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Asymmetric Synthesis of (1,3-Butadien-2-yl)methanols from Aldehydes via [1-(Silylmethyl)allenyl]methanols

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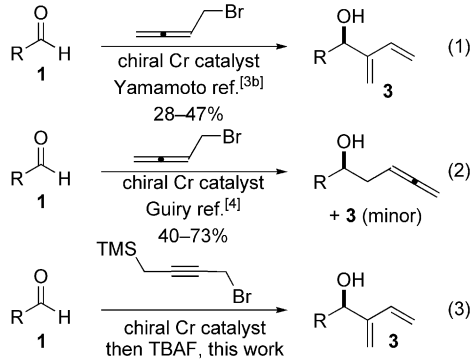
[1-(Silylmethyl)allenyl]methanols **2** were efficiently synthesized from aldehydes and (4-bromobut-2-ynyl)trimethylsilane in the presence of a catalytic amount of $CrCl_2$ and tridentate carbazole ligands. The desired compounds were obtained with good yields (43–88 %) and enantioselectivities (55–78 % *ee*). Alcohols **2** may be treated with TBAF or 2 M HCl in the case of aliphatic substrates, to provide (1,3-butadien-2-yl)methanols **3** in 43–81 % yields. This method allows the synthesis of dienes **3** with no regioselectivity problems, and it tolerates a large number of functionalities.

Introduction

In addition to appearing in the structures of numerous natural products, (1,3-butadien-2-yl)methanols **3** are versatile building blocks in organic synthesis.[1] Consequently, a number of methodologies have been developed for their synthesis.[2] Although recent methods have overcome regioselectivity problems presented by the early approaches, there are a limited number of enantioselective procedures, each of which is limited in some manner. Such limitations have included the use of non-readily available organometallic reagents, low functional-group tolerance, and low reactivity and product yields. A recent example is Yamamoto's asymmetric process [Equation (1)] based on the catalytic chromium system developed by Fürstner.[3] A complementary procedure reported by Guiry provides homoallenyl alcohols by a related proceess in which (1,3-butadienyl)-methanols **3** are observed only as minor byproducts (Scheme 1).[4]

Our work in this area focused on developing reaction conditions that tolerate a broad range of substrates, while avoiding issues of poor yields and poor regioselectivity. We realized that syntheses of **3** could be facilitated by the desilylation of {1-[(trimethylsilyl)methyl]allenyl}methanols **2**, which themselves may be obtained by allenylation of aldehydes. Because tridentate bis(oxazolinyl)carbazole ligands developed by Nakada and co-workers have shown to be excellent chiral ligands for chromium in catalyzed asymmetric allenylations of aldehydes with propargyl bromide (Figure 1),[5] we investigated their use for the synthesis of enantioenriched {1-[(trimethylsilyl)methyl]allenyl}methanols.



Scheme 1. Chromium-catalyzed syntheses of (butadienyl)methanols.

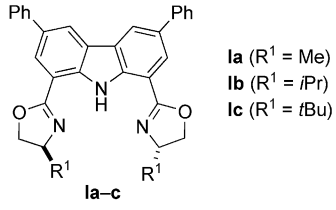


Figure 1. Tridentate carbazole ligands.

Results and Discussion

The reaction of benzaldehyde with (4-bromobut-2-ynyl)-trimethylsilane[6] in the presence of 10 mol-% $CrCl_3$ and carbazole ligand **Ib** was examined. After 20 h at room temp., the reaction was complete, and the desired product was obtained in 31 % *ee* (Table 1, Entry 1) after acidic workup. This result improved upon utilizing $CrCl_2$ as the catalyst (Table 1, Entry 2). MeCN was found to be a more

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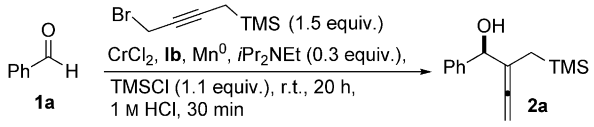
effective solvent than others (Entries 3 and 4). Additional optimization showed that decreasing the percentage of $CrCl_2$/ligand to 5 mol-% has no effect on the *ee* value, but the use of 2 equiv. of Mn^0 increased the enantiomeric excess to 78% *ee*. Use of other bis(oxazoline) ligands did not improve the enantioselectivity (Entries 7 and 8). Whereas ligand **Ia** afforded the desired product in 74% *ee*, the presence of a bulky *tert*-butyl group in ligand **Ic** drastically decreased the observed *ee* value, while increasing the necessary reaction time to 4 d.

Table 1. Optimization of catalytic reaction conditions.



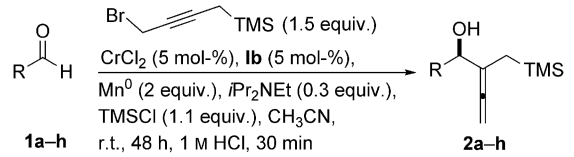
Entry	$CrCl_2$ [mol-%]	Mn [equiv.]	Solvent	Conv. [%][a]	*ee* [%][b]
1	10[c]	1.5	THF	> 99	31
2	10	1.5	THF	> 99	46
3	10	1.5	EtCN	95	48
4	10	1.5	CH_3CN	> 99	73
5	5	1.5	CH_3CN	> 99	72
6[d]	5	2	CH_3CN	> 99	78
7[e]	5	2	CH_3CN	91	74
8[f]	5	2	CH_3CN	86	20

[a] Determined by HPLC. [b] Enantiomeric excess determined by chiral HPLC. [c] $CrCl_3$ was used. [d] Reaction time: 36 h. [e] Ligand **Ia** was used in place of **Ib**. [f] Ligand **Ic** was used in place of **Ib** with a reaction time of 4 d.

The scope of the transformation was next examined. This allenylation is successful for both aromatic and aliphatic substrates. Aldehydes with *para* substituents afforded allenylmethanols **2b** and **2c** with high yields and enantioselectivities (Table 2, Entries 2 and 3). When *ortho* substituents are present, the products are obtained in good yields and enantioselectivities (Entries 4 and 5). Electron-deficient aldehyde **1f** successfully provided the corresponding adduct in 88% yield. The reaction proceeded more rapidly with aliphatic aldehydes, which provided the desired allenylmethanols with moderate yields and enantioselectivities, but in shorter reaction times (Entries 7 and 8).

Desilylation and isomerization of allenylmethanols **2** to provide the desired (butadienyl)methanols **3** was next examined. We were aware that {1-[(trimethylsilyl)methyl]-allenyl}methanols afford (1,3-butadien-2-yl)methanols in moderate yield in the presence of a relatively harsh HF/HCl mixture.[2j] In search of milder reaction conditions, we explored the use of basic fluoride as a viable reagent for this transformation. When tetrabutylammonium fluoride (TBAF) was combined with **2a** in THF, the desired diene **3a** was obtained in 54% yield (Table 3, Entry 1). The remaining allenylmethanols **2b**–**h** were successfully converted into the desired adducts in moderate to good yields. Only a slight decrease in the *ee* value of the products was observed under these reaction conditions.[7]

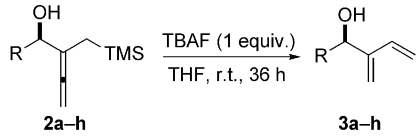
Table 2. Asymmetric chromium-catalyzed silylallenylation reaction.



Entry	R	Product	Yield [%][a]	*ee* [%][b]
1	Ph	**2a**	88	78
2	*p*-MeC_6H_4	**2b**	75	70
3	*p*-BrC_6H_4	**2c**	60	74
4	*o*-BrC_6H_4	**2d**	82	68
5[c]	*o*-MeC_6H_4	**2e**	77	59
6	*p*-$CF_3C_6H_4$	**2f**	88	72
7[d]	C_6H_{11}	**2g**	67	68
8[d]	$PhCH_2CH_2$	**2h**	58	55

[a] Isolated yields. [b] Enantiomeric excess determined by chiral HPLC. [c] (4-Bromobut-2-ynyl)trimethylsilane (3 equiv.), 50 h. [d] Reaction time: 36 h.

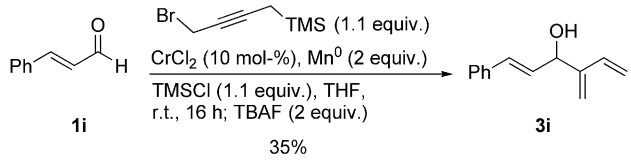
Table 3. Conversion of allenylmethanols to (1,3-butadien-2-yl)-methanols.



Entry	R	Product	Yield [%][a]	*ee* [%][b]
1	Ph	**3a**	54	70
2	*p*-MeC_6H_4	**3b**	86	65
3	*p*-BrC_6H_4	**3c**	72	73
4	*o*-BrC_6H_4	**3d**	82	77
5	*o*-MeC_6H_4	**3e**	79	68
6	*p*-$CF_3C_6H_4$	**3f**	59	69
7	C_6H_{11}	**3g**	84	64
8	$PhCH_2CH_2$	**3h**	43	48

[a] Isolated yields. [b] Enantiomeric excess determined by chiral HPLC.

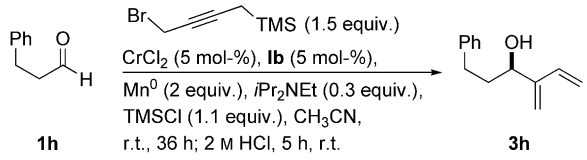
The acidic workup of the mixture resulting from the Cr-catalyzed reaction is not necessary and can be skipped in the case of acid-sensitive products. For example, cinnamaldehyde was combined with (4-bromo-2-ynyl)trimethylsilane in the presence of $CrCl_2$, and the corresponding allene was obtained after 16 h (Scheme 2). The crude silyl ether was directly treated with 2 equiv. TBAF in THF to afford the desired adduct.



Scheme 2. Synthesis of **3i** from cinnamaldehyde.

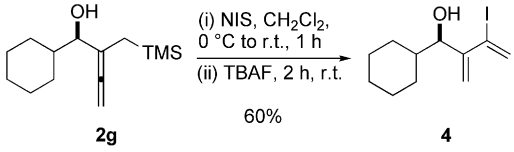
On the other hand, the TBAF step can be excluded by initial prolonged (5 h) treatment with aqueous HCl. For example, when intermediate [1-(silylmethyl)allenyl]methanol

2h was directly treated with acid by addition of 2 M HCl to the reaction flask, product **3h** was obtained from this one-pot procedure after 5 h in 56% yield (Scheme 3).



Scheme 3. One-pot synthesis of **3h** from 3-phenylpropionaldehyde.

The [1-(silylmethyl)allenyl]methanol intermediates **2** possess other useful reactivities that can be utilized for synthesis. To illustrate the versatility of these intermediates, **2g** was treated with NIS to give the iodinated adduct **4** (Scheme 4).[8] Furthermore, {1-[(trimethylsilyl)methyl]-allenyl}methanols may be treated with other electrophiles such as Br_2 or Selectfluor® to afford the corresponding halogenated derivatives.[2j,9]



Scheme 4. Iodination of {1-[(trimethylsilyl)methyl]allenyl}methanol **2g**.

Conclusions

We have developed an asymmetric synthesis (1,3-butadien-2-yl)methanols. This method is valuable for the synthesis of {1-[(trimethylsilyl)methyl]allenyl}methanols, valuable functionalized molecules that may be further converted to a variety of nonracemic small molecules. This work also further illustrates the utility of tridentate bis(oxazolinyl)carbazole ligands in chromium-catalyzed additions to aldehydes for the synthesis of asymmetric alcohols. The present method avoids regioselectivity problems of preceding protocols and tolerates a variety of functionalities. It is complementary to previous related reports that focus on the synthesis of the other regioisomers.

Experimental Section

General Method for the Preparation of the Allenylmethanols: Inside a nitrogen-filled drybox, a mixture of $CrCl_2$ (1.2 mg, 0.01 mmol), Mn powder (325-mesh; 22 mg, 0.4 mmol), and carbazole ligand **Ib** (5.5 mg, 0.01 mmol) was added to a 2-dram vial. Then, the vial was capped with a teflon lid, and it was removed from the drybox. Freshly distilled CH_3CN (2 mL) was added through a syringe, and a yellow suspension was formed. This was followed by addition of diisopropyl(ethyl)amine (7.5 mg, 0.06 mmol), and the mixture was stirred for 5 min. After this time, (4-bromo-2-butyn-1-yl)trimethylsilane (50 mg, 0.3 mmol) was added, and the solution was stirred for 30 min. Next, the aldehyde (0.2 mmol) and TMSCl (24 mg, 0.22 mmol) were successively added at 0 °C. The mixture was stirred at room temperature for 48 h or until the reaction was completed as judged by TLC. 1 M HCl was added, and the obtained green solution was stirred until the alcohol was completely deprotected as judged by TLC. The mixture was then extracted with EtOAc. The mixed organic phases were washed with brine, dried with Mg_2SO_4 and concentrated under reduced pressure to give a dark orange oil. The residue was purified by flash chromatography with EtOAc/hexanes (1:50 to 1:9) as eluent.

General Method for the Preparation of the (1,3-Butadien-2-yl)methanols from the Allenylmethanols: The allene (0.11 mmol) was dissolved in dry THF (1.5 mL). TBAF (1 M in THF, 0.1 mL, 0.1 mmol) was added, and the solution was stirred at room temp. for 36 h. After this time, a saturated solution of NH_4Cl (3 mL) was added, and the mixture was extracted with three portions of EtOAc. The combined organic fractions were washed with brine, dried with Mg_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography with EtOAc/hexanes (1:6).

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data.

Acknowledgments

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[7] The absolute configuration was assigned by direct comparison to known compounds or by conversion to known compounds (see Supporting Information for details).

[8] a) The synthesis of 2-iodo-1,3-dienes has also been reported to occur by treatment of (silylmethyl)allenes with I_2. See: T. Nishiyama, T. Esumi, T. Iwabuchi, H. Irie, S. Hatakeyama, *Tetrahedron Lett.* **1998**, *39*, 43–46; b) during this process, half of the alcohol was silylated in situ (by the TMSI byproduct generated), and the unpurified 1:1 mixture of free alcohol/silyl ether was converted into the pure alcohol in 60% yield by addition of TBAF.

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