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Catalytic Asymmetric Synthesis of Optically Active Allenes from Terminal Alkynes

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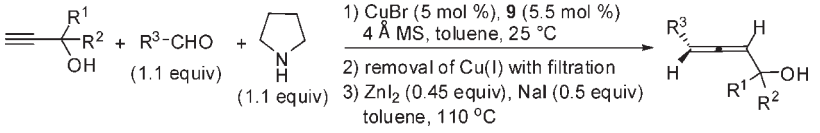
ABSTRACT



CuBr and ZnI_2 have been developed as catalysts or subcatalysts for the efficient asymmetric synthesis of axially chiral allenols with up to 97% ee from readily available propargylic alcohols, aliphatic or aromatic aldehyde, pyrrolidine, and commerically available ligands. The alcohol unit in the terminal alkynes plays a very important role for ensuring high enantioselectivity via coordination.

Allenes have been becoming more important in organic synthesis because of extensive exploration on the development of new highly selective reactions of allenes.[1,2] Of particular interest, because of the intrinsic axial chirality of allenes, the axial-to-central chirality transfer strategy has become an important approach for the synthesis of chiral products.[3] However, the known reports on the synthesis of axially chiral allenes are still largely limited.[2] On the basis of our recent observation that ZnI_2 may promote the reaction of terminal alkynes, aldehydes, and morpholine for the synthesis of 1,3-disubstituted allenes,[4] we reasoned that there are two approaches for the easy synthesis of optically active 1,3-disubstituted allenes from terminal alkynes and aldehydes: the chiral amine approach and catalytic asymmetric synthesis of propargylic amine approach (Scheme 1). In this paper, we wish to report our recent observation on the realization of such concepts.

In the first place, we tried the following proline-based commercially available cyclic chiral amines **4**–**6** for the ZnI_2-promoted reaction of terminal alkynes based on the earlier observation by Che et al. under the catalysis of $KAuCl_4$[5a] or $AgNO_3$[5b] salts from L-prolinol-based propargylic amines. After the extensive combinatorial reactions of the substrates in our original report[4] with amines **4**–**6**, it is interesting to note that the reaction of alkyne **1a** with *n*-BuCHO and the diphenyl-substituted prolinol **6** in

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(1) For most recent reviews on the chemistry of allenes, see: (a) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (b) Ma, S. *Aldrichimica Acta* **2007**, *40*, 91. (c) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. (d) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679. (e) Alcaide, B.; Almendros, P.; Campo, T. M. d. *Chem.—Eur. J.* **2010**, *16*, 5836. (f) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. (g) Inagaki, F.; Kitagaki, S.; Mukai, C. *Synlett* **2011**, 594. (h) López, F.; Mascareñas, J. L. *Chem.—Eur. J.* **2011**, *17*, 418.

(2) For reviews on the synthesis of allenes, see: (a) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133. (b) Krause, N., Hashmi, A. S. K., Eds.; *Modern Allene Chemistry*; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1 and 2. (c) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671. (d) Brummond, K. M.; Deforrest, J. E. *Synthesis* **2007**, 795. (e) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 259. (f) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384.

(3) For recent reviews on the chemistry of allenes involving axial-to-central chirality transfer, see: (a) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (b) Krause, N.; Belting, V.; Deutsch, C.; Erdsack, J.; Fan, H.; Gockel, B.; Hoffmann-Röer, A.; Morita, N.; Volz, F. *Pure Appl. Chem.* **2008**, *80*, 1063. (c) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. See also ref 1d.

(4) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786.

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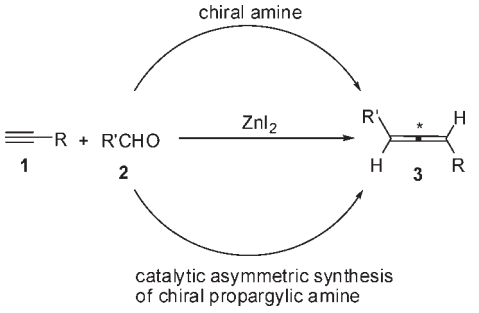
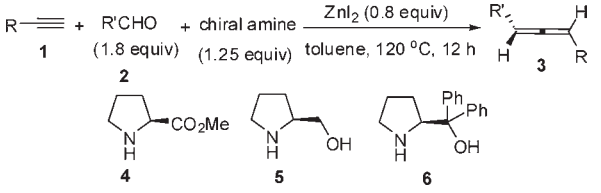
Scheme 1. Concepts for the Synthesis of Optically Active Allenes



toluene afforded allene **3aa** in 98% ee within 16 h (entry 3, Table 1).[6]

Table 1. Initial Efforts to Synthesize Axially Chiral Allenes Using Chiral Amines **4**–**6**: Selected Examples[a]



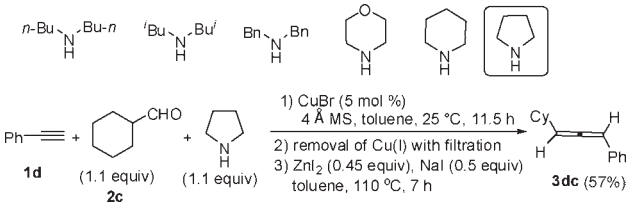
entry	R	R′	chiral amine	yield of **3** (%)[b,c]
1	*p*-$NO_2C_6H_4CH_2OH_2C$ (**1a**)	*n*-Bu (**2a**)	**4**	37 (**3aa**, 34% ee)[d]
2	*p*-$NO_2C_6H_4CH_2OH_2C$ (**1a**)	*n*-Bu (**2a**)	**5**	trace[e,f]
3	*p*-$NO_2C_6H_4CH_2OH_2C$ (**1a**)	*n*-Bu (**2a**)	**6**	46 (**3aa**, 98% ee)[g]
4	*p*-$NO_2C_6H_4CH_2OH_2C$ (**1a**)	*n*-Bu (**2a**)	**6**	63 (**3aa**, 94% ee)[h]
5	*n*-$C_{10}H_{21}$ (**1b**)	Ph (**2b**)	**6**	26 (**3bb**)[i,f]
6	HOH_2C (**1c**)	Cy (**2c**)	**6**	trace[f]

[a] The reactions were carried out on 1.0 mmol scale of **1** in 5 mL of toluene unless otherwise noted. [b] Isolated yield. [c] ee was determined by HPLC analysis using Chiralcel AD-H or OD-H column. [d] **4** (1.1 equiv) and toluene (3 mL) were used with 16% **1a** recovered. [e] **5** (1.1 equiv) and toluene (3 mL) were used with 40% **1a** recovered. [f] ee not determined. [g] 19% of **1a** was recovered with the reaction time of 16 h. [h] 3% of **1a** was recovered with the reaction time of 16 h at 130 °C. [i] NMR yield.

Because of the expensive nature of at least stoichiometric amounts of chiral amine **6** and an unsuccessful attempt with unprotected propargyl alcohol (entry 6, Table 1), we decided to pursue the second approach shown in Scheme 1. It is envisioned that the challenge will be the availability of a highly enantioselective method for the efficient synthesis of optically active propargylic amines.[5–9] Knochel et al.[7] reported CuBr-catalyzed synthesis of optically active propargylic amine from terminal alkyne, aldehyde, and dibenzyl or diallyl amine with (*R*)-quinap **7** as the chiral ligand, affording propargylic amines with 90–98% ee only with trimethylsilylacetylene; 25–89% ee were observed when alkyl- or aryl-substituted terminal alkynes were used. Besides, the reaction is very slow, taking 1–6 days to finish at room temperature; Carreira et al.[8] applied the ligand (*R*,*S*)-*N*-PINAP **8** and (*R*,*R*)-*N*-PINAP **9** to the same reaction, and higher enantioslelectivities were observed, yet the substrate scope is limited to *i*-alkyl carbinals and suffers from a long reaction time (3–5 days). In addition, we were also concerned with whether such optically active propargylic amines may be converted to chiral allenes highly stereoselectively in the presence of ZnI_2 and whether the two steps (chiral propargylic amine as well as allene formations) would share the same solvent.

After examining a series of secondary amines shown in Scheme 2, we were pleased to find that when *pyrrolidine* was employed, full conversion from terminal alkynes and aldehydes to propargylic amines can be realized within 12 h at room temperature. However, the second-step reaction with the direct addition of ZnI_2 is incomplete, albeit there is a decent conversion. During the preparation of racemic products, we noticed with control experiments that Cu(I) should be removed for a fast second step forming the allene. Thus, after simple filtration through a short pad of silica gel to remove Cu(I) with ether as the eluent, the ether was then evaporated, and the subsequent transformation from the crude propargylic amine to the allene **3dc** was conducted in the same solvent (toluene) in the presence of ZnI_2 very efficiently. NaI was added to ensure a higher yield.

Scheme 2. Amines Screened and Preparation of Racemic **3dc**



With the optimized protocol shown in Scheme 2, we examined several chiral ligands including (*R*)-quinap **7**,

(5) (a) Lo, V. K. Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2008**, *10*, 517. (b) Lo, V. K.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213.

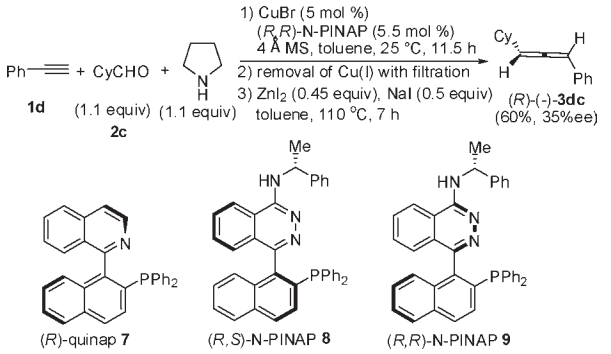
(6) This manuscript was originally submitted on December 18, 2011 to *J. Am. Chem. Soc.* (ja-2011-11789x). Periasamy et al. also submitted a manuscript containing the information of such a $ZnBr_2$-promoted reaction with amine **6** to *J. Am. Chem. Soc.* (ja-2011-11215r); thus, we did not pursue extending the scope of this reaction.

(7) (a) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (b) Gommermann, N.; Knochel, P. *Chem. Commun.* **2005**, 4175. (c) Gommermann, N.; Knochel, P. *Chem.—Eur. J.* **2006**, *12*, 4380.

(8) (a) Knöpfel, T. E.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (b) For the synthesis of optically active propaygylic amines using 4-piperidone hydrochloride hydrate as the amine, see: Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437.

(*R*,*S*)-*N*-PINAP **8**, and (*R*,*R*)-*N*-PINAP **9**. It was observed that when (*R*,*R*)-*N*-PINAP **9** was utilized as the chiral ligand, the reaction went smoothly, affording allene (*R*)**-3dc** in 60% yield; however, the enantiopurity of allene **3dc** was rather low (35%), although a very high enantioselectivity was observed by Carreira et al. for the preparation of chiral propargylic amines from structurally very similar aldehydes, i.e., *i*-PrCHO or *i*-BuCHO,[8] indicating a low efficiency of chirality transfer for the ZnI_2-promoted allene formation[4] (Scheme 3).

Scheme 3. Preparation of Optically Active (*R*)-(−)-**3dc**



Thus, we further reasoned that a hydroxyl group in propargylic alcohols may improve the stereoselectivity of the first as well as the second step reaction by the possible coordination of the hydroxyl oxygen with Cu or Zn (Scheme 4). Excitingly, this hypothesis is working: the reaction with unprotected propargylic alcohols did afford 2,3-allenols in moderate yields with a very practical ee. It was noted that the reaction with the tertiary proparylic alcohols yielded the axially chiral allenes in highest ee (Table 2). The scope of the aldehydes is quite general: *s*-alkyl (entries 1−9, Table 2), or *s*-alkylmethyl carbinal (entry 10, Table 2), normal aliphatic aldedyde (entry 11, Table 2), and benzaldehyde (entry 12, Table 2) may all be used with decent ee; with (*R*,*S*)-*N*-PINAP **8**, the enantiomers (*S*)-**3ec** and (*S*)-**3fc** may be conveniently prepared, indicating that the axial chirality in the ligand is largely determining the absolute configuration of the allene unit formed (entries 2−4, 6, Table 2). Control experiments showed that $ZnBr_2$ and $ZnCl_2$ provided similar levels of ee with much longer reaction times (entries 3 and 4, Table 2).

Control experiment showed that $KAuCl_4$[5a] and $AgNO_3$[5b] used by Che et al. failed to promote the allene formation reaction (Scheme 5).

Furthermore, the reaction is not limited to tertiary proparylic alcohols: the reaction of secondary proparylic alcohol **1i** yielded a pair of diastereoisomers (d.r. = 1:1) in slightly lower yet high ee (eq 1, Scheme 6). When the optically active propargylic alcohols with a central chirality such as (*S*)-**1i** and (*R*)-**1i** were used, all four diastereoisomers (*R*,*S*)-**3ic**, (*S*,*S*)-**3ic**, (*R*,*R*)-**3ic**, and (*S*,*R*)-**3ic** were prepared by this protocol conveniently with (*R*,*S*)-*N*-PINAP **8** or (*R*,*R*)-*N*-PINAP **9** as the ligand. The absolute configurations of allenes were assigned based on

(9) For recent reviews on the synthesis of propargylic amines from terminal alkynes and aldehydes in the presence of amines, see: (a) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263. (b) Li, C. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Feng, J.; Li, C. *Sci. Synth.* **2009**, *40a*, 579.

Scheme 4. Proposed Mechanism and Prediction of the Absolute Configuration of the Allene

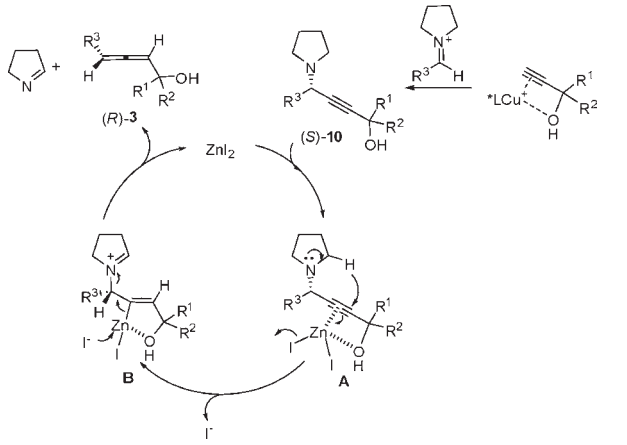
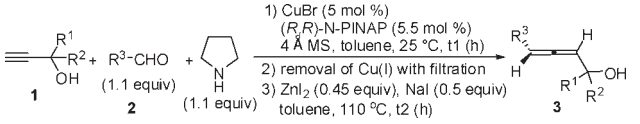


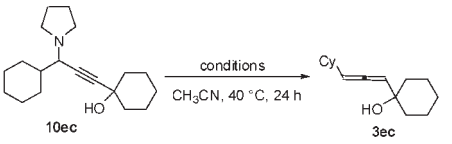
Table 2. Catalytic Asymmetric Synthesis of Chiral Allenols from Terminal Propargylic Alcohols, Aldehydes, And Pyrrolidine[a]



	1	2		3	
entry	R^1, R^2	R^3	t_1/t_2 (h)	yield (%)[b]	ee (%)[c]
1	$-(CH_2)_5-$ (**1e**)	Cy (**2c**)	12/8	68 (*R*-**3ec**)	96
2[d]	$-(CH_2)_5-$ (**1e**)	Cy (**2c**)	12/4	70 (*S*-**3ec**)	93
3[d,e]	$-(CH_2)_5-$ (**1e**)	Cy (**2c**)	12/12	58 (*S*-**3ec**)	94
4[d,f]	$-(CH_2)_5-$ (**1e**)	Cy (**2c**)	12/12	54 (*S*-**3ec**)	93
5	Me, Me (**1f**)	Cy (**2c**)	13/2	66 (*R*-**3fc**)	97
6[d]	Me, Me (**1f**)	Cy (**2c**)	12/1.5	71 (*S*-**3fc**)	95
7	$-(CH_2)_4-$ (**1g**)	Cy (**2c**)	12/2.5	69 (*R*-**3gc**)	95
8	Et, Et (**1h**)	Cy (**2c**)	12/1.5	77 (*R*-**3hc**)	96
9	$-(CH_2)_5-$ (**1e**)	*i*-Pr (**2d**)	19/2.7	50 (*R*-**3ed**)	95
10	$-(CH_2)_5-$ (**1e**	*i*-Bu (**2e**)	13/1.5	75 (*R*-**3ee**)	90
11	$-(CH_2)_5-$ (**1e**)	n-C_7H_{15} (**2f**)	20.5/1.4	54 (*R*-**3ef**)	92
12	$-(CH_2)_5-$ (**1e**)	Ph (**2g**)	17/4.5	78 (*R*-**3eg**)	93

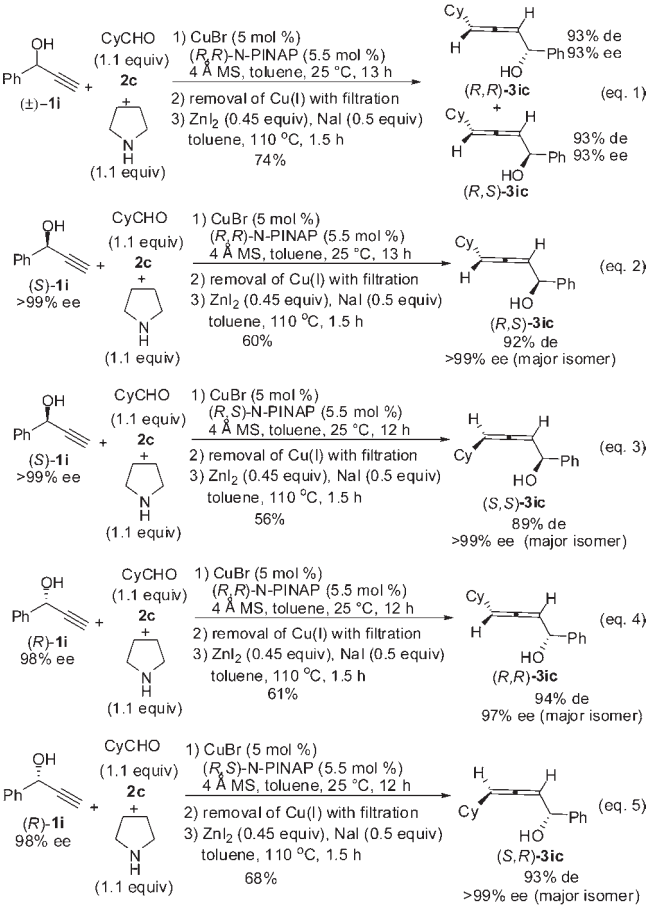
[a] The reactions were carried out on 1.0 mmol scale of **1**. [b] Isolated yield. [c] Determined by HPLC analysis using Chiralcel AD-H or OJ-H column. [d] (*R*,*S*)-*N*-PINAP **8** was used as the ligand. [e] $ZnBr_2$ (0.5 equiv) was used instead of ZnI_2 in the absence of NaI with 3% of propargylic amine recovered. [f] $ZnCl_2$ (0.5 equiv) was used instead of ZnI_2 in the absence of NaI with 3% of propargylic amine recovered.

Scheme 5. Control Experiments using $KAuCl_4$ or $AgNO_3$



conditions	NMR yield of **3ec** (%)	recovery of **10ec** (%)
$KAuCl_4$ (10 mol %)	trace	59
$AgNO_3$ (50 mol %)	trace	31

Scheme 6. Reactions of **2c** and Pyrrolidine with Racemic **1i**, (*S*)-**1i**, and (*R*)-**1i**



the Lowe–Brewster rule[10] and were further confirmed by the X-ray diffraction study of (*S*,*S*)-**3ic** (Figure 1).[11] A model to predict the absolute configuration of the allene moiety for the highly selective formation of allenes from terminal alkynes is shown in Scheme 4.[4,5,12,13]

(10) (a) Lowe, G. *Chem. Commun.* **1965**, 411. (b) Brewster, J. H. *Top. Stereochem.* **1967**, *2*, 1.

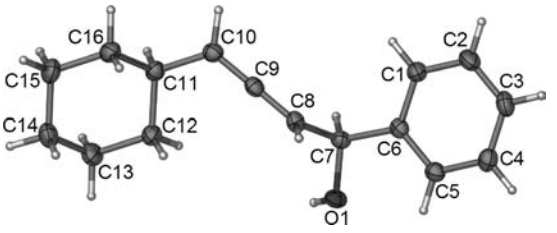


Figure 1. ORTEP representation of (*S*,*S*)-**3ic**.

In conclusion, we have developed an easy and efficient synthesis of allenes especially allenols with axial chirality by using the easily available or commercial starting materials and ligands. Because of the potentials of these chiral allenes,[14] it will be of high interest to the scientific community. In addition, it is interesting to observe that the alcohol unit in the terminal alkynes plays a unique role in this transformation, probably due to its coordination with Cu^+ in the propargylic amine formation step and with Zn^{2+} in both intermediates **A** and **B** as shown in Scheme 4. Further studies in this area are being actively pursued in our laboratory.

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Supporting Information Available. Detailed experimental procedures, characterization data for all the products, and the CIF file of (*S*,*S*)-**3ic**. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) Crystal data for compound (*S*,*S*)-**3ic**: $C_{16}H_{20}O$, MW = 228.32, monoclinic, space group *P*2(1), final *R* indices [$I > 2\sigma(I)$], *R*1 = 0.0266, *wR*2 = 0.0676; *R* indices (all data): *R*1 = 0.0267, *wR*2 = 0.0677; a = 11.7903(3) Å, b = 4.71280(10) Å, c = 12.0475(3) Å, α = 90°, β = 93.5840(10)°, γ = 90°, V = 668.11(3) Å^3, T = 133(2) K, Z = 2, reflections collected/unique: 9051/2212 (R_{int} = 0.0237), number of observations [$> 2\sigma(I)$] 2202, parameters: 163. CCDC 862647 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) (a) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1979**, 859. (b) Kazmaier, U.; Lucas, S.; Klein, M. *J. Org. Chem.* **2006**, *71*, 2429. (c) Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763.

(13) Nakamura, H.; Kamakura, T.; Ishiku, M.; Biellmann J.-F. *J. Am. Chem. Soc.* **2004**, *126*, 5958.

(14) For selected reports on the reactions of allenols, see: (a) Olsson, L.-I.; Claesson, A. *Synthesis* **1979**, 743. (b) Nikam, S. S.; Chu, K. H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 745. (c) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1990**, *55*, 2995. (d) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180. (e) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966. (f) Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, *41*, 8933. (g) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537. (h) Friesen, R. W.; Blouin, M. *J. Org. Chem.* **1993**, *58*, 1653. (i) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943. (j) Fu, C.; Li, J.; Ma, S. *Chem. Commun.* **2005**, 4119. (k) Li, J.; Fu, C.; Chen, G.; Chai, G.; Ma, S. *Adv. Synth. Catal.* **2008**, *350*, 1376. (l) Deng, Y.; Jin, X.; Ma, S. *J. Org. Chem.* **2007**, *72*, 5901. (m) Deng, Y.; Yu, Y.; Ma, S. *J. Org. Chem.* **2008**, *73*, 585.

The authors declare no competing financial interest.