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Enantioselective synthesis of allenyl carbinols by the CBS reduction in nitroethane: dramatic solvent effect for reactivity and enantioselectivity†

Chan-Mo Yu,* Chunsan Kim and Jae-Hong Kweon

Department of Chemistry and Lab for Metal-Catalysed Reactions, Sungkyunkwan University, Suwon 440-746, Korea. E-mail: cmyu@chem.skku.ac.kr; Fax: +82 31 290 7075; Tel: +82 31 290 7067

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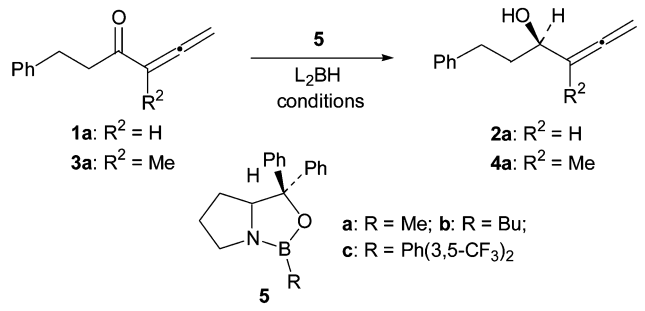
Dramatic solvent effect of nitroethane was observed in the catalytic asymmetric reductions of allenyl ketones and α,β-ynones using the oxazaborolidine cayalyst to yield the corresponding alcohols in high levels of enantioselectivity.

Structurally unique allenes are considerably distributed in nature and play a variety of biological roles.[1] Recently allene moieties have been utilized as useful substrates for a variety of chemical transformations.[2] As a consequence, considerable attentions have been paid to synthesize allenyl compounds.[1,2] As our continuous efforts to prepare and utilize allenyl functionality,[3] we disclosed the cyclization strategies to establish cyclic compounds using the allenyl-carbonyl functionalities through transition metal catalysis.[4] It was envisaged that the allenyl carbinols **2** could be a useful starting material for an asymmetric version of transition metal catalysis. However, there have been only few methods for the enantioselective synthesis of **2** mainly through the asymmetric allenylation of aldehydes.[5] As a consequence, we became quite interested in the practical and convenient synthesis of allenyl carbinols **2** from the corresponding allenyl ketones **1** and α,β-ynones **6** *via* asymmetric reduction methods. However, the lack of data concerning the catalytic asymmetric reduction of allenyl ketones to allenyl carbinols surprised us, in view of the expected similarity of such system to the well defined enone system.[6] This research led to the discovery of the remarkable solvent effects, which expedites the catalytic process of asymmetric reduction of **3** and **6** with high levels of enantioselectivity.

The first study for preliminary experiments focused on the feasibility of **1** for the asymmetric reduction to **2** with proper chiral reducing reagents. To investigate the sequence outlined in Scheme 1, we began with **1a** and **3a** as starting materials: these compounds were readily prepared by the modification of known procedures as described in the literature.[7] Initial attempts to reduction of **1a** with chiral borane reagents mainly employed for a ketone reduction indicated that the conversion to the corresponding lactone could not be satisfied with $(Ipc)_2BH$ and $(Ipc)_2BX$ (X = Cl or Br) under various reaction conditions mainly due to lower yields (less than 30%), enantioselectivity (less then 40% ee), and formation of side products.[8] Other methods including chirally modified Cp_2TiF_2/BuLi with silane and Co(II) complex with $NaBH_4$ turned out to be unsuccessfully for our approach.[9]



Scheme 1 Preliminary investigations of asymmetric reduction of **1** and **3**.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b407387h/

Fortunately, we found that the oxazaborolidine **5** known as the CBS catalyst[10] could promote reaction process without other reaction pathways. Initial experiments on the catalytic asymmetric reduction of **1a** with **5a** (10 mol%) by catecholborane under standard conditions (−78 °C for 20 h in toluene) afforded encouraging but marginal results. Although no side products were produced during the reaction, long reaction time, low chemical yield and enantioselectivity remained to be solved as outlined in Table 1 (entry 1). We subsequently speculated that solvent might be a control factor to regulate catalytic process. After surveying numerous conditions for orienting experiments as summarised in Table 1, several key findings emerged: (i) dramatic solvent effect was observed by introducing $EtNO_2$ compared to other solvents such as toluene, CH_2Cl_2 and THF in terms of reactivity and enantioselectivity; (ii) the oxazaborolidine **5a** was generally superior to **5b** and **5c** in terms of availability and efficacy; (iii) 10 mol% of **5a** was needed for optimum conditions whereas the reaction with reduced dosage resulted in diminished chemical yield and longer reaction times; (iv) catecholborane proved to be the most effective reagent compared to other reducing agents such as $BH_3{\cdot}SMe_2$, $BH_3{\cdot}THF$, $BH_3{\cdot}Et_2NPh$ and pinacolborane; (v) 2 equivalents of catecholborane was required for optimal conditions. Even though **4a** was obtained as an enantiomerically enriched product, enantiomeric excess of **2a** turned out to be 67% ee presumably due to a lack of steric bias. With the notion that this approach might lead to a general and efficient method for the synthesis of substituted allenyl carbinols **4**, we set out to determine the substituent effects with **3** to produce structurally various products. Indeed, the method is successful to yield **4** in high yields with high levels of enantioselectivity as it can be seen in Table 2. It is worthy of note that we could not detect any minor enantiomers for entry 3–6 in Table 1 as judged by ^1H NMR analysis of Mosher esters with racemic sample. Upon optimal conditions (entry 1 in Table 2), the reaction was conducted by a dropwise addition of catecholborane

Table 1 Selected preliminary investigations

Entry	1/3	5 (mol%)	L_2BH[a]	Solvent	T/°C	t/h	Yield (%)[b]	ee (%)[c]
1	**1a**	**a** (10)	CB	toluene	−78	20	47	41
2	**1a**	**b** (10)	CB	toluene	−78	20	44	38
3	**1a**	**a** (10)	BMS	CH_2Cl_2	−78	20	58	42
4	**1a**	**b** (10)	CB	THF	−78	20	53	15
5	**1a**	**a** (10)	CB	$EtNO_2$	−78	1	94	67
6	**3a**	**a** (10)	BTHF	CH_2Cl_2	0	20	56	22
7	**3a**	**a** (10)	CB	CH_2Cl_2	−78	16	47	66
8	**3a**	**a** (10)	BMS	CH_2Cl_2	−20	18	61	~0
9	**3a**	**a** (10)	CB	toluene	−78	18	44	56
10	**3a**	**a** (10)	CB	$EtNO_2$	−78	1	93	93

[a] CB = catecholborane, BMS = $BH_3{\cdot}SMe_2$, BTHF = $BH_3{\cdot}THF$ [b] Yields refer to isolated and purified yield. [c] Enantiomeric excesses were determined by HPLC analysis using chiral column (Chiracel OD-H, 3% Pr^iOH in hexane).

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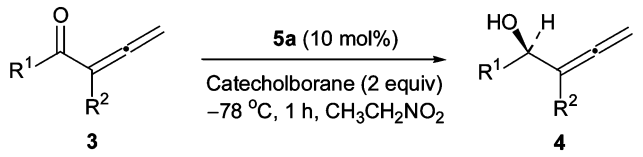
Table 2 Enantioselectve reduction of **3** to **4**



3 4

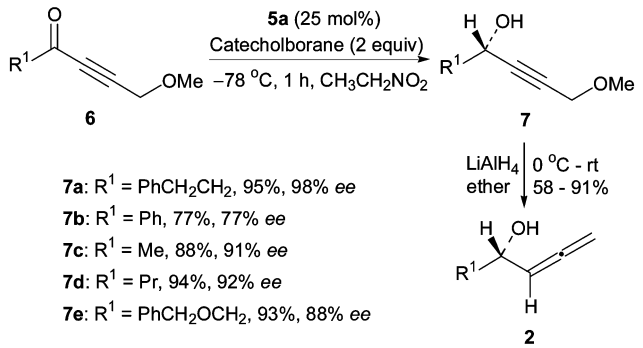
Entry	4	R^1	R^2	Yield (%)[a]	ee (%)[b]
1	**a**	$PhCH_2CH_2$	Me	93	93
2	**b**	$PhCH_2CH_2$	Et	95	92
3	**c**	Me_2CHCH_2	Me	86	>99
4	**d**	Me_2CHCH_2	Et	91	>99
5	**e**	*n*-C_5H_{11}	Me	93	>99
6	**f**	*n*-C_5H_{11}	Et	88	>99

[a] Yields refer to isolated and purified products. [b] Enantiomeric excesses were determined by preparation of (+)-MTPA ester derivatives, analysis by 500 MHz ^{1}H NMR (all entries), and by HPLC analysis using chiral column (Chiracel OD-H, 1 ~ 2% Pr^iOH in hexane, entries 1,2).

(2 equiv.) in $EtNO_2$ at −78 °C to a solution of the oxazaborolidine **5a** (0.1 equiv.) and **3a** (1 equiv.) in $EtNO_2$. Reaction was cleanly complete within 1 h. Work up and chromatography gave **4a** in 93% yield with 93% ee. The absolute configuration of the predominating enantiomer for adducts was unambiguously established by comparison of values of specific rotations and ^{1}H NMR spectra of Mosher ester with previously known alcohols.[3a] The absolute sense of asymmetric induction parallels previous observations on the CBS reduction of enone system.[6]

With our research scope of the catalytic asymmetric reduction of allenyl ketones **3**, we turned our attention next to examine the application of this approach with α,β-ynones **6** to extend the scope to the synthesis of **2** by two step sequence as illustrated in Scheme 2.[11] The CBS reduction of α,β-ynones to afford propargyl alcohols with high levels of enantioselectivity has been reported.[12] However, the reported methods were restricted by the use of 2 equivalents of the oxazaborolidine catalyst **5** or designed substrates of α,β-ynones for remote controlling of steric effects.

Our initial studies began with **6a** (R = $PhCH_2CH_2$) prepared from lithiated 3-methoxy-1-propyne with the corresponding Weinreb amide. We subsequently observed that the new condition of the CBS reduction could be also employed for this purpose. Reaction under the similar conditions in $EtNO_2$ except amount of **5a** (25 mol%) produced **7a** quickly in 95% yield with 98% ee as comparison to only 51% yield with 57% ee after 12 h at −78 °C in CH_2Cl_2. Additional experiments with various α,β-ynones were carried out and representative results are summarised in Scheme 2. Allenyl carbinols **2** were obtained from the reaction of **7** with



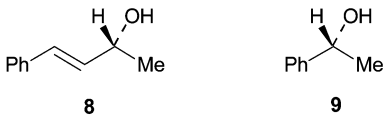
6 7 2

7a: R^1 = $PhCH_2CH_2$, 95%, 98% *ee*
7b: R^1 = Ph, 77%, 77% *ee*
7c: R^1 = Me, 88%, 91% *ee*
7d: R^1 = Pr, 94%, 92% *ee*
7e: R^1 = $PhCH_2OCH_2$, 93%, 88% *ee*

Scheme 2 The CBS reduction of α,β-ynones **6**.

$LiAlH_4$ at 0 °C to rt in ether in good yields (77–91%) except volatile **3c** (58% yield).

In the light of the above results for the enantioselective reductions of allenyl ketones and α,β-ynones depending on solvent, we tried to prove the generality of this solvent effect with simple enone and ketone. Indeed, the method is successful to yield **8** (**5a** 5 mol%, 2 h, 91% with 93% ee in $EtNO_2$; 35% with 88% ee in toluene)[13] and **9** (**5a** 5 mol%, 3 h, 91% with 94% ee in $EtNO_2$; 22% with 86% ee in toluene)[14] under the same conditions from the corresponding ketones.



8 9

Although the exact behavior of nitroethane has not been rigorously elucidated, the role of nitroethane as a solvent in accelerating the catalytic process and enhancing enantioselectivity may be interpreted by a consequence of dissociation of the product from reaction complex with regeneration of chiral catalyst.

In summary, we discovered dramatic solvent effect in enhancing reactivity and enantioselectivity on the CBS reduction of allenyl ketones and α,β-ynones. Further studies are in progress to enlarge the scope of this procedure with more complicated system.

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