DOI: 10.1002/chem.200902593

Stereoselective Restructuring of 3-Arylcyclobutanols into 1-Indanols by Sequential Breaking and Formation of Carbon–Carbon Bonds

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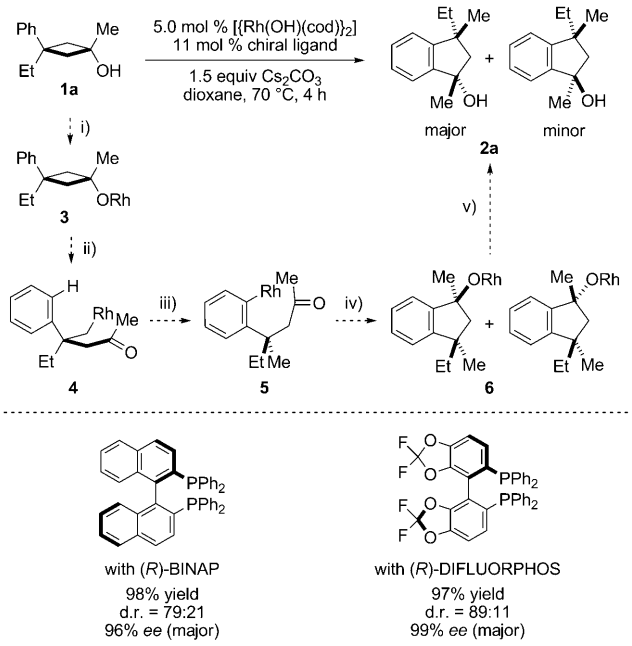
Transition-metal catalyzed reactions involving an elementary step in which a carbon–carbon bond is cleaved provide access to unique organic transformations that would otherwise be difficult to achieve.[1,2] Of particular interest is the desymmetrization of prochiral substrates through the enantioselective cleavage of a carbon–carbon bond, which produces enantiomerically enriched compounds.[3] We recently described a cascade-type reaction of 3-(2-hydroxyphenyl)cyclobutanones with electron-deficient olefins giving 5-alkylated 3,4-dihydrocoumarins.[4] Mechanistically, the reaction involves two contradictory elementary steps operating in sequence; the first one is breaking of a carbon–carbon bond of the four-membered carbocycle by β-carbon elimination[5] and the second one is a carbon–carbon bond formation by an intermolecular conjugate addition onto the electron-deficient alkene. Such sequences consisting of contradictory elementary steps are worth pursuing from the synthetic as well as mechanistic point of view. Herein, we describe the enantio- and diastereoselective synthesis of 1-indanols by restructuring of the carbon framework of 3-arylcyclobutanols.[6] Although construction of chiral quaternary carbon centers remains a significant challenge for synthetic chemists, the present reaction gives rise to two chiral quaternary centers in a highly enantiomerically enriched form in one pot.[7]

3-Ethyl-1-methyl-3-phenylcyclobutanol (**1a**), a symmetrical substrate, was heated at 70 °C in 1,4-dioxane in the presence of Cs_2CO_3 (1.5 equiv) and a rhodium(I) catalyst prepared from [{Rh(OH)(cod)}$_2$] (5 mol %) and (*R*)-BINAP (11 mol %). Restructuring of the carbon framework occurred to afford 3-ethyl-1,3-dimethylindan-1-ol (**2a**) as a mixture of diastereomers (*cis*/*trans* = 79/21)[8] in 98 % combined yield (Scheme 1). The enantiomeric purity of the major *cis* isomer was 96 % *ee*. Replacement of the BINAP ligand with (*R*)-DIFLUORPHOS[9] improved both stereoselectivities, such that the *cis*/*trans* ratio became 89:11, and importantly, the enantiopurity of the major isomer increased to 99 % *ee*.[10] A plausible mechanism is shown in Scheme 1; i) rhodium cyclobutanolate **3** is initially generated by deprotonation of the tertiary hydroxyl group of **1a** by rhodium hydroxide (or alkoxide), which acts as a base, ii) the four-membered ring carbocycle is opened by β-carbon elimination. The chiral ligand on rhodium induces selective cleavage of one of the two enantiotopic carbon–carbon bonds to generate a chiral quaternary center at the benzylic position, iii) the resulting alkylrhodium species **4** subsequently undergoes 1,4-rhodium shift[11] leading to the formation of arylrhodium intermediate **5**, iv) intramolecular 1,2-addition to the carbonyl group occurs to stereoselectively form the



Scheme 1. Rhodium-catalyzed reaction of cyclobutanol **1a**.

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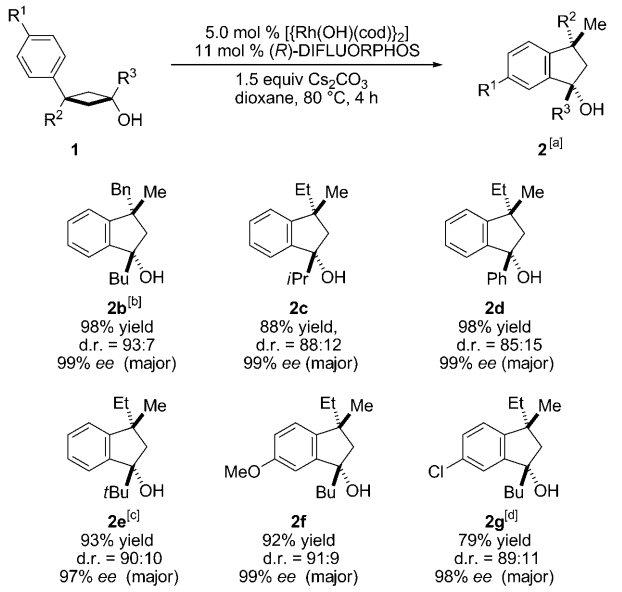
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902593.

second chiral quaternary center as the rhodium tertiary alcoholate,[12] v) the rhodium alcoholate acts as a base to deprotonate another molecule of the cyclobutanol **1a** to release the tertiary indanol **2a**.

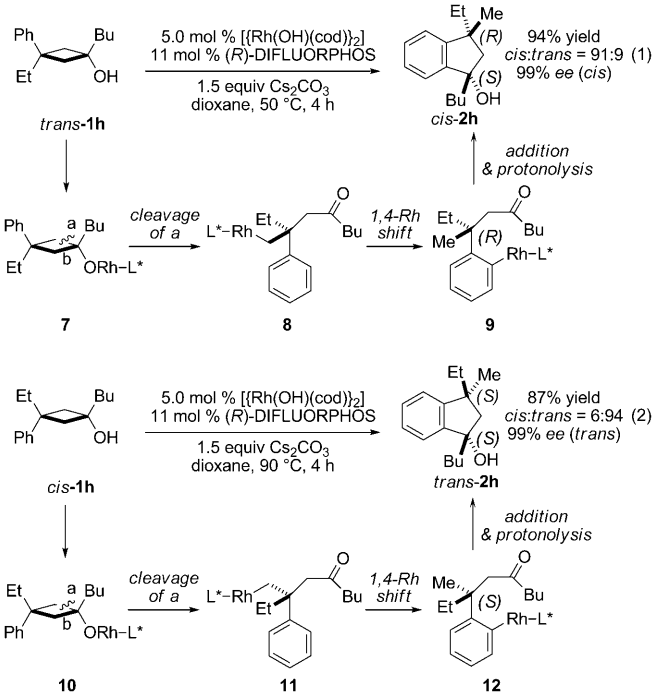
The generality of the method is illustrated with cyclobutanols **1b–g** having various substituents at the 1- and 3-positions (Scheme 2). Butyl-, isopropyl-, and phenyl-substituted



Scheme 2. Diastereo- and enantioselective synthesis of 1-indanols **2b–g**. a) Major isomer designated. b) The reaction was carried out at 60 °C. c) The reaction was carried out with 10 mol % [{Rh(OH)(cod)}$_2$] and 22 mol % (*R*)-DIFLUORPHOS. d) The reaction was carried out at 50 °C.

cyclobutanols **1b–d** gave the corresponding 1-indanols **2b–2d** in good yields with high diastereoselectivities and excellent enantioselectivities. The restructuring reaction of **1e** bearing a sterically demanding *tert*-butyl group required a higher catalyst loading, but still proceeded with high enantioselectivity. Methoxy- and chloro substituents were tolerated on the phenyl ring and the corresponding 1-indanols **2f** and **2g** were formed in good yields with high levels of enantiomeric excess.

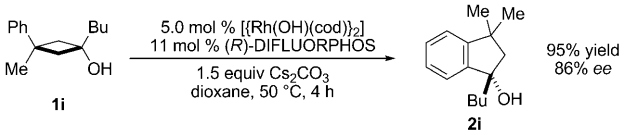
Both *trans* and *cis* isomers of cyclobutanol **1h** were subjected to the restructuring reaction to test its stereospecificity (Scheme 3). The reaction of *trans*-**1h** afforded *cis*-**2h** selectively (*cis*/*trans* = 91:9, 94 % combined yield) and the enantioselectivity observed with the major isomer was 99 % *ee*. On the other hand, the reaction of *cis*-**1h** produced *trans*-**2h** selectively (*trans*/*cis* = 94:6), again with an excellent enantioselectivity of 99 % *ee* for the major *trans* isomer.[13] Thus, a reasonable level of stereospecificity was observed between **1h** and the product of restructuring (**2h**). Comparison with authentic samples of the enantiomerically enriched 1-indanol **2h** prepared separately[14] revealed their absolute configurations to be (1*S*, 3*R*) for *cis*-**2h** and (1*S*, 3*S*) for *trans*-**2h**. These results led us to the following mechanistic interpretation, as depicted in Scheme 3. Two stereo-deter-



Scheme 3. Comparison between the stereoselectivities of the restructuring reactions of *trans*-**1h** and *cis*-**1h.**

mining steps are involved in the overall transformation. In the first stereo-determining step, carbon–carbon bond a is cleaved in preference to bond b by β-carbon elimination irrespective of the 3-substituent under the influence of the diphosphane ligand having (*R*)-axially chirality. As a result, *R* configuration arises at the benzylic carbon starting from *trans*-**1h**, and *S* configuration from *cis*-**1h.** In the second stereo-determining step, the *Re*-face of the carbonyl group is selectively attacked by the arylrhodium intermediate irrespective of the stereochemistry of the benzylic quaternary carbon center. In both stereo-determining steps, the axis chirality of the ligand on rhodium governs the stereochemical course of the reaction.

We carried out the reaction using 1-butyl-3-methyl-3-phenylcyclobutanol (**1i**) having a methyl group at the 3-position to confirm that the stereoselection made in the second stereo-determining step is controlled by the chiral ligand (Scheme 4). Thus, 1-indanol **2i** possessing only one chiral center was produced from the methyl-substituted cyclobutanol **1i**. The enantioselection in the carbonyl addition step can be ascribed only to the chiral ligand. The enantioselec-



Scheme 4. Rhodium-catalyzed synthesis of 1-indanol **2i** possessing only one chiral center.

tivity observed was 86% *ee*, supporting the assertion that the chiral ligand is the major factor in determining the stereochemical course of the carbonyl addition step with **1a**–**1h**.

In summary, we have developed a rhodium-catalyzed restructuring reaction of 3-arylcyclobutanols to 1-indanols possessing two chiral quaternary carbon centers with high diastereo- and enantioselectivities through a sequence of two contradictory elementary steps, that is, carbon–carbon bond cleavage and carbon–carbon bond formation, both occurring with high enantioselectivity.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research (Nos. 17750087 and 19205013) from the Ministry of Education, Culture, Sports, Science and Technology, Japan and the Asahi Glass Foundation. M.S. thanks the Japan Society for the Promotion of Science for a fellowship support.

Keywords: 1,2-addition · asymmetric synthesis · C–C activation · indanols · rhodium

[1] a) M. Murakami, Y. Ito, *Top. Organomet. Chem.* **1999**, *3*, 97–129; b) M. E. van der Boom, D. Milstein, *Chem. Rev.* **2003**, *103*, 1759–1792; c) C.-H. Jun, *Chem. Soc. Rev.* **2004**, *33*, 610–618; d) T. Kondo, T. Mitsudo, *Chem. Lett.* **2005**, *34*, 1462–1467.

[2] a) T. Kondo, M. Niimi, M. Nomura, K. Wada, T. Mitsudo, *Tetrahedron Lett.* **2007**, *48*, 2837–2839; b) T. Matsuda, T. Tsuboi, M. Murakami, *J. Am. Chem. Soc.* **2007**, *129*, 12596–12597; c) R. Shintani, K. Takatsu, T. Katoh, T. Nishimura, T. Hayashi, *Angew. Chem.* **2008**, *120*, 1469–1471; *Angew. Chem. Int. Ed.* **2008**, *47*, 1447–1449; d) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2008**, *130*, 5048–5049; e) M. P. Watson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 12594–12595; f) T. Matsuda, M. Shigeno, M. Murakami, *Org. Lett.* **2008**, *10*, 5219–5221; g) M. Tobisu, Y. Kita, Y. Ano, N. Chatani, *J. Am. Chem. Soc.* **2008**, *130*, 15982–15989; h) C. Nájera, J. M. Sansano, *Angew. Chem.* **2009**, *121*, 2488–2492; *Angew. Chem. Int. Ed.* **2009**, *48*, 2452–2456; i) Y. Hirata, T. Inui, Y. Nakao, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 6624–6631.

[3] a) T. Nishimura, S. Matsumura, Y. Maeda, S. Uemura, *J. Am. Chem. Soc.* **2003**, *125*, 8862–8869; b) T. Matsuda, M. Shigeno, M. Makino, M. Murakami, *Org. Lett.* **2006**, *8*, 3379–3381; c) T. Ohmura, H. Taniguchi, Y. Kondo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 3518–3519; d) B. M. Trost, J. Xie, *J. Am. Chem. Soc.* **2008**, *130*, 6231–6242; e) T. Seiser, N. Cramer, *Angew. Chem.* **2008**, *120*, 9435–9438; *Angew. Chem. Int. Ed.* **2008**, *47*, 9294–9297; f) C. Winter, N. Krause, *Angew. Chem. Int. Ed.* **2009**, *48*, 2460–2462.

[4] T. Matsuda, M. Shigeno, M. Murakami, *J. Am. Chem. Soc.* **2007**, *129*, 12086–12087.

[5] a) T. Nishimura, S. Uemura, *Synlett* **2004**, 201–206; b) T. Satoh, M. Miura, *Top. Organomet. Chem.* **2005**, *14*, 1–20; c) M. Murakami, M. Makino, S. Ashida, T. Matsuda, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1315–1321.

[6] A report on a similar reaction appeared on the Web during the preparation of this manuscript: T. Seiser, O. A. Roth, N. Cramer, *Angew. Chem.* **2009**, *121*, 6438–6441; *Angew. Chem. Int. Ed.* **2009**, *48*, 6320–6323.

[7] a) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037–2066; b) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; c) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597; d) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105–10146; e) J. D. Christopher, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367; f) *Quaternary Stereocenters* (Eds.: J. Christoffers; A. Baro), Wiley-VCH, Weinheim, **2005**; g) T. Rovis in *New Frontiers in Asymmetric Catalysis* (Eds.: K. Mikami, M. Lautens), Wiley, New York, **2007**, pp. 275–311; h) M. Hatano, K. Ishihara, *Synthesis* **2008**, 1647–1675; i) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853–2873.

[8] It was hardly possible to separate the diastereomers by preparative chromatography. The ratio was determined by HPLC analysis.

[9] S. Jeulin, S. Duprat de Paule, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion, P. Dellis, *Angew. Chem.* **2004**, *116*, 324–329; *Angew. Chem. Int. Ed.* **2004**, *43*, 320–325.

[10] The configuration was (1*S*, 3*R*). The enantiopurity of the minor diastereomer was 32% *ee* with dominance of (1*R*, 3*R*) configuration.

[11] a) S. Ma, Z. Gu, *Angew. Chem.* **2005**, *117*, 7680–7685; *Angew. Chem. Int. Ed.* **2005**, *44*, 7512–7517; b) Q. Huang, A. Fazio, G. Dai, M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 7460–7461.

[12] a) M. Sakai, M. Ueda, N. Miyaura, *Angew. Chem.* **1998**, *110*, 3475–3477; *Angew. Chem. Int. Ed.* **1998**, *37*, 3279–3281; b) H.-F. Duan, J.-H. Xie, W.-J. Shi, Q. Zhang, Q.-L. Zhou, *Org. Lett.* **2006**, *8*, 1479–1481; c) K. Suzuki, S. Ishii, K. Kondo, T. Aoyama, *Synlett* **2006**, 648–650; d) G. Liu, X. Lu, *J. Am. Chem. Soc.* **2004**, *126*, 7460–7461.

[13] The reaction of *cis*-**1h** required higher temperature than *trans*-**1h**.

[14] See the Supporting Information for details.

Received: August 24, 2009
Published online: November 2, 2009

