature. This method is general for aromatic, aliphatic and heterocyclic aldehydes, it tolerates a wide
spectrum of functional groups (including acid- and base-sensitive examples) and it leads to excellent isolated yields of aldol products. High stereoselectivity is achieved in the condensation reactions, yielding \textit{trans}-products in good to very good isolated yields. The selectivity of the two products upon changing the reaction conditions can be rationalized using the two-stage mechanism proposed by Kondo \textit{et al.} for the P4-tBu-catalyzed reactions of TMSEA with carbonyl compounds to synthesize $\alpha,\beta$-unsaturated esters.$^8$ In the 1st stage, the anion of a P4-tBu-TMS$^+$ CH$_2$CO$_2$Et (an intermediate formed from P4-tBu and TMSEA) 1,2-adds to a carbonyl to produce a silylated $\beta$-hydroxyester, which in the 2$^{\text{nd}}$ stage eliminates HP4-tBu$^+$ OTMS. This elimination product catalyzes formation of the $\alpha,\beta$-unsaturated ester from the silylated $\beta$-hydroxyester. Commercial availability of catalyst 1a and the environmentally desirable lack of metal usage in the syntheses reported here renders our methodology attractive. In comparing yields of $\beta$-hydroxyesters attained in our methodology with those found in the literature for the five of the methods cited in four entries of Table 2, we found that only one literature yield is higher than is attained with our method, four yields are lower, and three are comparable. In the case of the $\alpha,\beta$-unsaturated esters in Table 3, we compared two literature methods cited in three entries of this table, and found that one literature yield was higher than that attained with our methodology and two were lower. Our methodology was ineffective for the ketones (e.g., acetophenone, 4-chloro-acetophenone and benzophenone).
TABLE 3: Scope of the Condensation Reaction of Aldehydes with TMSEA Catalyzed by 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)^b</th>
<th>Lit. Yield (%)</th>
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</thead>
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<td><img src="..." alt="Image" />(CO2Et)</td>
<td>83</td>
<td>91^c</td>
</tr>
<tr>
<td>2</td>
<td><img src="..." alt="Image" />(MeO)</td>
<td><img src="..." alt="Image" />(CO2Et)</td>
<td>83</td>
<td>69^e</td>
</tr>
<tr>
<td>3</td>
<td><img src="..." alt="Image" />(O)</td>
<td><img src="..." alt="Image" />(CO2Et)</td>
<td>79</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td><img src="..." alt="Image" />(NC)</td>
<td><img src="..." alt="Image" />(CO2Et)</td>
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<td>-</td>
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<td>5</td>
<td><img src="..." alt="Image" />(CHO)</td>
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<td><img src="..." alt="Image" />(CHO)</td>
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<td><img src="..." alt="Image" />(CHO)</td>
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<td>-</td>
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<td>8</td>
<td><img src="..." alt="Image" />(CHO)</td>
<td><img src="..." alt="Image" />(CO2Et)</td>
<td>79</td>
<td>-</td>
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</table>

^aReaction conditions: (a) aldehyde (2 mmol), TMSEA (2.4 mmol), 1a (15 mol %), THF (2 mL), rt, 24 h, 1N HCl (3 mL). ^bIsolated yield after column chromatography. ^cSee ref 8a. ^dDetermined by NMR. ^eSee ref 8b.
Experimental Section

General Reaction Procedure for the Synthesis of $\beta$-Hydroxyesters and $\alpha,\beta$-Unsaturated esters. In a nitrogen-filled glove box, a round bottom flask was charged with 1 (2 mol % for $\beta$-hydroxyesters, 15 mol % for $\alpha,\beta$-unsaturated esters). Anhydrous THF (2.0 mL) was syringe under argon into the flask, followed by TMSEA (2.40 mmol) at 0 °C (r.t. for $\alpha,\beta$-unsaturated esters). The reaction mixture was stirred at 0 °C (r.t. for $\alpha,\beta$-unsaturated esters) for 15 min and then aldehyde (2.0 mmol) was added over 5–10 min. The reaction mixture was stirred for 24 h at 0 °C (r.t. for $\alpha,\beta$-unsaturated esters) and then it was quenched with 3 mL of aqueous HCl (1N). The reaction mixture was stirred at 0 °C (r.t. for $\alpha,\beta$-unsaturated esters) for 1 h and then it was neutralized with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (3 × 30 mL). The product was purified by column chromatography on silica gel using 10% EtOAc/hexanes, except for heterocyclic substrates (20–25% EtOAc/hexanes).

Acknowledgment

The National Science Foundation is gratefully acknowledged for financial support of this research in the form of grant 0750463. We also thank Dr. Ch. Venkat Reddy for helpful discussions.

References


(11) Proazaphosphatranes 1a, 1c, and 1d are commercially available.


CHAPTER 3. P(i-PrNCH₂CH₂)₃N: AN EFFICIENT CATALYST FOR TMS-1,3-DITHIANE ADDITION TO ALDEHYDES

Kuldeep Wadhwa and John G. Verkade


Abstract—Herein we report the use of P(i-PrNCH₂CH₂)₃N (1a) as an efficient catalyst for 2-trimethylsilyl-1,3-dithiane (TMS-dithiane) addition to aldehydes at room temperature. The catalyst loading required for these reactions (5 mol %) is the lowest recorded in the literature, and the majority of the reaction times for this transformation are the shortest thus far reported. A variety of functional groups are tolerated on the aryl aldehyde substrates.

Introduction

The addition of 1,3-dithiane (a masked acylcarbanion) to various electrophiles (e.g., aldehydes, ketones, alkyl halides) is one of the most practiced methodologies in synthetic organic chemistry for the formation of C-C bonds.¹⁻⁶ Also known as an “umpolung”, “dipole inversion” or “inversion of reactivity” reaction, this process at the S₂C carbon of the dithiane
allows facile generation of a carbonyl functionality under mild oxidation conditions using reagents such as \( \text{Hg(ClO}_4\text{)}_2 \), \( \text{CuCl}_2/\text{CuO} \), \( \text{AgNO}_3 \), \( \text{Tl(NO}_3\text{)}_3 \) and [bis(trifluoroacetoxy)iodo]benzene.\(^6\text{–}^{10}\) The most common deprotonating agent for converting a 1,3-dithiane to a nucleophile for addition to an electrophilic carbon center is the use of a stoichiometric amount of \( \text{BuLi} \).\(^1\text{–}^6\)

Umpolung of a dithiane for its addition to ketones and aldehydes has also been accomplished via catalytic activation of a silyl group in a 2-silyl-1,3-dithiane.\(^11\text{–}^{14}\) Thus Pollicino \textit{et al.} reported the use of a stoichiometric amount of cesium fluoride as a base in DMF solvent using 2-trimethylsilyl-4,6-dimethyl-1,3-dithiane and benzaldehyde to obtain a product yield of 72%, but the substrate scope was limited to benzaldehyde.\(^11\) Corey \textit{et al.} utilized an equivalent of \( \text{CsF} \) in a 1:1 mixture with \( \text{CsOH} \) at 0 °C for 2 h for the reaction of \( p \)-methoxybenzaldehyde with TMS-dithiane which achieved a product yield of 85%.\(^12\) A catalytic amount (10 mol %) of the fluoride ion source \( [n\text{-Bu}_4\text{N}][\text{Ph}_3\text{SiF}_2] \) was reported by DeShong \textit{et al.} to achieve a 96% yield of product from the reaction of benzaldehyde (the only substrate tested) with TMS-dithiane.\(^13\) Very recently, Mukaiyama \textit{et al.} reported that the use of 30 mol % of \( [n\text{-Bu}_4\text{N}][\text{OPh}] \) as a general catalyst for promoting the addition (TMS-dithiane at 0 °C in DMF to aldehydes and ketones to provide product yields of 60-97% and 63-93%, respectively.\(^14\) This significantly improved methodology does, however, require a highly polar aprotic solvent and a high mol % of catalyst.\(^14\)
We have found\textsuperscript{15} that proazaphosphatranes such as those in Figure 1 are strongly basic with \( pK_a \) values in the range 32-34 in MeCN for their P-protonated \( N_{\text{basal}}\rightarrow P \) transannulated conjugate acids.\textsuperscript{16} To the extent that \( N_{\text{basal}}\rightarrow P \) transannulation may be occurring during reactions catalyzed by 1, the nucleophilicity of the phosphorus may be enhanced.\textsuperscript{15b} We previously reported reactions in which proazaphosphatranes can activate silicon functionalities,\textsuperscript{17-23} as for example in the silylation of alcohols using tert-butyldimethylsilyl chloride,\textsuperscript{17,18} the synthesis of cyanohydrins from the addition of a trialkylsilylcyanide to carbonyl compounds,\textsuperscript{19,20} the desilylation of TBDMS ethers,\textsuperscript{21} and the nucleophilic aromatic substitution of aryl fluorides with aryl silyl ethers.\textsuperscript{22,23}

Because proazaphosphatranes activate silicon functional groups\textsuperscript{17-23} in addition to functioning as strong Lewis bases,\textsuperscript{15,16} it occurred to us that in view of the paucity of reports in which the catalytic activation of TMS-dithiane for carbonyl umpolung\textsuperscript{13,14} has been utilized, proazaphosphatranes might function well in such reactions. Here we report use of a proazaphosphatrane as an efficient catalyst for 1,3-dithiane addition to the carbonyl of aldehydes as shown in Scheme 1.
Scheme 1. General Reaction Scheme

Results and Discussion

For optimization studies (Table 1) we chose the reaction of an electron-neutral aldehyde (2) with TMS-dithiane (3). With 2 mol % of 1a, the isolated yield of product 4 was only 52% (entry 1). Increasing the catalyst loading to 5 mol %, however, augmented that yield to 98% (entry 2) over the same time period. Gratifyingly, this reaction time could be shortened to 30 min without compromising yield (entry 3). The conditions of entry 3 for proazaphosphatranes 1b-d also gave excellent yields of product 4 (Table 1, entry 4-6). Proazaphosphatranes 1a was our catalyst of choice, however, because of the combination of its superior performance, commercial availability, and ease in handling owing to its crystalline nature when purified by sublimation. It is noteworthy that our catalyst loading of 5 mol % is the lowest recorded in the literature for this methodology. According to NMR spectroscopy, no reaction was observed in the absence of catalyst (entry 7).

With the conditions in entry 3 of Table 1, a variety of aldehydes were screened to generalize the scope of catalyst 1a (Table 2). Electron donating groups such as methoxy (entry 1) and methyl (entry 2) resulted in excellent isolated product yields. Electron withdrawing and acid sensitive groups such as ester (entry 3) and cyano (entry 4) gave
excellent and good yields, respectively. A halogen-containing aryl aldehyde (entry 5) and an
enolizable aliphatic aldehyde (entry 6) provided excellent product yields. With the sterically
congested aldehyde 2-biphenyl carboxaldehyde (Table 2, entry 7) a good isolated yield of
product (81%) was realized.

Because only two heterocyclic aldehydes were previously examined in this reaction,\textsuperscript{14} we
examined five five- and two six-membered ring examples with our protocol, in which the
low catalyst loading of 5 mol % was maintained. The oxygen-containing benzofuran-2-carboxaldehyde participated in its reaction with dithiane (Table 2, entry 8) as did the
halogenated nitrogen heterocycle in entry 9 and the N- and S-containing heterocycle in entry
10; all giving excellent product yields. Although the heterocycle containing two nitrogens in
entry 11 gave a rather moderate yield of product, excellent product yields were achieved with
thiophene-2-carboxaldehyde (entry 12), 6-methyl-2-pyridinecarboxaldehyde (entry 13) and
N-methylindole-2-carboxaldehyde (entry 14).

**Table 1:** Survey of Proazaaphosphatranes (1)\textsuperscript{a}

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<tr>
<th>Entry</th>
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<tr>
<td>2</td>
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<td>5</td>
<td>24 h</td>
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</tr>
<tr>
<td>3</td>
<td>1a</td>
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<td>30 min</td>
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Table 1 continued

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<tr>
<th>Entry</th>
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<td>5</td>
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<td>7</td>
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<td>-</td>
<td>24 h</td>
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Reaction conditions: catalyst (x mol %), benzaldehyde (2.0 mmol), 3 (2.4 mmol), THF (2 mL), rt followed by 1N HCl (3 ml). \(^b\) Isolated yield after column chromatography. \(^c\) Lit. yield see refs 13 and 14.

From the variety of aldehydes included in the scope of our protocol, it appears that our methodology is general for those possessing electron withdrawing or donating groups and additionally for acid- or base-labile functional groups. Heterocyclic and enolizable aliphatic aldehydes are also amenable to our protocol.

Table 2: Reaction Scope of Aldehydes with 2-Trimethylsilyl-1,3-dithiane Catalyzed by 1a\(^a\)

<table>
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<th>Entry</th>
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|---|---
| 12 | ![Image](image1)
| 13 | ![Image](image2)
| 14 | ![Image](image3)

*Reaction conditions: aldehyde (2 mmol), 3 (2.4 mmol), THF (2 mL), 1a (5 mol %) rt, 30 min followed by 1N HCl (3 mL). bIsolated yield after silica gel column chromatography. cSee ref 12. dSee ref 14.*

A proposed mechanism for the addition of TMS-dithiane to aldehydes under our conditions is depicted in Scheme 2. Initially, 1 forms a pentacoordinated silicate TMS-dithiane adduct A which enriches the electron density on the silicon, consequently weakening the bonds around this atom and thus favoring ionization to species B and C. Thereafter, the dithiane anion C nucleophilically attacks the aldehyde carbon giving D which then nucleophilically attacks cation B giving intermediate E(Si). This intermediate is subsequently hydrolyzed in a second step to give the product E(H) with regeneration of the catalyst 1a.
Scheme 2. Proposed mechanism for TMS-1,3-dithiane addition reactions of aldehydes catalyzed by 1a

Conclusion

In summary, we found the nonionic strongly Lewis basic proazaphosphatrane 1a to be an efficient catalyst for the addition of 2-trimethylsilyl-1,3-dithiane to aldehydes. To the best of our knowledge, ours is the first report of a low catalyst loading for the synthesis of β-hydroxydithianes using a TMS-dithiane reagent. Our protocol operates efficiently at room temperature in 30 min with a commercially available catalyst, and product yields are generally excellent. Compared with literature reports of the highest yields for five of the products in Tables 1 and 2, our methodology gave a substantially higher yield in one instance and equal yields (within 1%) in the remaining 4 cases.
Experimental Section

General reaction procedure. A round-bottomed flask was charged with 1 (0.1 mmol, 5 mol \%) in a nitrogen filled glove-box. To this was added 2.0 mL of anhydrous tetrahydrofuran (THF) followed by the addition of aldehyde (2.0 mmol) at room temperature. The resulting solution was stirred at room temperature for 15 min and then 2-trimethylsilyl-1,3-dithiane 3 (2.4 mmol) was added over a period of two min. Progress of the reaction was monitored by proton NMR spectroscopy. The reaction mixture was stirred for 30 min and followed by quenching with 3 mL of an aq. solution 1N HCl. The mixture was stirred for an additional 1 h and then it was neutralized with saturated aq. NaHCO₃ solution and extracted with CH₂Cl₂ (3 × 30 mL). The combined organic extracts were dried over anhydrous MgSO₄. The crude product was purified by column chromatography using 30% EtOAc/hexane as eluent, whereas in the case of entry 11 of Table 2, 20% (v/v) MeOH/CH₂Cl₂ was employed.

Acknowledgment

The National Science Foundation is gratefully acknowledged for financial support of this research through grant 0750463. We also thank Dr. Ch. Venkat Reddy for helpful discussions.

References


24. Proazaphosphatranes 1a, 1c, and 1d are commercially available from sources such as Aldrich and Strem Chemicals.

CHAPTER 4. P(i-PrNCH$_2$CH$_2$)$_3$N AS A LEWIS-BASE CATALYST FOR THE SYNTHESIS OF β-HYDROXYNITRILES USING TMSAN

Kuldeep Wadhwa and John G. Verkade*

*J. Org. Chem. 2009 ASAP

Abstract: Proazaphosphatrane 1a was found to be an efficient catalyst for synthesis of β-hydroxynitriles via the reaction of trimethylsilylacetonitrile (TMSAN) with aldehydes under mild reaction conditions and typically low catalyst loading (ca. 2 mol %). A variety of functional groups were tolerated and good to excellent product yields were obtained.

Introduction

Carbon-carbon bond forming reactions are extensively utilized in modern organic synthesis$^1$ and one of the most common approaches to this process is via nucleophilic addition to carbonyl compounds.$^1$ β-Hydroxynitriles are important building blocks in many natural product syntheses$^2$ owing to the stability of nitriles to handling,$^3$ and the versatility of the nitrile group to conversion to a variety of other functionalities such as amines,$^{4a}$ amides,$^{4b}$ aldehydes,$^{4c}$ esters,$^{4d}$ alcohols$^{4e}$ or carboxylic acids.$^5$
Generally, β-hydroxynitriles have been synthesized with the aid of an equivalent amount of strong alkali metal base (for example, (CH₃)₂CHMgBr, BuLi, or alkali amides) to deprotonate the alpha proton of acetonitrile or benzyl nitrile to generate a nucleophile that attacks the carbonyl group. Low yields commonly encountered with these methods have been attributed to reversibility of the reaction or facile product dehydration to give α,β-unsaturated nitriles.

More recently, several other methods aimed at improving the yields of β-hydroxynitrile syntheses have appeared in the literature. Using an equivalent amount of n-BuLi, additional TMSCl was added to trap the alkoxide, resulting in a favorable shift of the equilibrium. Other reported methods include the use of toxic metal catalysts such as Mn/PbCl₂/TMSCl, Hg(ONC)₂ and PbCl₂/Ga. A two step synthesis of β-hydroxynitriles has been reported involving the prior generation of an aryl anion using aryl halide in an electrochemical cell, which then deprotonates acetonitrile for subsequent addition of the resulting anion to ketones, aldehydes, alkyl halides and esters. However, this method is cumbersome, providing only moderate product yields (52–74%). Another commonly utilized approach is the use of 1,2-epoxides in the presence of a nitrile or LiClO₄/KCN to promote nucleophilic ring opening of the epoxide. However, this method generally favors the use of aliphatic epoxides and yields vary from 35–98%. Additional reported methods for the synthesis of β-hydroxynitriles involve multi-step approaches.

TMSAN has been utilized for prior formation of the O-silyl ether in several attempts to overcome the reaction reversibility problem. In one such reaction, β-hydroxynitriles were produced in 70–73% yield via acid hydrolysis of the O-silyl adduct formed via the use of
toxic potassium cyanide as the catalyst.\textsuperscript{9a} The use of KF as a catalyst resulted in quantitative conversion of the $O$-silyl ether to product, but 25 mol % of KF was required, and only benzaldehyde was explored as a substrate.\textsuperscript{9b} KF (50 mol %) loaded on alumina with prior catalyst activation at 673 K using benzaldehyde as the sole substrate gave a low yield of product plus 15% of $\alpha,\beta$-unsaturated nitrile.\textsuperscript{9d} Utilizing 10 mol % of tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF) at -15 °C resulted in product yields of 20–93% for a variety of aldehydes and ketones.\textsuperscript{9c} Using 2.5 mol % of [Cu(PPh$_3$)$_3$][(EtO)$_3$SiF$_2$] as a catalyst in the presence of 1.2 equivalents of (EtO)$_3$SiF as an additive for the cyanomethylation of aldehydes using TMSAN,\textsuperscript{5} gave good product yields (75-100%), but no scope of functional groups was reported. The use of LiOAc and CsOAc as Lewis base catalysts has been described\textsuperscript{7} and although the yields are good, a high catalyst loading (10 mol %) as well as a relatively inconvenient solvent (DMF) is required. Piperidine (24 mol %) functioned as a catalyst under microwave conditions in the absence of solvent, but product yields were low to moderate (ca. 38-73%) and reactions were typically conducted at elevated temperature (85 °C).\textsuperscript{9e} Recently Kitazaki et al. reported the use of tris(2,4,6-trimethoxyphenyl)phosphine (10 mol %) for TMSAN addition to aldehydes and ketones with product yields of 56-99%, and to imines with 0-85% product yields in DMF and DMPU.\textsuperscript{9f}

\textbf{FIGURE 1.} Proazaphosphatranes

\begin{align*}
1a : R = i$-$Pr & (pK_a = 33.63) \\
1b : R = Bn \\
1c : R = i$-$Bu & (pK_a = 33.53) \\
1d : R = Me & (pK_a = 32.90)
\end{align*}
We found earlier that proazaphosphatranes (1) bearing various organic groups on the PN$_3$ nitrogens (Figure 1) are strongly basic with pK$_a$ values of the their P-protonated N$_{basal}$→P transannulated conjugate acids in the range 32-34 in MeCN. To the extent that N$_{basal}$→P transannulation may be occurring during reactions catalyzed by 1, the nucleophilicity of the phosphorus may be enhanced. We previously reported reactions in which proazaphosphatranes can activate silicon functionalities as, for example, in the silylation of alcohols using silyl chloride, synthesis of cyanohydrins from the addition of trimethylsilyl nitrile to carbonyl compounds, desilylation of TBDMS ethers, nucleophilic aromatic substitution of aryl fluorides with aryl silyl ethers, allylation of aromatic aldehydes, and reduction of aldehydes and ketones using poly(methylhydrosiloxane).

In the present work, we report the use of proazaphosphatrane 1a as an efficient catalyst for the synthesis of β-hydroxynitriles from aldehydes with TMSAN as shown in the scheme in the Abstract.

**Results and Discussion**

To optimize the reaction conditions, we chose the reaction of p-tolualdehyde with TMSAN (Table 1) as a model. We selected proazaphosphatrane 1a as the screening catalyst owing to its efficiency in this reaction and its commercial availability. Using 10 mol % of 1a at room temperature, dehydration to the corresponding α,β-unsaturated nitrile dominated β-hydroxynitrile formation (Table 1, entry 1). Lowering the temperature to 0 °C under the
same conditions increased the yield of the desired product to 46% (entry 2) but lowering the temperature to $-15^\circ$C revealed essentially no change in product yield (entry 3).

**TABLE 1.** Survey of Proazaphosphatranes as Catalysts for the Synthesis of $\beta$-Hydroxynitriles$^a$

![Reaction Scheme](attachment:image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Mol %</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^c$</td>
<td>1a</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>10</td>
<td>46</td>
</tr>
<tr>
<td>3$^d$</td>
<td>1a</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>5</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>4</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>2</td>
<td>91$^e$</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>1</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>2</td>
<td>87$^e$</td>
</tr>
<tr>
<td>9</td>
<td>1c</td>
<td>2</td>
<td>90$^e$</td>
</tr>
<tr>
<td>10</td>
<td>1d</td>
<td>2</td>
<td>90$^e$</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: (a) aldehyde (2.0 mmol), TMSAN (2.4 mmol), THF (2 mL), 0 $^\circ$C, 24 h, followed by 1$N$ HCl (3 mL). $^b$Isolated yield after silica gel column chromatography. $^c$Reaction was carried out at rt. $^d$Reaction was carried out at $-15^\circ$C. $^e$Average of three runs.

Since higher loading of a basic catalyst can lead to undesired formation of $\alpha,\beta$-
unsaturated nitrile via a Peterson olefination pathway,$^{14}$ we reduced the catalyst loading to 5 mol % and found that the yield of β-hydroxynitrile was substantially enhanced (Table 1, entry 4). Further lowering of the catalyst loading increased the yield of β-hydroxynitrile to 74 and 91% (entries 5 and 6, respectively). However, lowering the catalyst loading below 2% inhibited completion of the reaction, resulting in only a good product yield (86%, entry 7). Thus we decided to proceed with 2 mol % catalyst at 0 °C to screen proazaphosphatranes 1b–d, and those results are also summarized in Table 1 (entries 8–10). We found that changing the R group on the PN₃ nitrogens gave comparable yields of the desired product, although 1a was slightly better than the others. We do not have a reasonable explanation for this observation.

Given the higher activity of 1a as a catalyst and its commercial availability, we proceeded with 1a under the conditions optimized in Table 1, entry 6 to extend the scope of our protocol for the synthesis of β-hydroxynitriles. Thus a variety of aromatic and aliphatic aldehydes were employed under the optimized conditions in Table 1, entry 6. The product yields shown in Table 2 are comparable in most cases to those reported in the literature. Both electron donating and withdrawing groups afforded excellent isolated yields, with only a trace of, or no dehydrated product detectable by ¹H NMR spectroscopy. Electron donating groups such as methyl (Table 1, entry 6), methoxy at both para and ortho positions (Table 2, entries 2 and 3), and halogen (Table 2, entry 4) were tolerated under our conditions, giving excellent isolated product yields. Electron withdrawing groups such as p-nitro (entry 6), m-cyano (entry 7) and p-ester (entry 8) were also well tolerated, affording the desired respective products in excellent isolated yields. Trans-cinnamaldehyde gave the desired product in
good isolated yield (entry 9) with no observable evidence from NMR spectroscopy of the corresponding Michael addition product. Aliphatic enolizable aldehydes also gave good isolated product yields (Table 2, entries 10 and 11). Unfortunately our methodology was ineffective for the ketones tested (acetophenone, 4-chloro-acetophenone and benzophenone).

**TABLE 2.** Scope of the Reaction of Aldehydes with TMSAN Catalyzed by 1a$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
<th>Lit. Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td>OH</td>
<td>89</td>
<td>62-100$^{c-h}$</td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td>OH</td>
<td>83</td>
<td>80-96$^{c,f,g,i}$</td>
</tr>
<tr>
<td>3</td>
<td>CHO</td>
<td>OH</td>
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<tr>
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<td>OH</td>
<td>94</td>
<td>-</td>
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<tr>
<td>5</td>
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<td>OH</td>
<td>82</td>
<td>-</td>
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</tr>
<tr>
<td>7</td>
<td>CHO</td>
<td>OH</td>
<td>89</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2 continued

<table>
<thead>
<tr>
<th></th>
<th>Aldehyde Structure</th>
<th>Isolated Yield</th>
<th>Product Yields</th>
</tr>
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<tbody>
<tr>
<td>8</td>
<td><img src="image" alt="MeO₂C phenyl CHO" /></td>
<td>93</td>
<td>73⁺e</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Ph propargyl CHO" /></td>
<td>94</td>
<td>45-99⁺e,f,i</td>
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<tr>
<td>10</td>
<td><img src="image" alt="3-CHO" /></td>
<td>85</td>
<td>80f</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Cyclohexyl CHO" /></td>
<td>86</td>
<td>80-86f,g</td>
</tr>
</tbody>
</table>

⁺Reaction conditions: (a) aldehyde (2.0 mmol), TMSAN (2.4 mmol), 1a (2 mol %), THF (2 mL), 0 °C, 24 h, followed by 1N HCl (3 mL). Isolated yield after column chromatography. 
See ref 9a. 
See ref 9b. 
See ref 9c. 
See ref 5. 
See ref 7. 
See ref 9e. 
See ref 9f.

With a range of 5- and 6-membered ring heterocycle-bearing aldehydes possessing representation of O-, N- and S-heterocycle types, good to excellent yields of the desired product were obtained (Table 3). Thus the thiophenic aldehydes in entries 1 and 2 gave very good and excellent product yields, respectively; the pyridinyl aldehydes in entries 3 and 4; and quinolyl aldehyde in entry 5 afforded the corresponding products in excellent to good yields, respectively; N-containing 2-formyl-1-methylnindole gave an excellent isolated product yield (entry 6), the S,N-heterocycle in entry 7 facilitated an excellent yield of product; and the benzofuran, coumarin and furan carboxaldehydes in entries 8, 9 and 10 permitted a modest, moderate and good yield of products, respectively. The moderate
product yield in entry 9 was pleasantly surprising in view of the sensitivity of lactones to acid and base.

**TABLE 3.** Scope of the Reaction of Heterocyclic Aldehydes with TMSAN Catalyzed by 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td><img src="image1" alt="" /></td>
<td><img src="image2" alt="" /></td>
<td>88</td>
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<tr>
<td>2</td>
<td><img src="image3" alt="" /></td>
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<td><img src="image15" alt="" /></td>
<td><img src="image16" alt="" /></td>
<td>64</td>
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</tbody>
</table>
Table 3 continued

| 9 | \[
\begin{array}{c}
\text{CHO} \\
\text{CHO}
\end{array}
\]

| 70 | \[
\begin{array}{c}
\text{CN} \\
\text{CN}
\end{array}
\]

| 10 | \[
\begin{array}{c}
\text{CHO} \\
\text{CHO}
\end{array}
\]

| 81 | \[
\begin{array}{c}
\text{CN} \\
\text{CN}
\end{array}
\]

*Reaction conditions: (a) aldehyde (2.0 mmol), TMSAN (2.4 mmol), 1a (2 mol %), THF (2 mL), 0 °C, 24 h, followed by 1N HCl (3 mL). Isolated yield after column chromatography. See ref 7. See ref 9f.

A proposed mechanistic pathway for the addition of TMSAN to aldehydes is shown in Scheme 1. To obtain some insight into this pathway, we carried out $^{29}$Si NMR experiments at -40 °C in which a THF solution of TMSAN ($\delta^{29}$Si 5.02 ppm in THF) was treated with an equimolar amount of 1a. A new peak, which then appeared at $\delta^{29}$Si 9.16, was attributed to the tetracoordinate silicon species B in which the anionic CH$_2$CN$^{-}$ has been displaced. This chemical shift is in the same region as a peak we reported previously for a 1:1 mixture of TMSCN and 1d in C$_6$D$_6$ ($\delta^{29}$Si 7.5) in which CN$^{-}$ had been displaced. If the anion had not been displaced in both cases, an upfield rather than a downfield shift from the parent TMSX molecule would have been observed since the silicon would have become 5-coordinate.\textsuperscript{12c} We used similar reasoning to account for the formation of both $\alpha$- and $\gamma$-addition products in the reaction of crotlytrimethylsilane with aldehydes in the presence of 1a.\textsuperscript{12h} After transient A forms B in Scheme 1, an aldehyde molecule reacts with CH$_2$CN$^{-}$ to form the alkoxide shown, which after trimethylsilylation is acid-hydrolyzed to give the corresponding $\beta$-hydroxynitrile as the final product, plus the regenerated catalyst 1a.
Although we have $^{29}\text{Si}$ NMR evidence consistent with the formation of B, we have no convincing $^{31}\text{P}$ NMR evidence for this species. $^{31}\text{P}$ chemical shifts for PR$_4^+$ cations are generally in the range of 90-140 ppm. The chemical shift for B is 119 ppm at -40 °C in THF, which is virtually unchanged from the value of 1a under the same conditions. This result perhaps suggests a minimal perturbation of the phosphorus shielding environment as a result of a weak Si-P interaction.

Since six-coordinate silicon species are also well known, A in Scheme 1 may undergo nucleophilic attack by the carbonyl oxygen of the aldehyde to give rise to the six-coordinate intermediate C shown in Scheme 2. This intermediate may then decompose to product and regenerated catalyst 1a via the 4-center intermediate depicted in D. The unreactivity of ketones in our protocol can be rationalized on the basis of their increased steric hindrance in the formation of intermediates C and D.
Scheme 1. Proposed Mechanism of TMSAN Addition to Aldehydes

Conclusion

In summary, commercially available 1a is an excellent catalyst for the synthesis of β-hydroxynitriles via the reaction of TMSAN with aldehydes. Our reaction conditions are mild and our catalyst loadings are the lowest we were able to find in the literature for this transformation. In the case of aryl aldehydes, both electron withdrawing and donating groups are well tolerated, both heterocyclic and aliphatic aldehydes function well, and both acid- and base-sensitive functionalities favor the reaction. Comparing our yields to the maximum yields for seven different methods in the literature using seven different catalyst systems, our yields were lower in two cases, comparable (±5%) in four, and higher in one case. For the two literature yields that were larger than ours, one literature preparation involved the use of LiOAc in DMF and in the other, 2.5 mol % of [Cu(PPh₃)₃][(EtO)₃SiF₂] and 120 mol % of
(EtO)₃SiF as an additive were present. In Table 3 our yields for two substrates when compared to the maximum yields in the literature, were comparable in one case (±5%) and lower in the other, the literature method for these two cases involved the use of 10 mol % of LiOAc in DMF. From an environmental standpoint, it is worth noting that our catalyst is metal-free.

Scheme 2. Alternative Proposed Mechanism of TMSAN Addition to Aldehydes

Experimental Section

General reaction procedure. A round bottom flask was charged with the required amount of proazaphosphatrane (1) (2 mol %), in a nitrogen-filled glove-box. Anhydrous THF (2.0 mL) was added to the flask via syringe, followed by addition of TMSAN (2.40 mmol) at 0 °C via syringe under an argon atmosphere. The reaction mixture was stirred at 0 °C for 15 min and then aldehyde (2.0 mmol) was added over a period of 5–10 min. The reaction mixture was stirred for 24 h at 0 °C and then it was quenched with 3 mL of aqueous HCl (1N). The reaction mixture was stirred at 0 °C for 1 h and then it was neutralized with
saturated aq. NaHCO₃ and extracted with CH₂Cl₂ (3 × 30 mL). The crude product was purified by column chromatography on silica gel using 10% EtOAc/hexanes, except for heterocyclic substrates, in which case 20–25% EtOAc/hexanes was used as the eluent.

Acknowledgment

We are grateful to the Aldrich Chemical Co. for their generous gift of 1a. The National Science Foundation is gratefully acknowledged for financial support of this research through grant 0750463. We also thank Dr. Ch. Venkat Reddy for helpful discussions.

References


(13) Proazaphosphatranes 1a, 1c, and 1d are commercially available.


CHAPTER 5. P(PhCH₂NCH₂CH₂)₃N: AN EFFICIENT LEWIS-BASE CATALYST FOR THE SYNTHESIS OF PROPARGYLIC ALCOHOLS AND MORITA-BAYLIS-HILLMAN ADDUCTS VIA ALDEHYDE ALKynylation

Kuldeep Wadhwa, Venkat Reddy Chintareddy, John G. Verkade

Accepted in J. Org. Chem.

Abstract: Proazaphosphatrane P(PhCH₂NCH₂CH₂)₃N (1a) is an efficient catalyst for the addition of aryl trimethylsilyl alkynes to a variety of aromatic, aliphatic and heterocyclic aldehydes in THF at room temperature. The reaction conditions are mild and employ a low catalyst loading (ca. 5 mol %). Only propargylic alcohols were isolated in good to excellent isolated yields when electron-rich, electron-neutral, heterocyclic and aliphatic aldehydes were employed, whereas β-branched Morita-Baylis-Hillman (MBH) type adducts were isolated with electron-deficient aromatic aldehydes after conventional acid hydrolysis of the TMS ether products. Alkynes containing heterocyclic, and aromatic groups bearing electron-withdrawing or donating substituents underwent clean addition to
cyclohexanecarboxaldehyde and to electron-rich aromatic aldehydes to give propargylic alcohols in excellent isolated yields. β-Branched Morita-Baylis-Hillman (MBH) type adducts were isolated when electron-deficient aromatic aldehydes were employed. Reaction pathways to both types of products are proposed.

Introduction

Propargylic alcohols are useful in the synthesis of complex multi-functional natural products, such as (−)-Reveromycin B, Aspinolide B, (±)-Blastmycinone, (−)-Methylenolactocin, (+)-Sterpurene, and (−)-Chlorothricolide via carbon-carbon bond forming reactions.\textsuperscript{1-3} Several methods have been described in the literature over the decades for the synthesis of propargylic alcohols,\textsuperscript{4-7} and the most common technique for their synthesis is via the use of metal bases (\textit{e.g.}, \textit{n}-BuLi) to generate the acetylide ion.\textsuperscript{4-6} Heavy metals have also been used in the preparation of propargylic alcohols.\textsuperscript{5,6} For example, Carreira \textit{et al.} have worked extensively on stereoselective alkynylation of aldehydes, mainly with Zn metal-based catalytic systems.\textsuperscript{5} In addition, Ag-, In- and Ru-based catalyst systems for terminal alkyne addition have also been reported.\textsuperscript{6}

In recent years, several reports on Lewis-base activation of various organosilyl reagents to yield important organic intermediates have been published.\textsuperscript{8} Pertinent to the present work on activation of silyl-terminated alkynes to generate the corresponding acetylide nucleophiles, are past examinations of this process.\textsuperscript{7} In 1976, Kuwajima \textit{et al.} first reported the use of tetrabutylammonium fluoride (3-5 mol %) for the reaction between 1-trimethylsilyl-2-phenylacetylene with aldehydes and ketones, providing products in yields ranging from 5 to 87\%.\textsuperscript{7a,7b} Shioiri \textit{et al.} reported the use of a quaternary ammonium fluoride
salt derived from cinchonine (10 mol %) at -20 °C to facilitate the reaction of 1-trimethylsilyl-2-phenylacetylene with aldehydes, Morita-Baylis-Hillman (MBH) type adducts, were isolated in 23-92% yields. Among the eleven aldehydes screened, alkynylation product was obtained in the case of benzaldehyde and o-phthalaldehyde in minor quantities. Whereas alkynylation was observed as a major product with p-anisaldehyde and 3,4-dimethoxybenzaldehyde.\textsuperscript{7c} The use of 10 mol % of KOEt in THF as solvent at 0 °C was reported by Sheidt \textit{et al.} to provide good yields of alkynylated product when triethoxysilylacetylenes were used as reagents with aldehydes, ketones and imines.\textsuperscript{7d} In 2006, Mukaiyama \textit{et al.} reported that 10 mol % of [Bu\textsubscript{4}N][OPh] at -78 °C in THF as solvent gave 39-100% isolated alkynylated product yields with aldehydes and four ketone substrates.\textsuperscript{7e} Matsukawa \textit{et al.} reported the synthesis of propargylic alcohols using tris(2,4,6-trimethoxyphenyl)phosphine (10 mol %) as a catalyst for reaction between 1-trimethylsilyl-2-phenylacetylene and various aldehydes in DMF as solvent at 100–120 °C yielding product 74-96% isolated yield.\textsuperscript{7f} Tetrabutylammonium triphenyldifluorosilicate was used (10 mol %)\textsuperscript{7g} to promote the reaction between 1-trimethylsilyl-2-phenylacetylene and benzaldehyde yielded the alkynylated product in 81% yield. However, the generality of this process remains to be determined.\textsuperscript{7g} The use of tetraphenylphosphonium hydrogen difluoride (3-8 mol %) to catalyze the reaction of 1-trimethylsilyl-2-phenylacetylene with one aldehyde and three ketones in DMF solvent at 50 °C provided moderate product yields (46-64%).\textsuperscript{7h} Corey \textit{et al.} utilized a 1:1 mixture of CsF and CsOH for silyl activation of 1-trimethylsilyl-2-phenylacetylene in the alkynylation of two aldehydes, which gave good product yields (85 and 90%,) although 1.6 equiv. of fluoride ion was required.\textsuperscript{7i}
Discovered for the first time in our laboratories, proazaphosphatranes of the type shown in Figure 1 are strongly basic, with pK$_a$ values of 32–34 in CH$_3$CN for their P-protonated N$_{basal}$→P transannulated conjugated acids. If such transannulation occurs during a catalytic cycle, the nucleophilicity of the phosphorus center would be enhanced. The catalytic activation of silicon centers by the phosphorus of proazaphosphatranes has been invoked, for example, for silylation of alcohols using silyl chloride, for the synthesis of cyanohydrins by the addition of trimethylsilyl nitrile to carbonyl compounds, for desilylation of TBDMS ethers, for nucleophilic aromatic substitution of aryl fluorides with aryl silylethers, for allylation of aromatic aldehydes, and for the reduction of aldehydes and ketones with poly(methylhydrosiloxane).

Figure 1. Proazaphosphatranes

![Figure 1. Proazaphosphatranes](image)

Results and Discussion

In the present work, we report the use of proazaphosphatrane 1a as an efficient catalyst for the synthesis of propargylic alcohols using electron-rich, electron-neutral, heterocyclic and aliphatic aldehydes with trimethylsilylacetylenes, whereas β-branched Morita-Baylis-Hillman (MBH) type adducts are obtained as the sole products in the case of electron-deficient aromatic aldehydes (Scheme 1).
We first screened the reaction between benzaldehyde and 1-trimethylsilyl-2-phenylacetylene (2) (as shown in the Scheme in Table 1) using 1a as a catalyst. With 5 mol % catalyst and 1 equivalent of alkyne 2 in THF solvent, complete conversion to a mixture of 3a and 3b was observed by $^1$H NMR spectroscopy. Silica gel column chromatography allowed 3a to be isolated in 79% yield and the MBH type adduct 3b in 6% yield (Table 1, entry 1). We then attempted to minimize formation of the MBH product 3b by lowering the catalyst 1a loading to 3 mol % (Table 1, entry 2). Unfortunately, the corresponding alkynylation product 3a was isolated in only 20% yield and only starting aldehyde was recovered from the remainder of the reaction mixture. Gratifyingly, increasing the trimethylsilyl alkyne to two equivalents (Table 1, entry 3) increased the yield of the alkynylation product 3a to 82% with only a 2% yield of the MBH side product 3b. Lowering the temperature to 0 °C had no significant effect on the ratio of the two products (Table 1,
entry 4). We then screened proazaphosphatranes 1b-1d in the reaction in Table 1 using the best catalytic conditions reported in this table (entry 3) and the results are recorded in Table 1, entries 5-7. From these results, it is seen that 1a functioned best for making 3a under the conditions in entry 3 of Table 1. No reaction was observed under our conditions in the absence of catalyst (Table 1, entry 8).

**Table 1.** Survey of proazaphosphatranes as catalysts for the synthesis of propargylic alcohols.a

![Chemical structure diagram](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>mol (%)</th>
<th>2 (Equiv.)</th>
<th>temp (°C)</th>
<th>yield of 3a (%)b</th>
<th>yield of 3b (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>5</td>
<td>1.5</td>
<td>25</td>
<td>79</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>3</td>
<td>1.5</td>
<td>25</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>5</td>
<td>2.0</td>
<td>25</td>
<td>82</td>
<td>2</td>
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<td>(27-100)c-i</td>
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<tr>
<td>4</td>
<td>1a</td>
<td>5</td>
<td>2.0</td>
<td>0</td>
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<tr>
<td>5</td>
<td>1b</td>
<td>5</td>
<td>2.0</td>
<td>25</td>
<td>72</td>
<td>10f</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>5</td>
<td>2.0</td>
<td>25</td>
<td>42</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>1d</td>
<td>5</td>
<td>2.0</td>
<td>25</td>
<td>69</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
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<td>-</td>
<td>2.0</td>
<td>25</td>
<td>n.r. k</td>
<td>n.r. k</td>
</tr>
</tbody>
</table>

*a Reaction conditions: aldehyde (2.0 mmol), THF (2 mL), 24 h, followed by 1N HCl (3 mL).  
b Isolated yield after silica gel column chromatography.  
c 76% yield using 3 mol % Bu₄NF (ref 7a).  
d 76% yield using 5 mol % Bu₄NF (ref 7b).  
e 27% yield using 10 mol % of the quaternary ammonium fluoride salt derived from cinchonine (ref 7c).  
f 100% yield using 10
62

mol % NBu₄(OPh) (ref 7e). ²95% yield using 10 mol % tris(2,4,6-trimethoxyphenyl)phosphine (ref 7f). ³81% yield using 10 mol % NBu₄N(Ph₃SiF₂) (ref 7g). ⁴64% yield using 3 mol % Ph₄P(HF₂) (ref 7h). ⁵Determined by ¹H NMR spectroscopic integration. ⁶No reaction.

To examine the scope of this methodology a wide variety of aldehydes consisting of electron-rich, electron-poor, heterocyclic and aliphatic examples were screened under the optimized conditions in Table 1, entry 3, and the results are summarized in Tables 2 and 3. Electron-deficient o-fluorobenzaldehyde reacted efficiently with alkyne 2 to yield the desired alkynylation product in an excellent isolated yield (Table 2, entry 1). Aldehydes with electron-donating substituents, such as p-tolualdehyde (Table 2, entry 2), m-methoxybenzaldehyde (Table 2, entry 3) and m-tolualdehyde (Table 2, entry 4) resulted in very good isolated yields of alkynylation products, except in the case of m-tolualdehyde, wherein 6% of the MBH adduct was isolated. Pleasingly, excellent isolated yields with no observable MBH side product were obtained when sterically hindered aldehydes, such as o-phenylbenzaldehyde (Table 2, entry 5), o-tolualdehyde (Table 2, entry 6) and 2,6-dimethylbenzaldehyde (Table 2, entry 7) were employed under our conditions. The versatility of our protocol was extended to the heterocyclic aldehyde, thiophene-2-carboxaldehyde, providing a 91% yield of alkynylation product (Table 2, entry 8). Unfortunately, pyridine- and furan-2-carboxaldehyde gave complicated mixtures the reason for which is not clear at this time (Table 2, entry 9 and 10 respectively).
Table 2. Reactions of electron-rich aromatic, and heterocyclic aldehydes with 1-trimethylsilyl-2-phenylacetylene (2) using proazaphosphatrane 1a as the catalyst.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b}</th>
<th>Lit. Yield (%)</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{align*}
&\text{F} \\
&\text{CHO}
\end{align*}
\] | \[
\begin{align*}
&\text{F} \\
&\text{OH} \\
&\text{C} \equiv \text{C} \\
&\text{C}
\end{align*}
\] | 95 | - |
| 2 | \[
\begin{align*}
&\text{Me} \\
&\text{CHO}
\end{align*}
\] | \[
\begin{align*}
&\text{Me} \\
&\text{OH} \\
&\text{C} \equiv \text{C} \\
&\text{C} \\
&\text{Me}
\end{align*}
\] | 82 | 100\textsuperscript{c} |
| 3 | \[
\begin{align*}
&\text{MeO} \\
&\text{CHO}
\end{align*}
\] | \[
\begin{align*}
&\text{MeO} \\
&\text{OH} \\
&\text{C} \equiv \text{C} \\
&\text{C} \\
&\text{Me}
\end{align*}
\] | 91 | - |
| 4 | \[
\begin{align*}
&\text{Me} \\
&\text{CHO}
\end{align*}
\] | \[
\begin{align*}
&\text{Me} \\
&\text{OH} \\
&\text{C} \equiv \text{C} \\
&\text{C}
\end{align*}
\] | 83 | - |
| 5 | \[
\begin{align*}
&\text{CHO}
\end{align*}
\] | \[
\begin{align*}
&\text{OH} \\
&\text{C} \equiv \text{C} \\
&\text{C}
\end{align*}
\] | 91 | - |
| 6 | \[
\begin{align*}
&\text{CHO} \\
&\text{Me}
\end{align*}
\] | \[
\begin{align*}
&\text{OH} \\
&\text{C} \equiv \text{C} \\
&\text{Me}
\end{align*}
\] | 97 | 99\textsuperscript{c} |
| 7 | \[
\begin{align*}
&\text{Me} \\
&\text{CHO} \\
&\text{Me}
\end{align*}
\] | \[
\begin{align*}
&\text{Me} \\
&\text{OH} \\
&\text{C} \equiv \text{C} \\
&\text{Me}
\end{align*}
\] | 96 | - |
Table 2 continued

<table>
<thead>
<tr>
<th></th>
<th>Structure 1</th>
<th>Structure 2</th>
<th>Yield (%)</th>
<th>Isolated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td><img src="image1" alt="Structure 1" /></td>
<td><img src="image2" alt="Structure 2" /></td>
<td>91</td>
<td>87c</td>
</tr>
<tr>
<td>9d</td>
<td><img src="image3" alt="Structure 1" /></td>
<td><img src="image4" alt="Structure 2" /></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10d</td>
<td><img src="image5" alt="Structure 1" /></td>
<td><img src="image6" alt="Structure 2" /></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a Reaction conditions: aldehyde (2.0 mmol), 2 (4.0 mmol), 1a (5 mol %), THF (2 mL), rt, 24 h, followed by 1N HCl (3 mL). b Isolated yield after column chromatography. c 10 mol % NBu₄(OPh) (ref 7e). d Inseparable complex mixture was observed.

After screening aromatic aldehydes, we tested several aliphatic examples (Table 3). All the substrates in this table selectively gave propargylic alcohols, and MBH type adduct formation was not observed. We conjecture that this is because the intermediate E (shown in scheme 2) required for MBH type adduct formation cannot be stabilized by aliphatic aldehydes (vide infra). Cyclohexanecarboxaldehyde (Table 3, entry 1), isobutyraldehyde (Table 3, entry 2) and heptaldehyde (Table 3, entry 3) led to generally excellent isolated yields of alkynylation product (96, 94 and 84%, respectively). Interestingly, catalyst 1a was efficient in producing a high yield of alkynylation product with a long-chain unsaturated aliphatic aldehyde (Table 3, entry 4).
Table 3. Reactions of aliphatic aldehydes with 1-trimethylsilyl-2-phenylacetylene (2) using proazaphosphatrane 1a as the catalyst.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
<th>Lit. Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>96</td>
<td>79$^c$, 85$^d$, 88$^e$</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
<td>94</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>6</td>
<td>84</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>8</td>
<td>79</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: aldehyde (2.0 mmol), 2 (4.0 mmol), 1a (5 mol %), THF (2 mL), rt, 24 h, followed by 1N HCl (3 mL). $^b$ Isolated yield after column chromatography. $^c$ Using 10 mol % NBu$_4$(OPh) (ref 7e). $^d$ Using 3.2 equiv. of a 1:1 mixture of CsOH/CsF (ref 7i). $^e$ 88% yield using 10 mol % tris(2,4,6-trimethoxyphenyl)phosphine (ref 7f).

We next screened several electron-poor aldehydes and observed the β-branched MBH type adducts formed exclusively under our conditions (Table 4), this may be because of the formation of stabalized intermediate E as shown in scheme 2 (vide infra). Acid-sensitive electron-deficient methyl 4-formylbenzoate selectively gave the MBH adduct in good isolated yield (Table 4, entry 1). Electron-poor halogen-containing 3-iodobenzaldehyde
(Table 4, entry 2) and 4-bromobenzaldehyde (Table 4, entry 4) also stereoselectively afforded the MBH type adducts in good isolated yields and electron-deficient 4-(trifluoromethyl)benzaldehyde yielded the MBH adduct in excellent isolated yield (Table 4, entry 3).

**Table 4.** Reactions of electron-deficient aldehydes with 1-trimethylsilyl-2-phenylacetylene (2) using 1a as the catalyst.ª

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>79</td>
</tr>
</tbody>
</table>

ª Reaction conditions: aldehyde (2.0 mmol), 2 (4.0 mmol), 1a (5 mol %), THF (2 mL), rt, 24 h, followed by 1N HCl (3 mL). ° Isolated yield after column chromatography.

We then screened alkynes with various electron-withdrawing, electron-donating and heterocyclic functionalities. Gratifyingly they all tolerated our reaction conditions well, giving good to excellent isolated yields of alkynylation products (Table 5). We also examined substituents on the alkyne phenyl group. With an electron-donating methoxy...
group, an excellent isolated product yield of 92% was realized (Table 5, entry 1). An electron-deficient trifluoromethyl group at the para position (Table 5, entry 2) led to a good isolated yield of the desired product and halogens (both bromo and chloro at ortho and meta positions, respectively) resulted in good isolated product yields (Table 5, entry 4 and 5). Heterocyclic functionalities (such as pyridyl or thiophenyl) on the alkynes also underwent complete conversion, good to excellent isolated yields of the desired product under our reaction conditions (Table 5, entries 3 and 6). The use of terminally silylated aliphatic alkynes, such as hex-1-ynyltrimethylsilane (Table 5, entry 7), produced no observable product using the reaction conditions reported in Table 5, footnote a.

**Table 5.** Reactions of cyclohexanecaboxaldehyde with substituted 1-trimethylsilylacetylenes using 1a as the catalyst.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Alkyne</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Aldehyde 1" /></td>
<td><img src="image2.png" alt="Alkyne 1" /></td>
<td><img src="image3.png" alt="Product 1" /></td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4.png" alt="Aldehyde 2" /></td>
<td><img src="image5.png" alt="Alkyne 2" /></td>
<td><img src="image6.png" alt="Product 2" /></td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7.png" alt="Aldehyde 3" /></td>
<td><img src="image8.png" alt="Alkyne 3" /></td>
<td><img src="image9.png" alt="Product 3" /></td>
<td>88</td>
</tr>
</tbody>
</table>
Table 5 continued

<table>
<thead>
<tr>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td><img src="4.png" alt="Image" /></td>
<td><img src="5.png" alt="Image" /></td>
<td><img src="6.png" alt="Image" /></td>
<td><img src="7.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Table 5a

| 86 | 84 | 91 | nr<sup>c</sup> |

<sup>a</sup> Reaction conditions: aldehyde (2.0 mmol), 2 (4.0 mmol), 1a (5 mol %), THF (2 mL), rt, 24 h, followed by 1N HCl (3 mL).<sup>b</sup> Isolated yield after column chromatography. <sup>c</sup> No reaction.

Electron-rich aromatic aldehydes were also evaluated in the presence of a variety of aromatic-substituted alkynes (Table 6). Bulky 2,6-dimethylbenzaldehyde reacted with the electron-rich alkyne in entry 1 of Table 6 giving a quantitative conversion to the alkynylation product in excellent isolated yield (92%). A terminal silylated aromatic alkyne substituted with a bromine at the ortho or a chloro group at the meta position afforded the desired products with 2-biphenylcarboxaldehyde and o-tolualdehyde (Table 6, entries 2—4) in good to moderate isolated yields. o-Tolualdehyde in the presence of an electron-deficient or electron-rich alkyne (having a p-trifluoromethyl group or a p-methoxy group on the terminal phenylacetylene) gave good isolated yields of the alkynylation product (Table 6, entries 5 and 6, respectively). Heterocyclic alkynes, such as thiophenyl and pyridyl, also underwent...
complete conversion to give modest to good isolated yields of the desired product with o-tolualdehyde under our reaction conditions (Table 6, entries 7 and 8, respectively).

In accord with the results shown in Table 4, we obtained MBH type adducts stereoselectively as the cis-isomer (as determined by 2D NOESY NMR, Table 4, entry 2) when the reaction was carried out between electron-deficient aldehydes and substituted terminally-silylated alkynes (Table 7). Here the product yields ranged from modest (65%) to moderate (74%).

Table 6. Reactions of electron-rich aromatic aldehydes with variously substituted 1-trimethylsilylacetylenes using 1a as catalyst.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Alkyne</th>
<th>Product</th>
<th>Yield (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
<td>78</td>
</tr>
</tbody>
</table>
Table 6 continued

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<tbody>
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<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="image3" alt="Image" /></td>
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</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Image" /></td>
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<tr>
<td>8</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
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<table>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) Reaction conditions: aldehyde (2.0 mmol), 2 (4.0 mmol), 1a (5 mol %), THF (2 mL), rt, 24 h, followed by 1N HCl (3 mL). \( ^b \) Isolated yield after column chromatography.

A rationale for the selectivity in the formation of the two different types of products we observed, can be given using a combination of mechanisms for the two reactions\(^{11}\) (Scheme 2). After activation of the silyl group of 2 by proazaphosphatane 1a to form the activated pentacoordinated silicon species A, A dissociates to form the cationic intermediate B and the
acetylide counter anion. To obtain some insight into this pathway, we carried out \(^{29}\)Si NMR experiments at -40 °C in which we combined 1-trimethylsilyl-2-phenylacetylene (\(\delta ^{29}\)Si NMR, -18.5 ppm in THF) with proazaphosphatrane \(\text{1a}\) in equimolar ratio in THF. A new \(^{29}\)Si peak appeared at \(\delta 7.17\) ppm, which was attributed to the tetracoordinate silicon species \(\text B\) from which the acetylide anion had been displaced. This chemical shift accords with the previously reported value for a 1:1 mixture of TMSCN and \(\text{1d}\) in \(\text{C}_6\text{D}_6\) (\(\delta ^{29}\)Si 7.5 ppm) in which \(\text{CN}^-\) had presumably been displaced.\(^{10c}\) If the anion had not been displaced in both cases, an upfield rather than a downfield shift from the parent TMSCN molecule would have been observed since the silicon would have become 5-coordinate.\(^{10c}\) We used similar reasoning to account for the formation of both \(\alpha\)- and \(\gamma\)-addition products in the reaction of crotyltrimethylsilane with aldehydes in the presence of \(\text{1b}\).\(^{10h}\) The acetylide ion in Scheme 2 then nucleophilically attacks the aldehyde to give the ionic intermediate \(\text C\). Transfer of the silyl group to the alkoxide regenerates catalyst \(\text{1a}\) and the alkynylated product \(\text D\) is formed concomitantly. In the case of electron-deficient aldehydes, \(\text D\) can undergo a deprotonation step to form intermediate \(\text E\), followed by rearrangement of \(\text E\) to give the allenic anion \(\text F\). Anion \(\text F\) could abstract a proton from \(\text D\) to generate \(\text E\) and give allene \(\text G\), which has been previously isolated as a crude product and which, after addition of an aldehyde produced \(\text H\), which in turn was converted to the MBH type adduct upon acid hydrolysis.\(^{11}\)
Table 7. Reactions of electron-deficient aldehydes with substituted 1-trimethylsilylacetylenes using 1a as catalyst.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Alkyne</th>
<th>Product</th>
<th>Yield (%) \textsuperscript{b}</th>
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<td><img src="image9.png" alt="Image" /></td>
<td>72</td>
</tr>
</tbody>
</table>
Table 7 continued

| 4  | F₃C-PhCHO | TMS-≡C-THF | 68 |
| 5  | MeO₂C-PhCHO | TMS-≡C-PhCF₃ | 73 |
| 6  | Br-PhCHO | TMS-≡C-PhCF₃ | 65 |

*a* Reaction conditions: aldehyde (2.0 mmol), 2 (4.0 mmol), 1a (5 mol%), THF (2 mL), rt, 24 h, followed by 1N HCl (3 mL). *b* Isolated yield after column chromatography.
Scheme 2. Proposed Mechanism for the Alkynylation and MBH Reactions

Conclusion

We have found that the non-ionic Lewis basic proazaphosphatrane 1a is an efficient catalyst for addition of 1-aryl-2-(trimethylsilyl)acetylenes to aldehydes at room temperature. The selectivity of this reaction for the synthesis of propargylic alcohols is facilitated by electron-rich, electron-neutral, heterocyclic and aliphatic aldehydes, whereas MBH type adducts are isolated when electron-deficient aldehydes are employed, regardless of the substituents on the propargylic alcohol and despite the use of excess alkyne. Attempts to maximize yields of MBH type adducts by using a ratio of 0.5 equiv. of alkyne to aldehyde and by increasing the catalyst loading to 10 mol %, resulted in a 1:1 ratio of alkynylation to MBH product. We
believe our protocol will find many applications in organic syntheses, including the synthesis of a variety of useful polyfunctional aromatics. The use of low metal-free catalyst loading (ca. 5 mol %), the high isolated product yields, the broad scope, and room temperature reaction conditions are attractive features of this protocol.

**Experimental Section**

**General Procedure for Alkynylation and MBH reactions.** A flat bottom screw-capped vial was charged with proazaphosphatrane catalyst 1a (44.4 mg, 0.1 mmol, 5 mol %) in a nitrogen filled glove box. To the vial was added at room temperature, 2.0 mL of anhydrous THF, followed by the addition of aldehyde (2.0 mmol). The resulting solution was stirred at room temperature for 15 min and then aryl(trimethylsilyl)acetylene (4.0 mmol) was added over a period of two min. Progress of the reaction was monitored by TLC. The reaction mixture was stirred for 24 h and quenched with 3 mL of an aq. solution of HCl (1N). The mixture was stirred for an additional 1 h and then neutralized with saturated aq. NaHCO₃ solution. The crude product was extracted with CH₂Cl₂ (3 × 30 mL) and the combined organic extracts were dried over anhydrous MgSO₄ (ca. 2.0 g). The crude product was purified by column chromatography using 30% EtOAc/hexane as eluent.

**Acknowledgment**

The National Science Foundation is gratefully acknowledged for financial support of this research in the form of grant 0750463.
References


CHAPTER 6. P(PhCH$_2$NCH$_2$CH$_2$)$_3$N CATALYSIS OF MUKAIYAMA ALDOL REACTIONS OF ALIPHATIC, AROMATIC, HETEROCYCLIC ALDEHYDES AND TRIFLUOROMETHYL PHENYL KETONE

Venkat Reddy Chintareddy, Kuldeep Wadhwa, and John G. Verkade

*manuscript in preparation*

**Abstract**: Herein we find that proazaphosphatrane 1c is a very efficient catalyst for Mukaiyama aldol reactions of aldehydes with trimethylsilyl enolates in THF solvent. Only the activated ketone 2,2,2-trifluoroacetophenone underwent clean aldol product formation with a variety of trimethylsilyl enolates under similar conditions as the aldehydes. The reactions were carried out at room temperature using (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane, whereas the temperature was $-15 \, ^{\circ}C$ in the case of 1-phenyl-1-(trimethylsilyloxy)ethylene. The reaction conditions are mild and operationally simple, and a variety of aryl functional groups, such as nitro, amino, ester, chloro, trifluoromethyl, bromo, iodo, cyano, and fluoro groups are tolerated. Product yields are generally better than or
comparable to those in the literature. 1-Phenyl-1-(trimethylsilyloxy)ethylene, 1-(trimethylsilyloxy)cyclohexene and 2-(trimethylsilyloxy)furan underwent clean conversion to β-hydroxy carbonyl compounds under our reaction conditions. In the case of bulky (2,2-dimethyl-1-methylenepropoxy)trimethylsilane, only α,β-unsaturated esters were isolated. Heterocyclic aldehydes, such as pyridine-2-carboxaldehyde, benzofuran-2-carboxaldehyde, benzothiophene-2-carboxaldehyde, and 1-methyl-2-imidazolecarboxaldehyde gave good yields of Mukaiyama products. An optimized synthesis for the catalyst 1c is also reported herein.

Introduction

The Mukaiyama aldol reaction is a versatile carbon-carbon bond forming reaction, which occurs between an enoxysilane and a carbonyl compound to form β-hydroxy carbonyl compounds. The most common application of this transformation involves complex molecule synthesis (such as fragment coupling and chiral building block construction) and it has been the subject of intensive investigation for the past three decades. Moreover, the Mukaiyama reaction has significant advantages over the classical aldol reaction, such as mild reaction conditions, non-reversibility, good yields of aldol products and lower production of dehydrated side products. Initially, stoichiometric amounts of Lewis acids were used to promote Mukaiyama transformations, but it is now more common to employ catalytic loadings of these promoters whose role is believed to be the activation of the electrophilic carbonyl carbon substrate. Among the considerable number of such catalysts are Me3SiOTf, Me3SiI, Me3SiCl/SnCl2, Ph3CCl/SnCl2, Ph3CC1O4, trityl salts; various
rhodium complexes,\textsuperscript{13} trivalent lanthanum,\textsuperscript{14a} Ln(OTf)\textsubscript{3} (Ln = Yb\textsuperscript{14b}, Gd, Lu),\textsuperscript{14c} and scandium\textsuperscript{14e} triflates; Yb[C(SO\textsubscript{2}C\textsubscript{8}F\textsubscript{17})\textsubscript{3}] and Sc[C(SO\textsubscript{2}C\textsubscript{8}F\textsubscript{17})\textsubscript{3}],\textsuperscript{14f} iron,\textsuperscript{15a,15b} ruthenium,\textsuperscript{15c} palladium\textsuperscript{15c,15d} and bis((bis1,3-trimethylsilyl)cyclopentadienyl)ytterbium(III) chloride\textsuperscript{16a} complexes; and [Et\textsubscript{3}Si(toluene)]B(C\textsubscript{6}F\textsubscript{5})\textsubscript{4},\textsuperscript{16b} [Cp\textsubscript{2}Zr(OrBu)THF][BPh\textsubscript{4}],\textsuperscript{16c} BiCl\textsubscript{3}-NaI,\textsuperscript{16d} Sc(OTf)\textsubscript{3}-water,\textsuperscript{16e} (PfOBu\textsubscript{2}SnOSnBu\textsubscript{2}OPf)\textsubscript{2},\textsuperscript{16f} Bi(OTf)\textsubscript{3},\textsuperscript{16g} Bi(OTf)\textsubscript{3}/ionic liquids,\textsuperscript{16h} Cp\textsubscript{2}Zr(OTf)\textsubscript{3},\textsuperscript{16i} complexes of Ti(IV),\textsuperscript{17a} 1,3-dihalotetraalkyldistannoxane,\textsuperscript{17c} [Mo\textsubscript{2}(OAc)\textsubscript{4}]/O\textsubscript{2},\textsuperscript{17d} LnBr\textsubscript{3},\textsuperscript{17e} scandium trisdodecanesulfonate,\textsuperscript{17f} B-[3,5-bis(trifluoromethyl)phenyl]oxazaborolidine,\textsuperscript{17g} SmI\textsubscript{2},\textsuperscript{18a} MgI\textsubscript{2}-(OEt\textsubscript{2})\textsubscript{n},\textsuperscript{18b} polymer-supported Sc(OTf)\textsubscript{3},\textsuperscript{18c,d} titanium silicates,\textsuperscript{18e,f} montmorillonite K10,\textsuperscript{18g} SmCl\textsubscript{3},\textsuperscript{18h} FeCl\textsubscript{2},\textsuperscript{18i} zinc triflate,\textsuperscript{18j} Sc(OTf)\textsubscript{3} in PEG,\textsuperscript{18k,l} a dinuclear titanium(IV) complex of \textit{p}-\textit{tert}-butylthiacalix[4]arene,\textsuperscript{18m} aluminum bis(trifluoromethylsulfonyl)amides,\textsuperscript{18n} sulfated-metal oxides,\textsuperscript{18o} Sc(OTf)\textsubscript{3}/amphiphilic calix[6]arene complex,\textsuperscript{18p} InCl\textsubscript{3},\textsuperscript{18q} sulfated-ZrO\textsubscript{2},\textsuperscript{18r} MCM-41,\textsuperscript{18s} diphenyltin sulfide/silver perchlorate,\textsuperscript{18t} BF\textsubscript{3}-OEt\textsubscript{2},\textsuperscript{18u} Sn-MCM-48,\textsuperscript{18v} mesoporous-Mn\textsuperscript{2+} catalyst,\textsuperscript{18w} CuF·3PPh\textsubscript{3}·2EtOH/(EtO)\textsubscript{3}SiF,\textsuperscript{18x} and tris(pentafluorophenyl)boron.\textsuperscript{18y}

Lewis bases that have been employed to nucleophilically activate the enoxysilane substrate include 0.5 mol % of sodium phenoxide-phosphine oxides,\textsuperscript{19} 20 mol % tris(2,4,6-trimethoxyphenyl)phosphate,\textsuperscript{20} 1 mol % quaternary ammonium dendrimers containing iodide counterions,\textsuperscript{21a} 1 mol % SBA-15 functionalized TBD \{1,5,7-triazabicyclo[4.4.0]dec-5-ene\},\textsuperscript{21b} 20 mol % of DBU,\textsuperscript{21c} 10 mol % a polystyrene-bound-phosphoramido,\textsuperscript{21d} quaternary ammonium fluoride salts,\textsuperscript{21e} 5-10 mol % fluorides,\textsuperscript{22} 10 mol % lithium alkoxides,\textsuperscript{23a} 10 mol % lithium acetate,\textsuperscript{23b,23c} 10 mol % \textit{N}-oxides,\textsuperscript{24} and 10 mol % \textit{N}-methylimidazole.\textsuperscript{25} Mukaiyama \textit{et al.} also reported such reactions employing 1 equivalent of lithium amide\textsuperscript{26} or
10 mol % acetate catalysts\textsuperscript{27} and recently, Song \textit{et al.} reported a catalytic method with 0.5 mol % N-heterocyclic carbenes as catalysts.\textsuperscript{28}

It has also been reported that Mukaiyama aldol reactions can proceed without catalysts in highly polar solvents, such as DMF,\textsuperscript{29a} DMSO,\textsuperscript{29a} water,\textsuperscript{29b} and ionic liquids.\textsuperscript{29c} Another catalytic system utilizes iodine whose mechanism of action is suggested to involve an electron transfer pathway.\textsuperscript{30}

The activation of silyl enolates in which the Lewis acidity of the silicon atom has been enhanced by a Lewis base has been studied by Denmark \textit{et al.} who introduced phosphoramide Lewis bases to catalyze the aldol reaction of trichlorosilyl enolates with aldehydes.\textsuperscript{31} Similarly, Hosomi and co-workers reported a Mukaiyama reaction using a dimethylsilyl enolate in the presence of an aldehyde or imine substrate and CaCl\textsubscript{2} in dry or aqueous DMF solvent.\textsuperscript{32}

Previous work in our laboratories has established that bicyclic proazaphosphatranes\textsuperscript{33} (Figure 1) bearing methyl, \textit{iso}-butyl or benzyl groups on the PN\textsubscript{3} nitrogens are highly effective catalysts, promoters, and ligands for Pd-catalyzed cross-coupling reactions, such as Buchwald-Hartwig aminations,\textsuperscript{34a} Stille couplings,\textsuperscript{34b} and Suzuki reactions.\textsuperscript{34c}
Figure 1. Proazaphosphatranes (1) and imino-proazaphosphatranes (2).

Proazaphosphatranes are strongly basic, with pKₐ values of their P-protonated N_{basal→P} transannulated conjugate acids in the range 32-34 in MeCN.³⁴ To the extent that N_{basal→P} transannulation may be occurring during reactions catalyzed by 1, the nucleophilicity of the phosphorus may be enhanced.³³ Earlier we reported the activation of silicon-carbon bonds by strongly Lewis basic proazaphosphatranes in the silylation of alcohols with tert-butylidimethylsilyl chloride (TBDMSCl),³⁵ desilylation of TBDMS ethers,³⁶ addition of TMSCN to carbonyl compounds,³⁷ and nucleophilic aromatic substitution of aryl fluorides with aryl TBDMS (or TMS) ethers.³⁸ As part of our ongoing efforts to expand synthetic methodologies facilitated by the use of proazaphosphatranes as catalysts, we report here efficient activation of silicon in silyl enolates using 1c as a catalyst in Mukaiyama aldol reactions (Scheme 1).
Although we reported the synthesis of 1c previously, we now describe a more convenient set of reaction conditions (Scheme 2). Both synthetic methods involve three steps, but step 1 is now better optimized and in step 3 the more convenient base LiHMDS is employed instead of KO'Bu. Although our overall yield of 38% for 1c is lower than that obtained via our previously reported route (48%), the present protocol provides more consistent yields in the deprotonation step.
Results and Discussions

For optimization of the Mukaiyama reaction conditions, the room temperature aldol reaction of the electron-neutral aryl aldehyde shown in the model reaction in (Table 1) was chosen. All the proazaphosphatranes screened (1a-f) resulted in good to excellent isolated yields of aldol products, which were obtained after room temperature acid hydrolysis. Since catalysts 1b and 1c produced nearly the same product yield (entries 2 and 3, respectively), we reduced the catalyst loading to 0.5 mol % which revealed the somewhat better performance of 1c (entries 7 and 8). Although we found that the bulky catalyst 1d showed better activity in a variety of transformations, 33 1c was best in the present transformation, as well as in Stille reactions on which we reported earlier. 33b The origin of the beneficial influence of the benzyl groups of catalyst 1c and the i-Bu substituents of 1d on different reactions is not clear.

Very recently, we reported the synthesis of 2a 40a and 2b 40a and their applications as bulky, air-stable, and electron-rich ligands in both palladium-catalyzed Suzuki 40b and in
Buchwald-Hartwig aminations.\textsuperscript{40c} In the Mukaiyama aldol screening reaction in Table 1, both catalysts showed comparable results under the same reaction conditions (entries 9 and 10 in Table 1). The control experiment shown in Table 1, entry 11 reveals the need for a catalyst to presumably activate the silicon center in the Mukaiyama aldol reaction. It is interesting that 8 out of the 12 methods found in the literature employ 5–20 mol % of catalyst (see footnote c of Table 1 to reach moderate to high product yields. On the other hand, NHC’s\textsuperscript{28} and a 1,3-dihalotetraalkyldistannoxane\textsuperscript{17c} produced 83 and 99% product yields using only 0.5 and 0.025 mol % of catalyst, respectively.

Table 1. Survey of Proazaphosphatranes in a Mukaiyama Aldol Reaction using (1-Methoxy-2-methyl-1-propenyl)trimethylsilane.\textsuperscript{a}

\[
\text{CHO} \quad \text{OTMS} \quad \text{OMe} \quad \text{1. catalyst, THF, 25 °C} \quad \text{2. 1N HCl} \quad \text{OH} \quad \text{OMe}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)\textsuperscript{b}</th>
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<tbody>
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<td>1a</td>
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<td>2</td>
<td>1b</td>
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<tr>
<td>3</td>
<td>1c</td>
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Table 1 continued

<table>
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<td>91</td>
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<tr>
<td>11</td>
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</table>

*a Reaction conditions: catalyst (2.0 mol %), aldehyde (2 mmol), silyl ether (2.4 mmol), THF (4 mL), 24 h, room temperature, followed by 1N HCl (4.0 mL), 12 h. b Isolated yields after silica gel column chromatography. c Refs 15c, 17c, 18c, 20, 21c, 23a, 23b, 26a, 26c, 27b, 27c, and 28. d Using 0.5 mol % of the catalyst 1c. e nr = No reaction after 24 h.

A variety of aldehydes were tested (Table 2) using the optimized reaction conditions reported in footnote a of Table 1 (unless stated otherwise in Table 2). As is evident from Table 2, both electron-neutral and electron-donating aldehydes reacted with equal ease with Me₂C=C(OMe)OSiMe₃, affording the desired aldols in good to excellent yields. Electron-neutral aryl aldehydes, such as benzaldehyde (Table 2, entry 1), 1-napthaldehyde (entry 2), and o-phenylbenzaldehyde (entry 3) also underwent clean addition reactions with Me₂C=C(OMe)OSiMe₃ to give the expected aldol products in good to excellent yields. Aldehydes with electron-donating substituents, such as m-methoxybenzaldehyde (entry 4), o-tolualdehyde (entry 5), 2,6-dimethylbenzaldehyde (entry 6), p-methoxybenzaldehyde (entry 7), 3,4-dimethoxybenzaldehyde (entry 8), and 2-methoxy-1-naphthaldehyde (entry 9) resulted in moderate to excellent isolated yields of aldol products. Excellent isolated yields were obtained when sterically hindered aldehydes, such as o-tolualdehyde (Table 2, entry 5), 2,6-dimethylbenzaldehyde (entry 6), and o-phenylbenzaldehyde (entry 3) were employed under our reaction conditions. Di-substituted isophthalaldehyde also participated in this reaction by providing a 93% combined yield of mono- and di-substituted products (entry 10).
when the ratio of isophthaldehyde/(1-methoxy-2-methyl-1-propenyl)trimethylsilane was 1:2.4.

It is interesting to note that the reaction of $\text{Me}_2\text{C}=$C(OMe)OSiMe$_3$ with $p$-$(N,N$-

(dimethylamino)benzaldehyde gave a poor yield of product (47%) when the neutralization
work up step was carried out with saturated aqueous NaHCO$_3$. However, an excellent isolated yield (96%) was obtained when the product was isolated as the TMS-protected alcohol in a separate experiment. Using the stronger base NaOH, instead of NaHCO$_3$, gratifyingly gave an excellent isolated yield of aldol product (90%) (Table 2, entry 11).

**Table 2.** Scope of the Mukaiyama Aldol reaction of Aldehydes with (CH$_3$)$_2$C=C(OCH$_3$)OSi(CH$_3$)$_3$ Catalyzed by 1c

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
<th>Lit. Yield (%)</th>
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<td>![image]</td>
<td>81</td>
<td>82-97$^d$</td>
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<tr>
<td>3$^e$</td>
<td>![image]</td>
<td>![image]</td>
<td>92</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2 continued

| 4  | ![Chemical Structure 4](image1) | ![Chemical Structure 5](image2) | 88  | -  |
| 5c | ![Chemical Structure 6](image3) | ![Chemical Structure 7](image4) | 92  | 93f |
| 6  | ![Chemical Structure 8](image5) | ![Chemical Structure 9](image6) | 86  | -  |
| 7  | ![Chemical Structure 10](image7) | ![Chemical Structure 11](image8) | 90  | 44-98g |
| 8c | ![Chemical Structure 12](image9) | ![Chemical Structure 13](image10) | 91  | -  |
| 9c | ![Chemical Structure 14](image11) | ![Chemical Structure 15](image12) | 69  | -  |
| 10h| ![Chemical Structure 16](image13) | ![Chemical Structure 17](image14) | 93i | -  |
A variety of aldehydes bearing electron-withdrawing groups were screened with Me₂C=OmeOSiMe₃ under the optimized conditions mentioned in Table 1, entry 3, and the results are summarized in Table 3. o-Chlorobenzaldehyde and o-fluorobenzaldehyde provided excellent isolated product yields (entries 1 and 2, respectively), while 3-iodobenzaldehyde (Table 3, entry 3) and 4-bromobenzaldehyde (entry 4) both gave good yields of product. Electron-deficient 4-(trifluoromethyl)benzaldehyde gave a moderate yield (entry 5) as did the p-nitro (entry 6), m-cyano (entry 7) and p-cyano (entry 8) analogues. p-Chloro and ester-functionalized aldehydes underwent clean reactions giving good to excellent yields of products (entries 9 and 10, respectively).
Table 3. Scope of the Mukaiyama Aldol Reaction of Functionalized Aldehydes with (CH$_3$)$_2$C=O(CH$_3$)OSi(CH$_3$)$_3$ Catalyzed by 1c$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
<th>Lit. Yield (%)</th>
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<td>(65$^c$, &lt;5$^d$)</td>
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<tr>
<td>2</td>
<td>F</td>
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<td>77</td>
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<tr>
<td>3$^e$</td>
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<td>F$_3$C</td>
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<td>84</td>
<td>33-68$^h$</td>
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<tr>
<td>6</td>
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<td>32-97$^i$</td>
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<td>7$^f$</td>
<td>CN</td>
<td>![Product Image]</td>
<td>58</td>
<td>-</td>
</tr>
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</table>

$^a$ Catalyst: 1c
$^b$ Isolated yield
$^c$ Ref. 5
$^d$ Ref. 6
$^e$ Ref. 7
$^f$ Ref. 8
$^g$ Ref. 9
$^h$ Ref. 10
$^i$ Ref. 11
We then turned our attention to screening various heterocyclic and aliphatic aldehydes with Me2C=O(OMe)OSiMe3 (Table 4). Both 5- and 6- membered ring aldehydes bearing N, O or S heteroatoms afforded the expected aldol product in poor to excellent isolated yields. Sulfur-containing 2-benzothiophenecarboxaldehyde afforded an excellent isolated product yield (Table 4, entry 1), 2-benzofurancarboxaldehyde gave a very good yield (Table 4, entry 2), and an enolizable aliphatic aldehyde (entry 3) also provided a good yield of the corresponding aldol product. However, 2-pyridinecarboxaldehyde and cyclohexanecarboxaldehyde gave only modest isolated product yields (entries 4 and 5, respectively). Nevertheless, the yield in entry 5 exceeded that previously reported in the literature. The two 5-membered heterocyclic aldehydes in Table 4 (entries 6 and 7) gave only low yields of the corresponding products.

Table 3 continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde Structure</th>
<th>Yield (°C-°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td><img src="image" alt="Aldehyde 8" /></td>
<td>74</td>
</tr>
<tr>
<td>9_f</td>
<td><img src="image" alt="Aldehyde 9" /></td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Aldehyde 10" /></td>
<td>82</td>
</tr>
</tbody>
</table>

*Reaction conditions: aldehyde (2.0 mmol), TMS-ether (2.4 mmol), I_c (3.0 mol % unless otherwise stated), THF (4.0 mL), room temperature, 24 h.*

_b_ Isolated yields after silica-gel chromatography.

_c_ Ref 24.

_d_ Ref 15c.

_e_ Using 10 mol % of catalyst 1_c.

_f_ Using 6 mol % of catalyst 1_c.

_g_ Refs 15c, 17e, 23a, 26a, 26c.

_h_ Ref 17d.

_i_ Refs 17e, 18f, 21b, 23a, 23b, 24, 25, 26a, 26c, 26b, 27b, 27c, 28.

_j_ Refs 18f, 23a, 26a, 26c, 28.

_k_ Refs 15c, 17e, 18c, 21c, 23a, 23b, 24, 25, 26a, 26c, 27b, 27c, 28, 29c, 30.

_l_ Refs 23b, 27b.
Table 4. Scope of the Mukaiyama Aldol Reaction of Heterocyclic Aldehydes with (CH$_3$)$_2$C=C(OCH$_3$)OSi(CH$_3$)$_3$ Catalyzed by 1c$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
<th>Lit. Yield (%)</th>
</tr>
</thead>
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<td>1$^c$</td>
<td><img src="image1" alt="Aldehyde" /></td>
<td><img src="image2" alt="Product" /></td>
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<td><img src="image3" alt="Aldehyde" /></td>
<td><img src="image4" alt="Product" /></td>
<td>89</td>
<td>-</td>
</tr>
<tr>
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<td><img src="image5" alt="Aldehyde" /></td>
<td><img src="image6" alt="Product" /></td>
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<td>47-80$^d$</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Aldehyde" /></td>
<td><img src="image8" alt="Product" /></td>
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<td>53-97$^e$</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Aldehyde" /></td>
<td><img src="image10" alt="Product" /></td>
<td>67</td>
<td>35-48$^f$</td>
</tr>
<tr>
<td>6$^c$</td>
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<td><img src="image12" alt="Product" /></td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td>7$^c$</td>
<td><img src="image13" alt="Aldehyde" /></td>
<td><img src="image14" alt="Product" /></td>
<td>52</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: aldehyde (2.0 mmol), TMS-ether (2.4 mmol), 1c (3.0 mol % unless otherwise stated), THF (4 mL), room temperature. $^b$Isolated yields after silica-gel column chromatography. $^c$Using 10 mol % of catalyst 1c. $^d$Refs 14a, 18g, 18h. $^e$Refs 23b, 26b, 27b, 29b, 29c. $^f$Refs 20, 27b.
In screening the reaction of PhC(=CH₂)OSiMe₃ with o-anisaldehyde using proazaphosphatranes 1a-1d (Table 5, entry 1), 1c gave the best product yield (82%) in accord with the previous findings in the present work. We then screened several aldehydes with the same silyl enol ether. Thus, electron-rich p-tolualdehyde and electron-poor p-chlorobenzaldehyde gave a moderate and a modest yield of product, respectively (entries 2 and 3). A sterically bulky and an enolizable aliphatic acyclic aldehyde gave a modest and a good product aldol yield, respectively (entries 4 and 5) and C₆H₅OSiMe₃ with electron-deficient p-nitrobenzaldehyde provided an excellent isolated product yield as the syn isomer selectively (entry 6). Electron-neutral benzaldehyde and electron-rich o-anisaldehyde afforded good and excellent isolated product yields, respectively, with predominant syn isomer selectivity in both cases (entries 7 and 8).

**Table 5.** Scope of the Mukaiyama Aldol Reaction of Aldehydes with C₆H₅C(=CH₂)OSi(CH₃)₃ and C₆H₅OSi(CH₃)₃ Catalyzed by 1c

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>TMS-enolate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Lit. Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td>OTMS</td>
<td></td>
<td>82³</td>
<td>39-94¹⁴</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td></td>
<td></td>
<td>60³</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79²</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55²</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td>OTMS</td>
<td></td>
<td>77</td>
<td>74-89²⁹</td>
</tr>
</tbody>
</table>

Letter superscripts indicating data sources are given in the text.
Table 5 continued

<table>
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<tr>
<th>No.</th>
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<th>Structure 3</th>
<th>Yield (%)</th>
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<td><img src="image2" alt="Structure 4" /></td>
<td><img src="image3" alt="Structure 5" /></td>
<td>69</td>
</tr>
<tr>
<td></td>
<td><img src="image4" alt="Structure 6" /></td>
<td><img src="image5" alt="Structure 7" /></td>
<td><img src="image6" alt="Structure 8" /></td>
<td>48-93</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Structure 9" /></td>
<td><img src="image8" alt="Structure 10" /></td>
<td><img src="image9" alt="Structure 11" /></td>
<td>74</td>
</tr>
<tr>
<td></td>
<td><img src="image10" alt="Structure 12" /></td>
<td><img src="image11" alt="Structure 13" /></td>
<td><img src="image12" alt="Structure 14" /></td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td><img src="image13" alt="Structure 15" /></td>
<td><img src="image14" alt="Structure 16" /></td>
<td><img src="image15" alt="Structure 17" /></td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td><img src="image16" alt="Structure 18" /></td>
<td><img src="image17" alt="Structure 19" /></td>
<td><img src="image18" alt="Structure 20" /></td>
<td>91</td>
</tr>
<tr>
<td></td>
<td><img src="image19" alt="Structure 21" /></td>
<td><img src="image20" alt="Structure 22" /></td>
<td><img src="image21" alt="Structure 23" /></td>
<td>66-92</td>
</tr>
<tr>
<td>7</td>
<td><img src="image22" alt="Structure 24" /></td>
<td><img src="image23" alt="Structure 25" /></td>
<td><img src="image24" alt="Structure 26" /></td>
<td>76</td>
</tr>
<tr>
<td></td>
<td><img src="image25" alt="Structure 27" /></td>
<td><img src="image26" alt="Structure 28" /></td>
<td><img src="image27" alt="Structure 29" /></td>
<td>(94/6)</td>
</tr>
<tr>
<td>8</td>
<td><img src="image28" alt="Structure 30" /></td>
<td><img src="image29" alt="Structure 31" /></td>
<td><img src="image30" alt="Structure 32" /></td>
<td>91</td>
</tr>
<tr>
<td></td>
<td><img src="image31" alt="Structure 33" /></td>
<td><img src="image32" alt="Structure 34" /></td>
<td><img src="image33" alt="Structure 35" /></td>
<td>(78/22)</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: aldehyde (2.0 mmol), TMS-ether (2.4 mmol), 1c (3.0 mol %, otherwise stated), THF (4 mL), 0 °C, 72 h. \(^b\) Isolated yields after silica-gel chromatography. \(^c\) Using 3 mol % 1e \(^d\) Refs 17d, 18i, 18j. \(^e\) Using 3 mol % 1a. \(^f\) Using 3 mol % 1b. \(^g\) Using 3 mol % 1d. \(^h\) Refs 18k, 18l, 18m, 28. \(^i\) Refs 18j, 18k, 18l, 18m, 25, 28. \(^j\) Ref 18n. \(^k\) Refs 22b, 30. \(^l\) Using 6 mol % of catalyst 1c. \(^m\) The syn/anti ratio was determined by using proton NMR spectroscopy. \(^n\) Refs 1a, 14b, 14e, 15d, 16d, 17g, 18j, 18o, 18p, 18q, 18r, 18s, 18t, 18y, 21e, 22b, 30. \(^o\) Ref 18u.
The use of bulky Me₃CC(=CH₂)(OSiMe₃) was then investigated as shown in Table 6. To our surprise, the unsaturated ketone 7b was obtained, rather than the desired aldol product 7a when we carried out the reaction at 0 °C (Table 6, entry 1). An attempt to optimize the reaction to selectively produce aldol product by lowering the reaction temperature to –20 °C failed to give aldol product, and the same yield of dehydrated product (entry 2) was produced as was the case at 0 °C. Lowering the temperature to –78 °C did not produce any observable product and only starting materials were recovered (entry 3). At room temperature, this reaction did not proceed to complete conversion and only a moderate yield of α,β-unsaturated ketone 7b (entry 4) was isolated. We then expanded the scope of this trimethylsilyl enol ether to a diverse range of aldehydes using the conditions in entry 1 of Table 6.

**Table 6.** Scope of the Mukaiyama Aldol Reaction of 2-Fluorobenzaldehyde with (CH₃)₃CC(=CH₂)OSi(CH₃)₃ Catalyzed by 1c

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst 1c (mol %)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield 7a (%)b</th>
<th>Yield 7b (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>0</td>
<td>72</td>
<td>0</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>-20</td>
<td>72</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>-78</td>
<td>12</td>
<td>n.r.</td>
<td>n.r³</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>25</td>
<td>72</td>
<td>0</td>
<td>60a¹</td>
</tr>
</tbody>
</table>

²Reaction conditions: aldehyde (2.0 mmol), (2,2-dimethyl-1-methylenepropoxy)trimethylsilane (2.4 mmol), THF (2.0 mL), followed by 1N HCl. ³Isolated yields after silica-gel column chromatography. ⁴No reaction. ¹¹H NMR spectroscopy revealed that 40% of the reaction consisted of unreacted aldehyde.
As seen in Table 7, catalyst 1c gave good to excellent isolated yields of the corresponding \(\alpha,\beta\)-unsaturated bulky ketones for aldehydes bearing a variety of functional groups. Our methodology is compatible with fluoro (Table 6, entry 1), iodo (Table 7, entry 1), and acid-sensitive cyano (Table 7, entry 2) substituents; the heterocyclic aldehydes benzofuran-2-carboxaldehyde (entry 3), benzothiophene-2-carboxaldehyde (entry 4) and 4-methyl-2-thiazolecarboxaldehyde (entry 5); and also electron rich 4-methoxy-1-naphthaldehyde (entry 6) and \(o\)-tolualdehyde (entry 7). The bulky \(ortho\)-disubstituted aldehyde in entry 8 afforded a moderate product yield, and \(trans\)-cinnamaldehyde (entry 9) produced the conjugated bulky ketone shown in excellent isolated yield (95%). The latter yield exceeded that previously reported in the literature using 110 mol % CsF as catalyst at 80 ºC.\(^{41}\) The other products listed in this table have not, to our knowledge, been reported in the literature.

**Table 7.** Synthesis of \(\alpha,\beta\)-Unsaturated Bulky Ketones from Aldehydes with (CH\(_3\))\(_3\)CC(=CH\(_2\))OSi(CH\(_3\))\(_3\) Catalyzed by 1c\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>TMS-enolate</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{I-CHO})</td>
<td>(\text{I-TMS-\text{CHO}})</td>
<td>(\text{I-(\beta)-unsat-ketone})</td>
<td>95</td>
</tr>
</tbody>
</table>
Table 7 continued

<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>Reaction Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image1" alt="Structure" /></td>
<td>HCl (3.0 mL)</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td><img src="image2" alt="Structure" /></td>
<td>HCl (3.0 mL)</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td><img src="image3" alt="Structure" /></td>
<td>HCl (3.0 mL)</td>
<td>83</td>
</tr>
<tr>
<td>5c</td>
<td><img src="image4" alt="Structure" /></td>
<td>HCl (3.0 mL)</td>
<td>94</td>
</tr>
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<td>6</td>
<td><img src="image5" alt="Structure" /></td>
<td>HCl (3.0 mL)</td>
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</tr>
<tr>
<td>7c</td>
<td><img src="image6" alt="Structure" /></td>
<td>HCl (3.0 mL)</td>
<td>90</td>
</tr>
<tr>
<td>8c</td>
<td><img src="image7" alt="Structure" /></td>
<td>HCl (3.0 mL)</td>
<td>72</td>
</tr>
<tr>
<td>9c</td>
<td><img src="image8" alt="Structure" /></td>
<td>HCl (3.0 mL)</td>
<td>95</td>
</tr>
</tbody>
</table>

*Ref. 41.*

---

*Reaction conditions: aldehyde (2.0 mmol), (2,2-dimethyl-1-methylenepropoxy)trimethylsilane (2.4 mmol), 1c (6.0 mol %), THF (4.0 mL), 0 °C, 72 h, followed by 1N HCl (3.0 mL) *b* Isolated yields after silica-gel chromatography. *c* Using 10 mol % of 1c. *d* Ref. 41.
Our attempts to accomplish Mukaiyama aldol addition to acetophenone, benzophenone and 4-chloroacetophenone were unsuccessful. However, 2,2,2-trifluoroacetophenone reacted with a variety of trimethylsilyl enolates to provide products 8-11 in moderate to excellent yields as shown in Scheme 3. The reaction of Me₂C(=C)OMe)(OSiMe₃) with 2,2,2-trifluoroacetophenone afforded the corresponding Mukaiyama aldol product in 91% yield as the TMS-protected product 8. In a separate experiment, hydrolyzed product 9 was obtained in 78% yield. Interestingly, both 8 and 9 possess two vicinal quaternary carbon centers. Not surprisingly, 2,2,2-trifluoroacetophenone was found to be an excellent substrate for this reaction with PhC(=CH₂)(OSiMe₃) and product 10 was isolated in 93% yield, which is comparable to the yield reported in the literature.²⁸ The reaction of 2,2,2-trifluoroacetophenone with 2-(trimethylsilyloxy)furan gave a good yield of product 11 with a syn/anti ratio of 2:1. Neither 8 nor 11 have been previously reported in the literature.
**Scheme 3.** Mukaiyama Aldol Reaction of a Trifluoromethyl Ketone with a Variety of TMS Ethers Catalyzed by 1c.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CO}_2\text{F}_3 + \text{MeCO} & \xrightarrow{\text{catalyst, 1c}} \text{MeO} \cdot \text{C} \cdot \text{O} \cdot \text{CF}_3 \\
\text{MeO} \cdot \text{C} \cdot \text{O} \cdot \text{CF}_3 + \text{PhCO} & \xrightarrow{\text{catalyst, 1c}} \text{Ph} \cdot \text{Ph} \\
\text{MeO} \cdot \text{C} \cdot \text{O} \cdot \text{CF}_3 + \text{PhCO} & \xrightarrow{\text{catalyst, 1c}} \text{Ph} \cdot \text{Ph} \\
\text{MeO} \cdot \text{C} \cdot \text{O} \cdot \text{CF}_3 + \text{PhCO} & \xrightarrow{\text{catalyst, 1c}} \text{Ph} \cdot \text{Ph} \\
\text{MeO} \cdot \text{C} \cdot \text{O} \cdot \text{CF}_3 + \text{PhCO} & \xrightarrow{\text{catalyst, 1c}} \text{Ph} \cdot \text{Ph} \\
\end{align*}
\]

\( a \) Reaction conditions: aldehyde (2.0 mmol), TMS-ether (2.4 mmol), 1c (5 mol % for 8, 6 mol % for 9 and 10 mol % for 10), room temperature. \( b \) Isolated yields after silica-gel chromatography. \( c \) Ref. 28.

A mechanism suggested for the Mukaiyama aldol reaction of trimethylsilyl enolates with aldehydes under our conditions is depicted in Scheme 4. In the literature, the Lewis base-
catalyzed Mukaiyama aldol reaction is proposed to proceed through the formation of a pentavalent silicon complex via Lewis-base activation, which generates the naked enolate anion C in the presence of a large counter cation.\textsuperscript{22b,23,26a,27b,28} In Path 1, 1c initially forms a pentacoordinated silicon complex A in which the electron density on the silicon is enriched, consequently weakening the bonds around this atom, and thus favoring ionization to species B and C. Evidence for the existence of naked anion C was previously presented by our group to account for the formation of both \(\alpha\)- and \(\gamma\)-addition products in the reaction of crotyltrimethylsilane with aldehydes in the presence of 1a.\textsuperscript{43} Enolate anion C then nucleophilically attacks the aldehyde carbon giving the corresponding alkoxide E, which then nucleophilically attacks cation D giving the TMS-protected aldol product F. Product F is subsequently hydrolyzed in a separate step to give the desired aldol product G with accompanying regeneration of the catalyst 1c. Another proposed route is depicted in Path 2 in Scheme 4. Initially 1c forms a pentacoordinated silicate TMS-ketene acetal adduct A (as was suggested for Path 1), which then coordinates with the incoming aldehyde concomitantly to form hexacoordinated cyclic intermediate H\textsuperscript{44,20} in which a six-membered cyclic intermediate between the silyl enol ether and the aldehyde is formed. Subsequent steps are as discussed for Path 1 to give product and regenerated catalyst 1c.
Scheme 4. Proposed reaction pathway for the Mukaiyama aldol reaction of aldehydes with Me₂C=C(OMe)OSiMe₃ catalyzed by 1c.

To elucidate the nature of the active species in the mechanism in Scheme 4, we conducted ³¹P NMR spectroscopic experiments aimed at monitoring changes in the environment of 1c. Initially, we examined the room temperature ³¹P NMR spectrum of 1c in THF in the presence of equimolar amounts of Me₂C=C(OMe)OSiMe₃ and p-tolualdehyde. A peak at 24 ppm (~5-10% intensity) was observed, which was attributed to the corresponding oxide 12; a conclusion that was confirmed by synthesizing a sample of 12 as depicted in Scheme 5. The formation of 12 could arise from the formation of an epoxide due to the putative self-condensation of p-toluadehyde as was observed previously in the presence of 1a.⁴⁵ We then carried out a ²⁹Si NMR experiment at -40 °C on a THF solution of Me₂C= C(OMe)OSiMe₃ (δ²⁹Si 19.56, THF) in the presence of an equimolar amount of 1c. No change was observed in the ²⁹Si NMR chemical shift. Similarly, TMSOPh (δ²⁹Si 18.21 ppm
in THF) under the same conditions using 1c as a catalyst also produced no change in the $^{29}$Si NMR chemical shift. However, when we used the less bulky 1a, a new peak at $\delta^{29}$Si 6.98 ppm was observed after 2 h and 10 min, which we attribute to the tetracoordinate silicon species B in which the anionic species C has been displaced. This chemical shift is in the same region as a peak we reported previously for a 1:1 mixture of TMSCN and 1a in C$_6$D$_6$ ($\delta^{29}$Si 7.5 ppm) in which CN$^-$ had been displaced. If the anion had not been displaced in both cases, an upfield rather than a downfield shift from the parent TMSX molecule would have been observed, since the silicon would have become 5-coordinate.\textsuperscript{37a} We used similar reasoning to account for the formation of both $\alpha$- and $\gamma$-addition products in the reaction of crotyltrimethylsilane with aldehydes in the presence of 1a.\textsuperscript{43} After transient A forms B and C in Scheme 4, an aldehyde molecule reacts with C to form the alkoxide E, which after trimethylsilylation is acid-hydrolyzed to give the corresponding species G as the final product, plus the regenerated catalyst 1c. Although we have $^{29}$Si NMR evidence consistent with the formation of B, we have no convincing $^{31}$P NMR evidence for this species. $^{31}$P chemical shifts for PR$_4^+$ cations are generally in the range of 90-140 ppm.\textsuperscript{46} The $^{31}$P NMR chemical shift for B is 128 ppm at -40 °C in THF, which is virtually unchanged from the value of 1a under the same conditions. This result perhaps suggests a minimal perturbation of the phosphorus shielding environment as a result of a relatively weak Si-P interaction.
Scheme 5. Synthesis of the phosphorus oxide of catalyst 1c.

Conclusion

In summary, we have demonstrated that proazaphosphatrane 1c is an active catalyst for the C-C bond-forming Mukaiyama aldol transformation, furnishing aldol products in generally high yields. Our methodology is compatible with electron-donating and withdrawing aryl aldehyde functional groups (e.g., methoxy, nitro, trifluoromethyl, amino, cyano, bromo, ester, fluoro and chloro) and aliphatic and heterocyclic aldehydes, which also function well in these reactions. Moreover, a variety of silyl enol ethers are compatible with our reaction conditions. Our methodology using 1c represents an advantageous catalytic alternative to arylphosphines (wherein 20 mol % of catalyst is routinely employed). α,β-Unsaturated bulky ketone products were isolated in good to excellent yields under our reaction conditions.

From Table 8, it is seen that of the total of 26 known Mukaiyama aldol products we found in the literature, we have observed in this work higher yields for 5, comparable yields for 6 and lower yields for 15 of them. While the latter number might be considered somewhat disappointing, it is also to be noted from this table that our catalyst loadings were lower than the minimum catalyst loading (associated with the maximum yield) found in the literature in
well over half (68%) of all of the cases. It should also be mentioned that our protocol resulted in the synthesis of 24 new compounds of which 12 were obtained in excellent yields, 4 in good yields, 4 in moderate yields, 1 in only a modest yield and 3 in poor yields. The facile synthesis of catalyst 1c, the broad range of amenable silyl enol ethers and aldehydes which can be utilized, the relatively low catalyst loading and the environmentally desirable lack of metal usage in the syntheses reported here renders our methodology attractive.

**Table 8.** A Comparison of the Efficiency of our Catalytic Protocol with Literature Protocols.

<table>
<thead>
<tr>
<th>Table</th>
<th>No. of Our Products with Higher Yields and Our Catalyst Loadings compared with Lit.</th>
<th>No. of Our Products with Comparable Yields and Our Catalyst Loadings compared with Lit</th>
<th>No. of Our Products with Lower Yields and Our Catalyst Loadings compared with Lit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1</td>
<td>-</td>
<td>-</td>
<td>1 (higher)</td>
</tr>
<tr>
<td>Table 2</td>
<td>1</td>
<td>1</td>
<td>3 (lower)</td>
</tr>
<tr>
<td>Table 3</td>
<td>(higher)</td>
<td>(higher)</td>
<td>4</td>
</tr>
<tr>
<td>Table 4</td>
<td>(lower)</td>
<td>(lower)</td>
<td>1</td>
</tr>
<tr>
<td>Table 5</td>
<td>-</td>
<td>(lower)</td>
<td>2 (lower for 4; higher for 1)</td>
</tr>
<tr>
<td>Table 7</td>
<td>(lower)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 8 continued

<table>
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<tr>
<th>Scheme 3</th>
<th>1 (higher)</th>
<th>1 (higher)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (3 lower)</td>
<td>6 (3 lower)</td>
<td>15 (11 lower)</td>
</tr>
</tbody>
</table>

*Taken here to be within ± 5%.

**Experimental Section**

**General Considerations.** All reactions were performed under an atmosphere of argon in oven-dried glassware. Toluene, pentane and tetrahydrofuran (THF) were freshly distilled over sodium/benzophenone and stored over 4 Å molecular sieves under an argon atmosphere. $^1$H (300 or 400 Hz) and $^{13}$C (100.6 MHz) NMR spectra were recorded in CDCl$_3$ (unless otherwise stated); the chemical shifts are referenced to the residual peaks of CHCl$_3$ in CDCl$_3$. $^{31}$P NMR spectra were recorded at ambient temperature on a 400 MHz spectrometer using standard procedures. Thin layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates visualized with short-wavelength UV light (254 nm). Column chromatography was performed on silica gel (40–140 mesh) for purification of the product. Electron impact ionization experiments were performed on a triple quadrupole mass spectrometer fitted with a EI/CI ion source. Accurate mass measurements were performed using a double focusing MS-50 mass spectrometer. All commercially available reagents were used as received. All products described in Tables 1–7 and Schemes 2 and 3 are known in the literature (unless indicated otherwise) and were characterized by comparing their $^1$H and $^{13}$C NMR spectra to the previously reported data. In all cases, the comparisons were very favorable. New compounds were characterized by $^1$H, $^{13}$C, mass (EI) and HRMS analysis.
Preparation of P(PhCH$_2$NCH$_2$CH$_2$)$_3$N (1c):

Synthesis of tribenzyl-tren (4). To 14.6 g (0.100 mol, 1.0 equiv) of freshly distilled [tris(2-aminoethyl)amine] in 75 mL of MeOH was added (30.48 mL, 0.320 mol, 3.2 equiv) of benzaldehyde. The mixture was allowed to stir at room temperature over 8 h. To this mixture was added 100 mL MeOH and then the reaction mixture was cooled to 0-5 ºC using an ice bath. NaBH$_4$ (5.67 g, 0.150 mol, 1.5 equiv) was added slowly to the mixture portion-wise over a period of 1 h. Excess solvent was removed completely using a rotary evaporator, followed by dissolving the resultant slurry in 200 mL water and extracted with CH$_2$Cl$_2$ (3 × 100 mL). The organic extracts were combined and dried over anhydrous Na$_2$SO$_4$ and filtered to remove Na$_2$SO$_4$. Excess solvent was removed under reduced pressure using a rotary evaporator. The crude light yellow oil was purified using silica gel chromatography (eluent: 10 % MeOH/CH$_2$Cl$_2$) to afford 29.12 g (70%) of yellow oil.

Synthesis of [HP(PhCH$_2$NCH$_2$CH$_2$)$_3$N]Cl (5). Anhydrous acetonitrile (50 mL) was charged to a single-neck round bottom flask. The flask was cooled to 0–5 ºC in an ice bath. Hexamethylphosphorous triamide (HMPT, 4.72 mL, 26.7 mmol, 2.0 equiv) was added to the flask under argon and the mixture was stirred for 5 min. PCl$_3$ (1.13 mL, 13.33 mmol, 1.0 equiv) was then slowly added to the mixture via syringe. After stirring the mixture at 0–5 ºC for 15 minutes, tribenzyl-tren, 4 (16.6g, 40.05 mmol, 3.0 equiv) dissolved in 50 mL anhydrous acetonitrile was added slowly through a cannula under a positive flow of argon to remove the liberated by-product dimethylamine formed during the reaction. The reaction was continued under constant stirring overnight at room temperature. The excess solvent was then removed under reduced pressure using a rotary evaporator, and then 300 mL of ether and 5.0
mL of THF was added and the reaction mixture was stirred at room temperature for 1 h. The crystalline white solid obtained was filtered and washed with ethyl ether (200 mL) to remove any organic impurities. The product was further dried under reduced pressure to obtain a free-flowing white solid (19.05 g, 99%).

**Synthesis of P(PhCH\(_2\)NCH\(_2\)CH\(_2\))\(_3\)N (1c).** To a 500 mL round-bottom Schlenk flask was added [HP(PhCH\(_2\)NCH\(_2\)CH\(_2\))\(_3\)N]Cl (5) (7.684 g, 16.0 mmols) and lithium bis(trimethylsilyl)amide (6.21 g, 37.12 mmol) in an argon-filled glove-box. The flask was then evacuated under reduced pressure after which ca 50 mL of anhydrous THF was added to the heterogeneous reaction mixture under a flow of argon. The resulting light yellow solution was stirred for about 12 h at room temperature to complete the deprotonation process (while monitoring by \(^{31}\)P NMR spectroscopy). The reaction flask was then connected to a vacuum line and kept under reduced pressure for removal of volatiles, after which 200 mL of anhydrous pentane was added with further stirring for an additional 10 h at room temperature. The resulting solution was filtered through a frit under an argon atmosphere and volatiles were removed under reduced pressure on a vacuum line. The solid remaining (6.12 g) was recrystallized from anhydrous pentane three times (3 \(\times\) 100 mL). The colorless crystalline solid 1c was dried under vacuum for 3 h to give 3.89 g (55% yield) of product. \(^{31}\)P NMR (162.8 MHz, C\(_6\)D\(_6\)): 127.97 ppm.\(^{33b}\)

**General reaction procedure for the (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane:**

In a nitrogen-filled glove-box, a 10 mL flat-bottom flask equipped with a magnetic stir bar was charged with proazaphosphatrane catalyst 1 (2 mol % unless otherwise stated). The flask
was sealed with a rubber septum and then (1-methoxy-2-methyl-1-propenylloxy)trimethylsilane (2.4 mmols) was added, followed by the aldehyde [(2 mmols) (if solid, dissolved in 2 ml of anhydrous THF under an argon atmosphere)] and freshly distilled THF (2 mL) was then syringed into the solution. The reaction was magnetically stirred for a specified length of time (see Tables 1–4), and the progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, 5 mL of 2N HCl was added and after stirring for 12 h at room temperature, the reaction mixture was transferred into a 250 mL round-bottom flask. The reaction vessel was washed with ethyl acetate (3 × 10 mL) and then all organic solvents were removed under reduced pressure using a rotary evaporator apparatus. To the flask, 30 mL of dichloromethane was added, then its contents were transferred to a separatory funnel. The reaction mixture was neutralized with satd. aq. NaHCO₃ solution and the product was extracted with dichloromethane (3 × 30 mL). The combined organics were dried over anhydrous MgSO₄ (2.0 g) and then the solvent was removed under reduced pressure. The crude product was purified by using short-path silica gel (140 mesh) chromatography with ethyl acetate/hexanes as eluents in all cases.

**General reaction procedure for the silyl enol ethers 1-phenyl-1-(trimethylsilyloxy)ethylene and 1-(trimethylsilyloxy)cyclohexene:**

To a solution of proazaphosphatrane 1 (3 mol %) in 4 mL of anhydrous tetrahydrofuran (THF) at −20 °C was added the silyl enol ether [1-phenyl-1-(trimethylsilyloxy)ethylene or 1-(trimethylsilyloxy)cyclohexene (2.4 mmol)] and then the mixture was stirred at the same temperature for 30 min. The aldehyde (2.0 mmol) was then added and then the reaction mixture was brought to −5 °C and stirring was continued for 72 h. Addition of 1N HCl
solution (3 mL) to this mixture and further stirring for 3 h at −5 °C, was followed by bringing the reaction mixture to room temperature. The reaction mixture was neutralized with satd. aq. NaHCO$_3$ solution and then it was extracted with ethyl acetate (3 × 30 mL). The organic layers were collected and dried over anhydrous Na$_2$SO$_4$ followed by solvent removal under reduced pressure using a rotary evaporator apparatus. The crude product was purified by flash chromatography (hexane:ethyl acetate = 90:10) on silica gel (140 mesh) to give the desired aldol product.

**Methyl 3-hydroxy-3-(2-biphenyl)-2,2-dimethylpropionate (Table 2, entry 3).** The general procedure was followed using 2-biphenylcarboxaldehyde (0.323 mL, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), 1c (56.0 mg, 6 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 20% ethyl acetate/hexanes) to afford 0.527 g (92%) of the desired product as a white solid. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.58 (d, 1H, $J = 8.0$ Hz), 7.42–7.30 (m, 7H), 7.20 (d, 1H, $J = 7.6$ Hz), 5.27 (s, 1H), 3.75 (bs, 1H), 3.64 (s, 3H), 1.02 (s, 3H), 0.83 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 178.8, 142.5, 141.9, 137.7, 130.5, 129.9, 128.5, 127.7, 127.7, 127.4, 127.1, 74.1, 52.4, 48.4, 24.2, 19.5 ppm; HRMS m/z Calcd for C$_{18}$H$_{20}$O$_3$: 284.14124. Found: 284.14179.

**Methyl 3-hydroxy-3-(3-methoxyphenyl)-2,2-dimethylpropionate (Table 2, entry 4).** The general procedure was followed using 3-methoxybenzaldehyde (0.272 g, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), 1b (12.00 mg, 2 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 15% ethyl acetate/hexanes) to afford 0.418 g (88%) of the desired
product as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.26–7.21 (m, 1H), 6.88–6.82 (m, 3H), 4.86 (d, 1H, $J$ = 4.4 Hz), 3.79 (s, 3H), 3.72 (s, 3H), 3.05 (d, 1H, $J$ = 4.0 Hz), 1.15 (s, 3H), 1.12 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.3, 159.3, 141.9, 128.9, 120.3, 113.6, 113.3, 78.8, 55.4, 52.3, 47.9, 23.2, 19.4 ppm; HRMS m/z Calcd for C$_{13}$H$_{18}$O$_4$: 238.12050. Found: 238.12115.

**Methyl 3-hydroxy-3-(2,6-dimethylphenyl)-2,2-dimethylpropionate (Table 2, entry 6).**

The general procedure was followed using 2,6-dimethylbenzaldehyde (0.268 g, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), 1c (18.32 mg, 2 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 8% ethyl acetate/hexanes) to afford 0.407 g (86%) of the desired product as a white solid. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.06–6.99 (m, 3H), 5.59 (s, 1H), 3.73 (s, 3H), 2.95 (s, 1H), 2.56 (s, 3H), 2.38 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.8, 138.6, 137.5, 135.5, 131.3, 128.6, 127.4, 76.1, 52.5, 50.3, 24.2, 22.6, 20.9 ppm; HRMS m/z Calcd for C$_{14}$H$_{20}$O$_3$: 236.14124. Found: 236.14177.

**Methyl 3-hydroxy-3-(3,4-dimethoxyphenyl)-2,2-dimethylpropionate (Table 2, entry 8).**

The general procedure was followed using 3,4-dimethylbenzaldehyde (0.332 g, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), 1c (56.0 mg, 6 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 8% ethyl acetate/hexanes) to afford 0.489 g (91%) of the desired product as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 6.86–6.83 (m, 2H), 6.75 (s, 1H), 5.25 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.66 (s, 3H), 1.29 (s, 3H), 1.07 (s, 3H) ppm; $^{13}$C
NMR (CDCl$_3$, 100 MHz): $\delta$ 175.8, 149.2, 148.4, 129.9, 121.6, 112.2, 110.3, 68.8, 56.1, 56.1, 52.4, 49.9, 23.3, 20.3 ppm; HRMS $m/z$ Calcd for C$_{14}$H$_{20}$O$_5$: 268.13107. Found: 268.13179.

**Methyl 3-hydroxy-3-(2-methoxynaphthalen-1-yl)-2,2-dimethylpropanoate (Table 2, entry 9).** The general procedure was followed using 2-methoxy-1-naphthaldehyde (0.372 g, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), 1c (54.0 mg, 6 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 8% ethyl acetate/hexanes) to afford 0.397 g (69%) of the desired product as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.10 (bs, 1H), 7.81−7.74 (m, 2H), 7.46 (t, 1H, $J = 8.0$ Hz), 7.32 (t, 1H, $J = 8.0$ Hz), 7.27−7.23 (m, 1H), 5.90 (d, 1H, $J = 8.0$ Hz), 4.90 (bs, 1H), 3.94 (s, 3H), 3.67 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 177.5, 155.5, 133.1, 130.2, 129.3, 128.6, 126.6, 123.6, 119.9, 112.8, 75.2, 55.9, 52.0, 50.3, 24.1, 20.7 ppm; HRMS $m/z$ Calcd for C$_{17}$H$_{20}$O$_4$: 288.13615. Found: 299.13656.

**Methyl 3-(3-formylphenyl)-3-hydroxy-2,2-dimethylpropanoate (Table 2, entry 10, 6a).** The general procedure was followed using isophthalaldehyde (0.268 g, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), 1c (88.8 mg, 10 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 20% ethyl acetate/hexanes) to afford 0.221 g (49%) of the desired product as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.95 (s, 1H), 7.76−7.73 (m, 2H), 7.54−7.52 (m, 1H), 7.44 (t, 1H, $J = 8.0$ Hz), 4.93 (s, 1H), 3.67 (s, 3H), 3.48 (bs, 1H), 1.01 (s, 3H), 1.06 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 192.4, 177.9, 141.2, 135.9, 133.8, 129.2, 128.9, 128.5, 76.8, 52.3, 47.7, 22.7, 19.1 ppm; HRMS $m/z$ Calcd for C$_{13}$H$_{16}$O$_4$: 236.10485. Found: 236.10533.
Dimethyl 3,3’-(1,3-phenylene)bis(3-hydroxy-2,2-dimethylpropanoate) (Table 2, entry 10, 6b). The general procedure was followed using isophthalaldehyde (0.268 g, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), 1c (88.8 mg, 10 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 20% ethyl acetate/hexanes) to afford 0.301 g (44%) of the desired product as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.15–7.14 (m, 4H), 4.79 (d, 1H, $J = 4.4$ Hz), 3.64 (s, 6H), 3.48 (bs, 1H), 1.05 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.2, 139.7, 139.6, 127.2, 127.2, 127.1, 126.9, 78.5, 78.4, 52.2, 47.8, 47.8, 23.1, 22.8, 19.2, 19.1 ppm; HRMS m/z Calcd for C$_{18}$H$_{26}$O$_6$: 338.17293. Found: 338.17906.

Methyl 3-hydroxy-3-(2-chlorophenyl)-2,2-dimethylpropionate (Table 3, entry 1): The general procedure was followed using 2-chlorobenzaldehyde (0.224 mL, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), 1c (28.0 mg, 3 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.440 g (91%) of the desired product as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.46–7.44 (m, 1H), 7.27–7.14 (m, 3H), 5.45 (s, 1H), 3.66 (s, 3H), 3.54 (bs, 1H), 1.12 (s, 3H), 1.10 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.3, 137.9, 133.5, 129.6, 129.3, 128.8, 126.5, 73.4, 52.3, 48.6, 23.1, 18.7 ppm; HRMS m/z Calcd for C$_{12}$H$_{15}$ClO$_3$: 242.07097. Found: 242.07153.

Methyl 3-hydroxy-3-(2-fluorophenyl)-2,2-dimethylpropionate (Table 3, entry 2). The general procedure was followed using 2-fluorobenzaldehyde (0.210 mL, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), 1c (28.0 mg, 3 mol
%, and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.350 g (77%) of the desired product as a colorless oil. \( ^1 H \) NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.47–7.43 (m, 1H), 7.27–7.23 (m, 1H), 7.16–7.12 (m, 1H), 7.03–6.98 (m, 1H), 5.28 (d, 1H, \( J = 4.4 \) Hz), 3.73 (s, 3H), 3.37 (d, 1H, \( J = 5.7 \)Hz), 1.15 (s, 3H), 1.14 (s, 3H) ppm; \( ^{13}C \) NMR (CDCl\(_3\), 100 MHz): \( \delta \) 178.4, 160.1 (d, \( J = 260 \) Hz), 129.4, 129.3 (d, \( J = 4.2 \) Hz), 127.4 (d, \( J = 12.9 \) Hz), 124.0 (d, \( J = 3.3 \) Hz), 115.2 (d, \( J = 22.8 \) Hz), 71.7, 52.4, 48.2, 23.1, 18.8 ppm; HRMS \( m/z \) Calcd. for C\(_{12}\)H\(_{15}\)FO\(_3\): 226.10052. Found: 226.10078.

**Methyl 3-hydroxy-3-(3-iodophenyl)-2,2-dimethylpropionate (Table 3, entry 3).** The general procedure was followed using 3-iodobenzaldehyde (0.464 g, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), \( 1c \) (88.0 mg, 10 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 20% ethyl acetate/hexanes) to afford 0.637 g (95%) of the desired product as a colorless oil. \( ^1 H \) NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.63–7.58 (m, 2H), 7.23 (d, 1H, \( J = 8.0 \) Hz), 7.02 (t, 1H, \( J = 8.0 \) Hz), 4.79 (d, 1H), 3.70 (s, 3H), 3.13 (bs, 1H), 1.10 (s, 3H), 1.08 (s, 3H) ppm; \( ^{13}C \) NMR (CDCl\(_3\), 100 MHz): \( \delta \) 178.1, 142.4, 136.8, 136.6, 129.5, 127.0, 93.9, 76.8, 52.3, 47.7, 22.9, 19.2 ppm; HRMS \( m/z \) Calcd. for C\(_{12}\)H\(_{15}\)IO\(_3\): 334.00659. Found: 334.00734.

**Methyl 3-hydroxy-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)propanoate (Table 3, entry 5):** The general procedure was followed using 4-(trifluoromethyl)benzaldehyde (0.272 mL, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), \( 1c \) (28.0 mg, 3 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.463 g (84%) of the desired product as a white solid. \( ^1 H \) NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.52 (d, 2H, \( J = 8.0 \) Hz),
7.36 (d, 2H, J = 8.0 Hz), 4.87 (d, 2H, J = 2.8 Hz), 3.66 (s, 3H), 3.50 (d, 2H, J = 4.0 Hz), 1.08 (s, 3H), 1.04 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 177.9, 144.1, 129.9 (q, J = 32.2 Hz), 128.0, 124.2 (q, J = 270.4 Hz), 124.6 (q, J = 3.7 Hz), 77.9, 52.2, 47.6, 22.7, 19.0 ppm; HRMS m/z Calcd for C$_{13}$H$_{15}$F$_3$O$_3$: 276.09732. Found: 276.09812.

**Methyl 3-hydroxy-3-(3-cyanophenyl)-2,2-dimethylpropionate (Table 3, entry 7).** The general procedure was followed using 3-cyanobenzaldehyde (0.262 g, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), 1c (28.0 mg, 3 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.271 g (58%) of the desired product as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.58 (s, 1H), 7.55–7.50 (m, 2H), 7.40 (t, 1H, J = 7.6 Hz), 4.89 (d, 1H, J = 3.6 Hz), 3.69 (s, 3H), 3.53 (d, 1H, J = 3.6 Hz), 1.09 (s, 3H), 1.06 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 177.9, 141.8, 132.4, 131.6, 131.5, 128.8, 119.0, 112.1, 77.7, 52.6, 47.9, 22.8, 19.3 ppm; HRMS m/z Calcd for C$_{13}$H$_{15}$NO$_3$: 233.10519. Found: 233.10548.

**Methyl 3-(benzo[b]thiophen-2-yl)-3-hydroxy-2,2-dimethylpropanoate (Table 4, entry 1).** The general procedure was followed using 2-benzothiophenecarboxaldehyde (0.324 g, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), 1c (88.8 mg, 10 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.488 g (92%) of the desired product as a pale yellow solid. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.79 (d, 1H, J = 7.6 Hz), 7.72 (d, 1H, J = 8.0 Hz), 7.36–7.29 (m, 2H), 7.18 (s, 1H), 5.15 (d, 1H, J = 4.0 Hz), 3.76 (s, 3H), 3.51 (d, 1H, J = 4.8 Hz), 1.28 (s, 6H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): δ
Methyl 3-(benzofuran-2-yl)-3-hydroxy-2,2-dimethylpropanoate (Table 4, entry 2). The general procedure was followed using 2-benzofurancarboxaldehyde (0.242 mL, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), Ic (28.0 mg, 3 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.442 g (89%) of the desired product as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.53 (d, 1H, $J = 7.6$ Hz), 7.44 (d, 1H, $J = 8.4$ Hz), 7.28–7.20 (m, 2H), 6.64 (s, 1H), 4.94 (s, 1H), 3.75 (s, 3H), 3.71 (bs, 1H), 1.28 (s, 3H), 1.27 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 177.8, 156.9, 154.8, 128.1, 124.4, 123.1, 121.2, 111.5, 105.0, 74.0, 52.5, 47.4, 23.1, 20.5 ppm; HRMS m/z Calcd. for C$_{14}$H$_{18}$O$_5$S: 264.08202. Found: 264.08256.

Methyl 3-hydroxynonanoate (Table 4, entry 3): The general procedure was followed using heptaldehyde (0.280 mL, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), Ic (28.0 mg, 3 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.345 g (80%) of the desired product as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.67 (s, 3H), 3.57 (d, 1H, $J = 4.0$ Hz), 1.26–1.14 (m, 16H), 0.87–0.84 (m, 4H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.3, 76.7, 51.9, 47.2, 31.8, 31.7, 29.3, 26.7, 22.7, 22.3, 20.4, 14.1 ppm; HRMS m/z Calcd. for C$_{12}$H$_{24}$O$_3$: 216.17254. Found: 216.17291.

Methyl 3-hydroxy-2,2-dimethyl-3-(4-methylthiazol-2-yl)propanoate (Table 4, entry 6). The general procedure was followed using 4-Methyl-2-thiazolecarboxaldehyde (0.254 g, 2.0
mmol), (1-methoxy-2-methyl-1-propenyl)trimethylsilane (0.486 mL, 2.4 mmol), 1c (56.0 mg, 6 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.153 g (36%) of the desired product as a pale yellow solid. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 6.81\) (s, 1H), 5.08 (d, 1H, \(J = 4.0\) Hz), 4.22 (d, 1H, \(J = 8.0\) Hz), 3.71 (s, 3H), 2.38 (s, 3H), 1.21 (s, 3H), 1.21 (s, 3H) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 177.5, 170.3, 152.1, 114.0, 76.4, 52.4, 48.1, 21.6, 20.9, 17.2\) ppm; HRMS \(m/z\) Calcd. for C\(_{10}\)H\(_{15}\)NO\(_3\)S: 229.07726. Found: 229.07763.

**Methyl 3-hydroxy-2,2-dimethyl-3-(1-methyl-1H-imidazol-2-yl)propanoate (Table 4, entry 7).** The general procedure was followed using 1-Methyl-2-imidazolecarboxaldehyde (0.220 g, 2.0 mmol), (1-methoxy-2-methyl-1-propenyl)trimethylsilane (0.486 mL, 2.4 mmol), 1c (28 mg, 3 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: methanol) to afford 0.221 g (52%) of the desired product as a colorless solid. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 6.82\) (d, 1H, \(J = 1.2\) Hz), 6.72 (d, 1H, \(J = 0.8\) Hz), 4.73 (s, 1H), 4.50 (bs, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 177.9, 147.0, 127.2, 121.5, 71.7, 52.3, 47.5, 33.5, 23.1, 21.3\) ppm; HRMS \(m/z\) Calcd. for C\(_{10}\)H\(_{16}\)N\(_2\)O\(_3\): 212.11609. Found: 212.11649.

**3-Hydroxy-1-phenyl-1-nonanone (Table 5, entry 5):** The general procedure was followed using heptaldehyde (0.280 mL, 2.0 mmol), 1-phenyl-1-trimethylsiloxyethylene (0.486 mL, 2.4 mmol), 1c (28.0 mg, 3 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.374 g (80%) of the desired product as a colorless oil. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta 7.97–7.94\) (m, 2H), 7.60–7.44 (m, 3H), 4.21 (bs, 1H), 3.26–2.98 (m, 3H), 1.63–1.29 (m, 10H), 0.89–0.86
(m, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 201.3, 131.9, 133.8, 128.9, 128.3, 68.0, 45.2, 36.7, 32.0, 29.5, 25.7, 22.8, 14.3 ppm; HRMS m/z Calcd. for C$_{10}$H$_{16}$N$_2$O$_3$: 212.11609. Found: 212.11649.

*(E)-1-(2-Fluorophenyl)-4,4-dimethylpent-1-en-3-one (Table 6, entry 1).* The general procedure was followed using 2-fluorobenzaldehyde (0.248 g, 2.0 mmol), 3,3-dimethyl-2-trimethylsiloxy-1-butene (0.518 mL, 2.4 mmol), 1c (54.0 mg, 6 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.380 g (92%) of the desired product as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.75 (d, 1H, $J = 16$ Hz), 7.54 (t, 1H, $J = 8$ Hz), 7.34–7.29 (m, 1H), 7.22 (d, 1H, $J = 16.0$ Hz), 7.13 (t, 1H, 8.0 Hz), 7.07 (t, 1H, $J = 8.0$ Hz), 1.21 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 204.3, 161.8 (d, $J = 250$ Hz), 135.8 (d, $J = 2.0$ Hz), 131.6 (d, $J = 9$ Hz), 129.9 (d, $J = 3.0$ Hz), 124.6 (d, $J = 3.0$ Hz), 123.5 (d, $J = 7$ Hz), 123.2 (d, $J = 12.0$ Hz), 116.4 (d, 22.0 Hz), 43.4, 26.4 ppm; HRMS m/z Calcd for C$_{13}$H$_{15}$FO: 206.11069. Found: 206.11108.

*(E)-1-(3-Iodophenyl)-4,4-dimethylpent-1-en-3-one (Table 7, entry 1).* The general procedure was followed using 3-iodobenzaldehyde (0.348 g, 1.5 mmol), 3,3-dimethyl-2-trimethylsiloxy-1-butene (0.432 mL, 2.0 mmol), 1c (40.0 mg, 6 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.443 g (95%) of the desired product as a yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.88 (s, 1H), 7.65 (d, 1H, $J = 8.0$ Hz), 7.51 (d, 1H, $J = 16.0$ Hz), 7.47 (d, 1H, $J = 8.0$ Hz), 7.10–7.05 (m, 2H), 1.20 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz):
δ 204.0, 141.3, 139.0, 137.3, 136.8, 130.7, 128.0, 122.0, 95.0, 43.5, 26.5 ppm; HRMS m/z Calcd for C_{13}H_{15}O: 314.0176. Found: 314.0168.

**(E)-3-(4,4-Dimethyl-3-oxopent-1-enyl)benzonitrile (Table 7, entry 2).** The general procedure was followed using 3-cyanobenzaldehyde (0.262 g, 2.0 mmol), 3,3-dimethyl-2-trimethylsiloxy-1-butene (0.518 mL, 2.4 mmol), 1c (54.0 mg, 6 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.402 g (94%) of the desired product as a colorless oil. \(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 7.82 (s, 1H), 7.74 (d, 1H, J = 8.0 Hz), 7.62–7.60 (m, 1H), 7.58 (d, 1H, J = 16.0 Hz), 7.48 (t, 1H, J = 8.0 Hz), 7.15 (d, 1H, J = 16.0 Hz), 1.21 (s, 9H) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): δ 203.8, 140.2, 136.3, 133.2, 132.6, 131.4, 129.9, 123.2, 118.4, 113.4, 43.6, 26.3 ppm; HRMS m/z Calcd for C_{14}H_{15}NO: 213.11536. Found: 213.11582.

**(E)-1-(Benzofuran-2-yl)-4,4-dimethylpent-1-en-3-one (Table 7, entry 3).** The general procedure was followed using 2-benzofurancarboxaldehyde (0.292 g, 2.0 mmol), 3,3-dimethyl-2-trimethylsiloxy-1-butene (0.518 mL, 2.4 mmol), 1c (54.0 mg, 6 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.362 g (77%) of the desired product as a yellow oil. \(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 7.53 (d, 1H, J = 16.0 Hz), 7.53 (bs, 1H), 7.47 (d, 1H, J = 8.0 Hz), 7.31 (dt, 1H, J = 8.0 Hz, J = 1.2 Hz), 7.24 (d, 1H, J = 16.0 Hz), 7.20 (d, 1H, J = 8.0 Hz), 6.90 (s, 1H), 1.24 (s, 9H) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): δ 204.0, 155.6, 153.2, 129.5, 128.7, 126.6, 123.5, 121.9, 121.3, 112.0, 111.5, 43.5, 26.5 ppm; HRMS m/z Calcd for C_{15}H_{16}O\(_2\): 228.11503. Found: 228.11549.
(E)-1-(Benzo[b]thiophen-2-yl)-4,4-dimethylpent-1-en-3-one (Table 7, entry 4). The general procedure was followed using 2-benzothiophenecarboxaldehyde (0.326 g, 2.0 mmol), 3,3-dimethyl-2-trimethylsiloxy-1-butene (0.518 mL, 2.4 mmol), 1c (54.0 mg, 6 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.404 g (83%) of the desired product as a yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.87 (d, 1H, $J = 16.0$ Hz), 7.79–7.74 (m, 2H), 7.49 (s, 1H), 7.39–7.33 (m, 2H), 6.95 (d, 1H, $J = 16.0$ Hz), 1.24 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 203.9, 140.4, 140.1, 139.8, 136.1, 129.5, 126.4, 125.0, 124.6, 122.6, 122.2, 43.4, 26.5 ppm; HRMS m/z Calcd for C$_{15}$H$_{16}$OS: 244.09219. Found: 244.09266.

(E)-4,4-Dimethyl-1-(4-methylthiazol-2-yl)pent-1-en-3-one (Table 7, entry 5). The general procedure was followed using 4-methyl-2-thiazolecarboxaldehyde (0.254 g, 2.0 mmol), 3,3-dimethyl-2-trimethylsiloxy-1-butene (0.518 mL, 2.4 mmol), 1c (90.0 mg, 10 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.391 g (94%) of the desired product as a yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.60 (d, 1H, $J = 16.0$ Hz), 7.35 (d, 1H, $J = 16.0$ Hz), 6.96 (s, 1H), 2.45 (s, 3H), 1.18 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 203.8, 163.2, 155.3, 133.8, 124.2, 116.7, 43.6, 26.3, 17.4 ppm; HRMS m/z Calcd for C$_{11}$H$_{15}$NOS: 209.08743. Found: 209.08770.

(E)-1-(4-Methoxynaphthalen-1-yl)-4,4-dimethylpent-1-en-3-one (Table 7, entry 6). The general procedure was followed using 4-methoxy-1-naphthaldehyde (0.372 g, 2.0 mmol), 3,3-dimethyl-2-trimethylsiloxy-1-butene (0.518 mL, 2.4 mmol), 1c (54.0 mg, 6 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel.
(eluent: 10% ethyl acetate/hexanes) to afford 0.421 g (78%) of the desired product as a white solid. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 8.49\) (d, 1H, \(J = 15.6\) Hz), 8.31 (d, 1H, \(J = 8.0\) Hz), 8.20 (d, 1H, \(J = 8.0\) Hz), 7.79 (d, 1H, \(J = 8.0\) Hz), 7.61–7.50 (m, 2H), 7.14 (d, 1H, \(J = 16.0\) Hz), 6.83 (d, 1H, \(J = 8.0\) Hz), 4.04 (s, 3H), 1.27 (s, 9H) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 204.4, 157.6, 140.0, 133.0, 125.8, 124.9, 123.5, 122.8, 121.3, 103.8, 55.9, 43.4, 26.7\) ppm; HRMS m/z Calcd for C\(_{18}\)H\(_{20}\)O\(_2\): 268.14632. Found: 268.14673.

\(\text{(E)-4,4-Dimethyl-1-o-tolylpent-1-en-3-one (Table 7, entry 7).}\) The general procedure was followed using o-tolualdehyde (0.240 g, 2.0 mmol), 3,3-dimethyl-2-trimethylsiloxy-1-butene (0.518 mL, 2.4 mmol), 1c (90.0 mg, 10 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.364 g (90%) of the desired product as a white solid. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 7.99\) (d, 1H, \(J = 16.0\) Hz), 7.60 (d, 1H, \(J = 8.0\) Hz), 7.27–7.19 (m, 3H), 7.05 (d, 1H, \(J = 16.0\) Hz), 2.44 (s, 3H), 1.24 (s, 9H) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 204.5, 140.7, 138.4, 134.2, 131.1, 130.1, 126.5, 126.4, 122.1, 43.5, 26.6, 20.1\) ppm; HRMS m/z Calcd for C\(_{14}\)H\(_{18}\)O: 202.13576. Found: 202.13610.

\(\text{(E)-1-(2,6-Dimethylphenyl)-4,4-dimethylpent-1-en-3-one (Table 7, entry 8).}\) The general procedure was followed using 2,6-dimethylbenzaldehyde (0.268 g, 2.0 mmol), 3,3-dimethyl-2-trimethylsiloxy-1-butene (0.518 mL, 2.4 mmol), 1c (88.8 mg, 10 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.310 g (72%) of the desired product as a white solid. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 7.80\) (d, 1H, \(J = 16.0\) Hz), 7.12–7.06 (m, 3H), 6.74 (dd, 1H, \(J = 16.0\) Hz, \(J = 1.2\) Hz), 2.34 (s, 6H), 1.21 (s, 9H) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\)
204.4, 141.4, 136.9, 135.1, 128.4, 128.3, 127.1, 43.4, 26.3, 21.3 ppm; HRMS \( m/z \) Calcd for \( \text{C}_{15}\text{H}_{20}\text{O} \): 216.15141. Found: 216.15173.

**(4E,6E)-2,2-Dimethyl-7-phenylhepta-4,6-dien-3-one (Table 7, entry 9).** The general procedure was followed using \textit{trans}-cinnamaldehyde (0.264 g, 2.0 mmol), 3,3-dimethyl-2-trimethylsiloxy-1-butene (0.518 mL, 2.4 mmol), \textit{1c} (90.0 mg, 10 mol %), and THF (4.0 mL). The reaction mixture was purified by column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.412 g (95%) of the desired product as a yellow oil. \( ^1\text{H} \) NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta \) 7.50−7.46 (m, 3H), 7.37−7.30 (m, 3H), 6.94−6.92 (m, 2H), 6.69 (d, 1H, \( J = 12.0 \text{ Hz} \)), 1.20 (s, 9H) ppm; \( ^{13}\text{C} \) NMR (CDCl\textsubscript{3}, 100 MHz): \( \delta \) 204.6, 143.1, 141.3, 136.4, 129.2, 129.0, 127.3, 127.1, 124.5, 43.3, 26.6 ppm; HRMS \( m/z \) Calcd for \( \text{C}_{15}\text{H}_{18}\text{O} \): 214.13576. Found: 214.13625.

**Methyl 4,4,4-trifluoro-2,2-dimethyl-3-phenyl-3-(trimethylsilyloxy)butanoate (Scheme 3, product 8).** The general procedure was followed using 2,2,2-trifluoroacetophenone (0.348 g, 2.0 mmol), (1-methoxy-2-methyl-1-propenyloxy)trimethylsilane (0.486 mL, 2.4 mmol), \textit{1c} (54.0 mg, 6 mol %), and THF (4.0 mL). The reaction mixture was purified by flash column chromatography on silica gel (eluent: 10% ethyl acetate/hexanes) to afford 0.633 g (91%) of the desired product as yellow oil. \( ^1\text{H} \) NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta \) 7.48−7.45 (m, 2H), 7.35−7.33 (m, 3H), 3.60 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H), 0.14 (s, 9H) ppm; \( ^{13}\text{C} \) NMR (CDCl\textsubscript{3}, 100 MHz): \( \delta \) 174.8, 136.5, 128.5, 127.8, 127.3, 126.1 (q, \( J = 288 \text{ Hz} \)), 84.6 (q, \( J = 26.9 \text{ Hz} \)), 51.9, 50.9, 26.8, 22.7, 1.8 ppm; HRMS \( m/z \) Calcd for \( \text{C}_{16}\text{H}_{17}\text{F}_{3}\text{O} \): 348.13686. Found: 348.13754.
5-(2,2,2-Trifluoro-1-hydroxy-1-phenylethyl)furan-2(5H)-one (Scheme 3, product 11).
The general procedure was followed using 2,2,2-trifluoroacetophenone (0.348 g, 2.0 mmol),
2-(trimethylsiloxy)furan (0.403 mL, 2.4 mmol), 1c (54.0 mg, 6 mol %), and THF (4.0 mL).
The reaction mixture was purified by column chromatography on silica gel (eluent: 10%
ethyl acetate/hexanes) to afford a combined isolated yield of 0.404 g (83%). Syn isomer
(white solid) $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.61–7.60 (m, 2H), 7.49–7.45 (m, 3H), 6.84–
6.82 (m, 1H), 6.18–6.16 (m, 1H), 5.71 (t, 1H, $J = 4.0$ Hz), 4.1 (s, 1H) ppm; $^{13}$C NMR
(CDCl$_3$, 100 MHz): $\delta$ 173.0, 152.5, 133.4, 129.8, 129.2, 125.6, 124.5 (q, $J = 280$ Hz), 124.0,
83.6, 76.6 (q, $J = 29$ Hz) ppm; HRMS m/z Calcd for C$_{12}$H$_9$F$_3$O$_3$: 258.05038. Found:
258.05075. Anti isomer (yellow oil) $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.56–7.54 (m, 3H),
7.42–7.39 (m, 3H), 6.04–6.02 (m, 1H), 5.58 (s, 1H), 3.66 (s, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz):
$\delta$ 172.2, 152.5, 133.3, 129.8, 128.9, 126.4, 124.5 (q, $J = 280$ Hz), 124.0, 83.2,
77.9 (q, $J = 20$ Hz) ppm; HRMS m/z Calcd for C$_{12}$H$_9$F$_3$O$_3$: 258.05038. Found: 258.05076.

2,8,9-Trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane 1-oxide (12): To a
solution of 1c (0.133 g, 0.30 mmol) in 4.0 mL of toluene was added excess Me$_3$SiOOSiMe$_3$
(0.320 g, 1.80 mmol). The resulting clear solution was stirred at 40–50 °C. After 38 h, all the
volatiles were removed under vacuum giving an off-white residue which upon recrystallization from anhydrous pentane yielded 12 as a colorless solid (0.130 g, 94%). $^{31}$P
NMR (CDCl$_3$, 162 MHz): 24.24 ppm. $^1$H NMR (CDCl$_3$, 400 MHz): 7.61–7.59 (m, 6H),
7.37–7.26 (m, 9H), 4.25 (d, 6H, $J = 8.0$ Hz), 2.88–2.79 (m, 12H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz):
139.9 (d, $J = 2.3$ Hz), 128.9, 128.5, 127.4, 50.9 (d, $J = 5.0$ Hz), 50.0, 47.4 (d, $J =$
3.3 Hz) ppm. HRMS m/z calcd for C$_{27}$H$_{33}$N$_4$OP: 460.23919. Found: 460.24045.
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References


[31] For an excellent review of the reactions of trichlorosilyl enolates with aldehydes, see:


CHAPTER 7. DETERMINATION OF THE STRUCTURE OF A NOVEL ANION EXCHANGE FUEL CELL MEMBRANE BY SOLID-STATE NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

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Abstract: A novel anion exchange fuel cell membrane was successfully synthesized by chemically attaching proazaphosphatranium/phosphatranium cations under microwave treatment to the sulfonic groups of Nafion-F®. Solid-state nuclear magnetic resonance (NMR) techniques were employed to determine the actual structure and composition of this anion exchange membrane. $^{31}$P NMR showed two main signals with a 2:1 intensity ratio and chemical shift changes of +89 ppm and +46 ppm, respectively, from the main peak of phosphatranium chloride. $^1$H–$^{31}$P heteronuclear correlation (HetCor) NMR and $^1$H–$^{31}$P recoupling experiments indicated that the proton originally bonded to phosphorus in phosphatranium chloride is replaced in the major component of the Nafion®–proazaphosphatranium/phosphatranium composite. $^{19}$F NMR experiments showed that the fluorine in the –SO$_2$F group of the Nafion-F® precursor is fully replaced. $^{31}$P{$^{19}$F} rotational-echo double resonance (REDOR) experiments measured a P–F internuclear distance of ~0.4 nm, which showed that the proazaphosphatranium is covalently attached to Nafion® through a S–P bond. $^{13}$C NMR and $^1$H–$^{13}$C HetCor spectra indicated that the proazaphosphatranium
structure is maintained even after the microwave treatment at 180 °C and also showed the presence of entrapped dimethylformamide solvent.

**Keywords**: Nafion®; Phosphatranium; Proazaphosphatranium, Solid-state nuclear magnetic resonance spectroscopy; Fuel cell; Anion exchange membrane;

**Introduction**

The increasing demand for alternative sources of energy\textsuperscript{1-4} has placed direct methanol-based fuel cells (DMFCs) at the forefront of the search for alternatives to fossil fuels. DMFCs are projected to be the first fuel cells that will be commercially available for use by the general population. Among the advantages of DMFCs are their high energy density (5–10 times greater than that of commonly available batteries), moderate operating temperatures, and easy replacement of the methanol fuel cartridge; all of which make DMFCs ideal for usage in portable electronic devices.\textsuperscript{5-7} In many modern fuel cells, a proton exchange membrane (PEM) is utilized to transport protons produced in the anodic half reaction for consumption on the cathodic side of the cell (Scheme 1a). However, PEMs in DMFCs suffer from (i) parasitic crossover of methanol, which leads to a lowering of cell voltage and efficiency; (ii) electro-osmosis of water from anode to cathode, which causes severe flooding at the cathode; (iii) reduced catalyst kinetics in the acidic environment requiring high loadings of costly precious-metal catalysts, e.g. platinum.\textsuperscript{8} For these reasons, alkaline fuel cells (AFCs) with the same net reaction but exploiting different half reactions as shown in Scheme 1b have become attractive to investigate. The most important advantages of AFCs are that they can operate at a lower catalyst loading owing to more facile methanol oxidation in alkaline media,\textsuperscript{9-11} and that they may utilize a broader range of catalysts, such as nickel and silver.\textsuperscript{12-14}
Scheme 1: Half-reactions and the overall net reaction in a methanol fuel cell. (a) Protonic half reactions in a conventional fuel cell. (b) Reactions in an alkaline fuel cell.

In the past, methanol was not suitable as a fuel in AFCs because such cells utilized liquid alkaline electrolytes such as hydroxide ion conductors, which are vulnerable to precipitation of carbonate (e.g. K$_2$CO$_3$) that destroys the catalyst layer, which forms from CO$_2$ released in the cell reaction (Scheme 1b).$^{15-17}$ As a result, solid alkaline anion exchange membranes (AAEMs) containing hydroxide ions were developed. They combine the advantages of PEMs (flexibility, durability, small volume, and no leakage) and traditional AFCs (good catalyst kinetics) and they can operate when carbonate species are present.$^8$. Some efforts have been
made to use fluorinated polymers as AAEMs. For example, poly(vinylidene fluoride) (PVDF) and poly(tetrafluoroethene-co-hexafluoropropylene) (FEP) have been grafted with 4-vinylbenzyl chloride, followed by modification of the benzyl chloride functionality with trimethylamine to give the trimethylbenzyl ammonium salt, which was then tested as an AAEM. While the FEP-based AAEM gave conductivities of ca. 0.02 S/cm at ambient temperature and an atmospheric relative humidity of 100%, the PVDF-based AAEM degraded on subsequent amination and hydroxide ion exchange.

**Scheme 2.** a) Representation of the average chemical structure of Nafion® and Nafion-F®. b) Representation of Nafion® polymer segments attached to proazaphosphatranium functional groups A+. c) Representation of the same Nafion® polymer segments bonded to phosphatranium functional groups B+. 
An important feature of AAEMs is that their conductivities are directly proportional to the ionophore densities. Commonly studied ionophores tethered to AAEM backbones are quaternary ammonium salts. However, these salts experience relatively intense cation–anion interactions which further impede hydroxide ion mobility. Here we report the synthesis and characterization of a potentially improved AAEM that incorporates novel types of phosphonium cations as depicted in Scheme 2b and 2c. These ionophores have a reduced charge density due to their resonance structures that distribute the positive charge (Scheme 3) and thus diminish ionic interaction, which should facilitate hydroxide ion mobility.

These phosphonium sidegroups have been attached to Nafion® (Scheme 2a), a tetrafluoroethylene copolymer bearing sulfonic acid (-SO₂OH) functional groups that is extensively used as a PEM in fuel cells. Being perfluorinated and semicrystalline, Nafion® (a proton cation conductor commercially derived via base hydrolysis of Nafion-F®) and its precursor, Nafion-F® (which contains -SO₂F functionalities), possess good thermal and mechanical stability, which are particular advantages of Nafion® compared with many other potential PEM materials. Nafion® is stable up to 300 °C.¹⁹ Its excellent conductivity stems from its combination of a hydrophobic polymer backbone and hydrophilic functional groups which self-organize to form water channels of ~2.5-nm diameter through which small ions can be easily transported.²⁰
Scheme 3: Resonance structures for a proazaphosphatranium cation.

The synthesis steps for our material are summarized in Scheme 4, wherein Phan denotes the incorporation into the Nafion\textsuperscript{®} (Naf) polymer of the two structurally different types of phosphorus cations [i.e., proazaphosphatranium (A\textsuperscript{+} in Scheme 2) and phosphatranium (B\textsuperscript{+} in Scheme 2)] and "X" designates the anions Cl\textsuperscript{−} or F\textsuperscript{−}. Solid state nuclear magnetic resonance (NMR) is a promising tool for assessing the relative levels of A\textsuperscript{+}, B\textsuperscript{+} or other functionalities incorporated, and for detailing their chemical structure, since the material is rich in NMR-active spin-1/2 isotopes, namely \textsuperscript{1}H, \textsuperscript{13}C, \textsuperscript{31}P, \textsuperscript{19}F and \textsuperscript{15}N. The characteristic chemical shifts of the \textsuperscript{31}P, \textsuperscript{1}H, \textsuperscript{19}F, \textsuperscript{13}C and \textsuperscript{15}N in Naf-Phan-X were detected in quantitative direct polarization (DP) experiments (for \textsuperscript{31}P and \textsuperscript{19}F) and in cross polarization (CP) experiments (for \textsuperscript{31}P, \textsuperscript{13}C, and \textsuperscript{15}N). The potential bonding of the three latter isotopes to hydrogen was determined by recoupling the dipolar interaction with \textsuperscript{1}H. The correlations between phosphorus or carbon and their nearest protons were determined by 2D \textsuperscript{1}H–\textsuperscript{31}P and \textsuperscript{1}H–\textsuperscript{13}C heteronuclear correlation (HetCor) NMR. The bonding between Nafion\textsuperscript{®} and
proazaphosphatranium/phosphatranium moieties was elucidated using $^{31}$P{$^{19}$F} rotational echo double resonance (REDOR)$^{25}$. $^{13}$C spectra were edited with CH and CH$_2$ selection sequences$^{33,34}$ to identify such segments unambiguously.

Scheme 4: Synthesis of Naf-Phan-X and Naf-Phan-OH.

Experimental Section

Samples. Nafion-F$^\circ$ membrane (6 cm x 6 cm), with a 0.9 mmol/g loading of SO$_2$F functionality and a thickness of 25 microns (a product of Du Pont supplied by Ion Power Inc.) was charged to a microwave vial. To this was added excess phosphatranium chloride (Phan-Cl in Scheme 4; 500 mg, 2.3 mmol) prepared according to a literature method$^{21}$ and dry dimethyl formamide (ca 8 mL) such that the membrane was completely immersed in the solution. The mixture was microwaved at 180 $^\circ$C for 5 hours using a 300 watt CEM Discover apparatus and then the membrane was washed with copious amounts of methanol to remove any unreacted phosphatranium salt, HX and solvent. For solid state NMR characterization, the Naf-Phan-X membrane was dried at room temperature under reduced pressure. For
electrical measurements (to be reported in due course) the Naf-Phan-X membrane was soaked in aq. NaOH to exchange the halide ions for hydroxide, giving Naf-Phan-OH in Scheme 4. The change in counterion is unlikely to result in significant structural changes of the polymer or sidegroups.

**NMR parameters.** All NMR experiments were performed on a Bruker DSX-400 spectrometer at a resonance frequency of 400 MHz for $^1$H, 100 MHz for $^{13}$C, 162 MHz for $^{31}$P, 376 MHz for $^{19}$F and 40.5 MHz for $^{15}$N, using double-resonance or triple-resonance magic-angle spinning (MAS) probes. $^{13}$C experiments were performed in 7-mm rotors at 6.5 kHz with a 90° pulse length of 4 µs, and with 3-s recycle delays. $^{31}$P experiments were performed in 4-mm rotors at 7 kHz with a 90° pulse length of 4 µs, and with either 2-s recycle delay for cross polarization or 100 s for direct polarization. $^{19}$F experiments were performed in 2.5-mm rotors at 30 kHz, which reduces $^{19}$F dipolar couplings enough to resolve various sidegroup- and backbone signals in Nafion®, with a 90° pulse length of 1.85 µs, and with 3-s recycle delays. $^{15}$N experiments were performed in 7-mm rotors at 5 kHz with a 90° pulse length of 9.2 µs, and with 2.5-s recycle delays; the number of scans was 6,144 for phosphatranium chloride and 28,672 for Naf-Phan-X. Two-pulse phase-modulation (TPPM) was used for $^1$H–$^{13}$C, $^1$H–$^{31}$P, or $^1$H–$^{15}$N heteronuclear dipolar decoupling. $^{31}$P and $^{15}$N chemical shifts were indirectly referenced to H$_3$PO$_4$ and NH$_4^+$, respectively, using hydroxyapatite ($^{31}$P chemical shift at +3 ppm) and N-acetyl valine ($^{15}$N chemical shift at +122 ppm). All experiments were carried out at ambient temperature.

$^1$H–$^{31}$P and $^1$H–$^{13}$C HetCor. Two-dimensional (2D) $^1$H–$^{31}$P and $^1$H–$^{13}$C heteronuclear correlation (HetCor) NMR experiments were performed at spinning frequencies of 7 kHz.
and 6.5 kHz, respectively. Frequency-switched Lee-Goldburg\textsuperscript{24} homonuclear decoupling was applied during the evolution period $t_1$. Lee-Goldburg cross polarization was used to suppress $^1$H–$^1$H spin diffusion during polarization transfer and to show mostly one- and two-bond $^1$H–$^{13}$C connectivities. For $^1$H–$^{31}$P HetCor, the cross polarization time was 0.7 ms, the number of scans was 128, and the number of $t_1$ increments was 100. For $^1$H–$^{13}$C HetCor, the cross polarization time was 0.2 ms, the number of scans was 128, and the number of $t_1$ increments was 72.

$^{31}$P/$^{19}$F REDOR. $^{31}$P/$^{19}$F REDOR experiments\textsuperscript{25} were performed in 2.5-mm rotors at a spinning frequency of 30 kHz, which avoids excessive dephasing losses and allows semi-quantitative $^{31}$P/$^{19}$F distance measurements. The dephasing of $^{31}$P magnetization in the field of the $^{19}$F spins was observed. $^{19}$F composite 180° pulses were applied spaced by $t_r/2$ during a period of $Nt_r$ in order to recouple the dipolar interaction between $^{31}$P and $^{19}$F. EXORCYCLE was used for the single 180° pulse on the $^{31}$P channel.\textsuperscript{26} The recoupling $^{19}$F pulses were turned off to obtain the reference signal $S_0$.

**Results and Discussion**

$^{31}$P NMR: chemical bonding of phosphorus. The $^{31}$P MAS NMR spectra (Figure 1a, b) of phosphatranium chloride (Phan-Cl) show a dominant centerband at an isotropic chemical shift of $-48$ ppm with spinning sidebands (labeled with asterisks) spaced by the spinning frequency $\omega_r$. The signal was quickly dephased by the H–P dipolar coupling during gated recoupling, see Figure 1c, as expected for a P-H group (“protonated phosphorus”). The $^{31}$P chemical shift is close to the value of $-43$ ppm for the phosphatranium ion in solution as reported in the literature.\textsuperscript{27} Peaks at 0 ppm and $+41$ ppm must be assigned to impurities or
more likely degradation products due to decomposition of Phan-Cl in the presence of water; these peaks do not appear in solution spectra of fresh Phan-Cl in organic solvents. In the spectra of the product Naf-Phan-X (Figure 1d, e), two major peaks at +41 ppm and ~ +5 ppm are observed, with an area ratio of 2:1 in the quantitative DP spectrum. The peak at 41 ppm is associated with a non-protonated phosphorus as indicated by slow CP and slow dephasing by gated recoupling (see Figure 1f). The peak near 5 ppm consists of two components (which are confirmed by $^1$H-$^{13}$C correlation below): (i) a broader band at centered at 3 ppm, with significant spinning sidebands, and fast H-P dephasing indicative of P bonded to H, and (ii) the peak at 5 ppm, which shows slower H-P dephasing that may suggest a phosphorus close to a proton but with a smaller H–P dipolar coupling due to a larger internuclear distance or motional averaging. The peak at 41 ppm is assigned to Naf-Phan-X of functionality A$^+$. This assignment is proven below using $^1$H-$^{31}$P HetCor spectra, and further supported by chemical-shift analysis. The peaks at ~5 ppm can be tentatively assigned to the B$^+$ functionality; the ~3-ppm variation in chemical shifts might be due to different hydrogen bonding. According to the peak areas in the quantitative $^{31}$P NMR spectrum, the Naf-Phan-X functionality A$^+$ accounts for 67% of the total phosphorus content in our sample.
Figure 1. $^{31}\text{P}$ spectra of phosphatranium chloride (Phan-Cl, a - c) and Naf-Phan-X membrane (d - f). For Phan-Cl, a) direct polarization (DP) at $v_r = 12$ kHz with a recycle delay of 100 s and b) $^1\text{H} - ^{31}\text{P}$ cross polarization (CP) at $v_r = 7$ kHz with a recycle delay of 100 s show the centerband of the main $^{31}\text{P}$ signal with an isotropic chemical shift of $-48$ ppm; its spinning sidebands are labeled with asterisks. A sideband of the +41-ppm peak is labeled “ssb”. c) CP spectrum after gated recoupling for one rotation period, which confirms that the peak at $-48$ ppm is the signal of a protonated phosphorus. For the Naf-Phan-X membrane, the DP spectrum d) at $v_r = 12$ kHz with a recycle delay of
100 s, shows two resolved $^{31}$P peaks (at 41 ppm and ~5 ppm) with an area ratio of 2:1. e) CP spectrum at $v_r = 7$ kHz. Sidebands of the shoulder at 3 ppm are labeled by asterisks. f) CP spectrum after gated recoupling for one rotation period.

In order to identify $^1$H near phosphorus, two-dimensional $^1$H–$^{31}$P HetCor experiments (Figure 2) were performed with mixing times of 0.05 ms (nearest $^1$H) and 50 ms ($^1$H within ~3 nm). For phosphatranium chloride, the proton bonded to the phosphorus resonates at 5.6 ppm, which is shown by the stronger cross peak to the $^{31}$P at ~48 ppm and its spinning sideband in the spectrum of Figure 2a. In the spectrum after 50 ms of spin diffusion (Figure 2b), the cross peaks for longer distance $^1$H–$^{31}$P correlation, i.e. between phosphorus and protons in NH and NCH$_2$ groups ($^1$H chemical shift at ~3 ppm), surpass those for the direct P–H bonding, due to their larger number. The $^1$H band of protons in P–NH groups, whose chemical shift varies between ~ 4 and 5.1 ppm in the literature, is not clearly recognizable in the 2D HetCor spectra. For Naf-Phan-X, the phosphorus at 41 ppm correlates only to the NH and NCH$_2$ protons. The phosphorus at 5 ppm seems to be close to a proton at ~10 ppm (Figure 2c), which might suggest a strongly H-bonded proton (P – H…X where X = O or N). This could occur in structure B$^+$, wherein the presence of a five-membered -N-S-O-H-P- ring is conceivable. Further, a distinct set of cross peaks is seen at +3 ppm in the $^{31}$P dimension and ~ 6 ppm in $^1$H, assigned to P-H groups, confirming the presence of two components resonating near 5 ppm in the $^{31}$P spectrum of Naf-Phan-X. It is interesting to note that an impurity with quite similar $^{31}$P and $^1$H chemical shifts is visible in the spectrum of Phan-Cl,
see Figure 2a.

Figure 2. $^1$H–$^{31}$P HetCor spectra of (a, b) phosphatranium chloride (Phan-Cl) and (c, d) Naf-Phan-X with a CP time of 0.7 ms and at $\nu_r = 7$ kHz for mixing times of 5 $\mu$s and 50 ms. For Phan-Cl, the HetCor spectra show the centerband at $-48$ ppm in the $^{31}$P dimension, a spinning sideband (“ssb”) near $-5$ ppm, and an impurity peak at +1 ppm. The centerband positions are indicated by dashed lines at the top of the figure.
**19F and 31P{19F} REDOR NMR: changes in the Nafion® sidechain.** The 31P NMR results have proven the change in phosphorus bonding from protonated to non-protonated for the primary product A+ in the Naf-Phan-X sample. 19F NMR spectra (Figure 3) show that the fluorine in SO2F groups in the precursor Nafion-F®, which originally resonated at +46.5 ppm, have totally disappeared in the 19F spectrum for Naf-Phan-X membrane. This confirms that Nafion® side-chains have reacted by losing a fluorine atom. In addition, the 19F spectral lines have become broader, which indicates reduced mobility of the perfluoropolymer matrix 29, likely due to attached large molecules.

![Figure 3](image)

**Figure 3.** 19F NMR spectra of a) Nafion-F® and b) Naf-Phan-X by direct polarization at νr = 30 kHz. The peak of the 19F directly bonded to sulfur at +46.5 ppm in Nafion-F® has disappeared in the Naf-Phan-X sample. In addition, the 19F peaks of the Naf-Phan-X sample are broader than those of Nafion-F®, which indicates reduced mobility. Spinning sidebands of the (CF2)n peak are labeled “ssb” and those of the main
sidegroup signal by asterisks.

**Figure 4.** $^{31}\text{P}^{(19}\text{F})$ REDOR spectra of Naf-Phan-X at $N_{tr} = 1$ ms with recycle delay of 30 s and 256 scans. a) Reference spectrum ($S_0$) and b) spectrum after recoupling (S) which shows dephasing for $^{31}\text{P}$ peak at 41 ppm of 50% but little, if any, dephasing for the peak at 5 ppm. c) REDOR $S/S_0$ curve of Naf-Phan-X (circles) with comparison to fluoroapatite (triangles), which has an F–P distance of ~ 0.36 nm.
Dashed lines are simulation curves, with a closest $^{31}\text{P}-^{19}\text{F}$ distance of 0.4-nm for Naf-Phan-X (further details see text).

$^{31}\text{P}\{^{19}\text{F}\}$ REDOR experiments (Figure 4) were performed to confirm the bonding between the perfluoropolymer matrix and the proazaphosphatranium cations by estimating the distance between phosphorus and fluorine. Figures 4a and 4b show $^{31}\text{P}\{^{19}\text{F}\}$ REDOR reference ($S_0$) and dephased (S) spectra, respectively, for Naf-Phan-X at $Nt_r = 1$ ms. The $^{31}\text{P}$ peak at 41 ppm, tentatively assigned to $A^+$ functionality from $^1\text{H}-^{31}\text{P}$ spectra, was dephased to 50%, while the peak at 5 ppm, (possibly associated with $B^+$ from $^1\text{H}-^{31}\text{P}$ spectra) showed no significant dephasing. The REDOR experiment was also run at $Nt_r = 2$ ms, where the peak at 41 ppm had dephased to about 17% (circles in Figure 4c). The dephasing rate was compared to that of fluoroapatite, a crystalline mineral solid with a F–P distance of ~0.36 nm, analogous to simulations described in ref. [31] and [32]. A time scaling factor of 0.73 was used, as determined from the fluoroapatite dephasing and consistent with the expected finite-pulse length effects (75% of a rotation period are without pulses). Adequate fits of the dephasing in Naf-Phan were obtained for a closest $^{31}\text{P}-^{19}\text{F}$ distance of 0.4 ± 0.1 nm. Thus, the 41 ppm feature is again consistent with $A^+$ functionality, while the 5 ppm feature matches the
larger P-F distance of the $B^+$ functionality.

**Figure 5.** $^{13}$C spectra of phosphatranium chloride (Phan-Cl, a-d) and Naf-Phan-X membrane (e-h). (a, e) CP and (b, f) CP/gated decoupling experiments, run at $v_r = 6.5$ kHz; (c, g) CH$_2$- and (d, h) CH-selection experiments at $v_r = 5.787$ kHz. For phosphatranium chloride, two peaks of CH$_2$ bonded to nitrogen are seen, at 34 ppm and 51 ppm. For Naf-Phan-X, the two CH$_2$ peaks shift to 46 ppm and 54 ppm, respectively. In addition, a protonated carbonyl group and a nitrogen-bonded methyl group are present in a ~1:1 ratio. These are most likely from the swelling
agent N,N-dimethyl formamide (DMF) trapped in the membrane. The structure of DMF is shown, with solution state $^{13}$C chemical shifts indicated.

$^{1}$H–$^{13}$C NMR: structure of the proazaphosphatranium cation. To ensure that the primary structure of the phosphatranium chloride has not been altered during the synthesis of the Naf-Phan-X membrane, a set of one-dimensional NMR spectra with spectral editing$^{33,34}$ was recorded (Figure 5). For phosphatranium chloride, the $^{13}$C spectra clearly show two NCH$_2$ signals, at 34 ppm and 51 ppm. This assignment is confirmed by spectral editing that selects signals of CH$_2$ groups, see Figure 5c. The $^{13}$C chemical shifts are in good agreement with literature values (see below). However, for Naf-Phan-X, four $^{13}$C peaks were observed. In addition to signals at 54 ppm and 46 ppm, assigned to NCH$_2$ groups of the proazaphosphatranium cations bonded to Nafion®, additional bands are seen at 159 ppm, from a protonated carbonyl group (aldehyde, HC=O), and at 37 ppm, from a methyl group which persists in the spectrum after gated decoupling due to motional averaging of C-H coupling by fast uniaxial rotation. The carbonyl and methyl groups are most likely from dimethylformamide (DMF), the swelling agent used, which may be trapped in the membrane. The structure and solution state $^{13}$C chemical shifts of DMF are shown in Figure 5. As expected, in the $^{1}$H–$^{13}$C HetCor spectra (Figure 6) the carbonyl carbon correlates to a proton at ~8 ppm, and all other carbons correlate to NCH$_n$ protons at ~3 ppm. Interestingly, one methyl group of DMF, which resonates at 31.3 ppm, is not observed in the $^{13}$C spectra of Naf-Phan-X. The second correlation of the 159 ppm $^{13}$C resonance to a $^1$H at 3 ppm is consistent with a more distant coupling to NCH$_n$ protons, as confirmed by its relative prominence with a longer delay for spin diffusion, see Fig. 6(b).
**Figure 6.** $^1$H–$^{13}$C HetCor spectra of Naf-Phan-X with spin-diffusion times of a) $10 \, \mu s$ and b) $50$ ms at $v_r = 6.5 \, \text{kHz}$. $^{13}$C signal positions are indicated by dashed lines at the top of the figure. Solution state $^1$H NMR chemical shifts for DMF are shown with the structure.

$^{15}$N NMR. The $^{15}$N NMR spectrum of phosphatranium chloride obtained by cross
polarization from $^1$H (Figure 7) shows a peak at 50 ppm (referenced to liquid NH$_4^+$) from protonated nitrogen, and a peak at 37 ppm from non-protonated (tertiary) nitrogen, so assigned due to signal persistence in the CP/gated experiment, see Fig 7b. A small signal is also observed at 23 ppm, but due to limited sensitivity it is uncertain whether this is protonated or not. The relative peak areas are 1.6:1:0.5, which does not match the expected 3:1 ratio. However, it should be noted that a significant level of degradation products are detected in the $^{31}$P spectrum of this sample, see Figure 1a, and similar degradation might account for the 23 ppm $^{15}$N resonance. The signal of the protonated nitrogen has been shifted to 25 ppm in the spectrum for Naf-Phan-X (Figure 7c). No peak of non-protonated nitrogen is seen, which may be due to low cross-polarization efficiency of this tetra-coordinated nitrogen strongly diluted in the polymer matrix; the cross-polarization condition may have shifted due to power absorption by the slightly conductive sample. The $^{15}$N peak at 116 ppm can be assigned to an amide (N-C=O) structure; it may come from DMF, but the nitrogen appears to be protonated (HN-C=O).
Figure 7. $^{15}$N spectra of phosphatranium chloride (a, b) and Naf-Phan-X (c, d) obtained after CP and CP with recoupled gated decoupling, respectively, at $v_r = 5$ kHz. Dashed horizontal lines in d) mark the intensity expected if the N observed in c) was not protonated.
Figure 8. Chemical shifts of structures similar to phosphatranium chloride from reference 26. $^{31}$P chemical shifts are in italics, while $^{13}$C chemical shifts are in regular font. The results from our experiments are given in parentheses.

**Analysis of chemical shifts.** In Figure 8, literature chemical shift values$^{27}$ of $^{31}$P (in italics) and $^{13}$C (in regular font) are listed for phosphatranium chloride and its derivatives. For phosphatranium chloride, the literature values agree well with the results from our experiments (given in parentheses). Though none of the derivatives have the same structure as Naf-Phan-X, we can analyze them to obtain insights into chemical shift trends. For example, substituting the proton on phosphorus by a sulfur (from structure d to c) changes the $^{31}$P chemical shift by +87 ppm, which is similar to the change by +89 ppm from phosphatranium chloride to the chemical shift assigned to the proazaphosphatranium functionality A$^+$ in Naf-Phan-X. In addition, the similar $^{13}$C chemical shifts for structures b, c, e and Naf-Phan-X may
indicate elongation of the cage-like molecular structure of the proazaphosphatranium functionality $A^+$ in Nafion-Phan-X. Such elongation is relative to structures a (Phan-X) and d of Fig. 8, with their shorter P-N distances due to transannular donation of a nitrogen lone pair to phosphorous. This bonding yields correspondingly unique $^{13}$C shifts and a P-N distance of $\sim0.2$ nm, in contrast to $\sim0.3$ nm for structures b, c and e, $^{35}$ whose $^{13}$C shifts are more akin to the Naf-Phan-X system.

**Structural implications.** The new AAEM possesses several interesting features which we now discuss. Resonance structures of proazaphosphatranium cations of type $A^+$ in Scheme 2b can distribute the positive charge in the P–N bonds surrounding the phosphorus (Scheme 3). Such resonance structures minimize coulombic attractions between the cations and anions, and hence can improve the mobility of the anion. It is interesting that analogous cations representative of $A^+$ and $B^+$ (i.e., $[-\text{CS(O)}_2\text{P(N–)}_3]^+$ and $[-\text{CS(O)}_2\text{N(C)}\text{P(N–)}_2]^+$, respectively) are completely unprecedented in the literature. The robust mechanical, oxidative, hydrolytic and thermal stability of the Nafion$^\text{®}$ framework, the diffuse distribution of positive charge and hydrolytic stability of 4-coordinate proazaphosphatranium and 5-coordinate phosphatranium cations are combined in the novel "hybrid" AAEM depicted in Scheme 2. Thus we have in a formal sense transformed Nafion$^\text{®}$ from a PEM material into a halogenide- and a hydroxide-containing AAEM. We accomplished this "ion polarity inversion" of Nafion$^\text{®}$ by a simple experimental procedure using commercially available Nafion-F$^\text{®}$ as shown in Scheme 4. The Naf-Phan-OH film may be an excellent candidate in AFC fuel cell applications according to preliminary studies showing that it retains good conductivity under strongly basic conditions as well as at elevated temperatures.
Conclusions

A Nafion®–proazaphosphatranium/phosphatranium composite cationic film, a potential anion exchange membrane for direct methanol-based fuel cells, was successfully synthesized via a microwave process from Nafion-F® and phosphatranium chloride. Most of the latter was converted to proazaphosphatranium cations attached to the Nafion® via a P–S bond (structure A⁺), as shown by ³¹P{¹H}, ¹⁹F, and ³¹P{¹⁹F} REDOR NMR. These ionophores have a reduced charge density due to resonance structures that distribute positive charge to diminish ionic interaction, which should facilitate hydroxide ion mobility. Electrical measurements to complement the present structural study and further test these hypotheses are underway. The 4-coordinate stereochemistry of phosphorus in the novel proazaphosphatranium cation was substantiated by ¹³C and ¹⁵N NMR. About 1/3 of phosphatranium is converted into two other structures, with S not bonded to P but most likely to N as in structure B⁺. In addition, moieties derived from the solvent, DMF, were found in the final product. Efforts to inhibit formation of these impurities are underway.

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References


CHAPTER 8. SYNTHESIS OF LINEAR OR BRANCHED POLYMERS
POSSESSING CHEMICALLY BONDED PHOSPHATRANIUM NITRATE AS
EFFICIENT NITRATE CONDUCTING MEMBRANES

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In Collaboration with Energetics Inc.

Objective

Synthesize materials that possess high nitrate ion mobility for anionic electrically conducting membranes containing linear or branched polymers bearing cationic phosphatranium cations bonded to the backbone framework (Figure 1) with nitrate counter ions (X⁻).

Figure 1. Polymer Bound Phosphatranium Salt

Introduction

Fuel cells using either metal hydrides or methanol solutions have seen significant research and development in recent years. The Direct Methanol Based Fuel Cell (DMFC) is the dominant candidate to replace the Li-ion battery. Several companies are already involved in the R & D of fuel cell technologies for providing power to portable electronic devices.
instruments. However, none of these firms are developing direct-oxidation ammonia fuel cells because of the technical and environmental issues associated with this approach.\textsuperscript{5-10} Considerable attention has been focused in recent years on research on the DMFC. However, current DMFC technology requires high catalyst loading of precious metals such as Pt and Ru, and an expensive cationic membrane. Methanol is one of the most electroactive organic fuels in the low temperature range mainly because it has low carbon content, it possesses a readily oxidizable group (hydroxyl) and it has high solubility in aqueous electrolytes. The advantages of the DMFC are that methanol is a liquid which is quite soluble in water, thus reducing concentration polarization problems associated with gaseous fuels; methanol is cheap and easy to handle and store, and it has good electroactivity even though it is an organic fuel. Aqueous ammonia solutions have not been considered to date for fuel cells, even though the good energy potential and hydrogen-storage density of ammonia is widely recognized.\textsuperscript{11-13} Ammonia is nitrogen hydride which is cheaply manufactured in bulk. Ammonia is the second largest synthetic commodity product of the chemical industry, with world production exceeding 140 million metric tons. Although ammonia is a toxic noxious gas, ammonia and its derivatives are potential fuels for portable fuel cells. Thus ammonia is a major source of hydrogen, containing 17.6\% by weight of hydrogen in its anhydrous state.\textsuperscript{14}

Forty-five percent of the world’s ammonia production is used to manufacture urea (carbamide). Urea is a major worldwide source of ammoniacal fertilizer, which is environmentally benign and safe in transit and storage. Ammonia derived from urea is a low-cost, readily available, environmentally clean, high-density hydrogen storage medium. Urea contains 8.7 wt\% H\textsubscript{2}. There exists an extensive knowledge base in industry for the hydrolysis of urea to ammonia. The cost per kWh for ammonia is comparable to methanol,
and lower than high purity hydrogen. Carbamide (urea) solutions are safe, benign, transportable and environmentally acceptable sources of ammonia.

The proposed Carbamide Fueled Electrochemical Cell (CFC) (Figure 2) has several advantages including:

- Higher energy density, particularly the higher efficiency of alkaline fuel cells [as compared to acid electrolyte methanol fuel cells and hydrogen-based proton exchange membrane (PEM) fuel cells].
- The activation polarization of CFC’s is substantially lower than methanol in a DMFC.
- The CFC exhibits significant advantages over the Nickel Metal Hydride, Zinc-Air, and Lithium-Ion / Lithium Polymer battery systems, owing to their higher energy and power density, easy replenishment of fuel, and lower costs.
- The CFC provides significant advantages over other primary hydride-based fuel cells using metal hydrides and borohydrides in terms of cost, safety and environmental considerations.

The development of a direct-oxidation, high energy density, carbamide-derived aqueous-ammonia electrochemical cell (CFC) takes advantage of the high hydrogen content of the ammonia molecule (17.6 wt%) and its high electrochemical reactivity in alkaline media to improve energy density. This technology solves both technical and environmental hurdles by providing a novel integration of existing technology (the use of enzymes to liberate ammonia benignly from urea in bio-reactors) and new technologies (anionic membranes with high conductivity, ammonia coordination chemistry for low activation energy losses, non-noble
catalysts for lower costs, and a novel electrochemistry to yield high cell voltages). This will result in a high-energy, high-power density battery / fuel cell system.

**Figure 2.** Conceptual Carbamide Fueled Electrochemical Cell (CFC)

There are several technical and environmental risks associated with the proposed CFC:

- The conversion of carbamide to ammonia, with high efficiency / throughputs, and its safe containment, involves major engineering and scientific challenges.
• The low ideal voltages for ammonia oxidation reported in literature need to be appreciably improved by at least a factor of two, for successful commercialization of these fuel cells, thus requiring new cell chemistry for such improvements.

• Low ionic conductivities in current anionic membranes have limited their applications in fuel cells, and will need to be improved by a factor of one hundred.

• The high costs of catalysts and their high loading in the electrodes of current fuel cells will need to be decreased by a factor of one hundred for successful commercialization.

**Proposed cell chemistry:** The successful Air Force-funded proposal generated in collaboration with Energetics Inc involved the use of ferric nitrate as the oxidizer/catholyte, nitrate-selective salts / membranes as a solid polymer electrolyte, and cuprated carbamide solutions (with urease-immobilized membranes) as the anolyte (for safe and benign ammonia generation). The expected fuel cell reactions are as follows:

Anode: \(2\text{NH}_3 + \text{NO}_3^- \rightarrow \frac{3}{2} \text{N}_2 + 3\text{H}_2\text{O} + e^-\) \(E^o = 5.842 \text{ volts}\)

Cathode: \(\text{Fe}^{+++} + e^- \rightarrow \text{Fe}^{++}\) \(E^o = 0.771 \text{ volt}\)

Net: \(2\text{NH}_3 + \text{Fe}^{+++} + \text{NO}_3^- \rightarrow \frac{3}{2} \text{N}_2 + 3\text{H}_2\text{O} + \text{Fe}^{++}\) \(E^o = 6.613 \text{ volts}\)

The anodic reaction consists of the following sub-reactions:

\(\text{NO}_3^- + 3\text{H}_2\text{O} + 5e^- \rightarrow \frac{1}{2} \text{N}_2 + 6\text{OH}^-\) \(E_{1}^o = 0.248 \text{ volts}\)

\(2\text{NH}_3 + 6\text{OH}^- \rightarrow \text{N}_2 + 6 \text{H}_2\text{O} + 6e^-\) \(E_{2}^o = 0.767 \text{ volts}\)

Net anodic reaction \(2\text{NH}_3 + \text{NO}_3^- \rightarrow \frac{3}{2} \text{N}_2 + 3\text{H}_2\text{O} + e^-\)
Since there is a net loss of electrons, the thermodynamic voltage for the net reaction can be determined as follows using free energy calculations:

\[ nE^0 = 5E_{1^0} + 6E_{2^0} = 5(0.248) + 6(0.767) = 5.842 \text{ v}, \text{ where } n = 1. \text{ Therefore, } E^0 = 5.842 \text{ volts}. \]

The preferred electrolyte for the above described fuel cell chemistry would be a solid polymer anion exchange membrane. The following anionic membranes were tested by Energetics in the past, and their comparison to Nafion® is also shown in the table below. The main technical hurdles were membrane thickness and aerial resistance. If improved specific conductivity can be achieved, the higher efficiency of anionic fuel cells would be an enormous advantage to the proposed CFC.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Designation</th>
<th>Aerial Resistance (ohm-cm²)</th>
<th>Thickness (microns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranes Intl.</td>
<td>AMI-7001</td>
<td>22 +/- 1</td>
<td>457.2</td>
</tr>
<tr>
<td>Electropure</td>
<td>I-200</td>
<td>5-10</td>
<td>320-340</td>
</tr>
<tr>
<td>Excellion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sybron Chemicals</td>
<td>MA-3475</td>
<td>25</td>
<td>400</td>
</tr>
<tr>
<td>DuPont Chemicals</td>
<td><em>Nafion</em>®</td>
<td><strong>0.05</strong></td>
<td><strong>50</strong></td>
</tr>
</tbody>
</table>

In order to synthesize materials that possess high nitrate mobility for membranes and chemically modified electrodes, our objective was to synthesize linear polymers containing
phosphatranium derivatives bonded to the backbone framework (as shown schematically in Figure 1) in which the anion $X^-$ is nitrate. In Figure 3 is shown the variety of bicyclic precursors, the vast majority of them having been made for the first time in our laboratories.

![Structure of various proazaphosphatranes and phosphatranium ions](image)

Figure 3. Structure of various proazaphosphatranes and phosphatranium ions

All of the proazaphosphatrane precursors are readily converted to the phosphatranium salts in which the phosphorus is protonated as depicted on the right side of Figure 3. Because these phosphatranium cations are very weak acids (having pKa values of 33 to 34 in acetonitrile)$^{15}$ the precursors shown are very strong bases; a property which has led us to uncover a very rich chemistry of these species in effecting a wide variety of important Arrhenius or Lewis base-dependent organic reactions both stoichiometrically and catalytically.$^{16}$ It may be noted, that we have, in a single step, synthesized several examples of phosphatranium salts in which the axial H substituent is replaced by F, Cl or OP(O)Ph$_2$ which also were shown to exhibit strong transannular N→P bonds. We were also successful in chemically bonding to a Merrifield resin in one step, a phosphatranium cation of the type
shown in Figure 3 where $X^-$ is nitrate. That work was aimed at carrying out aza-Michael and thia-Michael reactions catalyzed by nitrate. This was very successful and it was found that the polymeric catalyst is very stable and highly recyclable. Even when the catalyst dies, it is readily regenerated. The results of this work showed that the nitrate in our resin is superior to that in commercially available nitrate anion exchange resins, and we attribute this improved action to the poor anion-cation interaction in our phosphatranium salts.

The justification for the use of phosphatranium cations of the type shown in Figure 1 is that there is a large body of experimental evidence garnered over the past ten years supporting the following four conclusions:

1) The cations represented in the structure shown in Figure 3 are very robust to air and moisture owing in large measure to their chelated strainless configuration and the existence of the very stabilizing bridgehead-bridgehead nitrogen-to-phosphorus bond.

2) Anions are effectively inhibited from forming interactive ion pairs with these types of cations, owing to extensive resonance delocalization of the positive charge among the four nitrogens and the phosphorus in the cage moiety of the cation shown in Figure 4.

3) Phosphatranium ions can be “decorated” with a wide variety of substituents on the cage core.

4) The upper axial substituent on the phosphatranium cation can be not only a hydrogen, but also a chlorine or a phosphinate group

Conclusion 1 bodes well for stability of the systems we proposed to investigate, and conclusions 3 and 4 offer possibilities for increasing stability through steric hindrance of the
phosphatranium skeleton. Conclusion 2 bodes well for unimpeded membrane transport and hence providing high conductivity of nitrate anions in our proposed system.

Our objective for developing a suitable conducting film for a membrane or chemically modified electrode entailed two strategies:

1) Development of a nitrate salt that will meet the requirements for withstanding the temperature and the aqueous, basic and oxidative environment of the fuel cell for the period of time required.

2) Development of a polymer backbone that will also meet the requirements for withstanding the temperature and the aqueous, basic and oxidative environment of the fuel cell for the period of time required.
We used various polymeric backbones containing benzyl chloride or alkyl chloride functionalities to attach trihydrophosphatranium chloride to the polymeric backbone via C-N linkages. We synthesized cationic polymer membranes 1-6 as shown in Figure 5 and then tested them for their conductive properties.

Figure 5. Structure of cationic polymers
Experimental

**Scheme 1.** Synthesis of 1

**Synthesis of 7:** Polymer backbone 7 was synthesized (Scheme 1) according to a literature procedure.\textsuperscript{18} To a solution of styrene (20.0 g, 194 mmol) and 4-(chloromethyl)styrene (0.91 g, 6 mmol) in benzene (70 mL) was added 2,2'-azobisobutylnitrile (AIBN) (0.16 g, 1 mmol). The vessel was purged of oxygen using a vacuum/nitrogen evacuation flushing cycle (3 times) and then the solution was stirred at 70 °C for 40 h. The mixture was poured into methanol drop wise to obtain a THF soluble chloromethylated polystyrene 7 (Cl = 0.3 mmol/g via elemental analysis).

**Synthesis of 1a:** To the solution of chloromethylated polystyrene 7 (1 g, 0.3 mmol chlorine/g) and trihydrophosphatranium chloride (0.084 g, 0.4 mmol) in dry DMF (20 mL) was added triethylamine (0.04 g, 0.4 mmol). The vessel was purged of oxygen using a vacuum/nitrogen evacuation cycle (3 times) and the solution was stirred at 110 °C for 72 h (Scheme 1). The mixture was poured into methanol drop wise to obtain DMF/MeOH (1:1)-
soluble polymer-bound phosphatrane chloride 1a in quantitative yield. This product was then washed with aq. NaNO$_3$ solution to replace the chloride ions with nitrate anion.

**Synthesis of 1b:** To the solution of chloromethylated polystyrene 7 (3 g, 0.3 mmol of chlorine/g) and trihydrophosphatranium chloride (1.44 g, 6.8 mmol) in dry DMF (20 mL) was added triethylamine (6.8 mmol). The vessel was purged of oxygen using a vacuum/nitrogen evacuation cycle (3 times) and the solution was stirred at 110 °C for 72 h (Scheme 1). The mixture was poured into methanol drop wise to obtain soluble polymer bound phosphatrane chloride 1b in quantitative yield. This was then washed with aq. NaNO$_3$ solution to replace the chloride ions with nitrate anion.

![Scheme 1](image1.png)

**Scheme 2.** Synthesis of 2

**Synthesis of 8:** To a solution of poly(methylhydrosiloxane) (PMHS, 0.2-0.3M, 1 equiv.) under argon, was added 4-vinylbenzylchloride (1.3 equiv.) followed by dichlorodi(cyclopentadienyl)platinum(II) (1 mg) as a catalyst (Scheme 2). The mixture was stirred at 60–65 °C for 40 h. The reaction mixture was then cooled to room temperature after which the reaction mixture was added drop-wise into a large volume (ca 50 mL) of hexanes. The precipitate was collected via centrifugation/decantation. Then the precipitated polymer
was collected and dissolved in the minimum amount of THF needed to dissolve the crude polymer completely. The polymer was re-precipitated in hexanes for a repeat of the purification process after which this process was repeated 2–3 times to remove monomer from the crude polymer. Residual solvents were removed under reduced pressure (Cl content = 3.7 mmol/g via elemental analysis).

**Preparation of 2:** To a solution of 8 (3.2 g, 3.7 mmol/g via elemental analysis) in toluene was added trihydrophosphatranium chloride (4.62 g, 22 mmol) followed by triethylamine (2.2 g, 22 mmol) (Scheme 2). The solution was refluxed for 3 days and then the mixture was cooled to room temperature and the product was added drop-wise to excess methanol. The product was filtered, washed with methanol and dried under vacuum to obtain 2.

![Scheme 3. Synthesis of 3a and 3b](image)

**Synthesis of 9:** Functionalized silica 9 was prepared according to a literature procedure (Scheme 3).\(^{19}\) a suspension of 5.96 g of (3-chloropropyl)trimethoxysilane and 20 g of activated silica gel\(^{20}\) in 100 mL of dry toluene was refluxed with stirring. After 1.5 h ca 25 mL methanol containing some toluene was distilled from the mixture. After an additional hour of refluxing, an additional 25 mL methanol–toluene was distilled out. Finally the
mixture was refluxed for one hour, cooled and filtered, and then the silica was washed several times with skelly F and air dried (Cl content = 1.29 mmol/g via elemental analysis).

**Synthesis of 3a:** Trihydrophosphatranium chloride (1.05 g, 5 mmol) was reacted with 2 g of 9 (Scheme 3) in refluxing toluene for 3 days in the presence of triethylamine (0.5 g, 5 mmol). After cooling to room temperature, the reaction mixture was filtered and the solid product was washed with THF, methanol and ether.

**Synthesis of 3b:** Phosphatranium chloride (1.05 g, 5 mmol) was reacted with 2 g of 9 (Scheme 3) in refluxing DMF for 3 days in the presence of triethylamine (0.5 g, 5 mmol). After cooling to room temperature, the reaction mixture was filtered and the solid product was washed with THF, methanol and ether.

![Scheme 4](image.png)

**Scheme 4.** Synthesis of 4a and 4b

**Synthesis of 10:** Activated silica gel21 10 g (Scheme 4) was immersed in a DMF solution (6 mL) containing chloromethylstyrene (6.6 g), divinylbenzene (0.7 g) and AIBN (0.1 g). The mixture was allowed to stand for 30 min while cooling at -5 °C and then filtered. The vinyl monomers on the silica surface were copolymerized by heating the beads at 80 °C for 5
h under Ar atmosphere. The product was washed with benzene for 6 h in a Soxhlet extractor and dried under reduced pressure (Cl content = 1.40 mmol/g via elemental analysis).

**Preparation of 4a:** A mixture of trihydrophosphatranium chloride (1.16 g, 5.54 mmol), 10 (2 g) and triethylamine (0.554 g, 5.54 mmol) was heated in toluene at 110 °C for 72 h (Scheme 4). The solid product was filtered off after cooling the reaction mixture to room temperature and washed with copious amounts of THF, methanol and ether.

**Preparation of 4b:** A mixture of trihydrophosphatranium chloride (1.16 g, 5.54 mmol), 10 (2 g) and triethylamine (0.554 g, 5.54 mmol) was heated in DMF at 110 °C for 72 h (Scheme 4). The solid product was filtered off after cooling the reaction mixture to room temperature and washed with copious amounts of THF, methanol and ether.
Scheme 5. Synthesis of 13

Synthesis of Hexakis(4-formylphenoxy)cyclotriphosphazene 11: To a solution of hexakischlorophosphazene (10.2 g, 0.03 mol) in THF was added a solution of \( p \)-hydroxybenzaldehyde (23 g, 0.19 mol) and triethylamine (24.1 g, 0.24 mol) in THF. The mixture was refluxed for 48 h. After filtration, the solvent was removed under reduced pressure and the residue was recrystallized to give hexakis(4-formylphenoxy)cyclotriphosphazene 11.

Synthesis of Hexakis(4-hydroxymethylphenoxy)cyclotriphosphazene 12: To a solution of hexakis(4-formylphenoxy)cyclotriphosphazene 11 (2 g, 2.3 mmol) in THF-MeOH (140
mL, 1:1) was added sodium borohydride (0.56 g, 15 mmol) at room temperature (Scheme 5). The reaction mixture was stirred overnight at room temperature. After evaporation of the solvents, the resulting solids were recrystallized from 90% ethanol to give 1.5 g (75% yield) of hexakis(4-hydroxymethylphenoxy)cyclotriphosphazene 12.

**Synthesis of Hexakis(4-chloromethylphenoxy)cyclotriphosphazene 13**: To a solution of hexakis(4-hydroxymethylphenoxy)cyclotriphosphazene 12 (5.0 g, 5.7 mmol) was added thionyl chloride (82 g, 0.69 mol). The solution was stirred at room temperature for 24 h (Scheme 5) and after removal of excess of thionyl chloride under reduced pressure, the product was recrystallized from chloroform in quantitative yield.

![Scheme 6. Synthesis of 5a-d](image)

**Synthesis of 5a-d**: To a solution of hexakis(4-chloromethylphenoxy)cyclotriphosphazene 13 (0.67 g, 0.68 mmol), phosphatranium chloride (0.79 g, 3.7 mmol) in DMF or toluene (Scheme 6), was added a base (see Table 6) (3.7 mmol). The reaction mixture was stirred at
110 °C for 72 h. The product was then precipitated in ethyl ether and filtered off. Impurities were removed by extracting the product with copious amounts of methanol, acetone and THF.

**Synthesis of 6a:** Compound 14 was prepared *in situ* using a literature procedure (Scheme 7). To a solution of phosphatranium triflate (0.648 g, 2 mmol) in THF was added 3.1 equivalents of *n*-BuLi (3.1 equiv., 2.5 mL in hexane) at –78 °C. To this mixture was slowly added a solution of polyvinyl chloride (2.0 g) in 10 mL of THF at –78 °C. The reaction mixture was stirred while allowing it to come to room temperature slowly. Polymer 6a was precipitated by adding the reaction mixture drop-wise to ethanol.

![Reaction Scheme](image)

**Scheme 7. Synthesis of 6a**

**Synthesis of 6b:** Phosphatranium triflate (0.648 g, 2 mmol) prepared according to a literature procedure was dissolved in 10 mL of THF. *n*-BuLi (1.5 equiv., 1.25 mL in Hexane) at –78 °C (Scheme 8) was then added followed by slow addition of a solution of polyvinyl chloride (2.0 g) in 10 mL of THF at –78 °C. The reaction mixture was stirred while allowing it to come to room temperature slowly. The polymer was precipitated by adding the reaction mixture drop-wise to ethanol.
Results and Discussion

Results of AC impedance test of 1a: A solution of 1 g of polymer 1a in a minimum amount of DMF/MeOH was coated on a pre-existing solid mesh nylon support.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Resistivity (Ohm cm)</th>
<th>Resistance (ohm)</th>
<th>Conductivity (Ohm$^{-1}$ cm$^{-1}$)</th>
<th>Cross Over$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>431,000</td>
<td>700</td>
<td>$2 \times 10^{-6}$</td>
<td>No</td>
</tr>
</tbody>
</table>

$^a$Diffusion of ammonia through the anion exchange membrane from the anode to the cathode compartment.

Results for AC impedance test of 1b: Sample 1b was cast as a membrane using two different techniques:

1b: A Polymer solution of 1b in DMF/MeOH (details as above) was coated on a nylon mesh support as above.
1b': A membrane was cast via molten solid casting with a 1:2 mixture of 1b and Low Density Polyethylene (LDPE).

Table 2: AC impedance tests of 1b and 1b’

<table>
<thead>
<tr>
<th>Sample</th>
<th>Resistivity (Ohm cm)</th>
<th>Resistance (ohm)</th>
<th>Conductivity (Ohm(^{-1}) cm(^{-1}))</th>
<th>Cross Over</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>105,000</td>
<td>19</td>
<td>1 x 10(^{-3})</td>
<td>No</td>
</tr>
<tr>
<td>1b’</td>
<td>420,000</td>
<td>86</td>
<td>2 x 10(^{-6})</td>
<td>No</td>
</tr>
</tbody>
</table>

Discussion:

1. The mechanical strength of the polymer was poor mainly because the polymer was of low molecular weight.

2. The resistances of both 1a and 1b were very high, although, when the loading of phosphatrane was increased in 1b, the resistance was 10 times lower. The conductivity of both membranes was low.

3. The membrane did not show any crossover of ammonia in the fuel cell.

4. Attempts were made to react other amines such as triethylamine and tributylamine with polymer 7, but unfortunately all the polymers with quaternary ammonium salts were soluble in water.

Results for AC impedance test of 2:

A membrane was cast via molten solid casting with a 1:4 mixture of 2 and Low Density Polyethylene (LDPE).
**Table 3:** AC impedance test of 2

<table>
<thead>
<tr>
<th>Sample</th>
<th>Thickness (micron)</th>
<th>Resistance (ohm)</th>
<th>Conductivity (Ohm$^{-1}$ cm$^{-1}$)</th>
<th>Cross Over</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>58.6</td>
<td>56.07</td>
<td>2.72 x 10$^{-6}$</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Discussion:

1. The resistance of 2 was very high and its conductivity was low.

2. The most important drawback was crossover of ammonia, which decreases the shelf life of fuel cells.

Results of AC impedance test of 3a/3b: Sample 3a and 3b was cast into membrane via molten solid casting with a 20% w/w mixture of 3a or 3b and polyvinylchloride (PVC).

**Table 4:** AC impedance tests of 3a and 3b

<table>
<thead>
<tr>
<th>Sample</th>
<th>Resistivity (Ohm cm)</th>
<th>Resistance (ohm)</th>
<th>Conductivity (Ohm$^{-1}$ cm$^{-1}$)</th>
<th>Cross Over</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>6750</td>
<td>9.6</td>
<td>1.5 x 10$^{-4}$</td>
<td>Yes</td>
</tr>
<tr>
<td>3b</td>
<td>10316</td>
<td>1.8</td>
<td>1 x 10$^{-4}$</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Discussion:

1. The mechanical strength of the polymer membrane was good up to <30% w/w conc with PVC. Brittleness was observed at higher concentrations.
2. The resistance of both 3a and 3b was very low with good conductivity for both membranes.

3. Unfortunately crossover of ammonia in the fuel cell was observed.

Results of AC impedance tests of 4a/4b: A sample of 4a was cast into a membrane via molten solid casting as a 1:2 mixture by weight with polystyrene, and 4b was cast as a 10% mixture by weight with polymethylmethacrylate.

Table 5: AC Impedance tests of 4a and 4b

<table>
<thead>
<tr>
<th>Sample</th>
<th>Resistivity (Ohm cm)</th>
<th>Resistance (ohm)</th>
<th>Conductivity (Ohm(^{-1}) cm(^{-1}))</th>
<th>Cross Over</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>1035</td>
<td>1.5</td>
<td>9 x 10(^{-4})</td>
<td>Yes</td>
</tr>
<tr>
<td>4b</td>
<td>7430</td>
<td>10.5</td>
<td>1.3 x 10(^{-4})</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Discussion:

1. The mechanical strength of 4a was poor because it was very brittle. On the other hand, 4b had good mechanical strength.

2. The resistance of both 4a and 4b was very low. High conductivity and low resistance was observed for 4b but its membrane strength was poor.

3. Unfortunately crossover of ammonia in the fuel cell was observed.

Results of AC impedance tests of 5a-d: Samples of 5a-d were cast into membranes via molten solid casting as follows:
5a: 20% w/w blended with polymethylmethacrylate.

5b: 1:2 weight ratio with low density polyethylene (LDPE).

5c: 1:3 weight ratio with low density polyethylene (LDPE).

5d: 20% w/w blended with polymethylmethacrylate.

Table 6: AC impedance tests of 5a-d/polymer blends

<table>
<thead>
<tr>
<th>Sample</th>
<th>Solvent</th>
<th>Base</th>
<th>Resistance (ohm)</th>
<th>Conductivity (ohm cm⁻¹)</th>
<th>Resistivity (ohm cm)</th>
<th>Cross over</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Toluene</td>
<td>Et₃N</td>
<td>30</td>
<td>6 x 10⁻⁶</td>
<td>170,262</td>
<td>No</td>
</tr>
<tr>
<td>5b</td>
<td>DMF</td>
<td>Et₃N</td>
<td>25</td>
<td>6 x 10⁻⁵</td>
<td>21,240</td>
<td>No</td>
</tr>
<tr>
<td>5c</td>
<td>DMF</td>
<td>Bu₃N</td>
<td>20</td>
<td>1 x 10⁻⁵</td>
<td>116.463</td>
<td>No</td>
</tr>
<tr>
<td>5d</td>
<td>DMF</td>
<td>-</td>
<td>11</td>
<td>2 x 10⁻⁵</td>
<td>60,864</td>
<td>No</td>
</tr>
</tbody>
</table>

Discussion:

1. Base was used to quench HCl liberated in the reaction between the amine and the benzyl chloride group.

2. The mechanical strengths of 5a-d were good but the membranes became brittle when the loading of 5 was increased.

3. Resistances were high and conductivities were low.
4. The best conductivity and lowest resistance was obtained when only phosphatranium chloride was used in DMF as solvent.

The AC impedance test of 6a and 6b: Samples 6a and 6b were cast as membranes via solution casting using THF as solvent.

Table 7: AC impedance tests of 6a, 6b and 6b'

<table>
<thead>
<tr>
<th>Sample</th>
<th>Phosphatrane loading (w.r.t PVC)</th>
<th>Resistance (ohm)</th>
<th>Conductivity (ohm(^{-1})cm(^{-1}))</th>
<th>Cross Over</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>5 mol %</td>
<td>6</td>
<td>5 x 10(^{-5})</td>
<td>No</td>
</tr>
<tr>
<td>6b</td>
<td>6.25 mol %</td>
<td>1</td>
<td>6 x 10(^{-4})</td>
<td>No</td>
</tr>
<tr>
<td>6b'</td>
<td>12.5 mol %</td>
<td>-</td>
<td>9 x 10(^{-5})</td>
<td>No</td>
</tr>
</tbody>
</table>

Discussion:

1. The mechanical strengths of the 6a, 6b and 6b' membranes were excellent and the membranes were easy to handle.
2. Resistances were low and good conductivities were observed.
3. However, fluctuation in the conductivity was observed was observed in 6b when a duplicate run was carried out.
Conclusion

A wide variety of polymeric samples with phosphatranium nitrate attached to the polymer backbone were prepared. Moderate to good values of conductivities were obtained and the best conductivities were obtained for samples 3, 4, 5 and 6. Our results suggest that 6 was the best candidate for fuel cell application. This result suggests that a halogenated polymeric backbone provides low resistances and greater thermolytic stability. Phosphatranium nitrate as shown above is a good candidate for a nitrate ion conductor owing to its bulky cationic nature which reduces anion-cation interactions. A more detailed study of these polymers should be carried out to better understand the relationship between their structures and their properties as anion transport membranes.

Reference


CHAPTER 9. PROAZAPHOSPHATRANE CATALYSTS MOUNTED ON PERHALOGENATED POLYMERS

Kuldeep Wadhwa, Venkat Reddy Chintareddy, and John G. Verkade

Introduction

Biodiesel, obtained from plant oils, is an advantageous alternative to fossil diesel fuel.\textsuperscript{1-15} It has many advantages such as biodegradability, biorenewability, very low sulfur content and toxicity, low volatility/flamability, good transport and storage properties, higher cetane number, and its good atmospheric CO\textsubscript{2} balance for production. Transesterification of plant oils with methanol is the most common approach to biodiesel production. The byproduct glycerin, formed during transesterification, also has numerous applications in the food, cosmetic, and pharmaceutical sectors.\textsuperscript{16,17} Biodiesel not only has applications as a diesel fuel additive, but it also has a market as green industrial degreasing solvents; as diluents for pigments, paints, and coatings; and for fuel applications in military engines.\textsuperscript{18,19}

The most common catalysts for the transesterification of plant oils to biodiesel have included the use of homogeneous strong-base catalysts, such as alkaline metal hydroxides, alkoxides, and acid catalysts, such as HCl and H\textsubscript{2}SO\textsubscript{4}.\textsuperscript{9,15,20-28} Alkaline alkoxides and hydroxides are more effective catalysts than acid catalysts and operate at lower temperatures.\textsuperscript{29-31} However, the most common disadvantage of homogeneous alkaline catalysts is soap formation, leading to product loss and problems with product separation and purification. Heterogeneous catalysts for biodiesel production have various advantages such as reusability and eco-
compatibility. Moreover, product separation from a heterogeneous catalyst is easier and since no water washes are required during work up, product purity is good. Some heterogenous catalysts have been reported in the literature such as guanidines or amines anchored to the backbone of organic polymers. Their main drawback is that they operate at the reflux temperature of the solvent used for the reaction.\textsuperscript{32-35} Recently, the use of WO\textsubscript{3}/ZrO\textsubscript{2} (stable up to 100 h at 250 °C) has been employed as a heterogeneous solid acid catalyst at 250 °C to produce biodiesel.\textsuperscript{36} However, the recyclability of this catalyst was not reported. Other drawbacks that heterogeneous catalyst systems possess are insufficient catalyst reusability, handling difficulties, the need for elevated temperatures, multistep catalyst synthesis, and, most importantly, frequent problems with adaptability to large-scale preparations.

First discovered in our laboratory, proazaphosphatranes\textsuperscript{37} 1\textsuperscript{a–d} are exceedingly strong commercially available nonionic bases (pK\textsubscript{a} 32–34 in CH\textsubscript{3}CN\textsuperscript{38b}) which are useful as homogeneous catalysts and as stoichiometric reagents in a wide variety of important organic transformations, including transesterifications.\textsuperscript{38a} Though catalyst 1 is a very efficient catalyst for transesterification, the trivalent aminophosphine moiety in 1 is fairly sensitive to
oxygen and proton sources (including water). However, modification of this catalyst system to less basic but stable iminophosphoranes 2a (Figure 1) was found to be effective.\textsuperscript{39} Subsequently it was found that these structures were erroneously reported as imines\textsuperscript{39} and that the correct structures had the azidopropazaphosphatrane 2b framework as determined by X-ray crystallography for a member of this class of compounds.\textsuperscript{40} We also demonstrated that a dendrimer functionalized with an azidopropazaphosphatrane (3) shown in Figure 2 is a good catalyst for C-C bond-forming Michael and Henry reactions.\textsuperscript{41} As part of our efforts to develop green chemical methods for organic synthesis, homogeneous proazaphosphatranes (1) were converted to heterogeneous Merrifield resin-bound analogs of type 4 (Figure 3).\textsuperscript{39,40}
Heterogeneous catalysts of type 4 have been shown by us to be useful in the acetylation of alcohols with vinyl acetate\textsuperscript{39} and in 1,4 addition reactions.\textsuperscript{42} Verkade \textit{et al.} reported the use of catalyst 4 in the synthesis of biodiesel and showed it to be deactivated after 11 cycles.\textsuperscript{40} It was then found by solid state $^{13}$C NMR techniques (in collaboration with Professor Schmidt-Rohr of this Department) that the catalyst was plugged with organic impurities accumulated during the catalyst cycles, thereby deactivating the catalyst by blocking the active sites.\textsuperscript{43}

![Figure 3](image)

\textbf{Figure 3}

To overcome the recyclability problem of catalyst 4,\textsuperscript{40} we proposed a heterogeneous catalyst composed of a molecule such as 4 bonded to a Teflon\textsuperscript{®} substrate for the transesterification of plant oils to biodiesel as depicted in Figure 4. The proposed catalyst would have the following advantages.
The highly robust nature of azidoproazaphosphatranes, which we had already shown in the past to be efficient catalysts for transesterification as well as a number of other organic transformations.\textsuperscript{39-42}

2) These catalysts would be attached to perhalogenated polymer backbones, such as Teflon®️, which would enable this catalyst system to be stable to elevated temperatures and hydrolytic conditions.

3) These catalyst systems would be highly recyclable since they would have no lipophilic pores for plugging by organic impurities.

**Figure 4.** Structure of Teflon®️ bound azidoproazaphosphatranes
Results and Discussion

Scheme 1. Synthesis of Nafion®-bound azidopraza-porphosphatrane

As shown in Scheme 1, commercially available Nafion-CO₂H® (5) resin was reacted with p-aminophenethyl alcohol to form amide linkages (6), followed by conversion of the Nafion®-bound-phenethyl alcohol (6) to the corresponding mesylate (8), which was then converted to a phenethyl azide linkage (9) using NaN₃. Nafion® bound-phenethyl alcohol (6) along with formation of 7 as side product were observed using solid state $^{13}$C NMR spectroscopy. The formation of 7 was rationalized as shown in Scheme 2. Nafion®-bound azidopraza-porphosphatrane (10) was prepared in a procedure similar to that employed for the synthesis of Merrifield-resin bound azidopraza-porphosphatrane. However, in the present case,
we noticed cleavage of the amide linkage in the $^1$H NMR spectrum. At this stage it is not clear what causes the cleavage of this linkage.

Scheme 2

In an attempt to synthesize a Teflon®-bound azidoproazaphosphatrane as shown in Figure 4, free radicals were generated on the surface of Teflon® (11) in the presence of $p$-vinylbenzyl chloride (VBC) using high-energy electron beam (EB) radiation (Scheme 3) yielding 12.\textsuperscript{44} Compound 12 was converted to 13 using NaN$_3$. Compound 13 was then reacted with proazaphosphatrane (1d) to generate a Teflon®-bound azidoproazaphosphatrane (14). We obtained a $^{31}$P NMR peak at 37 ppm that we assigned to 14, which is in accordance with $^{31}$P NMR of 2b.\textsuperscript{40} When 14 was tested in a reaction of SBO with MeOH to obtain the transesterification product, no reaction was observed by $^1$H NMR spectroscopy. We attribute
this disappointing result to the very low content of the azidoproazaphosphatrane present in the polymer (ca. < 0.17 mmol/g via phosphorus elemental analysis).

Scheme 3. Synthesis of Teflon®-bound azidoproazaphosphatrane

In these EB grafting experiments, reactions were carried out in a reaction vessel exposed to a radiation dose of 20-100 kGy. Table 1 shows the trend of VBC grafting to Teflon® (12-100 micron mesh). The highest loading we obtained was 0.77 mmol/g of benzyl chloride as shown by elemental analysis of chlorine retained. Unfortunately, this loading was not high enough to display observable catalytic activity for the transesterification of soybean oil with methanol.
Table 1. Grafting of VBC on Teflon® Powder\textsuperscript{a} Using EB Radiation

<table>
<thead>
<tr>
<th>Sample</th>
<th>Size (micron)</th>
<th>Dosage (kGy)</th>
<th>Chlorine (wt %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>22.32</td>
<td>0.4</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>22.32</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>22.32</td>
<td>0.2</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>22.32</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>47.49</td>
<td>2.4</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>47.49</td>
<td>1.7</td>
</tr>
<tr>
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<td>55</td>
<td>76.22</td>
<td>2.5</td>
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<td>2.1</td>
</tr>
<tr>
<td>9</td>
<td>55</td>
<td>93.0</td>
<td>2.7</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>93.0</td>
<td>1.9</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Teflon® powder was obtained from Aldrich.

Conclusion

In conclusion, we have shown that a new perhalogenated polymer-bound azidoproazaphosphatrane catalyst for the transesterification of plant oil was synthesized successfully. However, the loading of the catalytic sites on the polymer is very low and needs significant improvement. The use of gamma radiation to graft VBC to Teflon\textsuperscript{®} is underway in a collaboration with Dr. Inderjeet Kaur, Himachal Pradesh University, Simla, India, who has demonstrated this technology for VBC-Teflon\textsuperscript{®} grafting.\textsuperscript{45} Switching the source of energy for EB to gamma radiation from \textsuperscript{60}Co has dramatically increased the VBC loading
from 0.77 to 28.5–42.8 mmol/g Cl for a sample of Teflon® (55 micron particle size) which we sent her. A one-gram sample of the 150% grafted sample is projected to be sent to us by Dr. Kaur at the end of June, after which we will attach the azidoprazaphosphatrane. If this effort is successful, we hope that the new heterogeneous catalyst for the transesterification of soybean oil as well as other important organic transformations will be efficient and highly recyclable.

Experimental

**Synthesis of 6:** Nafion-CO₂H® 5 (2 g, 3.6 mmol) was weighed in nitrogen filled glove box in a round-bottom flask. To this was added \( p \)-amino-phenethyl alcohol (1 g, 7.2 mmol), DCC (1.48 g, 7.2 mmol) or EDC (1.1 g, 7.2 mmol), N-hydroxybenzotriazole (0.972 g, 7.2 mmol) in 30 mL DMF. This was heated in a closed vessel at 110 °C for 48 h. Product 6 was filtered and washed with excess water and methanol and then dried under vacuum.

**Synthesis of 8:** To 6 was added triethylamine (1 g, 10.0 mmol) and MsCl (1.14 g, 10.0 mmol) in a round-bottom flask. The solution was stirred at room temperature for 24 h and then filtered under vacuum. The filtered solid was washed with excess water and methanol. Product 8 was dried under vacuum.

**Synthesis of 9:** In a dry round-bottomed flask was added NaN₃ (1.3 g, 20.0 mmol), 8 (1.0 g) and 20 mL of anhydrous DMF. The flask was submerged in a pre-heated (80 °C) oil bath for 48 h. The polymer was filtered and washed with excess water and methanol. Product 9 was dried under vacuum.
**Synthesis of 10**: To a 50 mL round-bottomed flask under inert atmosphere charged with 9 (1.0 g) was added proazaphosphatrane 1c (3.42 g, 10 mmol) and dry toluene (5 mL) which was added via syringe. The mixture was stirred at room temperature for 48 h and then it was filtered and washed with dry toluene under an inert atmosphere.

**Synthesis of 12**: To a thick-walled glass tube was added Teflon® powder (11) (2 g) and VBC such that the polymer was completely immersed in the VBC. The tubes were then sealed under vacuum. These tubes were exposed to EB radiation for a total dose of 60-100 kGy and then they were heated in an oil bath at 60 °C for 24 h. The polymer was then filtered and washed with copious amounts of toluene to remove any unreacted or homopolymerized VBC. The polymer was then dried under vacuum to obtain the grafted polymer 12. The maximum grafting of VBC on the polymer was 2.7% (Table 1, entry 9).

**Synthesis of 13**: In a dry round-bottomed flask was added NaN₃ (1.3 g, 20 mmol) and 12 (1.0 g, Cl = 0.77 mmol/g via elemental analysis). To this was added dry DMF (20 mL) and the mixture was heated in a closed flask at 80 °C for 48 h. The polymer was filtered and then washed with excess water, THF and acetone. Product 13 was then dried under vacuum.

**Synthesis of 14**: To a 50 mL round-bottomed flask charged with 13 (0.77 mmol/g) under inert atmosphere was added proazaphosphatrane (1d, 340 mg, 1.54 mmol) followed by the addition of 10 mL of dry toluene via syringe. The mixture was stirred at room temperature for 48 h and then the solid was filtered and washed with dry toluene under inert atmosphere. The phosphorus loading on polymer 14 was found to be <0.16 mmol/g of phosphorus via elemental analysis.
General Procedure for Transesterification of SBO to Biodiesel. A round-bottom flask containing the catalyst 14 (0.5 g) was equipped with a rubber septum and two magnetic stir bars for stirring efficiency. After the tube was flushed with argon, SBO (2 mL) and MeOH (5 mL) were added separately via a syringe. The reaction mixture was stirred vigorously at room temperature (23-25 °C), and the progress of the reaction was monitored by solution $^1$H NMR spectroscopy. The reaction mixture was centrifuged and the vast majority of the supernatant was carefully removed by cannulation to avoid disturbing the catalyst. Excess methanol was removed from the separated supernatant liquid via rotavapor, leaving the biodiesel, which was subjected to $^1$H NMR analysis. The relevant signals chosen for integration were those of methoxy groups in the biodiesel (3.66 ppm, singlet) and those of the R-methylene protons present in the triglycerides (2.3 ppm, triplet) of the SBO.\(^{40}\) Conversion of SBO to biodiesel was also observed visually by the disappearance of the mutually immiscible SBO and methanol phases. As noted above, however, no SBO transesterification was observed for 14.

References


43) In collaboration with Professor K. Schmidt-Rohr at Iowa State University.


CHAPTER 10. GENERAL CONCLUSIONS AND FUTURE WORK

1. General conclusions and future possibilities for silyl activation using proazaphosphatranes

The work in Chapters 2–6 further demonstrates that proazaphosphatranes are potentially capable of becoming widely used catalysts for the synthesis of various organic intermediates. In those chapters, we showed that proazaphosphatranes are efficient catalysts for the synthesis of β-hydroxyesters, α,β-unsaturated esters, β-hydroxynitriles, propargylic alcohols, Morita-Baylis-Hillman (MBH) type adducts and Mukaiyama aldols, and for catalytic umpolung addition of dithiane to aldehydes. Our group is currently developing syntheses of chiral proazaphosphatranes. It will be interesting to apply these P-center chiral catalysts for enantioselective syntheses of some of the aforementioned intermediates.

In Chapters 5 and 6, we demonstrated the use of N-benzyl substituted proazaphosphatranes as an efficient catalyst for Mukaiyama aldol reactions and for the synthesis of propargylic alcohols and Morita-Baylis-Hillman (MBH) type adducts. These studies suggest that the synthesis of other analogs of proazaphosphatranes will be of interest to explore for potentially expanding the growing list of transformations catalyzed by such Lewis bases. Such analogues might also grow the commercial market for phosphatranes beyond the three that are currently available from Aldrich and Strem.

2. General conclusions and future plans for the use of phosphatranium salts in ion transport membranes
In Chapter 7 is described a potentially important discovery regarding the synthesis of a Nafion®-proazaphosphatrane composite membrane. Initial studies have shown that it is an excellent conductor of hydroxide ion with a low resistance of 0.5 ohm and a high conductivity of 2-5 mS/cm. It is interesting to note here that the membrane contains impurities that seem to be associated with DMF, which may be a factor in lowering the conductivity. Further work is planned aimed at improving the purity of the membrane and optimizing it to obtain very high conductivities of hydroxide or nitrate ion. Such membranes would have the potential to be used in fuel cell applications.

3. General conclusions and future plans for the use of Teflon®-bound azidoproazaphosphatranes and proazaphosphatranes as efficient catalysts

We have synthesized a new perhalogenated polymer-bound azidoproazaphosphatrane catalyst for biodiesel production. However, the loading of the catalytic sites on the polymer is low and needs substantial improvement. The use of gamma radiation to graft VBC to Teflon® is underway in a collaboration with Dr. Inderjeet Kaur, Himachal Pradesh University, Simla, India, who has successfully demonstrated this technology for VBC-Teflon® grafting. Switching the source of energy from EB to 60Co gamma radiation has dramatically increased the VBC loading from 0.77 to 28.5–42.8 mmol/g Cl for a sample of Teflon® (particle size 55 micron), which we sent to Dr. Kaur. A one gram sample of the 150% grafted sample is projected to be sent to us by Dr. Kaur, after which we will attach the azidoproazaphosphatrane. If this effort is successful, we hope that the new heterogeneous catalyst for the transesterification of soybean oil, as well as for other important organic transformations will be efficient and highly recyclable.
Recently, Fetterly et al. in our laboratory successfully demonstrated the utility of the Merrifield resin-bound proazaphosphatranes shown in Figure 1 for the efficient synthesis of diaryl ethers via nucleophilic substitution of fluoroarenes with trialkylsilyl ethers with good recyclability (20 times) of the catalyst. With the increasing demand for recyclable catalysts for economic and environmental reasons, it will be interesting to see if perhalogentated polymers grafted with 4-vinylbenzyl chloride, followed by proazaphosphatranes attachment, can meet these requirements. Perhalogenated polymer backbones for such catalysts can potentially increase the mechanical and thermal stability, as well as the recyclability of these catalyst systems.

![Figure 1](image)

**Figure 1**

4. **Proposed use of proazaphosphatranes for the synthesis of polydifluoroacetylene (PDFA)**

PDFA has attracted attention in the recent past owing to its numerous commercial applications as a semiconducting material and its unique optical and chemical properties. Initial studies have revealed that structural features of not only PDFA, but also of polymonofluoroacetylene (PMFA), make these polymers better alternatives to the more common non-fluorinated polyacetylene as an intrinsic semiconducting material.¹⁴
Advancement in the synthesis of PDFA has been largely hampered by handling problems with both the starting monomer and the target polymer.

Only a few literature reports of the synthesis of PDFA exist.\textsuperscript{5-7} Two patents have claimed the synthesis of the desired polymer,\textsuperscript{5,6} but the method the inventors described was irreproducible and the polymer obtained does not have the desired properties. Also, decomposition of the polymer was observed in the presence of the catalyst, which the inventors claimed for synthesis of the polymer.\textsuperscript{7}

Recently, an attempted synthesis of polydifluoroacetylene was published,\textsuperscript{7} involving the polymerization of the parent monomeric molecule difluoroacetylene under cryogenic polymerization conditions (chemical vapor deposition onto a substrate at a temperature of -198 °C to -90 °C). While this approach did yield the desired polymer, the most important drawback of this method is the difficulty in handling the difluoroacetylene monomer owing to its highly unstable nature. It decomposes at higher temperatures and is highly explosive even at liquid nitrogen temperature (-198 °C) in the presence of even trace amounts of oxygen.\textsuperscript{8,9}

Scheme 1. Proposed synthesis of PDFA

It was observed during the course of my research that a proazaphosphatrane can be effectively employed for the synthesis of PDFA at room temperature; however, we presently have no firm data to support this observation. When we treated polychlorotrifluoroethylene...
with an equivalent amount of proazaphosphatrane in dry toluene (Scheme 1), we observed the formation of a deep red polymer, which is the typical color of PDFA as described in the literature. When the solution was examined by $^{31}$P NMR spectroscopy, the formation of a fluorinated phosphatranium salt $\delta^{31}$P -40.9 (d, $J = 730.0$ Hz) with chlorine as a likely counterion as shown in Scheme 1 was observed. A related observation was made by Dr. Kingston in our group during the reaction of a proazaphosphatrane with pentafluorochlorobenzene, which he monitored by $^{31}$P NMR spectroscopy (Scheme 2). Attempts to trap the benzyne presumably formed (Scheme 2) were unsuccessful.

**Scheme 2. Reaction of pentafluorochlorobenzene with proazaphosphatrane**

When Teflon® was reacted with a proazaphosphatrane, no fluorinated phosphatranium salt was observed, and this was also the case when hexafluorobenzene was reacted with proazaphosphatrane. Although we have no proof for the identity of the counterion (Scheme 3), and we see that the fluorinated phosphatranium salt is formed only when there is chlorine adjacent to fluorine in the substrate. Thus, we believe the counterion to be chloride.
The advantages of our proposed synthesis compared with the competing methods are:

1) Handling monomeric difluoroacetylene is difficult as it is potentially explosive even at liquid nitrogen temperatures in the presence of trace amounts of oxygen.\(^8,9\) Whereas, our method employs a very stable starting material, namely, commercially available polychlorotrifluoroethane.

2) Handling the product PDFA is difficult, as it is also sensitive to air, light and water. Thus, it might be difficult to cast the polymer into the desired form after the polymer is synthesized by conventional methods. In our invention, we can cast the starting parent polymer polychlorotrifluoroethane and then carry out the transformation of this material in precast form to PDFA using a proazaphosphatrane.

References


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APPENDIX A

CHAPTER 2
General Information
References for known compounds and characterization data for the new compounds
$^1H$, $^{13}C$ and HRMS for all compounds
General Information

All reactions were carried out under inert atmosphere using oven dried glassware and a magnetic stirrer. THF was distilled and dried over sodium. Trimethylsilylethylacetate (TMSEA), proazaphosphatrane 1a and all aldehydes were purchased from Aldrich Chemical and used without further purification. Products were purified via column chromatography using hexane/ethyl acetate. $^1$H and $^{13}$C nmr spectra were obtained on a VXR-300 and a VXR-400 Varian NMR spectrometer, respectively. All NMR spectra were taken in CDCl$_3$. Thin layer chromatography was used to monitor reaction progress.

**Ethyl-3-hydroxy-3-(4-methylphenyl)propionate (Table 1, entry 7):**

![Ethyl-3-hydroxy-3-(4-methylphenyl)propionate](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 86% isolated yield.

**Ethyl-3-hydroxy-3-phenylpropionate (Table 2, entry 1):**

![Ethyl-3-hydroxy-3-phenylpropionate](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 71% isolated yield.

**Ethyl-3-hydroxy-3-(4-methoxyphenyl)propionate (Table 2, entry 2):**
The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 76% isolated yield.

**Ethyl-3-hydroxy-3-(2-methoxyphenyl)propionate (Table 2, entry 3)**:

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 77% isolated yield.

**Ethyl-3-hydroxy-3-(2-chlorophenyl)propionate (Table 2, entry 4)**:

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 87% isolated yield.

**Ethyl-3-hydroxy-3-(4-chlorophenyl)propionate (Table 2, entry 5)**:

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 78% isolated yield.

**Ethyl-3-hydroxy-3-(4-bromophenyl)propionate (Table 2, entry 6)**:
The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 87% isolated yield.

**Ethyl-3-hydroxy-3-(4-nitrophenyl)propionate (Table 2, entry 7):**

![Ethyl-3-hydroxy-3-(4-nitrophenyl)propionate](image)

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 92% isolated yield.

**Ethyl-3-hydroxy-3-(3-cyanophenyl)propionate (Table 2, entry 8):**

![Ethyl-3-hydroxy-3-(3-cyanophenyl)propionate](image)

The general procedure was followed for the synthesis and purification, affording the product as a colorless oil in 84% isolated yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.68 (s, 1H), 7.60 (d, 1H, \(J = 8.0\) Hz), 7.56 (d, 1H, \(J = 8.0\) Hz), 7.45 (t, 1H, \(J = 8.0\) Hz), 5.14 (t, 1H, \(J = 4.0\) Hz), 4.17 (q, 2H, \(J = 8.0\) Hz), 3.69 (bs, 1H), 2.70–2.68 (m, 2H), 1.25 (t, 3H, \(J = 8.0\) Hz) ppm; \(^1\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 172.2, 144.3, 131.6, 130.4, 129.6, 129.5, 118.9, 112.8, 69.5, 61.4, 43.3, 14.4 ppm; HRMS \(m/z\) Calcd. for C\(_{12}\)H\(_{13}\)NO\(_3\): 219.08954. Found: 219.09013.

**4-(2-Ethoxycarbonyl-1-hydroxy-ethyl)-benzoic acid methyl ester (Table 2, entry 9):**
The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 71% isolated yield.

**Ethyl-3-hydroxynonanoate (Table 2, entry 10):**

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 73% isolated yield. $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 173.4, 68.3, 60.9, 41.5, 36.7, 32.0, 29.4, 25.7, 22.8, 14.4, 14.3 ppm.

**Ethyl 3-cyclohexyl-3-hydroxypropanoate (Table 2, entry 11):**

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 77% isolated yield.

**Ethyl-3-Hydroxy-5-phenylpent-4-enoate (Table 2, entry 12):**

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 76% isolated yield.

**Ethyl-3-hydroxy-3-(2,6-dimethylphenyl)propionate (Table 2, entry 13):**
The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 87% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.07–6.99 (m, 3H), 5.64 (d, 1H, $J = 10.4$ Hz), 4.21 (q, 2H, $J = 8.0$ Hz), 3.09–2.97 (m, 2H), 2.58–2.53 (m, 1H), 2.46 (s, 6H), 1.29 (t, 3H, $J = 8.0$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 172.3, 137.3, 135.9, 129.2, 127.2, 67.4, 60.6, 39.7, 20.6, 14.0 ppm; HRMS $m/z$ Calcd. for C$_{13}$H$_{18}$O$_3$: 222.12559. Found: 222.12604.

**Ethyl-3-hydroxy-3-(2-biphenyl)propionate (Table 2, entry 14):**

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 78% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.67 (d, 1H, $J = 8.0$ Hz), 7.43–7.33 (m, 7H), 7.24 (d, 1H, $J = 8.0$ Hz), 5.27 (d, 1H, $J = 9.0$Hz), 4.13–4.07 (m, 2H), 3.45 (s, 1H), 2.73–2.52 (m, 2H), 1.21 (t, 3H, $J = 8.0$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 172.6, 141.0, 140.8, 139.9, 130.4, 129.4, 128.6, 128.2, 127.8, 127.5, 126.2, 67.0, 61.0, 42.8, 14.4 ppm; HRMS $m/z$ Calcd. for C$_{17}$H$_{18}$O$_3$: 270.12559. Found: 270.12608.

**Ethyl-3-hydroxy-3-(2-thienyl)-propionate (Table 2, entry 15):**

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 78% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.67 (d, 1H, $J = 8.0$ Hz), 7.43–7.33 (m, 7H), 7.24 (d, 1H, $J = 8.0$ Hz), 5.27 (d, 1H, $J = 9.0$Hz), 4.13–4.07 (m, 2H), 3.45 (s, 1H), 2.73–2.52 (m, 2H), 1.21 (t, 3H, $J = 8.0$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 172.6, 141.0, 140.8, 139.9, 130.4, 129.4, 128.6, 128.2, 127.8, 127.5, 126.2, 67.0, 61.0, 42.8, 14.4 ppm; HRMS $m/z$ Calcd. for C$_{17}$H$_{18}$O$_3$: 270.12559. Found: 270.12608.
The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 76% isolated yield.

**Ethyl-3-hydroxy-3-(6-methylpyridin-2-yl)propanoate (Table 2, entry 16):**

\[ \text{ethyl}-3\text{-hydroxy-3-(6-methylpyridin-2-yl)propanoate} \]

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 81% isolated yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.59 (t, 1H, \(J = 8.0\) Hz), 7.15 (d, 1H, \(J = 8.0\) Hz), 7.04 (d, 1H, \(J = 8.0\) Hz), 5.12 (d, 1H, \(J = 4.0\) Hz), 4.53 (d, 1H, \(J = 4.0\) Hz), 4.15 (q, 2H, \(J = 8.0\) Hz), 2.80–2.66 (m, 2H), 2.51 (s, 3H), 1.23 (t, 3H, \(J = 8.0\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 172.1, 159.9, 157.5, 137.3, 122.3, 117.3, 70.0, 60.9, 43.3, 24.5, 14.4 ppm; HRMS \(m/z\) Calcd. for C\(_{11}\)H\(_{15}\)NO\(_3\): 209.10519. Found: 209.10557.

**Ethyl-3-(benzofuran-2-yl)-3-hydroxypropanoate (Table 2, entry 17):**

\[ \text{ethyl}-3\text{-hydroxypropanoate} \]

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 79% isolated yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.53 (d, 1H, \(J = 8.0\) Hz), 7.45 (d, 1H, \(J = 8.0\) Hz), 7.28–7.19 (m, 2H), 6.66 (s, 1H), 5.28 (d, 1H, \(J = 8.0\) Hz), 4.19 (q, 2H, \(J = 8.0\) Hz), 3.71 (d, 1H, \(J = 4.0\) Hz), 2.95 (d, 1H, \(J = 4.0\) Hz), 1.26 (t, 3H, \(J = 8.0\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 172.1, 157.7, 155.0, 128.2, 124.5, 123.1, 121.4, 111.5, 103.2, 65.0, 61.3, 40.1, 14.4 ppm; HRMS \(m/z\) Calcd. for C\(_{13}\)H\(_{14}\)O\(_4\): 234.08921. Found: 234.08965.
Ethyl \((E)\)-3-(4-methylphenyl)-2-propenoate (Table 3, entry 1):

\[
\begin{array}{c}
\text{Me} \\
\text{O}
\end{array}
\begin{array}{c}
\text{O} \\
\text{Et}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 83% isolated yield.

Ethyl \((E)\)-3-(4-methoxyphenyl)-2-propenoate (Table 3, entry 2):

\[
\begin{array}{c}
\text{MeO}
\end{array}
\begin{array}{c}
\text{O} \\
\text{Et}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 83% isolated yield.

Ethyl-3-benzo[1,3]dioxol-5-yl-(\(E\))-acrylate (Table 3, entry 3):

\[
\begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{O} \\
\text{Et}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 79% isolated yield.

Ethyl \((E)\)-3-(3-cyanophenyl)-2-propenoate (Table 3, entry 4):

\[
\begin{array}{c}
\text{CN}
\end{array}
\begin{array}{c}
\text{O} \\
\text{Et}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 90% isolated yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.47 (s, 1H), 7.70–7.56 (m, 3H), 7.47 (t, 1H, \(J = 8.0\) Hz), 6.44 (d, 1H, \(J = 16.0\)Hz), 4.22 (q, 2H, \(J = 8.0\) Hz), 1.29 (t,
3H, \( J = 8.0 \text{ Hz} \) ppm; \(^{13}\text{C} \) NMR (CDCl\(_3\), 100.6 MHz): \( \delta \) 166.3, 141.9, 135.9, 133.3, 132.1, 131.5, 130.0, 121.7, 118.4, 113.5, 61.1, 14.5 ppm; HRMS \( m/z \) Calcd. for C\(_{12}\)H\(_{11}\)NO: 201.07897. Found: 201.07925.

**Ethyl (E,E)-5-phenylpenta-2,4-dienoate (Table 3, entry 5)**

![Ethyl (E,E)-5-phenylpenta-2,4-dienoate](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 84\% (9:1 mixture of EE/EZ) isolated yield.

**Ethyl (E)-3-(2,6-dimethylphenyl)-2-propenoate (Table 3, entry 6)**

![Ethyl (E)-3-(2,6-dimethylphenyl)-2-propenoate](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 80\% isolated yield.

**Ethyl-3-thiophen-3-yl-(E)-acrylate (Table 3, entry 7)**

![Ethyl-3-thiophen-3-yl-(E)-acrylate](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 89\% isolated yield.

**Ethyl (E)-3-(benzo[b]furan-2-yl)-2-propenoate (Table 3, entry 8)**

![Ethyl (E)-3-(benzo[b]furan-2-yl)-2-propenoate](image)
The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 79% isolated yield. $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 166.8, 155.7, 152.6, 131.4, 128.6, 126.6, 123.5, 121.9, 119.2, 111.6, 111.3, 60.9, 14.6 ppm.

Reference:

KW422, CDCl3
100 MHz
COLORLESS OIL
NOV 08 2007

Table 1, entry 7
KW453, CDC13
COLORLESS OIL
100 MHz
FEB 02 2008

Table 2, entry 1
KW452, CDCl3
100 MHz
COLORLESS OIL
JAN 29 2008

Table 2, entry 2
Table 2, entry 6
Table 2, entry 6

KIV456, CDCl3
75 MHz
COLORLESS OIL
Table 2, entry 7
Manual Peak Matching Report  
For Accurate Mass Determination  

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<td>219.09013</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only \(^{12}\text{C}, \(^{1}\text{H}, \(^{16}\text{O}, \(^{14}\text{N}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 2, entry 8
SPEC: fin084256.dat (18-FEB-09 10:42:07)
Samp: Kw491
Comm: DF 70 eV EI
Oper: kl
Study: ms services
Masses: 35.01 > 650.00
Peak: 1000.0 mnu
Intensity: 504804

Scan 24 @ 0.65 min (EI +Q1MS LNR UP LR) 5.0E+05

Table 2, entry 8

Date: Wed Feb 18 10:43:54 2009 ICIS: 8.3.0 SP2 for GSPI (V4.0) build 98-238 from 26-Aug-98
Table 2, entry 9

KW619, CDCl3
100MHz
COLORLESS OIL
KW487, CDCl3
300MHz
COLORLESS OIL

Table 2, entry 10
KW811, CDCl3
400 MHz
COLORLESS OIL
APR 01 2009

Table 2, entry 11
Table 2, entry 12

408 ppm, CDCl3
7.5 MHz, COLORLESS OIL
Manual Peak Matching Report
For Accurate Mass Determination

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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 2, entry 13
Table 2, entry 13
Table 2, entry 14
Manual Peak Matching Report
For Accurate Mass Determination

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* The deviation is obtained from the following equation:

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\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only \(^{12}\text{C}, \text{H}, \text{O}, \text{^{14}N}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 2, entry 14
Table 2, entry 14
Table 2, entry 15

KW616, CDCI3
100MHz
YELLOW OIL

Table 2, entry 15
Manual Peak Matching Report
For Accurate Mass Determination

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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 16
Table 2, entry 16

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<td>65</td>
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<td>209</td>
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Date: Mon May 15 10:45:23 2013  
ACS: 8.3.0 SP2 for CHPl (V4.0) Build 98-238 from 28-Aug-08
Manual Peak Matching Report
For Accurate Mass Determination

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<td>230.98562</td>
<td>1.9 ppm</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 17
Table 2, entry 17
Table 3, entry 2
Table 3, entry 3
Manual Peak Matching Report
For Accurate Mass Determination

<table>
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<th>PFK matching mass</th>
<th>Deviation*</th>
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<td>201.07925</td>
<td>180.98882</td>
<td>1.4 ppm</td>
</tr>
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</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 3, entry 4
Table 3, entry 6
Table 3, entry 8
APPENDIX B

CHAPTER 3

General Information
Reference for known compounds and characterization data for new compounds
$^1$H, $^{13}$C and HRMS for all compounds
General Information

All reactions were carried out under inert atmosphere using oven dried glassware and a magnetic stirrer. THF was distilled and dried over sodium. Trimethylsilyl-1,3-dithiane, proazaphosphatrane 1a and all aldehydes were purchased from Aldrich Chemical and used without further purification. Products were purified via column chromatography using hexane/ethyl acetate. $^1$H and $^{13}$C nmr spectra were obtained on a VXR-300 and VXR-400 Varian NMR spectrometer, respectively. All NMR spectra were taken in CDCl$_3$. Thin layer chromatography was used to monitor reaction progress.

1,3-Dithian-2-yl-phenylmethanol (Table 1, entry 1):

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 98% isolated yield.

$^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 140.4, 128.6, 128.5, 127.1, 74.9, 53.1, 28.5, 27.9, 25.6 ppm.

1,3-Dithian-2-yl-4-methoxyphenylmethanol (Table 2, entry 1):

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 95% isolated yield.

1,3-Dithian-2-yl-4-methylphenylmethanol (Table 2, entry 2):
The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 98% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.32–7.29 (m, 2H), 7.19–7.16 (m, 2H), 4.88 (d, 1H, $J$ = 8.0 Hz), 4.09 (d, 1H, $J$ = 8.0 Hz), 2.91–2.68 (m, 4H), 2.35 (s, 3H), 2.07–1.98 (m, 2H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 138.4, 137.3, 129.3, 126.9, 74.9, 53.2, 28.6, 28.0, 25.6, 21.5 ppm. HRMS m/z Calcd for C$_{12}$H$_{16}$OS$_2$: 240.06425. Found: 240.06462.

**Methyl 4-((1,3-dithian-2-yl)(hydroxy)methyl)benzoate** (Table 2, entry 3):

![Methyl 4-((1,3-dithian-2-yl)(hydroxy)methyl)benzoate](image)

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 93% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.94 (d, 2H, $J$ = 8.0 Hz), 7.42 (d, 2H, $J$ = 8.0 Hz), 4.90 (d, 1H, $J$ = 8.0 Hz), 4.02 (d, 1H, $J$ = 8.0 Hz), 3.84 (s, 3H) 3.52 (s, 1H), 2.75 (m, 2H), 2.69–2.61 (m, 2H), 1.97–1.89 (m, 2H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$167.0, 145.7, 130.0, 129.6, 127.1, 74.5, 52.8, 52.4, 28.5, 27.9, 25.5 ppm; HRMS m/z Calcd for C$_{13}$H$_{16}$O$_3$S$_2$: 284.05409. Found: 284.05447.

**1,3-Dithian-2-yl-3-cyanophenylmethanol** (Table 2, entry 4):

![1,3-Dithian-2-yl-3-cyanophenylmethanol](image)

The general procedure was followed for the synthesis and purification affording a colorless oil in 80% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.71 (s, 1H), 7.64 (d, 1H, $J$ = 8.0 Hz), 7.56 (d, 1H, $J$ = 8.0 Hz), 7.44 (t, 1H, $J$ = 8.0 Hz), 4.92 (dd, 1H, $J$ = 8.0 Hz, $J$ = 2.0 Hz), 3.94 (d, 1H, $J$ = 8.0 Hz), 3.36 (d, 1H, $J$ = 2.4 Hz), 2.94–2.91 (m, 2H), 2.75–2.66 (m, 2H), 2.06–1.96 (m, 2H) ppm; $^{13}$C NMR
(CDCl₃, 100.6 MHz): δ 142.0, 132.0, 131.6, 130.9, 129.1, 119.0, 112.3, 73.7, 52.4, 28.1, 27.4, 25.3 ppm; HRMS m/z Calcd for C₁₂H₁₃NOS₂: 251.04386. Found: 251.04414.

1,3-Dithian-2-yl-2-chlorophenylmethanol (Table 2, entry 5):

The general procedure was followed for the synthesis and purification affording a colorless oil in 96% isolated yield. ¹H NMR (CDCl₃, 400 MHz): δ 7.56–7.54 (m, 1H), 7.34–7.20 (m, 3H), 5.40 (q, 1H, J = 4.0 Hz), 4.12 (d, 1H, J = 4.0 Hz), 3.23 (s, 1H), 2.94–2.75 (m, 2H), 2.68–2.62 (m, 2H), 2.02–1.98 (m, 2H) ppm; ¹³C NMR (CDCl₃, 100.6 MHz): δ 138.3, 133.3, 129.5, 129.4, 128.4, 127.1, 71.2, 51.6, 28.9, 27.6, 25.6 ppm; HRMS m/z Calcd for C₁₁H₁₃ClOS₂: 260.00963. Found: 260.01002.

Cyclohexyl(1,3-dithian-2-yl)methanol (Table 2, entry 6):

The general procedure was followed for the synthesis and purification affording a colorless oil in 94% isolated yield. ¹H NMR (CDCl₃, 400 MHz): δ 4.06 (d, 1H, J = 8.0 Hz), 3.55 (s, 1H), 2.90–2.73 (m, 4H), 2.34 (s, 1H), 1.90–1.62 (m, 8H), 1.24–1.07 (m, 5H) ppm; ¹³C NMR (CDCl₃, 100.6 MHz): δ 76.5, 50.6, 39.9, 30.2, 29.2, 28.4, 26.9, 26.5, 26.1, 25.9 ppm; HRMS m/z Calcd for C₁₁H₂₀OS₂: 232.09555. Found: 232.09597.

1,3-Dithian-2-yl-2-biphenylmethanol (Table 2, entry 7):
The general procedure was followed for the synthesis and purification giving a colorless oil in 81% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.60 (d, 1H, $J = 8.0$ Hz), 7.42–7.35 (m, 7H), 7.26–7.25 (m, 1H), 5.17 (d, 1H, $J = 8.0$ Hz), 3.81 (d, 1H, $J = 8.0$ Hz), 3.19 (s, 1H), 2.76–2.70 (m, 1H), 2.52–2.47 (m, 1H), 2.29–2.24 (m, 1H), 2.08–2.04 (m, 1H), 1.88–1.81 (m, 2H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 142.8, 141.2, 138.1, 130.0, 129.9, 128.4, 128.1, 128.1, 127.2, 126.3, 69.1, 51.6, 26.8, 25.9, 25.2 ppm; HRMS m/z Calcd for C$_{17}$H$_{18}$OS$_2$: 302.07991. Found: 302.08031.

**Benzofuran-2-yl(1,3-dithian-2-yl)methanol** (Table 2, entry 8):

![Benzofuran-2-yl(1,3-dithian-2-yl)methanol](image)

The general procedure was followed for the synthesis and purification giving a white solid in 95% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.54 (d, 1H, $J = 8.0$ Hz), 7.47 (d, 1H, $J = 8.0$ Hz), 7.27 (t, 1H, $J = 8.0$ Hz), 7.21 (t, 1H, $J = 8.0$ Hz), 6.79 (s, 1H), 5.095 (q, 1H, $J = 4.0$ Hz), 4.38 (d, 1H, $J = 8.0$ Hz), 3.47 (d, 1H, $J = 4.0$ Hz), 2.90–2.85 (m, 2H), 2.69–2.63 (m, 2H), 1.98–1.92 (m, 2H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 155.3, 155.0, 128.1, 124.7, 123.1, 121.5, 111.6, 105.7, 69.5, 49.4, 28.1, 27.5, 25.5 ppm; HRMS m/z Calcd for C$_{13}$H$_{14}$O$_2$S$_2$: 266.04352. Found: 266.04411.

**(6-Bromopyridin-2-yl)(1,3-dithian-2-yl)methanol** (Table 2, entry 9):

![6-Bromopyridin-2-yl](image)

The general procedure was followed for the synthesis and purification giving a yellow oil in 92% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.56 (t, 1H, $J = 8.0$ Hz), 7.43–7.40 (m, 2H), 4.96 (bs, 1H), 4.21 (d, 1H, $J = 8.0$ Hz), 3.66 (bs, 1H), 3.00–2.72 (m, 4H), 2.10–1.88 (m, 2H) ppm; $^{13}$C NMR
(CDCl₃, 100.6 MHz): δ 160.4, 141.5, 139.0, 127.7, 120.9, 75.3, 52.5, 29.2, 28.8, 25.7 ppm; HRMS m/z Calcd for C₁₀H₁₂BrNOS₂: 305.95437. Found: 305.95475.

(1,3-Dithian-2-yl)(4-methylthiazol-2-yl)methanol (Table 2, entry 10):

The general procedure was followed for the synthesis and purification affording a yellow oil in 94% isolated yield. ¹H NMR (CDCl₃, 400 MHz): δ 6.89 (s, 1H), 5.25 (d, 1H, J = 8.0 Hz), 4.21 (d, 1H, J = 4.0 Hz), 3.72 (bs, 1H), 3.03−2.73 (m, 4H), 2.45 (s, 3H), 2.10−1.92 (m, 2H) ppm; ¹³C NMR (CDCl₃, 100.6 MHz): δ 170.0, 152.8, 114.4, 73.6, 51.9, 28.7, 28.2, 25.5, 17.3 ppm; HRMS m/z Calcd for C₉H₁₃NOS₂: 247.01593. Found: 247.01623.

(1,3-Dithian-2-yl)(1-methyl-1H-imidazol-2-yl)methanol (Table 2, entry 11):

The general procedure was followed for the synthesis and purification producing a white solid in 67% isolated yield. ¹H NMR (CDCl₃, 400 MHz): δ 7.02 (s, 1H), 6.81 (s, 1H), 5.21 (bs, 1H), 4.94 (d, 1H, J = 8.0 Hz), 4.49 (d, 1H, J = 8.0 Hz), 3.73 (s, 3H), 2.89−2.68 (m, 4H), 2.14−1.92 (m, 2H) ppm; ¹³C NMR (CDCl₃, 100.6 MHz): δ 147.1, 127.5, 121.7, 67.5, 50.5, 33.4, 28.3, 27.6, 25.6 ppm; HRMS m/z Calcd for C₉H₁₄N₂OS₂: 230.05476. Found: 230.05518.

1,3-Dithian-2-yl-2-thienylmethanol (Table 2, entry 12)¹:
The general procedure was followed for the synthesis and purification giving a white solid in 97% isolated yield.

(1,3-Dithian-2-yl)(6-methylpyridin-2-yl)methanol (Table 2, entry 13):

The general procedure was followed for the synthesis and purification giving a white solid in 98% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.52 (t, 1H, $J = 4.0$ Hz), 7.13 (d, 1H, $J = 8.0$ Hz), 7.02 (d, 1H, $J = 8.0$ Hz), 4.88 (bs, 1H), 4.84 (bs, 1H), 4.36 (d, 1H, $J = 3.6$ Hz), 2.84–2.65 (m, 4H), 2.46 (s, 3H), 2.00–1.86 (m, 2H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 157.4, 157.4, 137.0, 122.9, 118.8, 75.2, 53.6, 29.7, 29.4, 25.9, 24.5 ppm; HRMS $m/z$ Calcd for C$_{11}$H$_{15}$NOS$_2$: 241.0595. Found: 241.0600.

(1,3-Dithian-2-yl)(1-methyl-1H-indol-2-yl)methanol (Table 2, entry 14):

The general procedure was followed for the synthesis and purification affording a yellow oil in 94% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.61 (d, 1H, $J = 8.0$ Hz), 7.32–7.25 (m, 2H), 7.12 (t, 1H, $J = 8.0$ Hz), 6.61 (s, 1H), 5.10 (d, 1H, $J = 8.0$ Hz), 4.37 (d, 1H, $J = 8.0$ Hz), 3.78 (s, 3H), 3.11 (s, 1H), 2.96–2.71 (m, 4H), 2.05–1.91(m, 2H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 138.2, 138.0, 127.2, 122.2, 121.2, 119.9, 109.5, 101.5, 68.7, 50.9, 30.8, 28.6, 27.9, 25.5 ppm; HRMS $m/z$ Calcd for C$_{14}$H$_{17}$NOS$_2$: 279.07516. Found: 279.07569.
Reference

Table 1, entry 1
Manual Peak Matching Report  
For Accurate Mass Determination

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</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 2, entry 2
Table 2, entry 2
Table 2, entry 3
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>284.05409</td>
<td>284.05447</td>
<td>280.98242</td>
<td>1.3 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only 12C, 1H, 16O, 14N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 3
Table 2, entry 3
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>251.04386</td>
<td>251.04414</td>
<td>242.98562</td>
<td>1.1 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only \(^{12}\text{C}, \text{H}, \text{O}, \text{N}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 2, entry 4

\[\text{Diagram of chemical structure}\]
Table 2, entry 4
Table 2, entry 5

CH

S

S

Cl

COLORLESS OIL

K603 CDCL3

400MHz
KW603, CDCl3
100MHz
COLORLESS OIL

Table 2, entry 5
Manual Peak Matching Report  
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>260.00763</td>
<td>260.01002</td>
<td>260.98762</td>
<td>1.5 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 5
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>232.09557</td>
<td>232.09597</td>
<td>230.18562</td>
<td>1.8 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 6
Table 2, entry 6
Table 2, entry 7
Manual Peak Matching Report  
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>302.07991</td>
<td>302.08031</td>
<td>280.98242</td>
<td>1.3 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

\[
\begin{align*}
\text{Structure} & : & \text{Table 2, entry 7}
\end{align*}
\]
Table 2, entry 7
KW638, CDCl3
100MHz
YELLOW OIL

Table 2, entry 8
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>266.04352</td>
<td>266.04411</td>
<td>230.98562</td>
<td>2.2 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^{1}$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 2, entry 8
Table 2, entry 9
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>305.95437</td>
<td>305.95437</td>
<td>280.98242</td>
<td>1.3 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only 12C, 1H, 16O, 14N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 9
Table 2, entry 9

[Chemical Structure Image]

OH

Br
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>247.01543</td>
<td>247.01623</td>
<td>230.98862</td>
<td>1.2 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass corresponds to the mass of the most abundant isotope peak

Table 2, entry 10
Table 2, entry 10
Table 2, entry 11
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>230.05476</td>
<td>230.05518</td>
<td>218.94562</td>
<td>1.8 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc.

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 2, entry 11
Table 2, entry 11
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>241.05951</td>
<td>241.06000</td>
<td>230.18562</td>
<td>2 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc.

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 2, entry 13
Table 2, entry 13
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>279.07516</td>
<td>279.07589</td>
<td>242.98862</td>
<td>1.9 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only 12C, 1H, 16O, 14N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 14
Table 2, entry 14
APPENDIX C

CHAPTER 4

General Information

References for known compounds and characterization data for the new compounds

$^1$H, $^{13}$C and HRMS for all compounds
General Information

All reactions were carried out under inert atmosphere using oven dried glassware and a magnetic stirrer. THF was distilled and dried over sodium. Trimethylsilylacetonitrile (TMSAN), proazaphosphatrane 1a and all aldehydes were purchased from commercial sources and were used without further purification. Products were purified via column chromatography using hexane/ethyl acetate. $^1$H and $^{13}$C nmr spectra were obtained on a VXR-300 and a VXR-400 NMR spectrometer, respectively. All NMR spectra were taken in CDCl$_3$. Thin layer chromatography was used to monitor reaction progress.

$\beta$-Hydroxy-4-methyl- benzenepropanenitrile (Table 1, entry 6)$^1$:

![Chemical structure of $\beta$-Hydroxy-4-methyl- benzenepropanenitrile]

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 91% isolated yield.

$\beta$-Hydroxybenzenepropanenitrile (Table 2, entry 1)$^2$:

![Chemical structure of $\beta$-Hydroxybenzenepropanenitrile]

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 89% isolated yield.

$\beta$-Hydroxy-4-methoxy- benzenepropanenitrile (Table 2, entry 2)$^2$:
The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 83% isolated yield.

**β-Hydroxy-2-methoxy- benzene propanenitrile (Table 2, entry 3):**

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 77% isolated yield.

**β-Hydroxy-2-chlorobenzene propanenitrile (Table 2, entry 4):**

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 94% isolated yield.

**β-Hydroxy-1,3-benzodioxole-5-propanenitrile (Table 2, entry 5):**

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 82% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 6.86–6.76 (m, 3H), 5.95 (s, 2H), 4.93–4.89 (m, 1H), 2.81 (d, 1H, $J = 4.0$ Hz), 2.70–2.69 (m, 2H) ppm; $^{13}$C NMR
(CDCl₃, 100.6 MHz): δ 148.1, 135.1, 119.3, 117.6, 108.5, 106.1, 101.4, 69.9, 28.1 ppm; HRMS m/z Calcd. for C₁₀H₉NO₃: 191.05824. Found: 191.05876.

β-Hydroxy-4-nitrobenzenepropanenitrile (Table 2, entry 6):

\[
\begin{array}{c}
\text{O}_2\text{N} \\
\text{OH} \\
\text{CN} \\
\text{CN}
\end{array}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a yellow solid in 94% isolated yield.

β-Hydroxy-3-cyanobenzenepropanenitrile (Table 2, entry 7):

\[
\begin{array}{c}
\text{NC} \\
\text{OH} \\
\text{CN} \\
\text{NC}
\end{array}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 89% isolated yield. \(^1\)H NMR (CDCl₃, 400 MHz): δ 7.70 (s, 1H), 7.65–7.59 (m, 2H), 7.50 (t, 1H, \(J = 8.0\) Hz), 5.08 (q, 1H, \(J = 4.8\) Hz), 3.62 (d, 1H, \(J = 4.4\) Hz), 2.82–2.71 (m, 2H) ppm; \(^1^\)C NMR (CDCl₃, 100.6 MHz): δ 142.9, 132.4, 130.5, 129.9, 129.5, 118.7, 117.2, 112.7, 68.8, 28.3 ppm; HRMS m/z Calcd. for C₁₀H₈N₂O: 172.06366. Found: 172.06395.

Methyl 4-(2-cyano-1-hydroxyethyl)benzoate (Table 2, entry 8):

\[
\begin{array}{c}
\text{MeO}_2\text{C} \\
\text{OH} \\
\text{CN}
\end{array}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 93% isolated yield. \(^1\)H NMR (CDCl₃, 300 MHz): δ 8.99 (d, 2H, \(J = 8.0\) Hz).
Hz), 7.45 (d, 2H, J = 8.0 Hz), 5.07 (q, 1H, J = 4.0 Hz), 3.89 (s, 3H), 3.27 (d, 1H, J = 4.0 Hz), 2.76–2.74 (m, 2H) ppm; "C NMR (CDCl₃, 75 MHz): δ 166.9, 146.2, 130.5, 130.3, 125.8, 117.3, 117.3, 69.7, 52.6, 28.1 ppm; HRMS m/z Calcd. for C₁₁H₁₁NO₃: 205.07389. Found: 205.07416.

3-Hydroxy-5-phenyl-4-pentenenitrile (Table 2, entry 9)⁴:

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 94% isolated yield. "C NMR (CDCl₃, 100.6 MHz): δ 135.8, 133.1, 128.9, 128.7, 128.3, 127.0, 117.5, 68.8, 26.6 ppm.

3-Hydroxynonanenitrile (Table 2, entry 10)⁵:

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 85% isolated yield.

3-Cyclohexyl-3-hydroxypropionitrile (Table 2, entry 11)⁵:

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 88% isolated yield.

β-Hydroxy-2-thiophenepropanenitrile, (Table 3, entry 1)⁶:
The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 88% isolated yield.

β-Hydroxy-benzo[b]thiophene-2-propanenitrile (Table 3, entry 2):

The general procedure was followed for the synthesis and purification; product was afforded as a yellow solid in 93% isolated yield.

3-hydroxy-3-(6-methylpyridin-2-yl)propanenitrile (Table 3, entry 3):

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 92% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.61 (t, 1H, $J = 8.0$ Hz), 7.18 (d, 1H, $J = 8.0$ Hz), 7.10 (d, 1H, $J = 8.0$ Hz), 5.09 (s, 1H), 4.97 (t, 1H, $J = 4.0$ Hz), 2.87–2.75 (m, 2H), 2.51 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 157.9, 157.4, 137.8, 123.3, 117.6, 117.5, 68.6, 27.4, 24.4 ppm; HRMS m/z Calcd. for C$_9$H$_{10}$N$_2$O: 162.07931. Found: 162.07961.

3-(6-bromopyridin-2-yl)-3-hydroxypropanenitrile (Table 3, entry 4):
The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 87% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.62 (t, 1H, $J = 8.0$ Hz), 7.46 (d, 2H, $J = 4.0$ Hz), 5.03 (m, 1H), 4.02 (d, 1H, $J = 4.0$ Hz), 2.97−2.82 (m, 2H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 160.4, 141.7, 139.8, 128.1, 119.7, 117.3, 69.1, 27.0 ppm; HRMS m/z Calcd. for C$_8$H$_7$BrN$_2$O: 225.97417. Found: 225.97456.

$\beta$-hydroxy-2-Quinolinepropanenitrile (Table 3, entry 5)

The general procedure was followed for the synthesis and purification; product was afforded as a red oil in 93% isolated yield. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.25 (d, 1H, $J = 9.0$ Hz), 8.10 (d, 1H, $J = 9.0$ Hz), 7.87 (d, 1H, $J = 9.0$ Hz), 7.77 (t, 1H, $J = 9.0$ Hz), 7.59 (t, 1H, $J = 9.0$ Hz), 7.46 (d, 1H, $J = 9.0$ Hz), 5.25 (bs, 1H), 5.19 (bs, 1H), 2.96−2.93 (m, 2H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 157.8, 146.7, 138.1, 130.6, 129.1, 128.1, 127.9, 127.4, 118.1, 117.2, 68.9, 27.3 ppm; HRMS m/z Calcd. for C$_{12}$H$_{10}$N$_2$O: 198.07931. Found: 198.07973.

3-hydroxy-3-(1-methyl-1H-indol-2-yl)propanenitrile (Table 3, entry 6)

The general procedure was followed for the synthesis and purification; product was afforded as a yellow solid in 81% isolated yield. $^1$H NMR (CD$_3$CN, 400 MHz): $\delta$ 7.59 (d, 1H, $J = 8.0$ Hz), 7.41 (d, 1H, $J = 8.0$ Hz), 7.24 (t, 1H, $J = 8.0$ Hz), 7.09 (t, 1H, $J = 8.0$ Hz), 6.54 (s, 1H), 5.23 (q, 1H, $J = 8.0$ Hz), 3.97 (d, 1H, $J = 8.0$ Hz), 3.80 (s, 3H), 3.08−3.06 (m, 2H) ppm; $^{13}$C
NMR (CD_3CN, 100.6 MHz): \( \delta \) 139.9, 138.1, 127.3, 122.1, 120.8, 119.7, 118.2, 117.5, 109.6, 99.2, 62.6, 29.9, 25.3 ppm; HRMS \( m/z \) Calcd. for C_{12}H_{12}N_2O: 200.09496. Found: 200.09532.

3-Hydroxy-3-(4-methylthiazol-2-yl)propanenitrile (Table 3, entry 7):

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 95% isolated yield. \(^1\)H NMR (CDCl_3, 400 MHz): \( \delta \) 6.90 (s, 1H), 5.28 (s, 1H), 5.11 (s, 1H), 3.06–2.87 (m, 2H), 2.40 (s, 3H) ppm; \(^{13}\)C NMR (CDCl_3, 100.6 MHz): \( \delta \) 171.1, 153.1, 117.2, 114.8, 67.5, 27.2, 17.1 ppm; HRMS \( m/z \) Calcd. for C_7H_8N_2O: 168.03573. Found: 168.03606.

3-(Benzofuran-2-yl)-3-hydroxypropanenitrile (Table 3, entry 8):

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 64% isolated yield. \(^1\)H NMR (CDCl_3, 400 MHz): \( \delta \) 7.58–7.55 (m, 1H), 7.48–7.45 (m, 1H), 7.34–7.28 (m, 1H), 7.27–7.22 (m, 1H), 6.77 (s, 1H) 5.17 (q, 1H, \( J = 8.0 \) Hz), 3.05–2.91 (m, 3H) ppm; \(^{13}\)C NMR (CDCl_3, 100.6 MHz): \( \delta \) 155.4, 155.0, 127.8, 125.1, 123.4, 121.7, 117.1, 111.6, 104.4 64.4, 25.2 ppm; HRMS \( m/z \) Calcd. for C_{11}H_9NO_2: 187.06333. Found: 187.06371.

3-hydroxy-3-(2-oxo-2\textsubscript{H}-chromen-6-yl)propanenitrile (Table 3, entry 9):


The general procedure was followed for the synthesis and purification; product was afforded as a yellow solid in 70% isolated yield.$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.71–7.68 (m, 1H), 7.57–7.54 (m, 2H), 7.30–7.25 (m, 1H), 6.40 (d, 1H, $J = 12.4$ Hz), 5.13 (t, 1H, $J = 6.0$ Hz), 3.34 (s, 1H), 2.80 (d, 2H, $J = 4.0$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 160.7, 154.1, 143.3, 137.6, 129.2, 125.2, 119.1, 117.7, 117.6, 116.9, 115.5, 69.4, 28.4 ppm; HRMS $m/z$ Calcd. for C$_{12}$H$_9$NO$_3$: 215.05824. Found: 215.05862.

β-Hydroxy-2-furanpropanenitrile (Table 3, entry 10)$^7$:

![β-Hydroxy-2-furanpropanenitrile](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 88% isolated yield. $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 153.1, 143.1, 117.3, 110.8, 107.7, 63.9, 25.1 ppm.

Reference

KW460, CDCl3
400MHz
YELLOW OIL

Table 1, entry 6
KW465H1, ACETONE
WHITE SOLID
400MHz

Table 2, entry 3
Table 2, entry 4
Table 2, entry 4
Table 2, entry 5
Manual Peak Matching Report  
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>191.05824</td>
<td>191.05876</td>
<td>180.98882</td>
<td>2.7 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 5
Table 2, entry 5
KW489H, CDC13
400MHz
YELLOW OIL

Table 2, entry 7
KW489C, CDCl3
100MHz
YELLOW OIL

Table 2, entry 7
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>172.06366</td>
<td>172.06398</td>
<td>168.98852</td>
<td>1.7 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 7
SPEC: fin083791.dat (22-JUL-08 11:05:49)
Samp: RM489
Conc: SP 70 eV EI
Oper: Kh
Base: 131.91
Peak: 1000.0 mmu
Scan 73 @ 1.65 min (EI +QIMS LMR UP LR)

Study: MS services
Masses: 35.01 > 650.00
Intensity: 16777215

Client: Kuldup
Peaks: 651
RIC: 137516812

Table 2, entry 7
KW482, CDCl3
300MHz
YELLOW OIL

Table 2, entry 8
Manual Peak Matching Report  
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>245.07389</td>
<td>205.07416</td>
<td>180.98882</td>
<td>1.3 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only \(^{12}\text{C}, {^1}\text{H}, {^{16}}\text{O}, {^{14}}\text{N}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 8
Scan 60 @ 0.94 min (EI +Q1MS LMR UP LR)

Table 2, entry 8

Date: Mon Apr 6 14:47:58 2009   ICIS: 8.3.0 SP2 for OSFl (V4.0) build 98-238 from 26-Aug-98
Table 2, entry 9
KW494, CDCl3
100MHz
YELLOW OIL

Table 2, entry 9
KW486C, CDCl3
75 MHz
COLORLESS OIL

Table 2, entry 10
Table 3, entry 1
Table 3, entry 2

KW612, ACETONE
100 MHz, YELLOW SOLID
Table 3, entry 3
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>162.07931</td>
<td>162.07916</td>
<td>130.99201</td>
<td>1.8 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 3, entry 3
Table 3, entry 3
Table 3, entry 4
Manual Peak Matching Report  
For Accurate Mass Determination  

<table>
<thead>
<tr>
<th>Theoretical mass</th>
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<th>PFK matching mass</th>
<th>Deviation*</th>
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<tbody>
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<td>225.97417</td>
<td>225.97456</td>
<td>218.98562</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^{1}$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 3, entry 4
Table 3, entry 4

Date: Wed Jun 11 11:08:22 2008   ICIS: 8.3.0 SP2 for OSFI (V4.0) build 98-238 from 26-Aug-98
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
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<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>198.07931</td>
<td>198.07973</td>
<td>180.98882</td>
<td>2.1 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 3, entry 5

\[
\text{Table 3, entry 5}
\]
Manual Peak Matching Report
For Accurate Mass Determination

<table>
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<th>Theoretical mass</th>
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<th>PFK matching mass</th>
<th>Deviation*</th>
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</thead>
<tbody>
<tr>
<td>200.09496</td>
<td>200.09532</td>
<td>180.98882</td>
<td>1.8 ppm</td>
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</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}$H, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Table 3, entry 6]
Table 3, entry 6
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>168.03573</td>
<td>168.03606</td>
<td>130.99201</td>
<td>2 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only \(^{12}\text{C}, \, \text{H}, \, ^{16}\text{O}, \, ^{14}\text{N}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 3, entry 7

\[
\begin{array}{cc}
\text{S} & \text{CN} \\
\text{N} & \text{CN} \\
\text{OH} & \\
\end{array}
\]
Table 3, entry 7
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>187.06333</td>
<td>187.06371</td>
<td>180.98882</td>
<td>2 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only \(^{12}\text{C}, \, ^{1}\text{H}, \, ^{16}\text{O}, \, ^{14}\text{N} \text{ etc...}

Theoretical mass correspond to the mass of the most abundant isotope peak.

![Chemical structure](image)

Table 3, entry 8
Table 3, entry 8
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
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<tbody>
<tr>
<td>215.05824</td>
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<td>180.78882</td>
<td>1.8 ppm</td>
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</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 3, entry 9
\[^{29}\text{Si} \text{NMR of Trimethylsilylacetonitrile in THF at } -40^\circ \text{C}\]
$^{29}\text{Si NMR of Trimethylsilylacetonitrile and Proacaphosphatranen}$ 1a in THF at -40 °C
31P NMR of Trimethylsilylacetonitrile and Proacaphosphatrane 1a in THF at -40 °C
APPENDIX D

CHAPTER 5

General Information

References for known compounds and characterization data for the new compounds

$^1$H, $^{13}$C and HRMS for all compounds
**General Information**

All reactions were carried out under inert atmosphere using oven dried glassware and a magnetic stirrer. THF was distilled and dried over sodium. Aryltrimethylsilylacetylenes, and all aldehydes were purchased from commercial sources and were used without further purification. Proazaphosphatrane 1a was synthesized using literature procedure. Products were purified via column chromatography using hexane/ethyl acetate. $^1$H and $^{13}$C nmr spectra were obtained on a VXR-300, VXR 400 and DRX-400 NMR spectrometer, respectively. All NMR spectra were taken in CDCl$_3$. Thin layer chromatography was used to monitor reaction progress.

**1,3-Diphenylprop-2-yn-1-ol (Table 1, entry 3)**:

![1,3-Diphenylprop-2-yn-1-ol](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 82% isolated yield.

**1-(2-Fluorophenyl)-3-phenyl-prop-2-yn-1-ol (Table 2, entry 1)**:

![1-(2-Fluorophenyl)-3-phenyl-prop-2-yn-1-ol](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 95% isolated yield.
1-(4-Methylphenyl)-3-phenylprop-2-yn-1-ol (Table 2, entry 2):

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 82% isolated yield.

1-(3-Methoxyphenyl)-3-phenyl-prop-2-yn-1-ol (Table 2, entry 3):

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 91% isolated yield.

3-Phenyl-1-m-tolyl-prop-2-yn-1-ol (Table 2, entry 4):

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 83% isolated yield. $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 140.8, 138.6, 132.1, 129.5, 128.8, 128.5, 127.7, 124.1, 122.8, 89.3, 86.7, 65.3, 21.7 ppm.

1-(2-Phenylphenyl)-3-phenylprop-2-yn-1-ol (Table 2, entry 5):
The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 91% isolated yield.

3-Phenyl-1-o-tolyl-prop-2-yn-1-ol (Table 2, entry 6):

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 97% isolated yield.

1-(2,6-dimethylphenyl)-3-phenylprop-2-yn-1-ol (Table 2, entry 7):

The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 96% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.49–7.46 (m, 2H), 7.34–7.33 (m, 3H), 7.16–7.15 (m, 1H), 7.09–7.08 (m, 2H), 6.16 (s, 1H), 2.62 (s, 6H), 2.52 (s, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 136.9, 136.6, 131.9, 129.5, 128.7, 128.5,
128.4, 123.0, 88.9, 86.1, 61.1, 20.8 ppm; HRMS $m/z$ Calcd. for $C_{17}H_{16}O$: 236.12011. Found: 236.12053.

3-Phenyl-1-(2-thienyl)prop-2-yn-1-ol (Table 2, entry 8)$^2$:

![Chemical structure](image)

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 91% isolated yield.

1-Cyclohexyl-3-phenylprop-2-yn-1-ol (Table 3, entry 1)$^2$:

![Chemical structure](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 96% isolated yield.

4-Methyl-1-phenylpent-1-yn-3-ol (Table 3, entry 2)$^2$:

![Chemical structure](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 94% isolated yield.
1-Phenylnon-1-yn-3-ol (Table 3, entry 3)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 84% isolated yield.

1-Phenyltridec-12-en-1-yn-3-ol (Table 3, entry 4)

The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 79% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.44–7.42 (m, 2H), 7.31–7.30 (m, 3H), 5.86–5.76 (m, 1H), 5.01–4.91 (m, 2H), 4.59 (q, 1H, $J = 4.0$ Hz), 2.03 (q, 2H, $J = 8.0$ Hz), 1.85 (d, 1H, $J = 4.0$ Hz), 1.81–1.77 (m, 2H), 1.52–1.30 (m, 12H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 139.4, 131.9, 128.6, 128.5, 122.9, 114.3, 90.4, 85.1, 63.3, 38.1, 34.1, 29.7, 29.6, 29.5, 29.4, 29.2, 25.5 ppm; HRMS m/z Calcd. for C$_{19}$H$_{26}$O: 270.19835. Found: 270.19875.

(Z)-2-(hydroxy(4-(methoxycarbonyl)phenyl)methyl)-3-phenyl-1-(4-(methoxycarbonyl)phenyl)prop-2-en-1-one (Table 4, entry 1):
The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow oil in 85% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.96 (d, 2H, $J = 8.0$ Hz), 7.76 (d, 2H, $J = 8.0$ Hz), 7.61 (d, 2H, $J = 8.0$ Hz), 7.50 (d, 2H, $J = 8.0$ Hz), 7.07 (s, 1H), 7.03 (s, 4H), 5.81 (s, 1H), 3.94 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 199.8, 166.9, 166.3 146.2, 141.1, 139.5, 134.7, 133.9, 133.9, 130.1, 129.9, 129.6, 129.3, 129.2, 128.9, 128.5, 126.6, 76.6, 52.6, 52.4 ppm; HRMS $m/z$ Calcd. for C$_{26}$H$_{22}$O$_2$: 430.14164. Found: 430.14262.

(Z)-2-(hydroxy(3-iodophenyl)methyl)-1-(3-iodophenyl)-3-phenylprop-2-en-1-one (Table 4, entry 2):

The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 78% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.79 (s, 1H), 7.78 (s, 1H), 7.60 (d, 1H, $J = 8.0$ Hz), 7.56–7.51 (m, 2H), 7.35 (d, 1H, $J = 8.0$ Hz), 7.08–7.00 (m, 7H), 6.86 (t, 1H, $J = 8.0$ Hz), 5.64 (s, 1H), 3.40 (s, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 198.8, 143.3, 142.1, 140.9, 138.4, 137.8, 137.3, 135.6, 134.7, 133.6, 130.5, 130.1, 129.2, 128.8, 128.5, 126.0, 94.8, 94.2, 76.1 ppm; HRMS $m/z$ Calcd. for C$_{22}$H$_{16}$I$_2$O$_2$: 565.92398. Found: 565.92536.
(Z)-2-(hydroxy(4-(trifluoromethyl)phenyl)methyl)-3-phenyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (Table 4, entry 3):

The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 93% isolated yield. $^1$H NMR (CD$_3$CN, 400 MHz): $\delta$ 7.83 (d, 2H, J = 8.0 Hz), 7.64 (s, 4H), 7.55 (d, 3H, J = 8.0 Hz), 7.18 (s, 1H), 7.13 (s, 4H), 5.79 (s, 1H), 4.26 (d, 1H, J = 4.0 Hz) ppm; $^{13}$C NMR (CD$_3$CN, 100.6 MHz): $\delta$ 198.4, 146.6, 142.4, 139.7, 135.2, 133.4 (q, J = 32.0 Hz), 131.8, 131.7 (q, J = 32.0 Hz), 129.9, 129.0, 128.5, 127.6, 125.4 (q, J = 4.0 Hz), 125.3 (q, J = 4.0 Hz), 124.5 (q, J = 273.0 Hz), 123.9 (q, J = 270.0 Hz), 75.2 ppm; $^{19}$F NMR (CDCl$_3$, 376 MHz): $\delta$ -63.4, -64.1 ppm; HRMS m/z Calcd. for C$_{24}$H$_{16}$F$_6$O$_2$: 450.10545. Found: 450.10641.

(Z)-1-(4-bromophenyl)-2-((4-bromophenyl)(hydroxy)methyl)-3-phenylprop-2-en-1-one (Table 4, entry 4):

The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 79% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.48–7.42 (m, 4H), 7.31–7.26 (m, 4H), 7.08–7.06 (m, 5H), 6.97 (s, 1H), 5.67 (s, 1H), 3.28 (d, 1H, J = 4.0 Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 199.4, 141.1, 140.1, 134.9, 134.7, 133.2, 131.9, 129.9, 129.0, 128.5, 127.6, 125.4 (q, J = 4.0 Hz), 125.3 (q, J = 4.0 Hz), 124.5 (q, J = 273.0 Hz), 123.9 (q, J = 270.0 Hz), 75.2 ppm; $^{19}$F NMR (CDCl$_3$, 376 MHz): $\delta$ -63.4, -64.1 ppm; HRMS m/z Calcd. for C$_{24}$H$_{16}$F$_6$O$_2$: 450.10545. Found: 450.10641.
131.8, 131.0, 129.2, 128.9, 128.8, 128.5, 128.4, 122.2, 76.4 ppm; HRMS m/z Calcd. for C_{22}H_{16}Br_2O_2: 469.9517. Found: 469.9531.

**1-Cyclohexyl-3-(4-methoxyphenyl)prop-2-yn-1-ol (Table 5, entry 1):**

![Chemical Structure of 1-Cyclohexyl-3-(4-methoxyphenyl)prop-2-yn-1-ol](image)

The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 92% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.38 (d, 1H, $J$ = 8.0 Hz), 7.25–7.24 (m, 1H), 6.90–6.83 (m, 2H), 4.42 (d, 1H, $J$ = 4.0 Hz), 3.85 (s, 3H), 2.47 (bs, 1H), 1.94–1.66 (m, 6H), 1.24–1.17 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 160.2, 133.8, 129.9, 120.6, 112.2, 110.8, 93.8, 82.0, 67.9, 56.0, 44.5, 28.9, 28.4, 26.7, 26.2 ppm; HRMS m/z Calcd. for C$_{16}$H$_{20}$O$_2$: 244.14632. Found: 244.14668.

**1-Cyclohexyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol (Table 5, entry 2):**

![Chemical Structure of 1-Cyclohexyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol](image)

The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 84% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.55–7.49 (m, 4H), 4.38 (d, 1H, $J$ = 4.0 Hz), 2.37 (bs, 1H), 1.93–1.66 (m, 6H), 1.28–1.11 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 132.1, 130.2 (q, $J$ = 30.2 Hz), 126.8, 125.4, 125.4, 125.3,
124.0 (q, $J = 271.6$ Hz), 92.0, 84.5, 67.8, 44.4, 28.9, 28.4, 26.6, 26.1 ppm; $^{19}$F NMR (CDCl$_3$, 376 MHz): $\delta$ -63.3 ppm; HRMS $m/z$ Calcd. for C$_{16}$H$_{17}$F$_3$O: 282.12314. Found: 282.12345.

1-Cyclohexyl-3-(pyridin-3-yl)prop-2-yn-1-ol (Table 5, entry 3):

![Cyclohexyl-3-(pyridin-3-yl)prop-2-yn-1-ol](image)

The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 88% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.73 (s, 1H), 8.49 (d, 1H, $J = 4.0$ Hz), 7.71 (d, 1H, $J = 8.0$ Hz), 7.26–7.22 (m, 1H), 4.37 (d, 1H, $J = 4.0$ Hz), 4.01 (bs, 1H), 1.91–1.66 (m, 6H), 1.28–1.11 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 152.2, 148.4, 139.1, 123.3, 120.5, 115.5, 94.0, 82.0, 67.5, 44.5, 28.9, 28.6, 26.6, 26.2, 26.1 ppm; HRMS $m/z$ Calcd. for C$_{14}$H$_{17}$NO: 215.13101. Found: 215.13147.

3-(2-Bromophenyl)-1-cyclohexylprop-2-yn-1-ol (Table 5, entry 4):

![3-(2-Bromophenyl)-1-cyclohexylprop-2-yn-1-ol](image)

The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow oil in 86% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.56 (d, 1H, $J = 8.0$ Hz), 7.45 (d, 1H, $J = 4.0$ Hz), 7.23 (t, 1H, $J = 8.0$ Hz), 7.16 (t, 1H, $J = 8.0$ Hz), 4.44 (s, 1H), 2.30 (d, 1H, $J = 4.0$ Hz), 1.94–1.69 (m, 6H), 1.27–1.18 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 152.2, 148.4, 139.1, 123.3, 120.5, 115.5, 94.0, 82.0, 67.5, 44.5, 28.9, 28.6, 26.6, 26.2, 26.1 ppm; HRMS $m/z$ Calcd. for C$_{14}$H$_{17}$NO: 215.13101. Found: 215.13147.
100.6 MHz): $\delta$ 133.7, 132.6, 129.7, 127.2, 125.8, 125.1, 94.3, 84.3, 67.9, 44.5, 28.9, 28.3, 26.7, 26.2, 26.1 ppm; HRMS $m/z$ Calcd. for C$_{15}$H$_{17}$BrO: 292.04627. Found: 292.04691.

3-(3-Chlorophenyl)-1-cyclohexylprop-2-yn-1-ol (Table 5, entry 5):

The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow oil in 84% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.41 (s, 1H), 7.29–7.20 (m, 3H), 4.37 (s, 1H), 2.10 (s, 1H), 1.92–1.68 (m, 6H), 1.29–1.10 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 134.3, 131.7, 130.0, 129.7, 128.8, 124.7, 90.8, 84.5, 67.8, 44.5, 28.9, 28.5, 26.6, 26.1, 26.1 ppm; HRMS $m/z$ Calcd. for C$_{15}$H$_{17}$ClO: 248.09679. Found: 248.09739.

1-Cyclohexyl-3-(thiophen-3-yl)prop-2-yn-1-ol (Table 5, entry 6):

The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow oil in 91% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.24–7.19 (m, 2H), 6.97–6.94 (m, 1H), 4.38 (d, 1H, $J = 8.0$ Hz), 2.31 (s, 1H), 1.92–1.63 (m, 6H), 1.30–1.08 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 132.3, 127.1, 122.9, 93.5, 79.1, 68.0, 44.4, 28.9, 28.5, 26.6, 26.1 ppm; HRMS $m/z$ Calcd. for C$_{13}$H$_{16}$OS: 220.09218. Found: 220.09246.
1-(2,6-Dimethylphenyl)-3-(4-methoxyphenyl)prop-2-yn-1-ol (Table 6, entry 1):

![Structure Image]

The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow oil in 92% isolated yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.39 (d, 1H, \(J = 8.0\) Hz), 7.28 (t, 1H, \(J = 8.0\) Hz), 7.12–7.04 (m, 3H), 6.91–6.39 (m, 2H), 6.19 (s, 1H), 3.83 (s, 3H), 2.69 (s, 1H), 2.62 (s, 6H) ppm; \(^1^3\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 160.4, 137.1, 136.7, 133.8, 132.6, 130.4, 129.9, 129.8, 128.5, 128.1, 127.7, 127.2, 125.9, 124.9, 94.5, 85.3, 62.5 ppm; HRMS \(m/z\) Calcd. for C\(_{18}\)H\(_{18}\)O\(_2\): 266.13067. Found: 266.13699.

1-(Biphenyl-2-yl)-3-(2-bromophenyl)prop-2-yn-1-ol (Table 6, entry 2):

![Structure Image]

The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 81% isolated yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.05 (d, 1H, \(J = 8.0\) Hz), 7.59 (d, 1H, \(J = 8.0\) Hz), 7.51–7.40 (m, 8H), 7.34–7.17 (m, 3H), 5.74 (s, 1H), 2.47 (s, 1H) ppm; \(^1^3\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 141.2, 140.4, 138.2, 133.8, 132.6, 130.4, 129.9, 129.8, 128.5, 128.1, 127.7, 127.2, 125.9, 124.9, 94.5, 85.3, 62.5 ppm; HRMS \(m/z\) Calcd. for C\(_{21}\)H\(_{15}\)BrO: 362.03062. Found: 362.03139.
3-(2-Bromophenyl)-1-o-tolylprop-2-yn-1-ol (Table 6, entry 3):

![3-(2-Bromophenyl)-1-o-tolylprop-2-yn-1-ol](image)

The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow solid in 78% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.84–7.81 (m, 1H), 7.59–7.48 (m, 2H), 7.28–7.16 (m, 5H), 5.88 (d, 1H, $J = 4.0$ Hz), 2.53 (s, 3H), 2.46 (d, 1H, $J = 4.0$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 138.3, 136.3, 133.8, 132.6, 131.0, 129.9, 128.8, 127.2, 127.0, 126.5, 125.9, 124.9, 93.4, 85.3, 63.3, 19.3 ppm; HRMS $m/z$ Calcd. for C$_{16}$H$_{13}$BrO: 300.01497. Found: 300.01572.

3-(3-Chlorophenyl)-1-o-tolylprop-2-yn-1-ol (Table 6, entry 4):

![3-(3-Chlorophenyl)-1-o-tolylprop-2-yn-1-ol](image)

The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 72% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.70 (t, 1H, $J = 4.0$ Hz), 7.45 (s, 1H), 7.34–7.20 (m, 6H), 5.82 (s, 1H), 2.49 (s, 4H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 138.3, 136.3, 133.8, 132.6, 131.0, 129.9, 128.8, 127.2, 127.0, 126.5, 125.9, 124.9, 93.4, 85.3, 63.3, 19.3 ppm; HRMS $m/z$ Calcd. for C$_{16}$H$_{13}$ClO: 256.06549. Found: 256.06600.

1-o-Tolyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol (Table 6, entry 5):

![1-o-Tolyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol](image)
The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 83% isolated yield.  

\[ \text{H NMR (CDCl}_3, 400 \text{ MHz)}: \delta 7.71 (t, 1H, } J = 4.0 \text{ Hz), 7.59–7.54 (m, 4H), 7.29–7.21 (m, 3H), 5.84 (d, 1H, } J = 4.0 \text{ Hz), 2.52 (d, 1H, } J = 8.0 \text{ Hz), 2.50 (s, 3H) ppm;} \]  

\[ \text{13C NMR (CDCl}_3, 100.6 \text{ MHz): } \delta 138.2, 136.2, 132.4, 131.6, 130.5 (q, } J = 33 \text{ Hz), 128.9, 126.8, 126.6, 125.5, 125.4, 121.3 (q, } J = 270 \text{ Hz), 91.3, 85.3, 63.1, 19.2 \text{ ppm;} \]  

\[ \text{19F NMR (CDCl}_3, 376 \text{ MHz): } \delta -63.26 \text{ ppm;} \]  

\[ \text{HRMS m/z Calcd. for C}_{17}\text{H}_{13}\text{F}_3\text{O: 290.0906. Found: 290.0918.}\]  

3-(4-Methoxyphenyl)-1-\text{o-tolylprop-2-yn-1-ol (Table 6, entry 6):}  

The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow oil in 86% isolated yield.  

\[ \text{H NMR (CDCl}_3, 400 \text{ MHz): } \delta 7.82–7.80 (m, 1H), 7.43 (d, 1H, } J = 8.0 \text{ Hz), 7.32–7.21 (m, 4H), 6.92–6.85 (m, 2H), 5.87 (d, 1H, } J = 4.0 \text{ Hz), 3.85 (s, 3H), 3.70 (d, 1H, } J = 4.0 \text{ Hz), 2.51 (s, 3H) ppm;} \]  

\[ \text{13C NMR (CDCl}_3, 100.6 \text{ MHz): } \delta 160.4, 138.7, 136.4, 133.8, 130.9, 130.2, 128.5, 127.1, 126.4, 120.6, 110.9, 93.0, 83.1, 63.3, 56.0, 19.2 \text{ ppm;} \]  

\[ \text{HRMS m/z Calcd. for C}_{17}\text{H}_{16}\text{O}_2: 252.1148. \text{ Found: 252.1150.}\]  

3-(Thiophen-3-yl)-1-\text{o-tolylprop-2-yn-1-ol (Table 6, entry 7):}
The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow oil in 67% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.70 (t, 1H, $J$ = 4.0 Hz), 7.28–7.20 (m, 5H), 7.98 (t, 1H, $J$ = 4.0 Hz), 5.85 (d, 1H, $J$ = 8.0 Hz), 2.49 (s, 3H), 2.22 (d, 1H, $J$ = 8.0 Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 138.3, 136.2, 132.6, 131.1, 128.8, 127.6, 127.2, 126.8, 126.5, 122.6, 92.5, 80.1, 63.4, 19.3 ppm; HRMS $m/z$ Calcd. for C$_{14}$H$_{12}$OS: 228.0605. Found: 228.0609.

**3-(Pyridin-3-yl)-1-o-tolyprop-2-yn-1-ol (Table 6, entry 8):**

The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow solid in 88% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.73 (s, 1H), 8.42 (d, 1H, $J$ = 8.0 Hz), 7.71–7.69 (m, 2H), 7.26–7.20 (m, 4H), 5.84 (s, 1H), 5.35 (bs, 1H), 2.48 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 152.1, 148.4, 139.2, 138.7, 136.0, 130.9, 128.5, 126.7, 126.4, 123.4, 120.4, 93.7, 82.4, 62.5, 19.3 ppm; HRMS $m/z$ Calcd. for C$_{15}$H$_{13}$NO: 223.0992. Found: 223.0997.

**(Z)-3-(2-Bromophenyl)-2-(hydroxy(4-(trifluoromethyl)phenyl)methyl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (Table 7, entry 1):**

The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow oil in 67% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.70 (t, 1H, $J$ = 4.0 Hz), 7.28–7.20 (m, 5H), 7.98 (t, 1H, $J$ = 4.0 Hz), 5.85 (d, 1H, $J$ = 8.0 Hz), 2.49 (s, 3H), 2.22 (d, 1H, $J$ = 8.0 Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 138.3, 136.2, 132.6, 131.1, 128.8, 127.6, 127.2, 126.8, 126.5, 122.6, 92.5, 80.1, 63.4, 19.3 ppm; HRMS $m/z$ Calcd. for C$_{14}$H$_{12}$OS: 228.0605. Found: 228.0609.
The general reaction procedure was followed for the synthesis and purification; product was afforded as colorless oil in 68% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.63–7.59 (m, 6H), 7.38–7.25 (m, 4H), 6.91 (bs, 3H), 5.89 (s, 1H), 3.33 (s, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 198.3, 144.9, 142.3, 139.4, 135.5, 134.6, 134.2, 131.2, 130.6 (q, $J = 32.0$ Hz), 130.3, 129.3, 127.4, 127.0, 126.8 (q, $J = 270.0$ Hz), 126.2 (q, $J = 272.0$ Hz), 125.9, 124.8, 123.5, 76.5 ppm; $^{19}$F NMR (CDCl$_3$, 376 MHz): $\delta$ -63.0, -63.8 ppm; HRMS $m/z$ Calcd. for C$_{24}$H$_{15}$BrF$_6$O$_2$: 528.01595. Found: 528.01759.

(Z)-3-(3-Chlorophenyl)-2-(hydroxy(4-(trifluoromethyl)phenyl)methyl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (Table 7, entry 2):

The general reaction procedure was followed for the synthesis and purification; product was afforded as white solid in 74% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.66–7.40 (m, 8H), 7.01–6.89 (m, 5H), 5.80 (s, 1H), 3.22 (s, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$
198.7, 144.5, 142.4, 138.7, 136.1, 134.8 (q, \( J = 25.0 \) Hz), 134.4, 132.0, 130.7 (q, \( J = 32.0 \) Hz), 129.7, 129.4, 129.0, 128.8, 126.9, 126.8 (q, \( J = 290 \) Hz), 126.6 (q, \( J = 320 \) Hz), 125.7, 125.4, 75.8 ppm; \(^{19}\)F NMR (CDCl\(_3\), 376 MHz): \( \delta \) -63.1, -63.8 ppm; HRMS \( m/z \) Calcd. for C\(_{24}\)H\(_{15}\)ClF\(_6\)O\(_2\): 484.0644. Found: 484.0665.

(Z)-2-(hydroxy(4-(trifluoromethyl)phenyl)methyl)-1,3-bis(4-(trifluoromethyl)phenyl)prop-2-en-1-one (Table 7, entry 3):

The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow oil in 72% isolated yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.68 (d, 2H, \( J = 8.0 \) Hz), 7.60–7.53 (m, 4H), 7.41 (d, 2H, \( J = 8.0 \) Hz), 7.33 (d, 2H, \( J = 8.0 \) Hz), 7.16 (d, 2H, \( J = 8.0 \) Hz), 7.04 (s, 1H), 5.84 (d, 1H, \( J = 4.0 \) Hz), 3.18 (d, 1H, \( J = 4.0 \) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \( \delta \) 198.5, 144.5, 143.6, 138.9, 138.1, 134.9 (q, \( J = 32.0 \) Hz), 131.7, 130.7 (q, \( J = 32.0 \) Hz), 130.7 (q, \( J = 32.0 \) Hz), 129.6, 129.3, 127.1, 125.8, 125.4, 125.3, 124.1 (q, \( J = 271.0 \) Hz), 123.8 (q, \( J = 271.0 \) Hz), 123.4 (q, \( J = 271.0 \) Hz), 75.9 ppm; \(^{19}\)F NMR (CDCl\(_3\), 376 MHz): \( \delta \) -63.1, -63.5, -63.9 ppm; HRMS \( m/z \) Calcd. for C\(_{25}\)H\(_{15}\)F\(_9\)O\(_2\): 518.09283. Found: 518.09409.
The general reaction procedure was followed for the synthesis and purification; product was afforded as green oil in 69% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.85 (d, 2H, $J = 8.0$ Hz), 7.58–7.53 (m, 6H), 7.15 (d, 1H, $J = 8.0$ Hz), 7.00 (s, 1H), 6.84–6.79 (m, 2H), 5.75 (d, 1H, $J = 4.0$ Hz), 3.06 (d, 1H, $J = 4.0$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 198.5, 144.7, 139.3, 138.9, 137.1, 134.9 (q, $J = 33.0$ Hz), 130.8 (q, $J = 33.0$ Hz), 130.4, 129.8, 128.6, 128.1, 127.0, 125.7, 125.3, 124.1 (q, $J = 270.0$ Hz), 123.61 (q, $J = 271.0$ Hz), 76.2 ppm; $^{19}$F NMR (CDCl$_3$, 376 MHz): $\delta$ -64.7, -65.4 ppm; HRMS $m/z$ Calcd. for C$_{22}$H$_{14}$F$_6$O$_2$S: 456.06186. Found: 456.06315.
The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow oil in 73% isolated yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.97 (d, 2H, \(J = 8.0\) Hz), 7.80 (d, 2H, \(J = 8.0\) Hz), 7.63 (d, 2H, \(J = 8.0\) Hz), 7.50 (d, 2H, \(J = 8.0\) Hz), 7.30 (d, 2H, \(J = 8.0\) Hz), 7.15 (d, 2H, \(J = 8.0\) Hz), 7.03 (s, 1H), 5.84 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.35 (d, 1H, \(J = 4.0\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 198.9, 166.8, 166.1, 145.6, 143.8, 139.1, 134.4, 130.9, 130.1 (q, \(J = 33.0\) Hz), 129.8, 129.2, 126.7, 125.5, 124.4, 123.8 (q, \(J = 263.0\) Hz), 76.2, 55.6, 52.4 ppm; \(^{19}\)F NMR (CDCl\(_3\), 376 MHz): \(\delta\) -63.3 ppm; HRMS m/z Calcd. for C\(_{27}\)H\(_{21}\)F\(_3\)O\(_6\): 498.12902. Found: 498.13023.

\((Z)-1-(4-Bromophenyl)-2-((4-bromophenyl)(hydroxy)methyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one\) (Table 7, entry 6):

\[ \text{The general reaction procedure was followed for the synthesis and purification; product was afforded as yellow oil in 65\% isolated yield.} \]

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.49−7.44 (m, 4H), 7.34−7.26 (m, 6H), 7.16 (d, 2H, \(J = 8.0\) Hz), 6.94 (s, 1H), 5.69 (d, 1H, \(J = 4.0\) Hz), 3.08 (d, 1H, \(J = 4.0\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 198.5, 143.8, 139.6, 138.3, 134.7, 132.2, 132.1, 132.0, 130.9, 130.4, 129.3, 128.5, 125.5, 123.9 (q, \(J = 267\) Hz), 122.5, 76.0 ppm; \(^{19}\)F NMR (CDCl\(_3\), 376 MHz): \(\delta\) -63.2 ppm; HRMS m/z Calcd. for C\(_{23}\)H\(_{18}\)Br\(_2\)F\(_3\)O\(_2\): 537.9358. Found: 537.9391.
References


KW656, CDCL3
400MHz
COLORLESS OIL
20 JUNE 2008

Table 1, entry 3
444
Table 2, entry 4
Table 2, entry 4
Table 2, entry 6
Manual Peak Matching Report
For Accurate Mass Determination

<table>
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<th>PFK matching mass</th>
<th>Deviation*</th>
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<td>230.98542</td>
<td>1.8 ppm</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Diagram of molecule](image)

Table 2, entry 7
Table 2, entry 7
Table 2, entry 8
Table 3, entry 3
KW701, CDCl3  
100 MHz  
COLORLESS OIL  
SEP 22 2008

Table 3, entry 3
Table 3, entry 4
Manual Peak Matching Report
For Accurate Mass Determination

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<td>290.19875</td>
<td>230.98562</td>
<td>1.5 ppm</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 3, entry 4
SPEC: fin083989.dat (12-NOV-08 15:01:53)
Samp: KW711
Comm: 70 eV EI
Oper: KH
Study: MS Services
Base: 56.01
Masses: 35.01 > 650.00
Peak: 1000.0 mmu
Intensity: 3456369
Scan 28 @ 0.71 min (EI +Q1MS LMR UP LR)

Table 3, entry 4

Date: Wed Nov 12 15:03:42 2008
ICIS: 8.3.0 SP2 for OSF1 (V4.0) build 98-238 from 26-Aug-98
Manual Peak Matching Report
For Accurate Mass Determination

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<th>PFK matching mass</th>
<th>Deviation*</th>
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<td>430.14262</td>
<td>380.97603</td>
<td>2.3 ppm</td>
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</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only \(^{12}\text{C}, \text{H}, \text{O}, \text{N}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 4, entry 1
### Manual Peak Matching Report
For Accurate Mass Determination

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<th>PFK matching mass</th>
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<tbody>
<tr>
<td>565.92398</td>
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<td>530.96645</td>
<td>2.4 ppm</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Molecular Structure Image]

Table 4, entry 2
SPEC: fin083709.dat (22-JUL-08 10:52:27)
Samp: KX673
Comm: SP 70 eV EI
Oper: Kh  
Study: MS services
Base: 230.47  
Masses: 35.01 > 650.00
Peak: 1000.0 mmu  
Intensity: 2299958
Scan 277 @ 5.85 min (EI +QMS LMR UP LR)  

Table 4, entry 2

Date: Tue Jul 22 11:00:38 2008  
ICIS: 8.3.0 SP2 for OSF1 (V4.0) build 98-238 from 26-Aug-98
Table 4, entry 3

KW665, CD3CN
100MHz
WHITE SOLID
JUNE 26 2008
Table 4, entry 3

KW665, CD3CN
WHITE SOLID
376MHz
JUNE 26 2008
Manual Peak Matching Report
For Accurate Mass Determination

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<td>430.97284</td>
<td>2.1 ppm</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass corresponds to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 4, entry 3
SPBC: fin083770 (15-JUL-08 11:16:25)
Samp: 665
Comm: SP 70 eV EI
Oper: kh
Base: 144.92
Peak: 1000.0 mnu
REG #9 @ 1.48 min (EI+QLMS IMR UP LR) (+64>80)

Table 4, entry 3

Date: Tue Jul 15 11:18:59 2004
ICIS: 8.3.0 SP2 for OSF1 (V4.0) build 98-238 from 26-Aug-98
KW708, CDCl3
300 MHz
SEP 24 2008
WHITE SOLID

Table 4, entry 4
Manual Peak Matching Report
For Accurate Mass Determination

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<td>430.97284</td>
<td>3 ppm</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only 12C, 1H, 16O, 14N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure]

Table 4, entry 4
Table 4, entry 4
Manual Peak Matching Report
For Accurate Mass Determination

<table>
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<th>Deviation*</th>
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<td>244.14632</td>
<td>244.1468</td>
<td>230.98562</td>
<td>2.1 ppm</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only \(^{12}\text{C}, ^{1}\text{H}, ^{16}\text{O}, ^{14}\text{N}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Structure diagram](image)

Table 5, entry 1

\[\text{H}^n\]
KW745, CDCl₃
376 MHz
COLORLESS OIL
DEC 03 2008

Table 5, entry 2
Manual Peak Matching Report
For Accurate Mass Determination

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<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
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</thead>
<tbody>
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<td>282.12314</td>
<td>282.12345</td>
<td>268.98242</td>
<td>1.1 ppm</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only \(^{12}\text{C}, \, ^{1}\text{H}, \, ^{16}\text{O}, \, ^{14}\text{N}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 5, entry 2
Table 5, entry 2
KW746, CDCl3
100 MHz
COLORLESS OIL
DEC 04 2008

Table 5, entry 3
Manual Peak Matching Report
For Accurate Mass Determination

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<tbody>
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<td>180.98882</td>
<td>2.1 ppm</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^{1}$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 5, entry 3
Table 5, entry 3

Date: Tue Dec 16 10:25:31 2008  ICIS: 8.3.0 SP2 for OSF1 (V4.0) build 98-230 from 26-Aug-98
Manual Peak Matching Report
For Accurate Mass Determination

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<td>280.98242</td>
<td>2.2 ppm</td>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Table 5, entry 4](image-url)
KW755, CDCl3
100 MHz
YELLOW OIL
JAN 12 2008

Table 5, entry 5
Manual Peak Matching Report
For Accurate Mass Determination

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<tbody>
<tr>
<td>248.09679</td>
<td>248.09739</td>
<td>230.98562</td>
<td>2.4 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

$$\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}$$

Where nominal mass takes into account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 5, entry 5
Table 5, entry 5
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>220.07218</td>
<td>220.07244</td>
<td>208.98562</td>
<td>1.3 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 5, entry 6
Table 5, entry 6

Date: Thu Jan 22 11:19:50 2009   ICIS: 8.3.0 SP2 for OSF1 (V4.0) build 98-238 from 26-Aug-98
KW78I, CDCl3
100 MHz
YELLOW OIL
FEB 04 2009

Table 6, entry 1
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>266.13067</td>
<td>266.13379</td>
<td>280.98562</td>
<td>2.4 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...
Theoretical mass correspond to the mass of the most abundant isotope peak

\[
\text{Table 6, entry 1}
\]
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>362.03062</td>
<td>362.03139</td>
<td>330.94923</td>
<td>2.1 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 6, entry 2
KW780, CDCl₃
400 MHz
YELLOW SOLID
FEB 03 2009

Table 6, entry 3
KW780, CDCl3
100 MHz
YELLOW SOLID
FEB 03 2009

Table 6, entry 3
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>300.01497</td>
<td>300.01572</td>
<td>280.98242</td>
<td>2.5 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}, ^1\text{H}, ^{16}\text{O}, ^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 6, entry 3
Table 6, entry 4
Manual Peak Matching Report  
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>256.06549</td>
<td>256.06600</td>
<td>230.91512</td>
<td>2 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](attachment:image.png)

Table 6, entry 4
Table 6, entry 4
Table 6, entry 5
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0  Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions
74 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass)

<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBE</th>
<th>Score</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>290.0906</td>
<td>290.0907</td>
<td>-0.1</td>
<td>-0.4</td>
<td>14.0</td>
<td>1</td>
<td>C20 H12 F2</td>
</tr>
<tr>
<td>290.0918</td>
<td>290.0918</td>
<td>-1.2</td>
<td>-4.3</td>
<td>10.0</td>
<td>2</td>
<td>C17 H13 O F3</td>
</tr>
</tbody>
</table>

Table 6, entry 5
Table 6, entry 5
Elemental Composition Report

Multiple Mass Analysis: 3 mass(es) processed
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron ions
351 formula(e) evaluated with 7 results within limits (up to 50 closest results for each mass)

KW803
sv-05-05-04 903 (15.036) Cm (903.917)

<table>
<thead>
<tr>
<th>Mass</th>
<th>RA</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBE</th>
<th>Score</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>250.0996</td>
<td>35.84</td>
<td>250.0994</td>
<td>0.2</td>
<td>0.9</td>
<td>11.0</td>
<td>1</td>
<td>C17 H14 O2</td>
</tr>
<tr>
<td>251.0975</td>
<td>71.05</td>
<td>251.0972</td>
<td>0.3</td>
<td>1.2</td>
<td>10.5</td>
<td>1</td>
<td>C17 H15 O2</td>
</tr>
<tr>
<td>252.1148</td>
<td>100.00</td>
<td>252.1130</td>
<td>-0.2</td>
<td>-0.9</td>
<td>10.0</td>
<td>1</td>
<td>C17 H16 O2</td>
</tr>
</tbody>
</table>

Table 6, entry 6
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0  Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron ion
40 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Hudson_ KW0755
sv-03-12-02 126 (2.266) Cm (114:144)

TOF MS E+ 1.81e4

<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBE</th>
<th>Score</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>228.0505</td>
<td>228.0609</td>
<td>-0.4</td>
<td>-1.7</td>
<td>9.0</td>
<td>1</td>
<td>C14 H12 O S</td>
</tr>
</tbody>
</table>

Table 6, entry 7
Table 6, entry 8
Elemental Composition Report

Multiple Mass Analysis: 4 mass(es) processed
Tolerance = 7.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0  Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions
415 formula(e) evaluated with 7 results within limits (up to 50 closest results for each mass)

Table 6, entry 8
Table 7, entry 1
Manual Peak Matching Report  
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>528.01595</td>
<td>528.01759</td>
<td>480.96964</td>
<td>3 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only \(^{12}\text{C}, \text{H}^1, \text{O}^{16}, \text{N}^{14}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure Image]

Table 7, entry 1
Table 7, entry 1
KW792, CDCl₃
376 MHz
WHITE SOLID

Table 7, entry 2
Elemental Composition Report

Multiple Mass Analysis: 2 mass(es) processed
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoleptopic Mass, Odd and Even Electron Ions
737 formula(e) evaluated with 11 results within limits (up to 50 closest results for each mass)

Table 7, entry 2
Table 7, entry 2
KW787, CDCl3
100 MHz
YELLOW OIL
FEB 12 2009

Table 7, entry 3
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>518.09283</td>
<td>518.09409</td>
<td>492.96764</td>
<td>2.4 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

[Chemical structure diagram]

Table 7, entry 3
KW794, CDC13
376 MHz
GREEN OIL
FEB 27 2009

Table 7, entry 4
Manual Peak Matching Report  
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>456.06184</td>
<td>456.06315</td>
<td>430.97284</td>
<td>2.8 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 7, entry 4
Table 7, entry 4
Table 7, entry 5
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>498.1292</td>
<td>498.13023</td>
<td>490.9694</td>
<td>2.4 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 7, entry 5
Elemental Composition Report

Multiple Mass Analysis: 6 mass(es) processed
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions
42 formula(e) evaluated with 6 results within limits (up to 50 closest results for each mass)

<table>
<thead>
<tr>
<th>Mass</th>
<th>RA</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBE</th>
<th>Score</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>536.9314</td>
<td>44.31</td>
<td>536.9313</td>
<td>0.1</td>
<td>0.3</td>
<td>14.5</td>
<td>1</td>
<td>C23 H14 O2 P3 798 r2</td>
</tr>
<tr>
<td>537.9368</td>
<td>58.39</td>
<td>537.9351</td>
<td>-3.3</td>
<td>-6.1</td>
<td>14.0</td>
<td>1</td>
<td>C23 H15 O2 P3 798 r2</td>
</tr>
<tr>
<td>538.9299</td>
<td>92.95</td>
<td>538.9292</td>
<td>0.7</td>
<td>1.3</td>
<td>14.5</td>
<td>1</td>
<td>C23 H14 O2 P3 798 r</td>
</tr>
<tr>
<td>538.9353</td>
<td>100.00</td>
<td>539.9370</td>
<td>-1.7</td>
<td>-3.2</td>
<td>14.0</td>
<td>1</td>
<td>CHlor</td>
</tr>
<tr>
<td>540.9322</td>
<td>61.48</td>
<td>540.9272</td>
<td>5.0</td>
<td>9.3</td>
<td>14.5</td>
<td>1</td>
<td>C23 H14 O2 P3 818 r2</td>
</tr>
<tr>
<td>541.9333</td>
<td>48.27</td>
<td>541.9350</td>
<td>-1.7</td>
<td>-3.1</td>
<td>14.0</td>
<td>1</td>
<td>C23 H15 O2 P3 818 r2</td>
</tr>
</tbody>
</table>

Table 7, entry 6
After 48 h, THF, -40 °C
APPENDIX E

CHAPTER 6

General Information
References for known compounds and characterization data for the new compounds

$^1$H, $^{13}$C NMR and HRMS for all compounds
General Information

All reactions were carried out under inert atmosphere using oven dried glassware and a magnetic stirrer. THF was freshly distilled and dried over sodium/benzophenone. Trimethylsilylenolates, proazaphosphatrane $1b$ and all aldehydes were purchased from commercial sources and were used without further purification. Proazaphosphatrane $1a$, $1c$, $1d$ were synthesized according to our previous protocols. An optimized procedure was reported for proazaphosphatrane $1c$ in the manuscript. $^1H$ (300 or 400 Hz) and $^{13}C$ (100.6 MHz) NMR spectra were recorded in CDCl$_3$; the chemical shifts are referenced to the residual peaks of CHCl$_3$ in CDCl$_3$. $^{31}P$ NMR spectra were recorded at ambient temperature on a 400 MHz spectrometer using 85% $H_3PO_4$ as the external standard. Thin layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates visualized with short-wavelength UV light (254 nm). The column chromatography was performed using (40-140 mesh) silica gel for the purification of Mukaiyama products. Electron impact ionization experiments were performed on a triple quadrupole mass spectrometer fitted with a EI/CI ion source. Accurate mass measurements were performed using a double focusing MS-50 mass spectrometer. The reported yields are isolated yields after column chromatography unless otherwise stated. All commercially available reagents were used as received.
2,8,9-Tribenzyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (1c)\textsuperscript{1a}:

A three step optimized procedure is reported in the manuscript.

**Methyl 3-hydroxy-2,2-dimethyl-3-(4-methylphenyl)propionate (Table 1, entry 1)\textsuperscript{2}:**

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 92\% isolated yield.

**Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropionate (Table 2, entry 1)\textsuperscript{2}:**

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 93\% isolated yield.

**Methyl 3-hydroxy-2,2-dimethyl-3-(naphthalen-1yl)propionate (Table 2, entry 2)\textsuperscript{2}:**

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 81\% isolated yield.
Methyl 3-hydroxy-3-(2-biphenyl)-2,2-dimethylpropionate (Table 2, entry 3):

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 92% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.58 (d, 1H, $J = 8.0$ Hz), 7.42–7.30 (m, 7H), 7.20 (d, 1H, $J = 7.6$ Hz), 5.27 (s, 1H), 3.75 (bs, 1H), 3.64 (s, 3H), 1.02 (s, 3H), 0.83 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.8, 142.5, 141.9, 137.7, 130.5, 129.9, 128.5, 127.7, 127.4, 127.1, 74.1, 52.4, 48.4, 24.2, 19.5 ppm; HRMS m/z Calcd for C$_{18}$H$_{20}$O$_3$: 284.14124. Found: 284.14179.

Methyl 3-hydroxy-3-(3-methoxyphenyl)-2,2-dimethylpropionate (Table 2, entry 4):

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 95% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.26–7.21 (m, 1H), 6.88–6.82 (m, 3H), 4.86 (d, 1H, $J = 4.4$ Hz), 3.79 (s, 3H), 3.72 (s, 3H), 3.05 (d, 1H, $J = 4.0$ Hz), 1.15 (s, 3H), 1.12 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.3, 159.3, 141.9, 128.9, 120.3, 113.6, 113.3, 78.8, 55.4, 52.3, 47.9, 23.2, 19.4 ppm; HRMS m/z Calcd for C$_{13}$H$_{18}$O$_4$: 238.12050. Found: 238.12115.

Methyl 3-hydroxy-3-(2-methylphenyl)-2,2-dimethylpropionate (Table 2, entry 5):
The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 92% isolated yield.

**Methyl 3-hydroxy-3-(2,6-dimethylphenyl)-2,2-dimethylpropionate (Table 2, entry 6):**

```
    OH
   /   \
O   OMe
   
```

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 86% isolated yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.06–6.99 (m, 3H), 5.59 (s, 1H), 3.73 (s, 3H), 2.95 (s, 1H), 2.56 (s, 3H), 2.38 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 178.8, 138.6, 137.5, 135.5, 131.3, 128.6, 127.4, 76.1, 52.5, 50.3, 24.2, 22.6, 20.9 ppm; HRMS \(m/z\) Calcd for C\(_{14}\)H\(_{20}\)O\(_3\): 236.14124. Found: 236.14177.

**Methyl 3-hydroxy-3-(4-methoxyphenyl)-2,2-dimethylpropionate (Table 2, entry 7):**

```
    OH
   /   \
O   OMe
   
```

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 90% isolated yield.

**Methyl 3-hydroxy-3-(3,4-dimethoxylphenyl)-2,2-dimethylpropionate (Table 2, entry 8):**

```
    OH
   /   \
O   OMe
   
```

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 90% isolated yield.
The general procedure was followed for the synthesis and purification; product was afforded as colorless oil in 91% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 6.86–6.83 (m, 2H), 6.75 (s, 1H), 5.25 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.66 (s, 3H), 1.29 (s, 3H), 1.07 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 175.8, 149.2, 148.4, 129.9, 121.6, 112.2, 110.3, 68.8, 56.1, 56.1, 52.4, 49.9, 23.3, 20.3 ppm; HRMS $m/z$ Calcd for C$_{14}$H$_{20}$O$_5$: 268.13107. Found: 268.13179.

Methyl 3-hydroxy-3-(2-methoxynaphthalen-1-yl)-2,2-dimethylpropanoate (Table 2, entry 9):

![Methyl 3-hydroxy-3-(2-methoxynaphthalen-1-yl)-2,2-dimethylpropanoate](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 69% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.10 (bs, 1H), 7.81–7.74 (m, 2H), 7.46 (t, 1H, $J = 8.0$ Hz), 7.32 (t, 1H, $J = 8.0$ Hz), 7.27–7.23 (m, 1H), 5.90 (d, 1H, $J = 8.0$ Hz), 4.90 (bs, 1H), 3.94 (s, 3H), 3.67 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 177.5, 155.5, 133.1, 130.2, 129.3, 128.6, 126.6, 123.6, 119.9, 112.8, 75.2, 55.9, 52.0, 50.3, 24.1, 20.7 ppm; HRMS $m/z$ Calcd for C$_{17}$H$_{20}$O$_4$: 288.13615. Found: 299.13656.

Methyl 3-(3-formylphenyl)-3-hydroxy-2,2-dimethylpropanoate (Table 2, entry 10, 6a).

![Methyl 3-(3-formylphenyl)-3-hydroxy-2,2-dimethylpropanoate](image)
The general procedure was followed for the synthesis and purification; product was afforded as colorless oil in 49% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.95 (s, 1H), 7.76–7.73 (m, 2H), 7.54–7.52 (m, 1H), 7.44 (t, 1H, $J = 8.0$ Hz), 4.93 (s, 1H), 3.67 (s, 3H), 3.48 (bs, 1H), 1.01 (s, 3H), 1.06 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 192.4, 177.9, 141.2, 135.9, 133.8, 129.2, 128.9, 128.5, 76.8, 52.3, 47.7, 22.7, 19.1 ppm; HRMS m/z Calcd for C$_{13}$H$_{16}$O$_4$: 236.10485. Found: 236.10533.

**Dimethyl 3,3’-(1,3-phenylene)bis(3-hydroxy-2,2-dimethylpropanoate)** (Table 2, entry 10, 6b):

![Chemical Structure](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 44% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.15–7.14 (m, 4H), 4.79 (d, 1H, $J = 4.4$ Hz), 3.64 (s, 6H), 3.48 (bs, 1H), 1.05 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.2, 139.7, 139.6, 127.2, 127.2, 127.1, 126.9, 78.5, 78.4, 52.2, 47.8, 47.8, 23.1, 22.8, 19.2, 19.1 ppm; HRMS m/z Calcd for C$_{18}$H$_{26}$O$_6$: 338.17293. Found: 338.17906.

**Methyl 3-(4-(dimethylamino)phenyl)-2,2-dimethyl-3-(trimethylsilyloxy)propanoate** (Table 2, entry 11)$^4$:

![Chemical Structure](image)
The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 96% isolated yield.

**Methyl 3-hydroxy-3-(4-N,N-dimethylphenyl)-2,2-dimethylpropionate (Table 2, entry 11)**:

![Chemical Structure](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 90% isolated yield.

**Methyl 3-hydroxy-3-(2-chlorophenyl)-2,2-dimethylpropionate (Table 3, entry 1)**:

![Chemical Structure](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 91% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.46–7.44 (m, 1H), 7.27–7.14 (m, 3H), 5.45 (s, 1H), 3.66 (s, 3H), 3.54 (bs, 1H), 1.12 (s, 3H), 1.10 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.3, 137.9, 133.5, 129.6, 129.3, 128.3, 126.5, 73.4, 52.3, 48.6, 23.1, 18.7 ppm; HRMS $m/z$ Calcd for C$_{12}$H$_{15}$ClO$_3$: 242.07097. Found: 242.07153.

**Methyl 3-hydroxy-3-(2-fluorophenyl)-2,2-dimethylpropionate (Table 3, entry 2)**:

![Chemical Structure](image)
The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 77% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.47–7.43 (m, 1H), 7.27–7.23 (m, 1H), 7.16–7.12 (m, 1H), 7.03–6.98 (m, 1H), 5.28 (d, 1H, $J = 4.4$ Hz), 3.73 (s, 3H), 3.37 (d, 1H, $J = 5.7$Hz), 1.15 (s, 3H), 1.14 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.4, 160.1 (d, $J = 260$ Hz), 129.4, 129.3 (d, $J = 4.2$ Hz), 127.4 (d, $J = 12.9$ Hz), 124.0 (d, $J = 3.3$ Hz), 115.2 (d, $J = 22.8$ Hz), 71.7, 52.4, 48.2, 23.1, 18.8 ppm; HRMS m/z Calcd. for C$_{12}$H$_{15}$FO$_3$: 226.10052. Found: 226.10078.

Methyl 3-hydroxy-3-(3-iodophenyl)-2,2-dimethylpropionate (Table 3, entry 3):

![Methyl 3-hydroxy-3-(3-iodophenyl)-2,2-dimethylpropionate](image)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 95% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.63–7.58 (m, 2H), 7.23 (d, 1H, $J = 8.0$ Hz), 7.02 (t, 1H, $J = 8.0$ Hz), 4.79 (d, 1H), 3.70 (s, 3H), 3.13(bs, 1H), 1.10 (s, 3H), 1.08 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.1, 142.4, 136.8, 136.6, 129.5, 127.0, 93.9, 76.8, 52.3, 47.7, 22.9, 19.2 ppm; HRMS m/z Calcd. for C$_{12}$H$_{15}$IO$_3$: 334.00659. Found: 334.00734.

Methyl 3-hydroxy-3-(4-bromophenyl)-2,2-dimethylpropionate (Table 3, entry 4)$^4$:

![Methyl 3-hydroxy-3-(4-bromophenyl)-2,2-dimethylpropionate](image)

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 72% isolated yield.
Methyl 3-hydroxy-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)propanoate (Table 3, entry 5):

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 84% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.52 (d, 2H, $J = 8.0$ Hz), 7.36(d, 2H, $J = 8.0$ Hz), 4.87 (d, 2H, $J = 2.8$ Hz), 3.66 (s, 3H), 3.50 (d, 2H, $J = 4.0$ Hz), 1.08 (s, 3H), 1.04 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 177.9, 144.1, 129.9 (q, $J = 32.2$ Hz), 128.0, 124.2 (q, $J = 270.4$ Hz), 124.6 (q, $J = 3.7$ Hz), 77.9, 52.2, 47.6, 22.7, 19.0 ppm; HRMS m/z Calcd for C$_{13}$H$_{15}$F$_3$O$_3$: 276.09732. Found: 276.09812.

Methyl 3-hydroxy-3-(4-nitrophenyl)-2,2-dimethylpropionate (Table 3, entry 6)$^2$:

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 62% isolated yield.

Methyl 3-hydroxy-3-(3-cyanophenyl)-2,2-dimethylpropionate (Table 3, entry 7):

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 58% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.58 (s, 1H), 7.55–7.50 (m, 2H), 7.40 (t, 1H, $J = 7.6$ Hz), 4.89 (d, 1H, $J = 3.6$ Hz), 3.69 (s, 3H), 3.53 (d,
$1H, J = 3.6 \text{ Hz}$, 1.09 (s, 3H), 1.06 (s, 3H) ppm; $^{13}C$ NMR (CDCl$_3$, 100 MHz): $\delta$ 177.9, 141.8, 132.4, 131.6, 131.5, 128.8, 119.0, 112.1, 77.7, 52.6, 47.9, 22.8, 19.3 ppm; HRMS $m/z$ Calcd. for C$_{13}$H$_{15}$NO$_3$: 233.10519. Found: 233.10548.

**Methyl 3-hydroxy-3-(4-cyanophenyl)-2,2-dimethylpropionate (Table 3, entry 8):**

\[
\begin{array}{c}
\text{NC} \\
\text{OH} \\
\text{O} \\
\text{Me}
\end{array}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 74% isolated yield.

**Methyl 3-hydroxy-3-(4-chlorophenyl)-2,2-dimethylpropionate (Table 3, entry 9):**

\[
\begin{array}{c}
\text{Cl} \\
\text{OH} \\
\text{O} \\
\text{Me}
\end{array}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 91% isolated yield.

**Methyl 3-hydroxy-3-(4-methoxycarbonylphenyl)-2,2-dimethylpropionate (Table 3, entry 10):**

\[
\begin{array}{c}
\text{H}_2\text{CO} \\
\text{OH} \\
\text{O} \\
\text{Me}
\end{array}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 82% isolated yield.
Methyl 3-(benzo[b]thiophen-2-yl)-3-hydroxy-2,2-dimethylpropanoate (Table 4, entry 1):

The general procedure was followed for the synthesis and purification; product was afforded as a yellow solid in 92% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.79 (d, 1H, $J = 7.6$ Hz), 7.72 (d, 1H, $J = 8.0$ Hz), 7.36–7.29 (m, 2H), 7.18 (s, 1H), 5.15 (d, 1H, $J = 4.0$ Hz), 3.76 (s, 3H), 3.51 (d, 1H, $J = 4.8$ Hz), 1.28 (s, 6H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.1, 145.1, 139.7, 139.4, 124.5, 124.4, 123.7, 122.5, 122.4, 76.1, 52.6, 48.1, 23.0, 20.5 ppm; HRMS m/z Calcd. for C$_{14}$H$_{16}$O$_3$S: 264.0820. Found: 264.0825.

Methyl 3-(benzofuran-2-yl)-3-hydroxy-2,2-dimethylpropanoate (Table 4, entry 2):

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 89% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.53 (d, 1H, $J = 7.6$ Hz), 7.44 (d, 1H, $J = 8.4$ Hz), 7.28–7.20 (m, 2H), 6.64 (s, 1H), 4.94 (s, 1H), 3.75 (s, 3H), 3.71 (bs, 1H), 1.28 (s, 3H), 1.27 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 177.8, 156.9, 154.8, 128.1, 124.4, 123.1, 121.2, 111.5, 105.0, 74.0, 52.5, 47.4, 23.1, 20.5 ppm; HRMS m/z Calcd. for C$_{14}$H$_{16}$O$_4$: 248.1048. Found: 248.1053.

Methyl 3-hydroxynonanoate (Table 4, entry 3):
The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 80% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.67 (s, 3H), 3.57 (d, 1H, $J = 4.0$ Hz), 1.26–1.14 (m, 16H), 0.87–0.84 (m, 4H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 178.3, 76.7, 51.9, 47.2, 31.8, 31.7, 29.3, 26.7, 22.7, 22.3, 20.4, 14.1 ppm; HRMS $m/z$ Calcd. for C$_{12}$H$_{24}$O$_3$: 216.17254. Found: 216.17291.

Methyl 3-hydroxy-2,2-dimethyl-3-(2-pyridyl)propanoate (Table 4, entry 4):

\[
\text{\begin{tikzpicture}
    \node (n1) at (0,0) {O};
    \node (n2) at (0,-0.5) {Me};
    \node (n3) at (0.5,0) {N};
    \node (n4) at (0.5,-0.5) {C};
    \node (n5) at (1,0) {O};
    \node (n6) at (1,-0.5) {Me};
    \draw [->] (n1) -- (n2);
    \draw [->] (n1) -- (n3);
    \draw [->] (n1) -- (n4);
    \draw [->] (n1) -- (n5);
    \draw [->] (n1) -- (n6);
    \end{tikzpicture}}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 67% isolated yield.

Methyl 3-cyclohexyl-3-hydroxypropanoate (Table 4, entry 5):

\[
\text{\begin{tikzpicture}
    \node (n1) at (0,0) {O};
    \node (n2) at (0,-0.5) {Me};
    \node (n3) at (0.5,0) {OH};
    \node (n4) at (0.5,-0.5) {C};
    \draw [->] (n1) -- (n2);
    \draw [->] (n1) -- (n3);
    \draw [->] (n1) -- (n4);
    \end{tikzpicture}}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 67% isolated yield.

Methyl 3-hydroxy-2,2-dimethyl-3-(4-methylthiazol-2-yl)propanoate (Table 4, entry 6):

\[
\text{\begin{tikzpicture}
    \node (n1) at (0,0) {O};
    \node (n2) at (0,-0.5) {Me};
    \node (n3) at (0.5,0) {N};
    \node (n4) at (0.5,-0.5) {C};
    \draw [->] (n1) -- (n2);
    \draw [->] (n1) -- (n3);
    \draw [->] (n1) -- (n4);
    \end{tikzpicture}}
\]

The general procedure was followed for the synthesis and purification; product was afforded as a yellow solid in 36% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 6.81 (s, 1H), 5.08 (d, 1H, $J = 4.0$ Hz), 4.22 (d, 1H, $J = 8.0$ Hz), 3.71 (s, 3H), 2.38 (s, 3H), 1.21 (s, 3H), 1.21 (s, 3H)
ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 177.5, 170.3, 152.1, 114.0, 76.4, 52.4, 48.1, 21.6, 20.9, 17.2 ppm; HRMS m/z Calcd. for C$_{10}$H$_{15}$NO$_3$S : 229.07726. Found: 229.07763.

Methyl 3-hydroxy-2,2-dimethyl-3-(1-methyl-1H-imidazol-2-yl)propanoate (Table 4, entry 7):

![Chemical structure](attachment:structure.png)

The general procedure was followed for the synthesis and purification; product was afforded as a colorless solid in 77% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 6.82 (d, 1H, $J$ = 1.2 Hz), 6.72 (d, 1H, $J$ = 0.8 Hz), 4.73 (s, 1H), 4.50 (bs, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 177.9, 147.0, 127.2, 121.5, 71.7, 52.3, 47.5, 33.5, 23.1, 21.3 ppm; HRMS m/z Calcd. for C$_{10}$H$_{16}$N$_2$O$_3$: 212.11609. Found: 212.11649.

3-Hydroxy-3-(2-methoxy-phenyl)-1-phenyl-propan-1-one (Table 5, entry 1)$^8$:

![Chemical structure](attachment:structure.png)

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 82% isolated yield.

3-Hydroxy-1-phenyl-3-p-tolyl-propan-1-one (Table 5, entry 2)$^8$:

![Chemical structure](attachment:structure.png)
The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 77% isolated yield.

3-(p-Chlorophenyl)-3-hydroxy-1-phenylpropan-1-one (Table 5, entry 3): 

The general procedure was followed for the synthesis and purification; product was afforded as a colorless solid in 69% isolated yield.

3-Hydroxy-4,4-dimethyl-1-phenyl-1-pentanone (Table 5, entry 4): 

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 74% isolated yield.

3-Hydroxy-1-phenyl-1-nonanone (Table 5, entry 5): 

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 80% isolated yield. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.97–7.94 (m, 2H), 7.60–7.44 (m, 3H), 4.21 (bs, 1H), 3.26–2.98 (m, 3H), 1.63–1.29 (m, 10H), 0.89–0.86 (m, 3H) ppm; $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 201.3, 131.9, 133.8, 128.9, 128.3, 68.0, 45.2, 36.7, 32.0, 29.5, 25.7, 22.8, 14.3 ppm; HRMS $m/z$ Calcd. for C$_{15}$H$_{22}$O$_2$: 234.16197. Found: 234.16226.
2-[Hydroxy(4-nitrophenyl)methyl]-cyclohexanone (Table 5, entry 6)\textsuperscript{10}:

![Chemical Structure]

The general procedure was followed for the synthesis and purification; product was afforded as a yellow solid in 91\% isolated yield.

2-(Hydroxyphenylmethyl)-cyclohexanone (Table 5, entry 7)\textsuperscript{11}:

![Chemical Structure]

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 76\% isolated yield.

2-[Hydroxy(2-methoxyphenyl)methyl]-cyclohexanone (Table 5, entry 8)\textsuperscript{12}:

![Chemical Structure]

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 91\% isolated yield.

\textit{(E)}-1-(2-Fluorophenyl)-4,4-dimethylpent-1-en-3-one (Table 6, entry 1):

![Chemical Structure]

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 92\% isolated yield. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.75 (d, 1H, \(J = 16\) Hz), 7.54 (t, 1H, \(J = 8\) Hz), 7.34–7.29 (m, 1H), 7.22 (d, 1H, \(J = 16.0\) Hz), 7.13 (t, 1H, 8.0 Hz),
Hz), 7.07 (t, 1H, $J = 8.0$ Hz), 1.21 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 204.3, 161.8 (d, $J = 250$ Hz), 135.8 (d, $J = 2.0$ Hz), 131.6 (d, $J = 9$ Hz), 129.9 (d, $J = 3.0$ Hz), 124.6 (d, $J = 3.0$ Hz), 123.5 (d, $J = 7$ Hz), 123.2 (d, $J = 12.0$ Hz), 116.4 (d, $J = 22.0$ Hz), 43.4, 26.4 ppm; HRMS $m/z$ Calcd for C$_{13}$H$_{15}$FO: 206.11069. Found: 206.11108.

(E)-1-(3-Iodophenyl)-4,4-dimethylpent-1-en-3-one (Table 7, entry 1):  

![Chemical Structure](image)

The general procedure was followed for the synthesis and purifcation; product was afforded as a yellow oil in 95% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.88 (s, 1H), 7.65 (d, 1H, $J = 8.0$ Hz), 7.51 (d, 1H, $J = 16.0$ Hz), 7.47 (d, 1H, $J = 8.0$ Hz), 7.10–7.05 (m, 2H), 1.20 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 204.0, 141.3, 139.0, 137.3, 136.8, 130.7, 128.0, 122.0, 95.0, 43.5, 26.5 ppm; HRMS $m/z$ Calcd for C$_{13}$H$_{15}$OI: 314.0176. Found: 314.0168.

(E)-3-(4,4-Dimethyl-3-oxopent-1-enyl)benzonitrile (Table 7, entry 2):  

![Chemical Structure](image)

The general procedure was followed for the synthesis and purifcation; product was afforded as a colorless oil in 94% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.82 (s, 1H), 7.74 (d, 1H, $J = 8.0$ Hz), 7.62–7.60 (m, 1H), 7.58 (d, 1H, $J = 16.0$ Hz), 7.48 (t, 1H, $J = 8.0$ Hz), 7.15 (d, 1H, $J = 16.0$ Hz), 1.21 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 203.8, 140.2, 136.3, 133.2, 132.6, 131.4, 129.9, 123.2, 118.4, 113.4, 43.6, 26.3 ppm; HRMS $m/z$ Calcd for C$_{14}$H$_{15}$NO: 213.11536. Found: 213.11582.
(E)-1-(Benzofuran-2-yl)-4,4-dimethylpent-1-en-3-one (Table 7, entry 3):

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 77% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.53 (d, 1H, $J$ = 16.0 Hz), 7.53 (bs, 1H), 7.47 (d, 1H, $J$ = 8.0 Hz), 7.31 (dt, 1H, $J$ = 8.0 Hz, $J$ = 1.2 Hz), 7.24 (d, 1H, $J$ = 16.0 Hz), 7.20 (d, 1H, $J$ = 8.0 Hz), 6.90 (s, 1H), 1.24 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 204.0, 155.6, 153.2, 129.5, 128.7, 126.6, 123.5, 121.9, 121.3, 112.0, 111.5, 43.5, 26.5 ppm; HRMS m/z Calcd for C$_{15}$H$_{16}$O$_2$: 228.11503. Found: 228.11549.

(E)-1-(Benzothiophen-2-yl)-4,4-dimethylpent-1-en-3-one (Table 7, entry 4):

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 83% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.87 (d, 1H, $J$ = 16.0 Hz), 7.79–7.74 (m, 2H), 7.47 (s, 1H), 7.39–7.33 (m, 2H), 6.95 (d, 1H, $J$ = 16.0 Hz), 1.24 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 203.9, 140.4, 140.1, 139.8, 136.1, 129.5, 126.4, 125.0, 124.6, 122.6, 122.2, 43.4, 26.5 ppm; HRMS m/z Calcd for C$_{15}$H$_{16}$OS: 244.09219. Found: 244.09266.

(E)-4,4-Dimethyl-1-(4-methylthiazol-2-yl)pent-1-en-3-one (Table 7, entry 5):
The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 94% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.60 (d, 1H, $J = 16.0$ Hz), 7.35 (d, 1H, $J = 16.0$ Hz), 6.96 (s, 1H), 2.45 (s, 3H), 1.18 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 203.8, 163.2, 155.3, 133.8, 124.2, 116.7, 43.6, 26.3, 17.4 ppm; HRMS m/z Calcd for C$_{11}$H$_{15}$NOS: 209.08743. Found: 209.08770.

$(E)$-1-(4-Methoxynaphthalen-1-yl)-4,4-dimethylpent-1-en-3-one (Table 7, entry 6):

![Methoxynaphthalen-1-yl](image1)

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 78% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.49 (d, 1H, $J = 15.6$ Hz), 8.31 (d, 1H, $J = 8.0$ Hz), 8.20 (d, 1H, $J = 8.0$ Hz), 7.79 (d, 1H, $J = 8.0$ Hz), 7.61–7.50 (m, 2H), 7.14 (d, 1H, $J = 16.0$ Hz), 6.83 (d, 1H, $J = 8.0$ Hz), 4.04 (s, 3H), 1.27 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 204.4, 157.6, 140.0, 133.0, 125.8, 124.9, 123.5, 122.8, 121.3, 103.8, 55.9, 43.4, 26.7 ppm; HRMS m/z Calcd for C$_{18}$H$_{20}$O$_2$: 268.14632. Found: 268.14673.

$(E)$-4,4-Dimethyl-1-o-tolylpent-1-en-3-one (Table 7, entry 7):

![4,4-Dimethyl-1-o-tolyl](image2)

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 90% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.99 (d, 1H, $J = 16.0$ Hz), 7.60 (d, 1H, $J = 8.0$ Hz), 7.27–7.19 (m, 3H), 7.05 (d, 1H, $J = 16.0$ Hz), 2.44 (s, 3H),
1.24 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 204.5, 140.7, 138.4, 134.2, 131.1, 130.1, 126.5, 126.4, 122.1, 43.5, 26.6, 20.1 ppm; HRMS $m/z$ Calcd for C$_{14}$H$_{18}$O: 202.13576. Found: 202.13610.

**(E)-1-(2,6-Dimethylphenyl)-4,4-dimethylpent-1-en-3-one (Table 7, entry 8):**

![Image of (E)-1-(2,6-Dimethylphenyl)-4,4-dimethylpent-1-en-3-one](image)

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 72% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.80 (d, 1H, $J = 16.0$ Hz), 7.12–7.06 (m, 3H), 6.74 (dd, 1H, $J = 16.0$ Hz, $J = 1.2$ Hz), 2.34 (s, 6H), 1.21 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 204.4, 141.4, 136.9, 135.1, 128.4, 128.3, 127.1, 43.4, 26.3, 21.3 ppm; HRMS $m/z$ Calcd for C$_{15}$H$_{20}$O: 216.15141. Found: 216.15173.

**(4E,6E)-2,2-Dimethyl-7-phenylhepta-4,6-dien-3-one (Table 7, entry 9):**

![Image of (4E,6E)-2,2-Dimethyl-7-phenylhepta-4,6-dien-3-one](image)

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 95% isolated yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.50–7.46 (m, 3H), 7.37–7.30 (m, 3H), 6.94–6.92 (m, 2H), 6.69 (d, 1H, $J = 12.0$ Hz), 1.20 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 204.6, 143.1, 141.3, 136.4, 129.2, 129.0, 127.3, 127.1, 124.5, 43.3, 26.6 ppm; HRMS $m/z$ Calcd for C$_{15}$H$_{18}$O: 214.13576. Found: 214.13625.
Methyl 4,4,4-trifluoro-2,2-dimethyl-3-phenyl-3-(trimethylsilyloxy)butanoate (Scheme 3, product 8):

The general procedure was followed for the synthesis and purification; product was afforded as a yellow oil in 91% isolated yield. \( ^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.48–7.45 (m, 2H), 7.35–7.33 (m, 3H), 3.60 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H), 0.14 (s, 9H) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 174.8, 136.5, 128.5, 127.8, 127.3, 126.1 (q, \( J = 288 \) Hz) 84.6 (q, \( J = 26.9 \) Hz), 51.9, 50.9, 26.8, 22.7, 1.8 ppm; HRMS \( m/z \) Calcd for C\(_{16}\)H\(_{17}\)F\(_3\)O: 348.13686. Found: 348.13754.

Methyl 4,4,4-trifluoro-3-hydroxy-2,2-dimethyl-3-phenylbutanoate (Scheme 3, product 9):

The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 78% isolated yield.

\[ \text{4,4,4-Trifluoro-3-hydroxy-1,3-diphenyl-1-butanone (Scheme 3, product 10)} \]
The general procedure was followed for the synthesis and purification; product was afforded as a colorless oil in 93% isolated yield.

5-(2,2,2-Trifluoro-1-hydroxy-1-phenylethyl)furan-2(5H)-one (Scheme 3, product 11):

The general procedure was followed for the synthesis and purification; product was afforded as a white solid in 83% isolated yield. Syn isomer (white solid) \( ^1 \)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.61–7.60 (m, 2H), 7.49–7.45 (m, 3H), 6.84–6.82 (m, 1H), 6.18–6.16 (m, 1H), 5.71 (t, 1H, \( J = 4.0 \) Hz), 4.1 (s, 1H) ppm; \( ^{13} \)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 173.0, 152.5, 133.4, 129.8, 129.2, 125.6, 124.5 (q, \( J = 280 \) Hz), 124.0, 83.6, 76.6 (q, \( J = 29 \) Hz) ppm; HRMS \( m/z \) Calcd for C\(_{12}\)H\(_9\)F\(_3\)O\(_3\): 258.05038. Found: 258.05075. Anti isomer (yellow oil) \( ^1 \)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.56–7.54 (m, 3H), 7.42–7.39 (m, 3H), 6.04–6.02 (m, 1H), 5.58 (s, 1H), 3.66 (s, 1H) ppm; \( ^{13} \)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 172.2, 152.5, 133.3, 129.8, 128.9, 126.4, 124.5 (q, \( J = 280 \) Hz), 124.0, 83.2, 77.9 (q, \( J = 20 \) Hz) ppm; HRMS \( m/z \) Calcd for C\(_{12}\)H\(_9\)F\(_3\)O\(_3\): 258.05038. Found: 258.05076.

2,8,9-Tribenzyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane 1-oxide (12):

\( ^{31} \)P NMR (CDCl\(_3\), 162 MHz): 24.24. \( ^1 \)H NMR (CDCl\(_3\)): 7.61–7.59 (m, 6H), 7.37–7.26 (m, 9H), 4.25 (d, 6H, \( J = 8.0 \)Hz), 2.88–2.79 (m, 12H) ppm. \( ^{13} \)C NMR (CDCl\(_3\)): 139.9 (d, \( J = 2.3 \) Hz).
Hz), 128.9, 128.5, 127.4, 50.9 (d, J = 5.0 Hz), 50.0, 47.4 (d, J = 3.3 Hz) ppm. HRMS m/z calcd for C_{27}H_{33}N_{4}OP: 460.23919. Found: 460.24045.

References


Table 1, entry 1
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>284.14124</td>
<td>284.14179</td>
<td>280.93242</td>
<td>1.9 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 2, entry 3
Table 2, entry 3
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>238.12050</td>
<td>238.1215</td>
<td>230.97562</td>
<td>2.8 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

$$\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}$$

Where nominal mass takes into account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 4
Table 2, entry 4
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>236.14124</td>
<td>236.14177</td>
<td>230.98562</td>
<td>2.3 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 2, entry 6
Table 2, entry 6
CVR-2769
CDCl3, 100.6 MHz
Liquic OIl
20 AUG 2008

Table 2, entry 8
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>268.1307</td>
<td>268.1379</td>
<td>230.98562</td>
<td>2.7 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak.

![Chemical Structure]

Table 2, entry 8
CVR-2874
CDCL3, 100MHz
Oily liquid
06 DEC 2008

Table 2, entry 9
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>288.13615</td>
<td>288.13356</td>
<td>280.90242</td>
<td>1.4 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 9
Table 2, entry 10, 6a
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>236.10485</td>
<td>236.10533</td>
<td>230.98562</td>
<td>2 pm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass corresponds to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 2, entry 10, 6a
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>338.17293</td>
<td>338.17906</td>
<td>330.97923</td>
<td>1.8 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 2, entry 10, 6b

\[\begin{align*}
\text{HO} & \quad \text{O} \\
& \quad \text{OMe}
\end{align*}\]
Table 2, entry 10, 6b
CVR-2950
CDCl3, 400 MHz
White solid
12 April 2009

Table 2, entry 11
CVR-2955
CDCl3, 400MHz
White solid
Col: 20% Hex/EtOAc
24 APRIL 2009

Table 2, entry 11
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>242.07697</td>
<td>242.07153</td>
<td>230.98562</td>
<td>2.3 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure]

Table 3, entry 1
Table 3, entry 1

Date: Tue Jun 16 11:02:19 2009  TCIS: 8.3.0 SP2 for OBP1 (V4.0) build 98-238 from 26-Aug-98
Table 3, entry 2
Table 3 entry 2

CVR-2432
Colorless liquid
CDCl3, 100.6 MHz
30 JAN 2008
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>226.10052</td>
<td>226.10078</td>
<td>218.98562</td>
<td>1.2 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 3, entry 2
Table 3, entry 3
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>334.00457</td>
<td>334.00734</td>
<td>330.97923</td>
<td>2.2 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}, {^1}\text{H}, {^{16}}\text{O}, {^{14}}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](attachment:structure.png)

Table 3, entry 3
Table 3, entry 4

\[
\text{[Chemical structure image]}
\]
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>276.0932</td>
<td>276.09812</td>
<td>276.09862</td>
<td>2.9 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 3, entry 5
Table 3, entry 5
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>233.10519</td>
<td>233.10548</td>
<td>230.18562</td>
<td>1.3 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 3, entry 7
Table 3, entry 7
CVR-2765
CDCl3, 400MHz
Colorless Oil
20 AUG 2008

Table 3, entry 9
CVR-2765
CDCL3, 100.6MHz
Liquid OIi
20 AUG 2008

Table 3, entry 9
Table 3, entry 10
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>264.08202</td>
<td>264.08256</td>
<td>230.98562</td>
<td>2 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure image](Image)

Table 4, entry 1
Table 4, entry 1
CVR-2661
Liquid Oil
CDCl3, 400MHz
05 May 2008
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>248.10486</td>
<td>248.10539</td>
<td>230.98562</td>
<td>2.1 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 4, entry 2
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>216.17254</td>
<td>216.17291</td>
<td>180.98882</td>
<td>1.7 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only \(^{12}\text{C}, \text{H}, \text{O}, \text{N}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 4, entry 3
Table 4, entry 3
Table 4, entry 5
CVR-2674
Pale yellow oil
CDCl3, 400 MHz
19 May 2008
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>229.07726</td>
<td>229.07763</td>
<td>218.98512</td>
<td>1.14 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 4, entry 6
Table 4, entry 6
CVR-2682
White solid
CDCl3, 400MHz
31 MAY 2008

Table 4, entry 7
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>212.11609</td>
<td>212.11649</td>
<td>182.98882</td>
<td>1.9 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...
Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 4, entry 7
Table 4, entry 7
Table 5, entry 2
XW-360
Colorless oil
CDCl3, 75 MHz
May 02 2007

Table 5, entry 2
KW-378
Colorless oil
CDCl3, 300MHz
May-11-2007

Table 5, entry 5
Table 5, entry 5
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>234.16197</td>
<td>234.16226</td>
<td>230.98562</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only \(^{12}\text{C}\), \(^{1}\text{H}\), \(^{16}\text{O}\), \(^{14}\text{N}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 5, entry 5
Table 5, entry 5
Table 5, entry 7
Manul Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>206.11067</td>
<td>206.11108</td>
<td>180.988882</td>
<td>1.9 ppm</td>
</tr>
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* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 6, entry 1
Table 6, entry 1

F
\[\text{O} \]

Date: Wed Jul 2 13:13:59 2008  ICIS: 8.3.0 SP2 for OSF1 (V4.0) build 98-238 from 26-Aug-98
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM  /  DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0  Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions
39 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>m/z</th>
<th>PPM</th>
<th>DBE</th>
<th>Score</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>314.0176</td>
<td>314.0168</td>
<td>0.8</td>
<td>2.7</td>
<td>6.0</td>
<td>1</td>
<td>C13 H15 O I</td>
</tr>
</tbody>
</table>

Table 7, entry 1

![Chemical Structure](image_url)
Table 7, entry 1

KW 678
UV-08-28-18 212 (3.534) Cm (164:212:14:38x2:000)

TOF MS El+
1.73e6
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>213.11536</td>
<td>213.11582</td>
<td>180.48662</td>
<td>2.1 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Molecular structure](image)

Table 7, entry 2

\[\text{\textcopyright 20xx}\]
Table 7, entry 2
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>228.11583</td>
<td>228.11549</td>
<td>218.99912</td>
<td>2 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Table 7, entry 3](image)

\[\text{Table 7, entry 3}\]
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>244.09219</td>
<td>244.09261</td>
<td>230.98562</td>
<td>1.9 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^{1}$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 7, entry 4

![Chemical Structure](image)
Table 7, entry 4
Table 7, entry 5
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>209.08743</td>
<td>209.08770</td>
<td>180.98882</td>
<td>1.3 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 7, entry 5

\[
\text{H}_3\text{C} - \text{N} - \text{S} - \text{CH} = \text{CH} - \text{CH} = \text{CH} - \text{CO}
\]
Table 7, entry 5
<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>268.14632</td>
<td>268.14673</td>
<td>230.98362</td>
<td>1.5 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \left(\frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}\right) 
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 7, entry 6
Table 7, entry 6
KW717, CDCl3
400 MHz
WHITE SOLID
OCT 15 2008

Table 7, entry 7
Manual Peak Matching Report  
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>202.13576</td>
<td>202.13610</td>
<td>180.98882</td>
<td>1.7 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical structure](image)

Table 7, entry 7
Table 7, entry 8
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>216.15141</td>
<td>216.15173</td>
<td>180.98882</td>
<td>1.5 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviations} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}\text{C}$, $^{1}\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](image)

Table 7, entry 8
Table 7, entry 8
Table 7, entry 9
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>214.13576</td>
<td>214.13685</td>
<td>180.98882</td>
<td>2.3 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only 12C, 1H, 16O, 14N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

Table 7, entry 9
Table 7, entry 9
Scheme 3, product 8

MeO\text{OTMS}

OTMS

\text{CF}_3

1H-NMR (400 MHz, CDCl₃)
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>348.13686</td>
<td>348.13754</td>
<td>330.94923</td>
<td>1.9 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only $^{12}$C, $^1$H, $^{16}$O, $^{14}$N etc...

Theoretical mass correspond to the mass of the most abundant isotopes peak.

![Scheme 3, product 8](attachment:image.png)
Scheme 3, product 8
Scheme 3, product 10
Scheme 3, product 11, syn isomer
Scheme 3, product 11, syn isomer
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>258.05038</td>
<td>258.05075</td>
<td>242.98882</td>
<td>1.5 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only \(^{12}\text{C}, ^{1}\text{H}, ^{16}\text{O}, ^{14}\text{N}\) etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

\[
\begin{align*}
\text{Scheme 3, product 11, syn isomer}
\end{align*}
\]
Scheme 3, product 11, syn isomer
Scheme 3, product 11, anti isomer
Manual Peak Matching Report  
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>258.05038</td>
<td>258.06074</td>
<td>230.98562</td>
<td>1.5 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes into account only $^{12}\text{C}$, $^1\text{H}$, $^{16}\text{O}$, $^{14}\text{N}$ etc...

Theoretical mass correspond to the mass of the most abundant isotope peak

![Chemical Structure](attachment:image.png)

Scheme 3, product 11, anti isomer
Scheme 3, product 11, anti isomer
Manual Peak Matching Report
For Accurate Mass Determination

<table>
<thead>
<tr>
<th>Theoretical mass</th>
<th>Experimental mass</th>
<th>PFK matching mass</th>
<th>Deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>660.23919</td>
<td>660.24048</td>
<td>630.99284</td>
<td>2.7 ppm</td>
</tr>
</tbody>
</table>

* The deviation is obtained from the following equation:

\[
\text{deviation} = \frac{\text{experimental mass} - \text{theoretical mass}}{\text{nominal mass}}
\]

Where nominal mass takes in account only 12C, 1H, 16O, 14N etc...

Theoretical mass correspond to the mass of the most abundant isotope peak