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Abstract

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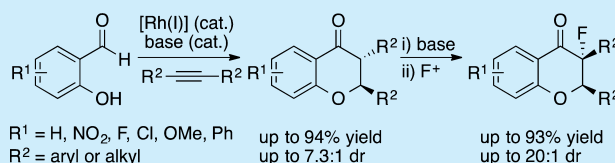
Tandem Alkyne Hydroacylation and Oxo-Michael Addition: Diastereoselective Synthesis of 2,3-Disubstituted Chroman-4-ones and Fluorinated Derivatives

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S Supporting Information

ABSTRACT: Tandem reactions involving Rh-catalyzed intermolecular hydroacylations of alkynes with salicylaldehydes followed by intramolecular oxo-Michael additions are described for the diastereoselective synthesis of 2,3-disubstituted chroman-4-ones. The tandem hydroacylation/oxo-Michael additions occur to form 2,3-disubstituted chroman-4-ones in high yields from a range of 1,2-disubstituted acetylenes and substituted salicylaldehydes. The resulting 2,3-disubstituted chroman-4-ones are readily fluorinated to form *trans*-3-fluoro-2,3-disubstituted chroman-4-ones in high yields with excellent diastereoselectivity.



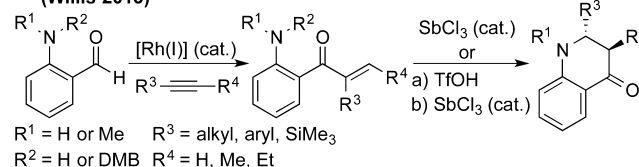
Tandem processes involving atom-economic, transition-metal-catalyzed alkene or alkyne hydroacylation have been developed as efficient routes to a variety of ketones.¹ However, examples of these tandem processes to form valuable heterocyclic ketones are rare.¹¹ The paucity of tandem reactions involving alkene and alkyne hydroacylation to form heterocyclic ketones is surprising because a variety of heteroatom-functionalized aldehydes, particularly 2-hydroxybenzaldehydes (salicylaldehydes),² 2-aminobenzaldehydes,³ 2-mercaptobenzaldehydes, and derivatives,⁴ are established as privileged substrates in transition-metal-catalyzed alkene and alkyne hydroacylation reactions.

The presence of heteroatom substitution in the aldehyde substrates is often viewed as a limitation of alkene and alkyne hydroacylation necessary to suppress catalyst deactivation pathways and minimize the formation of undesired products often observed in reactions of simple aldehydes.⁵ However, these heteroatom functional groups offer a handle to rapidly generate complex heterocycles when olefin hydroacylation reactions are coupled with additional reaction manifolds (Scheme 1).⁶ To this end, Willis developed a stepwise protocol for hydroacylation of alkynes with 2-aminobenzaldehydes followed by Lewis acid catalyzed, intramolecular aza-Michael addition to rapidly generate dihydroquinolones (Scheme 1A).³

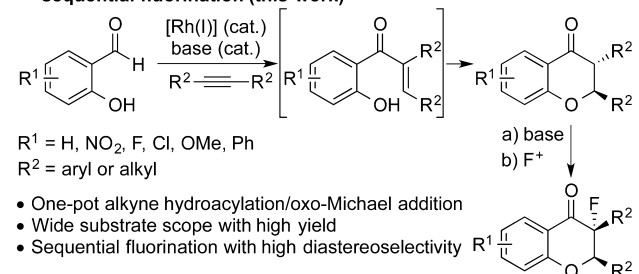
The development of related intermolecular hydroacylation of alkynes with salicylaldehydes followed by intramolecular oxo-Michael addition offers the potential to streamline traditional syntheses of chroman-4-ones.⁷ However, tandem alkyne hydroacylation/oxo-Michael addition processes to form chroman-4-ones are limited to two examples reported by Miura.^{2b,c} Hydroacylations of activated alkynes, ethyl hept-2-ynoate and 1-phenylhept-2-yn-1-one, and the subsequent oxo-Michael additions occur to form approximately 1:1 mixtures of chroman-4-one and benzofuran-3-(2*H*)-one products. To our knowledge, a general catalyst system to generate chroman-4-

Scheme 1. Synthesis of Dihydroquinolones and Chroman-4-ones by Hydroacylation of Alkynes

A) Sequential alkyne hydroacylation and aza-Michael addition (Willis 2013)



B) Tandem alkyne hydroacylation/oxo-Michael addition and sequential fluorination (this work)



ones with high regio- and diastereoselectivity by a tandem alkyne hydroacylation/oxo-Michael addition strategy has not been reported.

We now report a one-pot process to synthesize 2,3-disubstituted chroman-4-ones by hydroacylation of 1,2-disubstituted alkynes with salicylaldehydes followed by an intramolecular oxo-Michael addition (Scheme 1B). The 2,3-disubstituted chroman-4-one products of these tandem reactions are readily converted to *trans*-3-fluoro-2,3-disubsti-

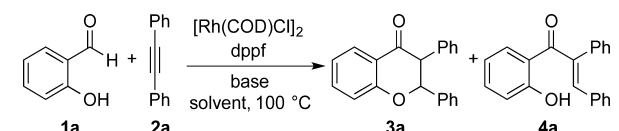
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tuted chroman-4-ones by a highly diastereoselective enolate fluorination.

2,3-Diarylchroman-4-ones are core structures present in a wide variety of biflavonoids⁸ and are valuable precursors to 2,3-diaryl-2H-1-benzopyrans that exhibit potent antiestrogenic activity.⁹ To develop a rapid entry into the 2,3-diarylchroman-4-one core, we studied the reaction of salicylaldehyde **1a** with 1,2-diphenylacetylene **2a** in the presence of a variety of bases and 5 mol % of catalyst prepared in situ from [Rh(COD)Cl]₂ and dppf (Table 1). The hydroacylation of

Table 1. Identification of Reaction Conditions for Tandem Alkyne Hydroacylation/Oxo-Michael Addition^a



entry	base (mol %)	solvent	yield 3a (%) ^{b,c}	dr (trans:cis) ^b	yield 4a (%) ^b
1	Na ₂ CO ₃ (200)	toluene	14	1.8:1	76
2	K ₃ PO ₄ (200)	toluene	78	3.6:1	15
3	CsF (20)	toluene	84	3.9:1	7
4	CsF (20)	DCE	85	3.2:1	10
5	CsF (20)	1,4-dioxane	65	2.6:1	22
6	CsF (20)	DMF	91	3.8:1	5
7	CsF (20)	MeCN	93	5.7:1	1
8	CsF (20)	MeNO ₂	81	1.8:1	0
9	CsF (20)	MeCN	70	3.0:1	8
10	CsF (10)	MeCN	95	5.0:1	4
11	CsF (8)	MeCN	94	5.0:1	4
12 ^d	CsF (8)	MeCN	94 (92) ^e	5.4:1	4

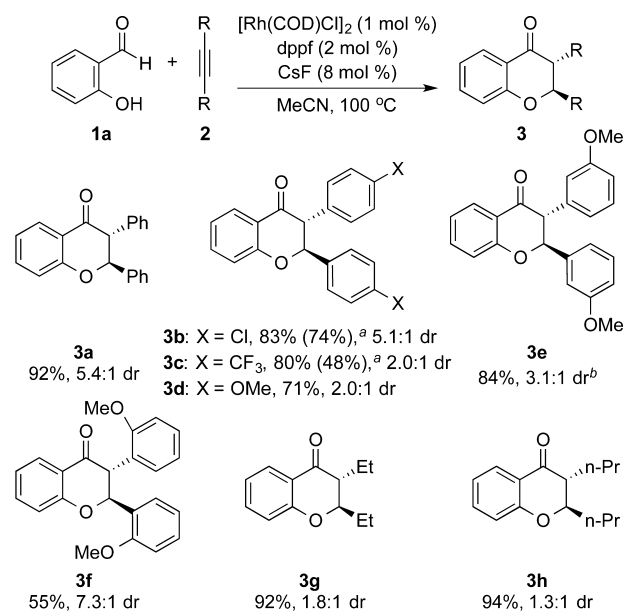
^aReaction conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), [Rh(COD)Cl]₂ (2.5 mol %), dppf (5 mol %), base, solvent (0.20 M), 100 °C. dppf = 1,1'-bis(diphenylphosphine)ferrocene. ^bDetermined by ¹H NMR spectroscopy of the crude reaction mixture with dibromomethane as the internal standard. ^cCombined yield of *trans*-**3a** and *cis*-**3a**. ^dReaction conducted with 2 mol % of Rh catalyst (0.5 M in MeCN). ^eCombined isolated yield of *trans*-**3a** and *cis*-**3a**.

2a in the presence of a variety of inorganic bases occurs in high yields (entries 1–3). These reactions form 2,3-diphenylchroman-4-one **3a** and (*E*)-1-(2-hydroxyphenyl)-2,3-diphenylprop-2-en-1-one **4a** in combined yields of ≥90% with 2 equiv of Na₂CO₃, K₃PO₄, or CsF as the base. However, the efficiency of the oxo-Michael addition to form **3a** is significantly impacted by the identity of the base. Product **3a** was generated in higher yield and with higher diastereoselectivity when CsF (20 mol %) was used as the base (entry 3).

The improved yield and diastereoselectivity observed with CsF as the base guided attempts to improve the yield and selectivity of the model reaction. To improve the diastereoselectivity of the intramolecular oxo-Michael addition of **4a** to **3a**, we evaluated the tandem reaction in a range of solvents (entries 4–9) and found the yield (93%) and diastereomeric ratio (5.7:1) of **3a** to be the highest in acetonitrile (entry 7). Conducting the model reaction in acetonitrile enabled us to lower the loading of CsF to 8 mol % with only a modest decrease in selectivity (entry 11). The loading of the Rh catalyst was reduced from 5 to 2 mol % without significantly impacting the yield or diastereoselectivity of the tandem reaction sequence (compare entry 12 with entry 11).

The scope of the tandem reaction sequence with regard to 1,2-disubstituted alkynes was then examined (Scheme 2).

Scheme 2. Scope of Tandem Alkyne Hydroacylation/Oxo-Michael Addition with 1,2-Disubstituted Acetylenes

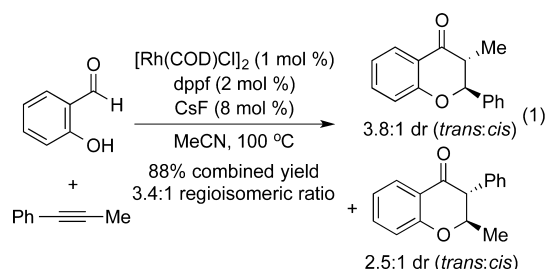


^aIsolated yield reported as mixtures of *trans*-**3** and *cis*-**3**. Yields in parentheses represent isolated yield of >20:1 *trans*-**3** after column chromatography. ^bReaction conducted with 1.0 equiv of 1,2-bis(3-methoxyphenyl)ethyne.

Reactions of **1a** with a variety of 1,2-diarylacetylenes occur to form the corresponding 2,3-diarylchroman-4-ones **3a–f** in good to excellent yields (55–92%). The diastereomeric ratio of 2,3-diarylchroman-4-ones **3a–f** was influenced by substitution on the alkyne. 2,3-Diarylchroman-4-ones derived from 1,2-diarylacetylenes with electron-neutral (R = Ph, 4-ClC₆H₄) or bulky (R = 2-MeOC₆H₄) aryl groups were isolated with greater than 5:1 diastereomeric ratios favoring *trans*-**3a**, **3b**, and **3f**. Tandem reactions of **1a** with 1,2-diarylacetylenes containing strongly electron-withdrawing (R = 4-F₃CC₆H₄), strongly electron-donating (R = 4-MeOC₆H₄), and *meta*-substituted (R = 3-MeOC₆H₄) aryl groups formed the corresponding 2,3-diarylchroman-4-ones **3c–e** with modest diastereoselectivities (2.0–3.1:1 *trans*-**3**:*cis*-**3**).

Although the tandem reactions form mixtures of *trans*:*cis* diastereoisomers, pure *trans*-**3** (>20:1) can be isolated by recrystallization or column chromatography. For example, *trans*-**3a** was isolated in 74% yield (2.22 g) after recrystallization from the reaction of **1a** (10.0 mmol, 1.22 g) with **2a**. *trans*-**3b** and *trans*-**3c** were isolated in 74% yield and 48% yield after column chromatography.

A tandem alkyne hydroacylation and oxo-Michael addition involving an unsymmetrical alkyne also occurs to form 2,3-disubstituted chroman-4-ones with modest levels of regio- and diastereoselectivity (eq 1). The reaction of 1-phenyl-1-propyne with salicylaldehyde occurs to form a 3.4:1 mixture of regioisomeric products 3-methyl-2-phenylchroman-4-one and 2-methyl-3-phenylchroman-4-one in 88% combined yield.¹⁰ 3-Methyl-2-phenylchroman-4-one is formed with a 3.8:1 diastereomeric ratio of *trans* and *cis* isomers, and 2-methyl-3-

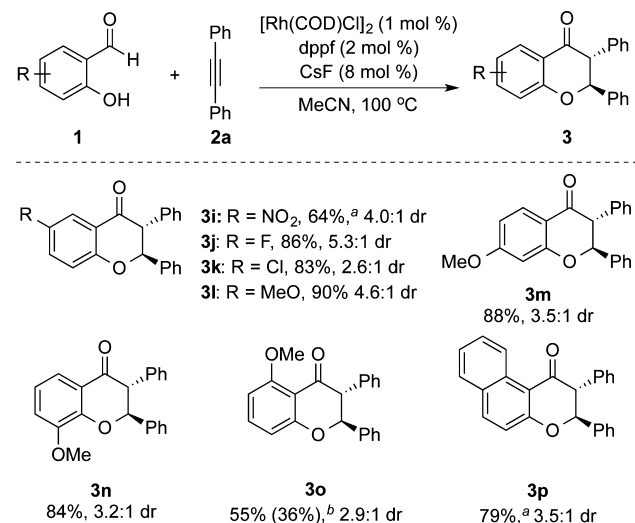


phenylchroman-4-one is formed with a 2.5:1 diastereomeric ratio of *trans* and *cis* isomers.

Reactions of salicylaldehyde with 1,2-dialkylacetylenes occur to form the corresponding 2,3-dialkylchroman-4-ones, which are found in a variety of naturally occurring chroman-4-ones¹¹ in higher yields than analogous reactions of 1,2-diarylacetylenes. For example, reactions of 3-hexyne and 4-octyne with salicylaldehyde occur to form 2,3-dialkylchroman-4-ones **3g** and **3h** in 92% and 94% yield. However, the diastereoselectivity of these reactions is modest, and the resulting 2,3-dialkylchromanones **3g** and **3h** were isolated as 1.8:1 and 1.3:1 mixtures of the *trans:cis* diastereomers.

The scope of tandem reactions of a variety of substituted salicylaldehydes with 1,2-diphenylacetylene **2a** is summarized in Scheme 3. Reactions of salicylaldehydes containing both

Scheme 3. Scope of Tandem Alkyne Hydroacylation/Oxo-Michael Addition with Substituted Salicylaldehydes



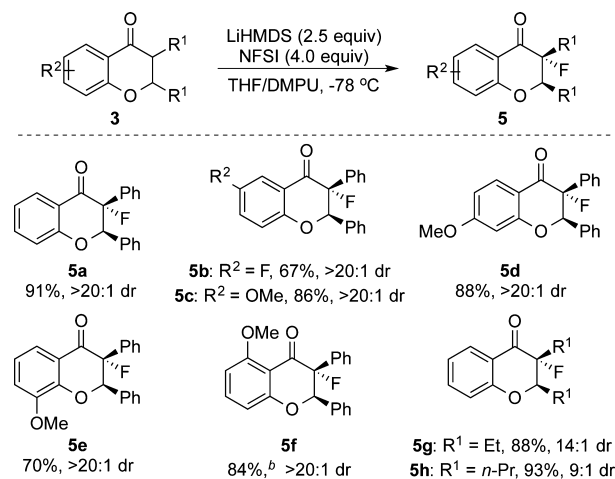
^aYield of *trans*-**3** with >20:1 diastereomeric ratio after recrystallization. ^bThe uncyclized hydroacylation product **4o** was isolated in 17% yield. *trans*-**3o** was isolated in 36% yield.

electron-withdrawing and electron-donating substituents with **2a** occur to form 2,3-diphenylchroman-4-ones in good yields with moderate diastereoselectivities. Reactions of 4-NO₂-, 4-F-, and 4-Cl-salicylaldehyde with **2a** form the corresponding 2,3-diphenylchroman-4-ones **3i–k** in 64–86% yield with diastereoselectivities ranging from 2.6:1 to 5.3:1. Reactions of 3-MeO-, 4-MeO-, 5-MeO-, and 6-MeO-salicylaldehydes with 1,2-diphenylacetylene generate 2,3-diphenylchroman-4-ones **3l–o** in 55–90% yield with 2.9:1 to 4.6:1 dr. The reaction of 6-methoxysalicylaldehyde with **2a** formed only 55% yield of 2,3-diarylchroman-4-one **3n**, while the initial alkyne hydroacylation product was isolated in 17% yield. The reaction of 2-hydroxy-1-

naphthaldehyde with **2a** formed **3p** with 3.5:1 dr. *Trans* diastereomers (>20:1 dr) of **3** are readily obtained by column chromatography or recrystallization. *trans*-**3i** and *trans*-**3p** were isolated in 64% yield and 79% yield after recrystallization. *trans*-**3o** was isolated in 36% after column chromatography.

With a tandem reaction strategy to form *trans*-2,3-disubstituted chroman-4-ones **3** in hand, we sought to develop a fluorination protocol to access pseudodiastereomeric *trans*-3-fluoro-2,3-disubstituted chroman-4-ones in which the 2,3-diaryl or 2,3-dialkyl substituents reside on the same face of the chromanone core. A direct fluorination protocol to synthesize *trans*-3-fluoro-2,3-disubstituted chroman-4-ones **5** is summarized in Scheme 4.¹² Deprotonation of diastereomeric mixtures

Scheme 4. Synthesis of 3-Fluoro-2,3-disubstituted Chroman-4-ones^b



^aNFSI = *N*-fluorobenzenesulfonimide. Isolated yields are reported as mixtures of diastereomers. Diastereomeric ratios determined by ¹⁹F NMR spectroscopy. ^bReaction conducted with 3.0 equiv of LiHMDS and 4.8 equiv of NFSI.

of chroman-4-ones **3** with LiHMDS and fluorination of the resulting enolate with NFSI from the opposite face of the C2 substituent selectively generates *trans*-**5** in high yields with excellent selectivities. Fluorinations of a variety of 2,3-diphenylchroman-4-ones **3** occur to form *trans*-**5a–f** in 67–91% yield with nearly perfect diastereoselectivity (>20:1). The relative stereochemistry of **5a** was confirmed by X-ray crystallographic analysis (Figure 1). Fluorinations of 2,3-dialkylchroman-4-ones form the corresponding *trans*-3-fluoro-2,3-dialkylchroman-4-ones **5g** (R¹ = Et) and **5h** (R¹ = *n*-Pr) in 88% and 93% yield as 14:1 and 9:1 diastereomeric mixtures.

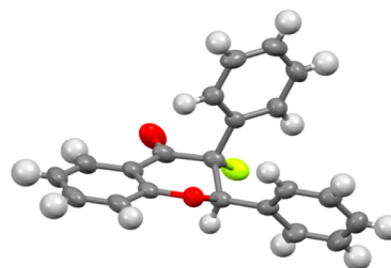


Figure 1. Relative stereochemistry and structure of **5a**.

In conclusion, we have developed a tandem alkyne hydroacylation/oxo-Michael addition process to synthesize *trans*-2,3-disubstituted chroman-4-ones from readily accessible starting materials in the presence of simple catalyst precursors. The 2,3-disubstituted chroman-4-one products are transformed to *trans*-3-fluoro-2,3-disubstituted chroman-4-ones in high yields and with excellent diastereoselectivities by a straightforward fluorination procedure. Studies to expand the scope of the tandem reaction to encompass unsymmetrical alkynes and to apply these reactions in total syntheses of natural products are ongoing in our laboratory.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, characterization data for all new compounds, and crystallographic data for compound **5a**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01447.

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Notes

The authors declare no competing financial interest.

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(10) Under identical reaction conditions, the analogous reaction of phenylacetylene with salicylaldehyde formed a mixture of 2-phenylchroman-4-one (34%), 3-phenylchroman-4-one (13%), and uncyclized 1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one in 21% yield.

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