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# Enantio- and Diastereoselective Tandem Zn-Promoted Brook Rearrangement/ Ene−Allene Carbocyclization Reaction

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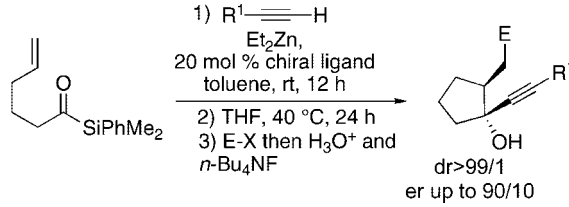
## ABSTRACT




**The zinc-catalyzed addition of various alkynes to acylsilanes followed by a Zn−Brook rearrangement and either the Zn−ene−allene or Zn−yne−allene cyclization led to the enantio- and diastereoselective formation of carbocycles in a single-pot operation.**

The preparation of enantioenriched tertiary alcohols represents a stimulating and dynamic area in organic synthesis. Although effective methods have been described for the catalytic enantioselective carbon−carbon bond-forming reactions of ketones, they are difficult substrates because of their low reactivity and the difficulty in controlling facial stereoselectivity.[1] Therefore, due to the synthetic challenge imposed by the difficulties in the creation of such quaternary stereocenters, most methods usually lead to the creation of a single carbon−carbon bond per chemical step.[2] Over the past few years, our laboratory has been involved in the development of alternative and efficient synthetic methodologies that create several carbon−carbon bonds and stereogenic centers, including quaternary stereocenters, in a single-pot operation,[3] and we recently questioned whether it might be possible to develop a simple synthetic solution to the challenging enantio- and diastereoselective intramolecular carbometalation reaction on unactivated alkenes[4] by using this principle. Indeed, only very few enantioselective carbometalations of alkenes are reported in the literature,[4]

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(1) (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445. (b) Ramon, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651. (c) Garcia, C.; La Rochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970. (d) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668. (e) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895. (f) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778. (g) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (h) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. (i) Garcia, C.; Larochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970. (j) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538. (k) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 8355.

(2) For some representative exceptions, see: (a) Marek, I. *Chem. Eur. J.* **2008**, *14*, 7460. (b) Hussain, M. H.; Walsh, P. J. *Acc. Chem. Res.* **2008**, *41*, 883.

(3) (a) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (b) Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *119*, 9451. (c) Sklute, G.; Marek, I. *J. Am. Chem. Soc.* **2006**, *128*, 4642. (d) Sklute, G.; Amsallem, D.; Shibli, A.; Varghese, J. P.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 11776.

(4) For reviews, see: (a) Hogan, A-M. L.; O'Shea, D. E. *Chem. Commun.* **2008**, *38*, 3839. (b) Perez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *New J. Chem.* **2008**, *32*, 594. (c) Marek, I. *J. Chem. Soc. Perkin Trans 1* **1999**, 535.

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particularly via asymmetric catalysis.[5] In this paper, we would like to report the first enantio- and diastereoselective Zn−ene−allene cyclization, via asymmetric catalysis, in which several carbon−carbon bonds including the challenging tertiary alcohol stereocenter were created in a single-pot operation. The intramolecular addition of propargyl/allenylzinc compounds to alkenes and alkynes, called zinc−ene−allene[6] and zinc−yne−allene[7] carbocyclization, respectively, leading to the unique formation of carbocycles in excellent yields as unique diastereoisomers was described from our research group and was successfully used for the stereoselective syntheses of polysubstituted tetrahydrofurans[8] and pyrrolidines[9] as well as for an efficient approach to angular and linear triquinane skeletons.[10]

This initial approach was further improved when it was found that a tandem Zn-promoted Brook rearrangement−carbocyclization reaction also leads to the cyclic product in similar yields and diastereoselectivities (Scheme 1).[11] However, to have an enantio- and diastereoselective Zn−ene−allene carbocyclization reaction, we have to address the challenging in situ preparation and cyclization of enantiomerically enriched allenylzinc species. The asymmetric alkyne addition on a model acysilane was reported in the literature,[12] and it has been shown that an enantioenriched silyl alkynol could be treated with a catalytic amount of *n*-BuLi to generate chiral allenyl silylether with minimal erosion of stereochemical information. However, the Brook rearrangement proceeds only when a catalytic amount of base is utilized, and the typically rapid and essentially irreversible reaction is by protonation of the carbanion by the starting alcohol.[13] Therefore, transfer of chirality into a *metallated* allenyl species through a stoichiometric amount of base for the Brook rearrangement[14] had no precedent, and that drove our curiosity. We first prepared enantioenriched propargyl silanol using a tridentate Schiff base ligand **3a** as reported by Scheidt,[12a] and our results are described in Table 1. We were pleased to see that the addition of phenyl acetylene **1a** ($R^1$ = Ph) to acylsilane **2a** ($R^2$ = Ph, $R^3$ = Me) proceeds smoothly to give the expected propargyl silanol **4a** in excellent yield and in fair enantiomeric ratio (94%, er 86:14, see Table 1, entry 1). Although the same behavior was found with acylsilane **2b** ($R^2 = R^3$ = Ph, er 88:12, entry 2,

**Scheme 1.** Tandem Zn-Promoted Brook Rearrangement/Ene−Allene Carbocyclization Reaction

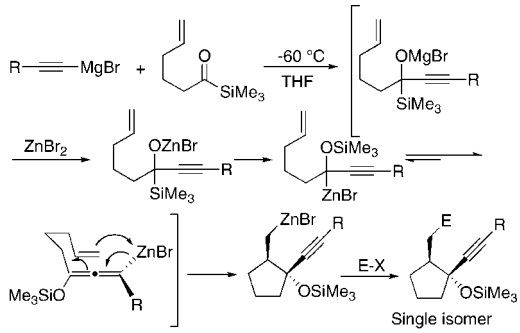
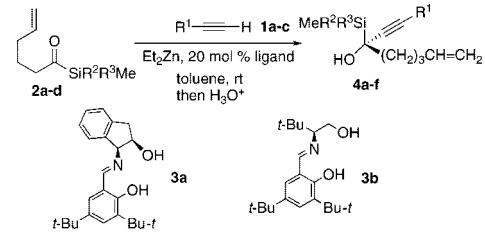



**Table 1.** Enantioselective Addition of Alkynes **1a**−**c** to Acylsilanes **2a**−**d**




| entry | $R^1$ | $R^2$ | $R^3$ | ligand | yield[a] (%) | er[b] |
|---|---|---|---|---|---|---|
| 1 | Ph (**1a**) | Ph | Me (**2a**) | **3a** | 94 (**4a**) | 86:14 |
| 2 | Ph (**1a**) | Ph | Ph (**2b**) | **3a** | 78 (**4b**) | 88:12 |
| 3 | Ph (**1a**) | Me | *t*-Bu (**2c**) | **3a** | 55 (**4c**) | 53:47 |
| 4 | Ph (**1a**) | Me | Me (**2d**) | **3a** | 96 (**4d**) | 76:24 |
| 5 | Ph (**1a**) | Ph | Me (**2a**) | **3b** | 93 (**4a**) | 90:10 |
| 6 | Hex (**1b**) | Ph | Me (**2a**) | **3a** | 80 (**4e**) | 84:16 |
| 7 | $SiMe_3$ (**1c**) | Ph | Me (**2a**) | **3a** | 87 (**4f**) | 67:33 |

[a] Isolated yields after column chromatography on silica gel. [b] Enantiomeric ratio determined by HPLC on chiral column. [c] Absolute configuration determined by comparison of experimentally measured and calculated CD.[15]

(5) Li chemistry: (a) Majumdar, S.; de Meijere, A.; Marek, I. *Synlett* **2002**, 423. (b) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem.−Eur. J.* **1999**, *5*, 2055. (c) Norsikian, S.; Marek, I.; Poisson, J. F.; Normant, J. F. *J. Org. Chem.* **1997**, *117*, 8853. (d) Klein, S.; Marek, I.; Poisson, J. F.; Normant, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 8853. Zn chemistry: (e) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437. (f) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978. Zr chemistry: (g) Liang, B.; Novak, T.; Tan, Z.; Negishi, E. *J. Am. Chem. Soc.* **2006**, *128*, 2770, and references cited therein. (h) Wipf, P.; Ribe, S. *Org. Lett.* **2002**, *4*, 395. (i) Heron, N. M.; Adams, J. A.; Hoveyda, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6205.

(6) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J. F. *J. Org. Chem.* **1995**, *60*, 863.

(7) Meyer, C.; Marek, I.; Normant, J. F.; Platzer, N. *Tetrahedron Lett.* **1994**, *35*, 5645.

(8) (a) Lorthiois, E.; Marek, I.; Meyer, C.; Normant, J. F. *Tetrahedron Lett.* **1995**, *36*, 1263. (b) Lorthiois, E.; Marek, I.; Normant, J. F. *Bull. Chem. Soc. Fr.* **1997**, *134*, 5317.

(9) Lorthiois, E.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1997**, *38*, 89.

(10) Meyer, C.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1996**, *37*, 857.

(11) (a) Unger, R.; Cohen, T.; Marek, I. *Org. Lett.* **2005**, *7*, 5313. (b) Unger, R.; Cohen, T.; Marek, I. *Eur. J. Org. Chem.* **2009**, 0000.

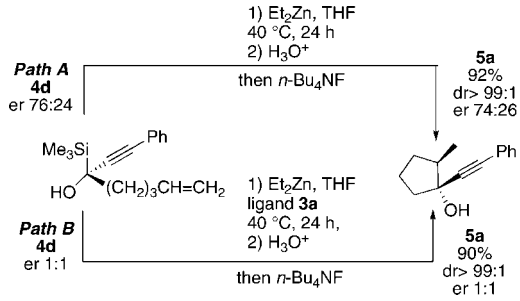
(12) (a) Reynolds, T. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 15382. (b) Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170.

(13) For representative examples, see: (a) Reich, H. J.; Eisenhart, E. K.; Olson, R. E.; Kelly, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 7791. (b) Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609.

(14) For recent reports on the Brook rearrangements, see: (a) Smith, A. B., III.; Kim, W.-S.; Wuest, W. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7082. (b) Smith, A. B., III.; Kim, D. S. *J. Org. Chem.* **2006**, *71*, 2547. (c) Smith, A. B., III.; Kim, D. S. *Org. Lett.* **2005**, *7*, 3247. (d) Smith, A. B., III.; Kim, D. S. *Org. Lett.* **2004**, *6*, 1493. (e) Reynolds, T. E.; Stern, C. A.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 2581. (f) Tsubouchi, A.; Onishi, K.; Takeda, T. *J. Am. Chem. Soc.* **2006**, *128*, 14268. (g) Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070. (h) Nicewicz, D. A.; Yates, C. M.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2652. (i) Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534. (j) Linghu, X.; Nicewicz, D. A.; Johnson, J. S. *Org. Lett.* **2002**, *4*, 2957.

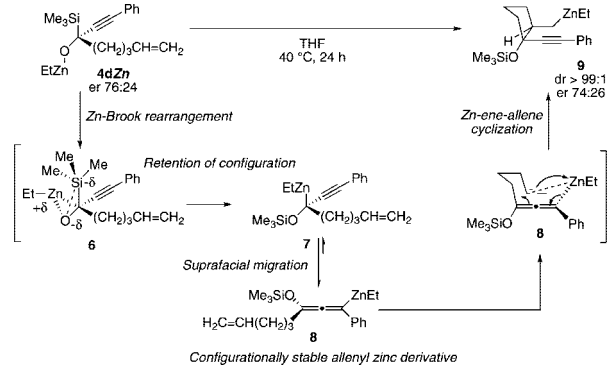
Table 1), the more sterically hindered ($R^2$ = Me, $R^3$ = *t*-Bu) as well as symmetrically substituted ($R^2$ = $R^3$ = Me) acylsilanes **2c**,**d** led to lower enantiomeric ratios (Table 1, entries 3 and 4, respectively). The enantiomeric ratio could be slightly improved for the reaction between **1a** and **2a** by using ligand **3b** instead of **3a** (er 90:10, Table 1, entry 5). In contrast to phenyl acetylene **1a** (Table 1, entry 1) and oct-1-yne **1b** ($R^1$ = Hex, Table 1, entry 6), the enantiomeric ratio of **4f**, resulting from the addition of trimethylsilylacetylene **1c** to **2a**, is only moderate (er 67:33, Table 1, entry 7). Having in hand propargyl silanol derivatives, we then investigated the transfer of chirality in the tandem Zn−Brook rearrangement followed by the Zn−ene−-allene carbocyclization reaction on the moderately enantioenriched **4d** as described in Scheme 2.

**Scheme 2.** Transfer of Chirality in the Sequence Zn-Brook Rearrangement/Zn-ene-allene Carbocyclization




We were pleased to see that when a solution of $Et_2Zn$ was added to enantioenriched **4d** (er 76:24) in THF and heated at 40 °C for 24 h,[16] the corresponding cyclic product **5a** was obtained in excellent yield with a similar enantiomeric ratio (er 74:26) *over three consecutive steps* (Zn−Brook rearrangement, Zn suprafacial migration, and Zn−ene−allene cyclization, see Scheme 2, path A).[17] On the other hand, when racemic **4d** was treated with $Et_2Zn$ in the presence of chiral ligand **3a**, only racemic **5a** was formed excluding a possible equilibration of racemic propargyl/allenylzinc into enantiomerically enriched species via interactions with chiral ligand (Scheme 2, path B). The stereochemical outcome of the first rearrangement, namely the 1,2-silyl migration, has been occasionally investigated and occurs with partial inversion of configuration for secondary and tertiary α-silyl benzyl alcohols, respectively, but with retention (>97%) of configuration if the phenyl substituent is replaced by an alkyl group.[18] However, silylalkyl anions were always in situ intercepted rapidly and irreversibly by using solvents containing water[19] or protic source.[13a] No report on the stereochemistry of the 1,2-Brook rearrangement was available, particularly for the formation of a propargylzinc species. Although more mechanistic investigations are needed to fully explore this rearrangement, the absolute configuration of the starting propargyl silanol **4d** and the final cyclic product **5a** led us to postulate the following mechanistic hypothesis: the oxygen atom of the zinc alcoholate **4d*Zn*** first interacts with the silicon atom to form an intermediate such as **6**,[19] the zinc countercation occupying the less sterically hindered face, adjacent to the alkyne (Scheme 3).

**Scheme 3.** Mechanistic Hypothesis




The zinc−Brook rearrangement would lead to the corresponding propargylzinc derivative **7**, with pure retention of configuration. The second rearrangement in our process, the metallotropic equilibrium with its allenic counterpart **8**, occurs via a suprafacial migration leading to the corresponding configurationally stable allenylzinc derivative **8** with pure retention of configuration.[20] The latter then undergoes the last step, a diastereoselective Zn−ene−allene cyclization reaction in which the allenyl metal moiety plays the role of the ene moiety and fixes the cis relationships of the two substituents to give the corresponding alkynyl cyclopentyl methylzinc derivative **9** (Scheme 3). Clearly, this whole sequence (three consecutive steps) proceeds with virtually complete transfer of chirality from **4d** with the creation of two new stereocenters, including the formation of the tertiary silyl ether as illustrated in **9**.

As in the alkynylation of the acylsilane, the Brook rearrangement and the carbocyclization involve only the zinc

(15) See the experimental part and (a) Masarwa, A.; Stanger, A.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 8039. (b) Simaan, S.; Masarwa, A.; Bertus, P.; Marek, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 3963.

(16) When the reaction mixture is warmed at higher temperature, the diastereoselectivity of the reaction decreases. However, in pure toluene, no significant Brook rearrangement product could be detected (<5%).

(17) For an easier determination of enantiomeric ratio by chiral HPLC, the silyl ether is transformed into free alcohol by treatment of the crude reaction mixture with a solution of tetra-*n*-butylammonium fluoride.

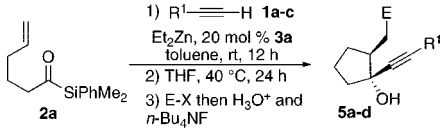
(18) For 1,2-silyl migration with retention of configuration, see: (a) Simov, B. J.; Wuggenig, F.; Mereiter, K.; Andres, H.; France, J.; Schnelli, P.; Hammerschmidt, F. *J. Am. Chem. Soc.* **2005**, *127*, 13934. (b) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809. (c) Hoffmann, R.; Brückner, R. *Chem. Ber.* **1992**, *125*, 2731. (d) Kapeller, D. C.; Brecker, L.; Hammerschmidt, F. *Chem. Eur. J.* **2007**, *13*, 9582. For 1,2-silyl migration with inversion of configuration, see: (f) Brook, A. G.; Pascoe, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 6224. (g) Biernbaum, M. S.; Mosher, H. S. *J. Am. Chem. Soc.* **1971**, *93*, 6221.

(19) For theoretical investigations, see: (a) Antoniotti, P.; Tonachini, G. *J. Org. Chem.* **1993**, *58*, 3622. (b) Wang, Y.; Dolg, M. *Tetrahedron* **1999**, *55*, 12751. (c) Yu, Y.; Feng, S. *J. Phys. Chem. A* **2004**, *108*, 7468.

(20) For configurationally stable allenylzinc derivatives, see: (a) Poisson, J.-F.; Normant, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4639. (b) Poisson, J.-F.; Chemla, F.; Normant, J. F. *Synlett* **2001**, 305. (c) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812. (d) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825.

species; we should therefore be able to perform the entire sequence in a single-pot operation as described in Table 2 via asymmetric catalysis.

**Table 2.** Formation of Carbocycles from Acylsilanes and Alkynes



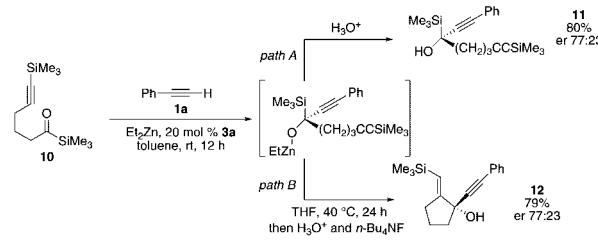

| entry | $R^1$ | E−X | yield[a] (%) | dr[b] | er[c,d] |
|---|---|---|---|---|---|
| 1 | Ph (**1a**) | $H_3O^+$ | 92 (**5a**) | >99:1 | 81:19 |
| 2 | Hex (**1b**) | $H_3O^+$ | 91 (**5b**) | >99:1 | 77:23[e] |
| 3 | Hex (**1b**) | $I_2$ | 65 (**5c**) | >99:1 | 77:23 |
| 4 | $Me_3Si$ (**1c**) | $H_3O^+$ | 87 (**5d**) | >99:1 | 61:39 |

[a] Isolated yields after column chromatography. [b] Diastereomeric ratio determined by chiral HPLC and by $^1$H NMR. [c] Enantiomeric ratio determined by HPLC on chiral column. [d] Absolute configuration determined by comparison of experimentally measured and calculated CD.[15] [e] The enantiomeric ratio of **5b** was determined by analogy with **5c** (enantiomers of **5b** could not be completely separated by HPLC).

When acylsilane **2a** was added to phenylacetylene **1a** in the presence of $Et_2Zn$ and 20 mol % of chiral ligand **3a**, as shown in Table 2, the corresponding cyclopentanol **5a** (E = H) was obtained in excellent isolated yield as a unique diastereoisomer with an almost complete transfer of chirality [from intermediate **4a** of er 86:14 (see Table 1, entry 1), to **5a** of er 81:19 (Table 2, entry 1)]. The same behavior was found when acylsilane **2a** was treated, under the same experimental conditions, with oct-1-yne **1b** (Table 2, entry 2) or trimethylsilylacetylene **1c** (Table 2, entry 4). The enantiomeric ratio determined after the alkynylation reaction (Table 1, entries 6 and 7, respectively) is practically the same as the one obtained for the cyclic products **5b**−**d**. The formation of a discrete organometallic species after carbocyclization was checked by iodinolysis (Table 2, entry 3).

The same principle could be extended to the first enantioselective Zn−yne−allene cyclization as described in Scheme 4. The addition of phenylacetylene **1a** to an acylsilane **10** possessing an electrophilic alkynylsilane moiety led to the corresponding propargylsilanol **11**, after hydrolysis, in excellent yield with an enantiomeric ratio of 77:23 (path A,

**Scheme 4.** Enantioselective Zn−Yne−Allene Cyclization




Scheme 4). By heating the reaction mixture before hydrolysis at 40 °C in THF for 24 h, the cyclic product **12**, resulting from the Brook rearrangement followed by suprafacial migration of the zinc along the carbon chain of the alkyne and then the Zn−yne−allene carbocyclization, was obtained in 80% yield with a complete transfer of chirality (er 77:23) and as a unique geometrical *E*-isomer.

In summary, the catalytic enantioselective alkynylation of an acylsilane followed by a zinc-promoted Brook rearrangement and finally the ene−allene or yne−allene cyclization represents a very efficient and powerful entry to enantiomerically enriched carbocycles with formation of synthetically challenging quaternary stereocenters, with the formation of three new bonds in a single-pot operation. One of the most remarkable features of this sequence is the highly efficient transfer of chirality in the formation of the organometallic product during the Zn−Brook rearrangement. Currently, our efforts are directed toward elucidating the mechanism of this new asymmetric transformation as well as improving the enantioselectivity of the alkynylation reaction.

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**Supporting Information Available:** Experimental procedure with description of $^1$H and $^{13}$C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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