ORGANIC LETTERS

2006
Vol. 8, No. 15
3379−3381

Enantioselective C–C Bond Cleavage Creating Chiral Quaternary Carbon Centers

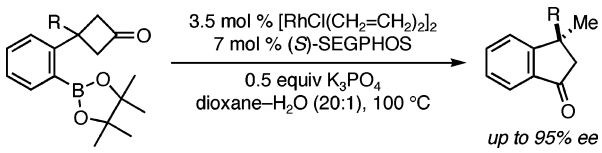
Takanori Matsuda, Masanori Shigeno, Masaomi Makino, and Masahiro Murakami*

Department of Synthetic Chemistry & Biological Chemistry, Kyoto University, Katsura, Kyoto 615-8510, Japan

murakami@sbchem.kyoto-u.ac.jp

Received June 3, 2006

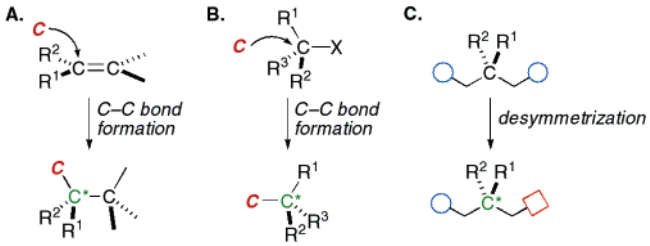
ABSTRACT



A chiral all-carbon benzylic quaternary carbon center is created by the asymmetric intramolecular addition/ring-opening reaction of a boryl-substituted cyclobutanone, which involves enantioselective *β*-carbon elimination from a symmetrical rhodium cyclobutanolate. The asymmetric reaction was successfully applied to a synthesis of sesquiterpene, (–)-α-herbertenol.

Chiral all-carbon quaternary centers are often contained in natural products and pharmaceuticals, yet the synthesis of such centers with control of asymmetry remains a significant challenge for synthetic chemists.[1] A few methods can be envisaged for the asymmetric construction of chiral quaternary centers (Scheme 1). A direct method to achieve this transformation is by the stereoselective introduction of a carbon−carbon bond onto an unsymmetrically *gem*-disubstituted sp^2 carbon of an olefin (**A**) or onto a tertiary sp^3 carbon with resident chirality (**B**). In these carbon−carbon bond-forming methods, the stereochemical information is installed at a highly sterically congested carbon. The desymmetrization of a preinstalled symmetrically substituted quaternary carbon center would also provide convenient access to chiral quaternary centers. This alternative pathway (**C**) dispenses with the need to form a carbon−carbon bond with control of asymmetry in the midst of significant steric congestion.

Scheme 1



We previously reported the rhodium-catalyzed intermolecular reaction of arylboronic acids with cyclobutanones, which produces arylated ketones through a 1,2-addition to the carbonyl group and subsequent ring-opening of the resulting rhodium cyclobutanolates by *β*-carbon elimination.[2] We envisioned that selective cleavage of one of the two prochiral carbon−carbon single bonds of a symmetrical cyclobutane skeleton would open an avenue for the asym-

(1) Reviews on asymmetric construction of quaternary carbon centers: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (d) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (e) Christopher, J. D.; Overman, L. E. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (f) Christoffers, J., Baro, A., Eds. *Quaternary Stereocenters*; Wiley-VCH: Weinheim, 2005.

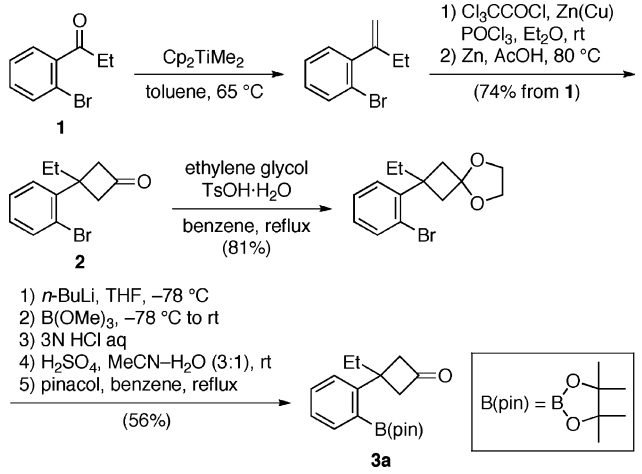
(2) (a) Matsuda, T.; Makino, M.; Murakami, M. *Org. Lett.* **2004**, *6*, 1257. (b) Matsuda, T.; Makino, M.; Murakami, M. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1528. (c) Matsuda, T.; Makino, M.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4608.

10.1021/ol061359g CCC: $33.50
Published on Web 06/20/2006

metric synthesis of chiral quaternary carbon centers via pathway **C** in Scheme 1.[3] In this paper, we report the rhodium-catalyzed asymmetric synthesis of 1-indanones having benzylic quaternary carbon centers[4] and the application of this method to a synthesis of a naturally occurring sesquiterpene, (−)-α-herbertenol.

To achieve the desymmetrization reaction, we prepared cyclobutanone **3a** having a 2-borylphenyl group at the 3-position (Scheme 2). An *o*-bromostyrene derivative was

Scheme 2. Synthesis of Boryl-Substituted Cyclobutanone **3a**[a]



prepared by methylenation of 2-bromophenyl ethyl ketone (**1**) with the Petasis reagent. Subsequent [2 + 2] cycloaddition with dichloroketene followed by dechlorination with zinc afforded cyclobutanone **2**. After the carbonyl group was protected as a cyclic ketal, the *o*-bromo group was transformed into a boronic acid functionality. Deprotection of the ketal group, followed by treatment with pinacol furnished **3a**, equipped with a symmetrically substituted quaternary center and two prochiral carbon−carbon single bonds which were potentially amenable to enantioselective cleavage.

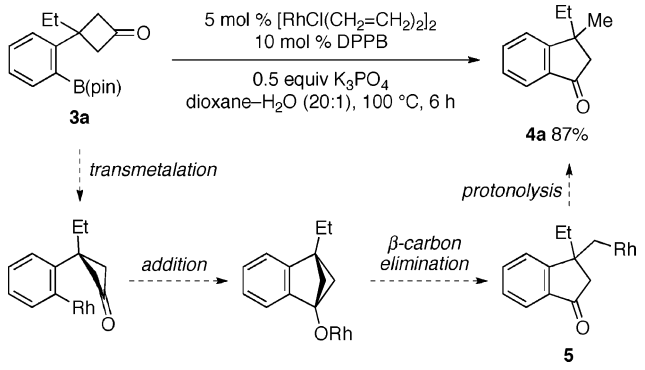
When boryl-substituted cyclobutanone **3a** was heated in 1,4-dioxane−H_2O (20:1) in the presence of a rhodium(I) catalyst (10 mol % of Rh, Rh/DPPB[5] = 1:1) at 100 °C for 6 h, an intramolecular addition/ring-opening reaction occurred to afford 3-ethyl-3-methyl-1-indanone (**4a**) in 87% yield (Scheme 3). Mechanistically, the reaction proceeds via (i) transmetalation of the boryl group of **3a** with rhodium(I), (ii) intramolecular addition of the arylrhodium species to the carbonyl group, forming a symmetrical bicyclo[2.1.1]hexane skeleton, (iii) ring-opening of the cyclobutanolate moiety by *β*-carbon elimination,[6] and (iv) protonolysis[7] to furnish a methyl group. Thus, the original symmetrically substituted quaternary carbon center at the benzylic position of **3a** was desymmetrized in **4a**.

(3) For analogous reaction creating a chiral center by *β*-carbon elimination from Pd(II) cyclobutanolate, see: Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862.

(4) For recent examples of asymmetric synthesis of 3,3-disubstituted 1-indanones, see: (a) Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2071. (b) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774.

(5) DPPB = 1,4-bis(diphenylphosphino)butane.

Scheme 3. Rhodium-Catalyzed Addition/Ring-Opening of **3a**

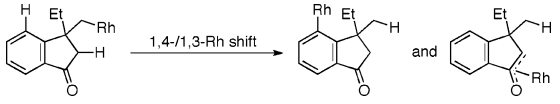


Our attention was then focused on an asymmetric version of the ring-opening reaction. Various chiral phosphine ligands were examined, and good enantioselectivities were observed with chiral biaryl diphosphine ligands. Representative results are listed in Table 1. The (*S*)-SEGPHOS ligand induced the best enantioselectivity of 95% ee for the reaction of **3a** (entry 1). The use of diphosphine ligands possessing a wider bite angle than SEGPHOS resulted in a decrease in enantioselectivity (entries 2 and 3).[8] The same trend was observed among the three chiral ligands in the reaction of **3b**, and product **4b** was obtained in 79% ee with SEGPHOS (entries 4−6). Cyclobutanone **3c**, having a bulky isopropyl group at the 3-position, also yielded **4c** in 94% ee although the reaction required higher catalyst loading and longer reaction time (entry 7).

The synthetic potential of the intramolecular addition/ring-opening reaction was demonstrated by application in the asymmetric synthesis of a sesquiterpene, (−)-α-herbertenol (**13**),[10] which exhibits a range of biological properties including antifungal activity.[11] In a manner similar to that for the synthesis of **3a** from **1** (Scheme 2), aryl ketone **7**, prepared from 2-bromo-5-methylbenzaldehyde (**6**), was transformed to the symmetrical cyclobutanone **8**, armed with an arylboronic acid moiety (Scheme 4). The rhodium-

(6) For recent examples of synthetic application of *β*-carbon elimination with transition metal cyclobutanolates, see: (a) Pd: Nishimura, T.; Uemura, S. *Synlett* **2004**, 201. (b) Ni: Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932.

(7) Deuterium labeling experiments revealed that 1,4- and 1,3-Rh shifts occurred prior to protonolysis. See the Supporting Information for further details.



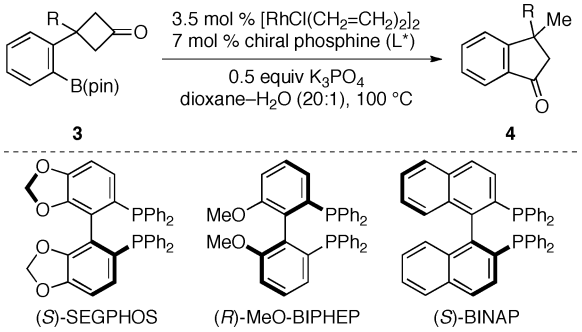
(8) Dihedral angles (*θ*) of free phosphines: SEGPHOS 67.2°; MeO-BIPHEP 72.3°; BINAP 86.2°. Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5799.

(9) **4a** (R = Et): Hill, R. K.; Newkome, G. R. *Tetrahedron* **1969**, *25*, 1249.

(10) For asymmetric total synthesis of **13**: (a) Abad, A.; Agulló, C.; Cuñat, A. C.; Perni, R. H. *J. Org. Chem.* **1999**, *64*, 1741. (b) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *J. Org. Chem.* **2003**, *68*, 5917. *ent*-**13**: (c) Srikrishna, A.; Babu, N. C.; Rao, M. S. *Tetrahedron Lett.* **2004**, *60*, 2125 and references therein.

(11) Matsuo, A.; Yuki, S.; Nakayama, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 701.

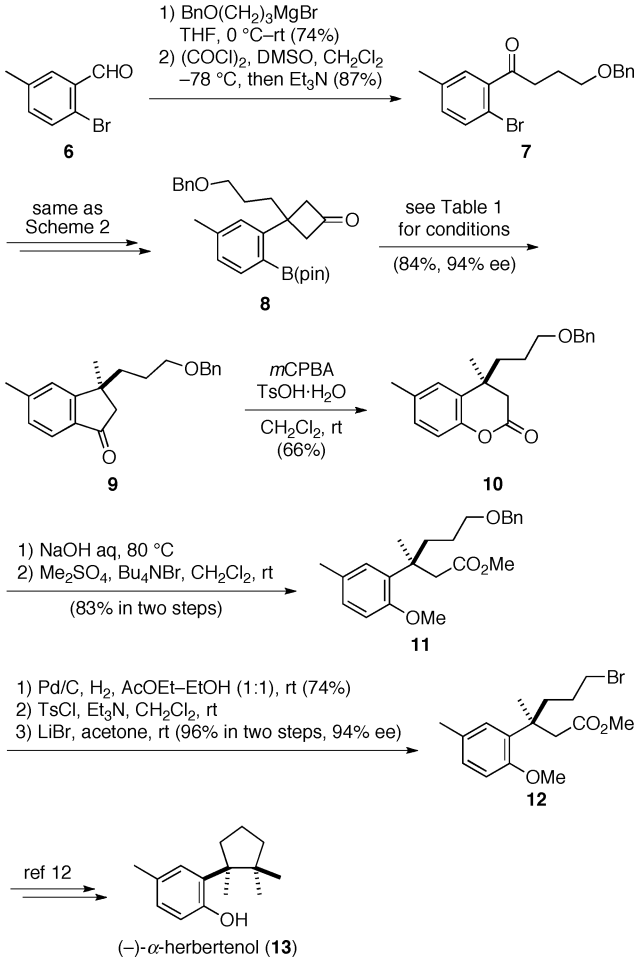
Table 1. Asymmetric Synthesis of Indanones **4**[a]



entry	**3**	R	L*	**4**	% yield[b]	% ee[c,d]
1	**3a**	Et	(*S*)-SEGPHOS	**4a**	96	95 (*S*)
2	**3a**	Et	(*R*)-MeO-BIPHEP	**4a**	98	75 (*R*)
3	**3a**	Et	(*S*)-BINAP	**4a**	93	69 (*S*)
4	**3b**	Ph	(*S*)-SEGPHOS	**4b**	93	79
5	**3b**	Ph	(*R*)-MeO-BIPHEP	**4b**	97	60
6	**3b**	Ph	(*S*)-BINAP	**4b**	97	36
7[e]	**3c**	*i*-Pr	(*S*)-SEGPHOS	**4c**	81	94

[a] The reaction was carried out with **3**, $[RhCl(CH_2{=}CH_2)_2]_2$ (3.5 mol %, 7 mol % Rh), chiral phosphine (7 mol %), and K_3PO_4 (0.5 equiv) in dioxane−H_2O (20:1) at 100 °C for 4−5 h. [b] Isolated yield by preparative TLC. [c] For **4a** and **4c**, the enantiomeric excess (ee) was determined by chiral GC analysis. For **4b**, the enantiomeric excess (ee) was determined by chiral HPLC analysis. [d] The absolute configuration in parentheses was determined by comparing optical rotation with reported value.[9] [e] 7 mol % of $[RhCl(CH_2{=}CH_2)_2]_2$ and 14 mol % of (*S*)-SEGPHOS for 12 h.

Scheme 4. Synthesis of (−)-α-Herbertenol (**13**)[a]



catalyzed asymmetric addition/ring-opening reaction of **8** using SEGPHOS afforded indanone **9** in 93.7% ee (84% chemical yield). Subsequent Baeyer−Villiger oxidation with *m*-CPBA caused migration of the aryl group to afford lactone **10**, whose ester linkage was then cleaved with NaOH. Both hydroxy and carboxy groups were methylated with Me_2SO_4. Finally, the benzyloxy group was transformed to a bromo group affording **12**. The bromo ester **12** was transformed to α-herbertenol **13** according to the procedure reported by Mukherjee[12] in order to determine the absolute configuration of the quaternary center. Measurement of the optical rotation of **13** established that the absolute stereochemistry was that of the natural enantiomer.

In summary, we have developed a method for the enantioselective cleavage of a carbon−carbon single bond by *β*-carbon elimination to create a chiral benzylic quaternary carbon center. The utility of the desymmetrization process was demonstrated by application to a synthesis of (−)-α-herbertenol.

Acknowledgment. We thank Takasago International Corp. for its generous gift of (*S*)-SEGPHOS. T.M. acknowledges a support by Eisai Award in Synthetic Organic Chemistry, Japan.

Supporting Information Available: Experimental procedures and NMR spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061359G

(12) Paul, T.; Pal. A.; Gupta, P. D.; Mukherjee, D. *Tetrahedron Lett.* **2003**, *44*, 737.