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Bimetallic Enantioselective Approach to Axially Chiral Allenes

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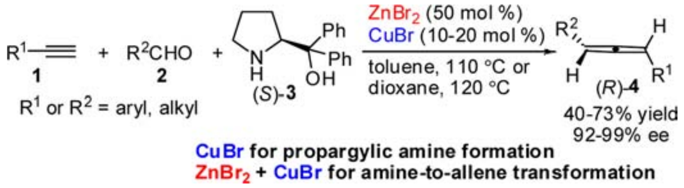
ABSTRACT



An efficient bimetallic Zn(II)/Cu(I)-mediated asymmetric synthesis of simple axially chiral allenes from terminal alkynes and aldehydes was realized by taking advantage of the chiral amine (*S*)-α,α-diphenylprolinol 3. This one-pot procedure is compatible with broad scopes of both terminal alkynes and aldehydes, providing axially chiral allenes in practical yields with an excellent enantioselectivity. Control experiments revealed that CuBr is responsible for the efficient formation of propargylic amine while the combination of CuBr and $ZnBr_2$ plays crucial roles in the amine-to-allene transformation.

Allenes, which had been considered as highly unstable, are now becoming more and more important in organic synthesis, pharmaceuticals, and materials science.[1] Thus, there is an urgent demand for efficient entries to optically active allenes.[2−6] Recently, we have developed a “chiral amine” approach enabling the synthesis of axially chiral 1,3-disubstituted allenes directly from terminal alkynes and aldehydes using (*S*)-α,α-diphenylprolinol **3** (a, Scheme 1).[4] However, extensive study in this group revealed

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(1) For most recent reviews on the chemistry of allenes, see: (a) Ma, S. *Aldrichimica Acta* **2007**, *40*, 91. (b) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. (c) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679. (d) Alcaide, B.; Almendros, P.; Campo, T. M. d. *Chem.—Eur. J.* **2010**, *16*, 5836. (e) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. (f) Inagaki, F.; Kitagaki, S.; Mukai, C. *Synlett* **2011**, 594. (g) López, F.; Mascareñas, J. L. *Chem.—Eur. J.* **2011**, *17*, 418. (h) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074.

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(3) For the synthesis of axially chiral allenes from enantioenriched propargylamines, see: (a) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529. (b) Lo, V. K.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2008**, *10*, 517. (c) Lo, V. K.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213. (d) Gurubrahamam, R.; Periasamy, M. *J. Org. Chem.* **2013**, *78*, 1463.

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(6) For selected most recent examples, see: (a) Vyas, D. J.; Hazra, C. K.; Oestreich, M. *Org. Lett.* **2011**, *13*, 4462. (b) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *Org. Lett.* **2011**, *13*, 6312. (c) Uehling, M. R.; Marionni, S. T.; Lalic, G. *Org. Lett.* **2012**, *14*, 362. (d) Yang, M.; Yokokawa, N.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2012**, *14*, 816. (e) Li, Z.; Boyarskikh, V.; Hansen, J. H.; Autschbach, J.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2012**, *134*, 15497. (f) Li, H.; Müller, D.; Guénée, L.; Alexakis, A. *Org. Lett.* **2012**, *14*, 5880.

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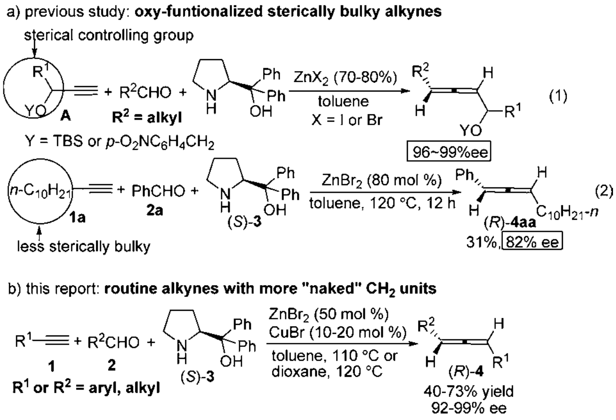
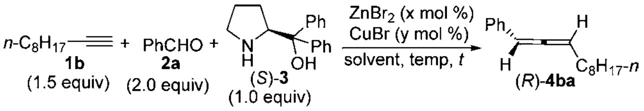
that the substrate scope is very limited: only the **A**-type of α-oxy-functionalized alkynes and aliphatic aldehydes may be applied (a, Scheme 1 and entry 1, Table 1);[4] with 1-dodecyne and benzaldehyde, the corresponding allene (*R*)-**4aa** was formed in 31% yield with a much lower ee (82%) (eq 2, Scheme 1).[5] Thus, it is still a challenge to prepare the optically active simple 1,3-disubstituted allenes from widely available terminal alkynes with much less sterically bulky "naked" CH_2 units adjacent to the C–C triple bond since the oxygen-containing unit ($CH(OY)R^1$) (eq 1, Scheme 1) acts as the enantioselective-dictating group based on our previous studies.[4] On the other hand, bimetallic catalysts, which are distinct from those of their monometallic counterparts, have been shown to exhibit unique activities in a wide range of organic transformations.[7] Given that Zn(II) salt alone showed low efficiency for the synthesis of simple axially chiral allenes, we thus envisaged that the bimetallic strategy might be a solution for higher reactivity and enantioselectivity for this reaction. Herein, we report a highly enantioselective bimetallic asymmetric approach to axially chiral allenes from both aromatic or aliphatic aldehydes, less sterically bulky alkynes, and chiral amine (*S*)-α,α-diphenylprolinol **3** (b, Scheme 1).

Scheme 1. Synthesis of Axially Chiral Allenes Using (*S*)-α,α-Diphenylprolinol **3**



After screening numerous additives to $ZnBr_2$ such as $FeCl_2$, $FeCl_3$, NaBr, LiBr, KBr, $HgCl_2$, $AuBr_3$, etc., we eventually observed that when 10 mol % CuBr was added to the reaction mixture of 1.5 equiv of 1-decyne **1b**, 2.0 equiv of benzaldehyde **2a**, 1.0 equiv of (*S*)-α,α-diphenylprolinol **3**, and 50 mol % $ZnBr_2$, the yield of (*R*)-**4ba** dramatically improved from 22% to 53% (entry 2 vs 1, Table 1); in addition, the enantiomeric excess also improved to 96% (cf. eq 2 in Scheme 1)! The reaction temperature was also found to be crucial for this transformation: Elevating the temperature to 120 °C led to an erosion in enantioselectivity (entry 3, Table 1) whereas lowering the temperature to 100 °C resulted in a very low yield of (*R*)-**4ba**, although the enantioselectivity improved slightly (entry 4, Table 1), which is expected. Notably, when the reaction was carried out with 50 mol % $ZnBr_2$ and 20 mol % CuBr in dioxane at 120 °C, (*R*)-**4ba** can be obtained in comparable yield with **98% ee** (entry 5, Table 1). Therefore, 50 mol % $ZnBr_2$, 10–20 mol % CuBr, 1.5 equiv of 1-alkyne, and 2 equiv of aldehyde in toluene at 110 °C (conditions A) or dioxane at 120 °C (conditions B) for 13 h were established as the standard conditions for further study.

Table 1. Optimization of the Reaction Conditions[a]



entry	*x*/*y*	solvent	temp (°C)/*t* (h)	yield of (*R*)-**4ba** (%)[b]
1	50/0	toluene	110 °C, 13 h	22[c]
2	50/10	toluene	110 °C, 13 h	53 (96% ee)
3	50/10	toluene	120 °C, 8.5 h	55 (92% ee)
4	50/10	toluene	100 °C, 24 h	30[d] (98% ee)
5	50/20	dioxane	120 °C, 13 h	50 (98% ee)

[a] The reactions were carried out with (*S*)-**3** (1.0 mmol), 1-decyne **1b** (1.5 mmol), benzaldehyde **2a** (2.0 mmol), and the indicated amounts of $ZnBr_2$ and CuBr in 3 mL of solvent. [b] Isolated yield of (*R*)-**4ba** based on (*S*)-**3**; ee was determined by chiral HPLC analysis. [c] NMR yield of (*R*)-**4ba**; ee not determined; 7% of the propargylic amine (*S*,*S*)-**5ba** (*vide infra*) was also formed as determined by ^1H NMR analysis of the crude reaction mixture. [d] 8% of the propargylic amine (*S*,*S*)-**5ba** was formed as determined by ^1H NMR analysis of the crude reaction mixture.

With the optimized reaction conditions in hand, the generality of the reaction was then explored, and representative results are summarized in Table 2. Gratifyingly, both electron-poor and -rich aromatic aldehydes are compatible under the optimized conditions: Aromatic aldehydes with a synthetically versatile Br, Cl, or F substituent at the *meta*- or *para*-position all underwent the reaction smoothly, affording the corresponding allene products (*R*)-**4bb**–(*R*)-**4bf** in moderate yields with up to 98% ee (entries 3–7, Table 2); aromatic aldehydes containing an electron-donating group such as CH_3 or MeO can also be transformed into the desired products (*R*)-**4bg**–(*R*)-**4bi** in practical yields with 93–98% ee (entries 8–10, Table 2). Notably, terminal alkyne **1d** with a chlorine atom at the 5-position was also tolerated, furnishing (*R*)-**4da** in 50% yield with 93% ee and 43% yield with 99% ee under conditions A and B, respectively (entry 12, Table 2). Moreover, phenylacetylene **1e** and aliphatic aldehyde **2j** may also be employed to afford axially chiral allene (*R*)-**4ej** in moderate yields with 99% ee (entry 13, Table 2). This protocol may also be extended to the alkynyl benzyl ether **1f**, affording axially chiral allene (*R*)-**4fj** in modest yield with 99% ee under the two sets of reaction conditions (entry 14, Table 2). Interestingly, reactions carried out in dioxane at 120 °C generally afforded the corresponding axially chiral allenes with higher enantioselectivity, albeit

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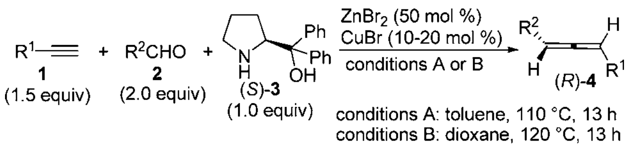
in a slightly lower yield (conditions B vs conditions A in Table 2).

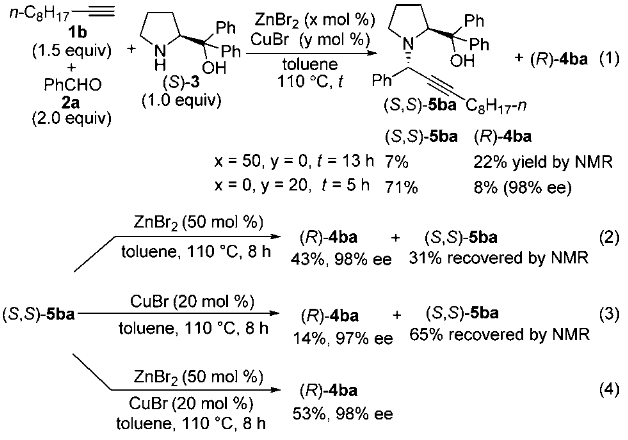
Table 2. Bimetallic Zn(II)/Cu(I)-Mediated Asymmetric Synthesis of Axially Chiral Allenes from 1-Alkyne, Aldehyde, and (*S*)-**3**[a]



entry	R^1 (**1**)/R^2 (**2**)	yield of (*R*)-**4** (%)[b]/(ee %)[c]	
		conditions A	conditions B
1	n-$C_{10}H_{21}$ (**1a**)/Ph (**2a**)	**4aa**, 48 (95)	–
2	n-C_8H_{17} (**1b**)/**2a**	**4ba**, 53[c] (96)	50 (98)
3	**1b**/p-BrC_6H_4 (**2b**)	**4bb**, 44 (95)	42 (98)
4	**1b**/m-BrC_6H_4 (**2c**)	**4bc**, 45 (95)	41 (96)
5	**1b**/p-ClC_6H_4 (**2d**)	**4bd**, 47 (95)	–
6	**1b**/m-ClC_6H_4 (**2e**)	**4be**, 45 (95)	41 (96)
7	**1b**/p-FC_6H_4 (**2f**)	**4bf**, 57 (92)	48 (96)
8	**1b**/p-$CH_3C_6H_4$ (**2g**)	**4bg**, 53[c] (93)	40 (97)
9	**1b**/m-$CH_3C_6H_4$ (**2h**)	**4bh**, 51[c] (95)	48 (98)
10	**1b**/m-$MeOC_6H_4$ (**2i**)	**4bi**, 52 (95)	46 (97)[d]
11	n-C_6H_{13} (**1c**)/**2a**	**4ca**, 46 (96)	40 (99)
12	$Cl(CH_2)_2CH_2$ (**1d**)/**2a**	**4da**, 50[e] (93)	43 (99)
13	Ph (**1e**)/Cy (**2j**)	**4ej**, 51 (99)	47 (99)
14	$BnOCH_2$ (**1f**)/Cy (**2j**)	**4fj**, 73 (98)	63 (99)

[a] The reactions were carried out with $ZnBr_2$ (50 mol %), CuBr (20 mol %), (*S*)-**3** (1.0 mmol), **1** (1.5 mmol), and **2** (2.0 mmol) in 3 mL of solvent unless otherwise noted. [b] Isolated yield of (*R*)-**4** based on (*S*)-**3**; ee was determined by chiral HPLC analysis. [c] CuBr (10 mol %) was used. [d] (*R*)-**4bi** was obtained in 47% yield and 97% ee on a 4 mmol scale of (*S*)-**3**. [e] Contaminated with minor impurities.

Scheme 2. Control and Mechanistic Experiments

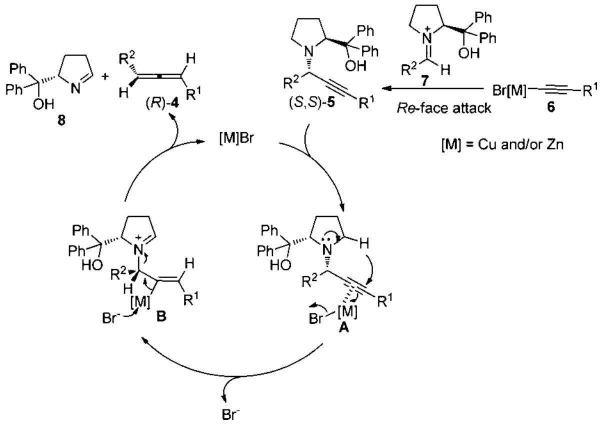


To gain insight into the roles of both $ZnBr_2$ and CuBr, control experiments were conducted (Scheme 2). When the reaction was carried out with 50 mol % $ZnBr_2$ in the absence of CuBr at 110 °C for 13 h, the allene product (*R*)-**4ba** was formed in only 22% yield as determined by ^{1}H NMR analysis (eq 1, Scheme 2). On the other hand, when the same reaction was carried out with only 20 mol % CuBr, (*R*)-**4ba** was obtained in only 8% yield with 98% ee and a 71% yield of propargylic amine (*S*,*S*)-**5ba**[3] was isolated (eq 1, Scheme 2). Based on these experimental data, we believe that *the catalytic amount of CuBr must play a much more important role than the 50 mol % of* $ZnBr_2$ *in furnishing the first step efficient and high-yielding formation of the* **5***-type propargylic amine ensuring an excellent de (cf. eq 2 in Scheme 1).*

When the isolated propargylic amine intermediate (*S*,*S*)-**5ba** was treated with 50 mol % $ZnBr_2$ for 8 h, (*R*)-**4ba** was obtained in 43% yield with 98% ee, with 31% of (*S*,*S*)-**5ba** being recovered (eq 2, Scheme 2); as a comparison, with 20 mol % CuBr, (*R*)-**4ba** was obtained only in 14% yield with 97% ee and 65% of the propargylic amine (*S*,*S*)-**5ba** was recovered after 8 h (eq 3, Scheme 2). These data clearly indicate that $ZnBr_2$ exhibits a higher activity for transforming the propargyl amine intermediate into the allene products as compared to CuBr. Importantly, it should be noted that it is the combination of 50 mol % $ZnBr_2$ and 20 mol % CuBr that efficiently converted the propargylic amine (*S*,*S*)-**5ba** to (*R*)-**4ba** in 53% yield with 98% ee within 8 h (eq 4, Scheme 2). Therefore, we may safely come to the conclusion that both $ZnBr_2$ and CuBr are responsible for the more efficient transformation of the chiral propargylic amine intermediate to the chiral allene product with a very high efficiency of central-to-axial chirality transfer.

The absolute configurations of allenes were assigned clearly based on the Lowe–Brewster rule[8] and the previous studies.[4] A model to predict the absolute configuration of the allene moiety for the highly enantioselective formation of (*R*)-**4** is shown in Scheme 3.[4,9] The alkynylmetal species **6**, which was formed by deprotonation of the corresponding alkyne in the presence of CuBr, $ZnBr_2$, and amine, reacted with the in situ generated iminium ion **7** via *Re*-face attack, furnishing highly enantioenriched propargylic amine intermediate (*S*,*S*)-**5**, which then undergoes highly stereoselective intramolecular 1,5-hydride transfer and

Scheme 3. Proposed Mechanism and Prediction of the Absolute Configuration of the Allene



β-elimination to generate the axially chiral allene unit under the cooperation of Cu(I) and $ZnBr_2$. As indicated by the aforementioned experimental results, CuBr may play an exclusive role in the efficient formation of chiral propargylic amine whereas both CuBr and $ZnBr_2$ are responsible for the formation of allene products.

In conclusion, we have developed a new bimetallic asymmetric approach for simple axially chiral allenes from terminal alkynes and aldehydes by taking advantage of the readily available and cheap chiral amine (*S*)-α,α-diphenylprolinol **3**. Due to the ready availability of all the starting materials, the potential of the axially chiral allene products,[1,10] and the respectable yields (> 70% per-step based on the mechanism shown in Scheme 3), this methodology will be of high interest for the synthetic community. Further studies to expand the scope of the reaction and gain a better understanding of the bimetallic system are ongoing in our laboratory.

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Supporting Information Available. Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.