

Copper Catalyzed Asymmetric Synthesis of Chiral Allylic Esters

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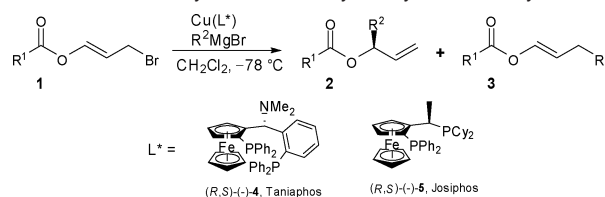
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Enantiomerically pure allylic alcohols and their derivatives are key building blocks in numerous synthetic applications.¹ Besides a number of multistep routes, catalytic methods have been developed involving kinetic resolution² or enantioselective addition of alkenyl zinc³ or boron⁴ reagents to carbonyl compounds. Recent breakthroughs for the preparation of optically active allylic alcohol derivatives are based on transition-metal catalyzed allylic substitution using oxygen nucleophiles. Most of these processes give allylic ethers,^{5,6} but the use of carboxylic acids as nucleophiles in the conversion of (Z)-allylic trichloroacetimidates provides allylic esters.⁷ Although these methods rely on asymmetric C–O bond formation, we envisioned that the construction of allylic esters through catalytic enantioselective C–C bond formation using simple organometallic reagents might provide a new, general and versatile addition to the current synthetic repertoire. In this context, it should be noted that Trost and Lee reported asymmetric Pd-catalyzed allylic substitutions of geminal dicarboxylates using soft carbon nucleophiles.⁸ Herein we report the highly enantioselective synthesis of optically active allylic esters via C–C bond formation in a Cu-catalyzed *hetero*-allylic asymmetric alkylation (*h*-AAA) with Grignard nucleophiles (Scheme 1).

We anticipated that the use of 3-bromopropenyl esters **1** as substrates in *h*-AAA would provide access to a wide range of protected chiral allylic alcohols **2** (Scheme 1). Recently it was shown^{9,10} that Cu-catalyzed AAA with Grignard reagents can be achieved with excellent regio- and enantioselectivities on C-substituted allylic substrates. However as ester groups are prone to be attacked by Grignard reagents and vinyl esters are commonly used in acyl transfer reactions due to the excellent leaving group ability of the enolate, a key question is if the ester moiety at the γ -position in **1** would be tolerated in S_N2' substitutions with organometallic reagents.

When *trans*-**1**¹¹ (R¹ = Ph), prepared in one step from benzoylbromide and acrolein, was treated with 1.15 eq of MeMgBr (*ca.* 3M in ether), (*R,S*)-Taniaphos **4** (6 mol %), and CuBr•Me₂S (5 mol %), (*S*)-**2**¹¹ (R² = Me) was obtained in 85% yield and 96% ee (Table 1, entry 1). Furthermore, **3** could not be detected by ¹H NMR spectroscopy (<1% by HPLC analysis). The use of (*R,S*)-(-)-Josiphos **5** instead of ligand **4** (Table 1, entry 2) gave 75% yield of regioisomers **2** and **3** (ratio 92:8) where **2** had significantly lower (80%) ee. Our previous studies on copper catalyzed asymmetric Grignard additions¹² illustrate that *t*-BuOMe may often be used in place of CH₂Cl₂. The use of *t*-BuOMe in the *h*-AAA of **1** (R¹ = Ph) surprisingly led to regioisomer **3** (36%, 12 h, Table 1, entry 3). The use of 2 eq of MeMgBr (Table 1, entry 4) in the reaction was also tolerated, as was a lower (0.8 mol %) catalyst loading (entry 5).

Reaction at –60 °C or even at –15 °C (Table 1, entries 6, 7) led only to a slight decrease in ee (94% and 90%, respectively). Curiously, at reaction temperatures lower than –80 °C (Table 1, entries 8, 9), the regioselectivity diminished significantly. The

Scheme 1. Cu-Catalyzed *Hetero*-Allylic Asymmetric Alkylation**Table 1.** Cu-Catalyzed *Hetero*-Allylic Alkylation of *trans*-**1** (R¹ = Ph) with MeMgBr

entry	catalyst	temp[°C]	2:3 ^a	yield[%] ^b	ee[%]
1	(–) 4	–68	99:1	85	(+) ^c 96
2	(–) 5	–75	92:8	75	(+) ^c 80
3 ^c	(–) 4	–73	8:92	36 ^d	n.d.
4 ^e	(–) 4	–74	99:1	85	(+) ^c 98
5 ^e	(–) 4 ^f	–74	99:1	83	(+) ^c 96
6	(–) 4	–15	99:1	76	(+) ^c 90
7	(–) 4	–60	99:1	77	(+) ^c 94
8	(+) 4	–80	99:1	78	(–) ^c 96
9	(+) 4	–82	79:21	67	(–) ^c 94
10	(–) 4	–85	37:63	76	n.d.
11 ^g	(–) 4	–74	n.a.	<5 ^h	n.d.

^a Regioselectivity determined by HPLC or ¹H NMR spectroscopy.^b Isolated yield. ^c *t*-BuOMe as solvent. ^d Conversion by ¹H NMR. ^e Two equivalents of MeMgBr. ^f With 0.8 mol % catalyst. ^g Reaction without copper. ^h Not isolated.

copper-catalyzed reaction at –85 °C favored the S_N2 product **3** (Table 1, entry 10).¹³

To investigate the steric influence of the R¹ group, compounds **1a** and **1b** were examined (Table 2, entries 1, 2). Cinnamyl derivative **1a** readily provided **2a**, with excellent regio- and enantioselectivities (>98:2, 98% ee). It should be emphasized that the selectivity in this catalytic conversion is remarkable. Whereas substrate **1a** has α,β -unsaturated ester, enol ester, and allyl bromide moieties and can undergo 1,4-addition, 1,2-addition, S_N2' and S_N2 substitution (among others), near-exclusive S_N2' substitution to a single enantiomer of **2a** takes place. Mesityl derivative **1b** (Table 2, entry 2) also afforded the desired compound (91% yield, 99:1, 96% ee).

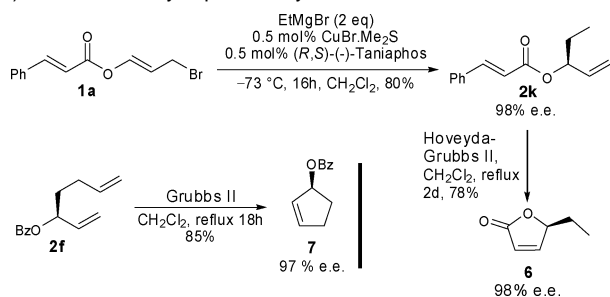
We next examined the addition of different Grignard reagents. Higher yields were obtained when using an excess (2 eq) of Grignard reagents. Regioisomers **3** were only observed in entries 3, 9, and 10, Table 2.¹¹ Simple primary saturated Grignard reagents (Table 2, entries 3, 4) afforded allylic esters in excellent yields (87 and 99%) and high ee's (98 and 97%, respectively). The formation of a long chain allylic ester (C₁₈H₃₇, entry 8) was readily achieved.

Functionalized Grignard reagents were also successfully used in the *h*-AAA reaction (Table 2, entries 6, 7). A limitation of the method appears to be the addition of more sterically demanding Grignard reagents: reaction with *i*-BuMgBr (Table 2, entry 5) did not afford the desired product.¹¹ Substrates bearing a β -methyl substituent also undergo Cu catalyzed *h*-AAA with excellent

Table 2. Use of Different Grignard Reagents and Ester Groups in the *h*-AAA Reaction

$ \begin{array}{c} \text{R}^1\text{C}(=\text{O})\text{OCH}=\text{CHCH}_2\text{Br} \\ \text{1} \end{array} \xrightarrow[\text{-75 } ^\circ\text{C, CH}_2\text{Cl}_2]{\begin{array}{c} \text{R}^2\text{MgBr (2 eq)} \\ 5 \text{ mol\% CuBr}\cdot\text{Me}_2\text{S or CuTC} \\ 5 \text{ mol\% (R,S)-(-)-Taniaphos} \end{array}} \begin{array}{c} \text{R}^1\text{C}(=\text{O})\text{OCH}(\text{R}^2)\text{CH}=\text{CHCH}_2\text{R}^3 \\ \text{2} \end{array} $						
entry	R ¹	R ²	R ³	2	yield[%] ^a	e.e[%]
1	Sty(1a)	Me	H	2a	80	(+) ⁹⁸
2	Mes(1b)	Me	H	2b	97	(+) ⁹⁶
3 ^b	Ph	C ₂ H ₅	H	2c	87	(+) ⁹⁸
4 ^c	Ph	C ₆ H ₁₁	H	2d	99	(-) ⁹⁷
5	Ph	<i>i</i> -bu	H	2e	n.d	—
6	Ph	C ₄ H ₇	H	2f	96	(+) ⁹⁷
7	Ph	C ₈ H ₉	H	2g	93	(+) ⁹³
8	Ph	C ₁₈ H ₃₇	H	2h	93	(+) ^d >95 ^e
9 ^f	Ph(1c)	C ₂ H ₅	Me	2i + 3i	97 ^g	97
10 ^f	Ph(1c)	C ₆ H ₁₁	Me	2j + 3j	96 ^g	98

^a Unless otherwise noted. ^b Trace amount of regioisomer was detected by ¹H NMR spectroscopy. ^c Ligand used: (S,R)-(+)-Taniaphos. ^d Based on optical rotation of the corresponding alcohol. ^e Ee determination by ¹H and ¹⁹F NMR analysis of the Mosher ester of the alcohol derived from 2h. ^f Ligand: O, O'-(R)-(1,1'-dinaphthyl)-2,2'-diyl-di-(R,R)-1-phenyl-ethylphosphoramidite, Metal: CuTC.¹¹ ^g A mixture of regioisomers 2i + 3i (2.5:1) and 2j + 3j (2:1) in favor of 2 was isolated.

Scheme 2. Synthesis of (S)-5-ethyl-2(5*H*)-furanone **6** and (S)-benzoic Acid-cyclopent-2-enyl Ester **7**

enantioselectivity (Table 2, entries 9, 10), albeit with a phosphoramidite¹⁴ as the optimal chiral ligand.¹¹ A notable feature of this method is the practical synthesis of the simplest optically active allylic alcohols, such as 1-buten-3-ol (Table 1, entry 4).¹⁵

We illustrate the synthetic utility of this new *h*-AAA in combination with RCM in the synthesis of two valuable chiral nonracemic building blocks: natural occurring butenolide (S)-**6**¹⁶ and cyclopentenyl ester (S)-**7**¹¹ (Scheme 2). The addition of EtMgBr to **1a** provided **2k** with excellent chemo-, regio-, and enantioselectivity (80% yield, 98% ee), despite the possibility of several competing reactions. This reaction was also run with 0.05 mol % catalyst loading with equal enantioselectivity. Subsequent RCM of **2k** to (S)-**6**¹¹ (78% yield, 98% ee) was accomplished by heating **2k** to reflux in CH₂Cl₂ in the presence of Hoveyda-Grubbs II catalyst¹⁷ to produce butenolide **6**. When **2f** was subjected to RCM conditions with Grubbs II catalyst,¹⁸ carbocycle (S)-**7**¹¹ was obtained in 85% yield and excellent ee (97%).

In conclusion, a practical catalytic route to optically active allylic esters with excellent stereocontrol based on asymmetric allylic alkylation with Grignard reagents has been found.

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Supporting Information Available: Detailed experimental procedures and characterization and ¹H and ¹³C NMR spectra of all products **2**. This material is available free of charge via the Internet at <http://www.pubs.acs.org>.

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