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Rhodium-Catalyzed C−C Bond Cleavage: Construction of Acyclic Methyl Substituted Quaternary Stereogenic Centers

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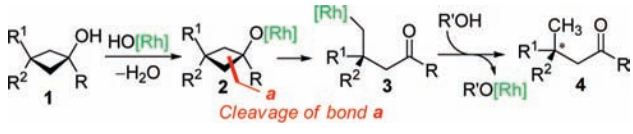
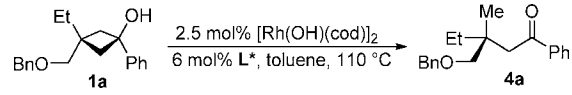
The catalytic and selective functionalization of carbon−hydrogen and carbon−carbon bonds by transition-metal complexes is a significant challenge for organometallic chemistry. The lack of required prefunctionalizations renders such processes ecologically and economically attractive. C−H activations are a vibrant and very active research area with impressive progress.[1] Compared to C−H activations, the development of related C−C activation reactions lags behind.[2] Examples for efficient enantioselective processes are scarce.[3] Hartwig and co-workers recently showed that triarylcarbinols and rhodium complexes are in equilibrium with the corresponding diarylketones and arylrhodium species.[4] Substrates having a stronger bias toward this β-carbon elimination pathway can provide an attractive entry into highly reactive organometallic species. In this respect, strained tertiary alcohols are performing substrates to generate alkyl metals.[5] Especially symmetrically substituted cyclobutane derivatives are an attractive substrate class, as a selective insertion into one of the two enantiotopic C−C bonds of the cyclobutane ring opens opportunities for enantioselective activations. We[6] and others[7] investigated this reactivity to access transient enantioenriched organometallic species and subsequently capitalized on their reactivity in downstream reactions. The significance and vast occurrence of methyl substituted quaternary stereogenic centers in natural products prompted us to explore the applicability of rhodium-catalyzed β-carbon cleavages for their selective construction.[8] Murakami obtained linear ketones with racemic tertiary methyl substituents by rhodium(I)-catalyzed addition of arylboronic acids to cyclobutanones.[9] This process was extended toward an enantioselective construction of benzocyclopentanones and dihydrocoumarines with cyclic stereocenters using an intramolecular addition.[7c,d] Herein we report the construction of *acyclic* quaternary stereogenic centers from cyclobutanol derivatives using a chiral rhodium(I) catalyst. We anticipated accessing crucial rhodium cyclobutanoxide **2** through ligand exchange of cyclobutanol **1** and a rhodium(I) hydroxy complex. Subsequent enantioselective β-carbon cleavage of **2** would lead to alkyl rhodium(I) species **3**, that might hydrolyze in the presence of a suitable proton source or **1** itself (Scheme 1).

Scheme 1. Rh-Catalyzed Ring-Opening/Protonation Process



Heating *trans*-**1a** in the presence of catalytic amounts of [Rh(OH)(cod)]$_2$ and (*R*)-Binap (**L1**) in toluene resulted in the anticipated ring-opening and gave ketone **4a** in excellent yield albeit very poor enantioselectivity (Table 1, entry 1). A short survey of chiral ligands led to the identification of DTBM-Segphos (**L8**) as the most selective ligand, providing ketone **4a** in 87% *ee* (Entry 8).[10] Using dioxane as solvent and 15 equivalents of water further improved the selectivity to 92% *ee* (entries 9−11).

Table 1. Optimization of the C−C Cleavage/Protonation Reaction[a]



entry	ligand L*	yield [%][b]	*ee* [%][c]
1	(*R*)-Binap (**L1**)	93	7
2	(*R*)-H8-Binap (**L2**)	96	10
3	(*R*)-MeOBiphep (**L3**)	94	16
4	(*R*)-Segphos (**L4**)	99	20
5	(*R*)-Difluorphos (**L5**)	83	19
6	(*R*)-DM-Segphos (**L6**)	87	29
7	(*R*)-DTBM-MeOBiphep (**L7**)	94	79
8	(*R*)-DTBM-Segphos (**L8**)	93	87
9[d]	(*R*)-DTBM-Segphos (**L8**)	93	91
10[e]	(*R*)-DTBM-Segphos (**L8**)	98	90
11[d,e]	(*R*)-DTBM-Segphos (**L8**)	99	92

[a] Conditions: 0.1 mmol **1a**, 2.5 mol % [Rh(OH)(cod)]$_2$, 6.0 mol % **L***, toluene (0.25 M), 110 °C, 2 h. [b] Isolated product. [c] *ee*'s were determined by HPLC with a chiral stationary phase. [d] 15 equiv of H_2O. [e] Dioxane.

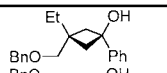
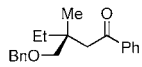
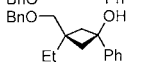
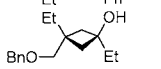
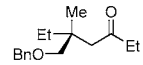
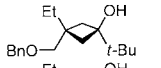
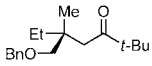
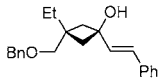
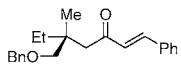
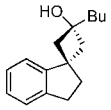
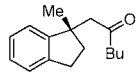
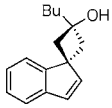
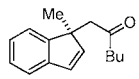
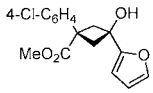
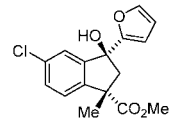
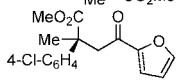
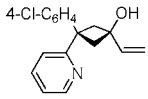
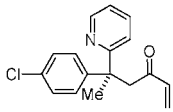
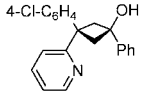
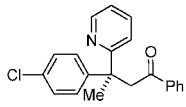
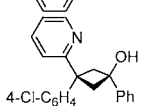
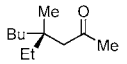
With these optimized conditions, we then explored the scope of the process (Table 2). The selectivity of the cleavage is largely independent from the substitution pattern on the 1-position of the cyclobutanol (Entries 1−5). Cyclobutanols bearing aromatic substituents in the 3-position generally give rise to indanols through a 1,4-rhodium shift/1,2-addition sequence.[6b] For example, indanol **5** was obtained exclusively with Difluorphos (**L5**) from **1g** (entry 8). Notably, the bulky DTBM-MeOBiphep (**L7**) mostly suppresses this pathway and instead provides **4g** in good yields (entry 9). A 2-pyridyl substituent as well blocks this 1,4-Rh shift by forming a stable chelate with the nitrogen atom and providing the ketones **4h** and **4i** (entries 10−12). Conformationally restricted spirocyclic substrates yield the linear ketone **4e** and **4f** (entries 6−7).

We subsequently applied this reaction for an enantioselective synthesis of 4-ethyl-4-methyl-octane (**7**), the simplest unbranched saturated hydrocarbon with a quaternary stereogenic center (Scheme 2).[11] **1j** provides under the aforementioned conditions ketone **4j** in 99% yield and an *ee*-value of 93% (entry 13). Additionally, **1j** can be directly converted *via* a one pot reaction into its dithiane derivative **6** in 86% yield over both steps. Subsequent Raney-nickel promoted desulfurization gave (*S*)-4-ethyl-4-methyl-octane (**7**) in 99% yield.

Deuterium-labeling experiments of *trans*-**1a** revealed that the protonation does not occur as originally proposed at the alkyl-

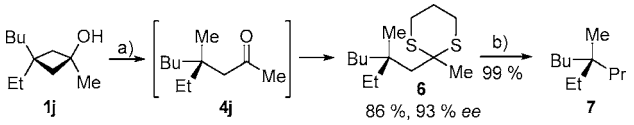
10.1021/ja101469t

Table 2. Scope of the C−C Cleavage/Protonation Process[a]

entry	1	4		yield[b] (%)	ee[c] (%)
1[d]			**4a**	99	92
2[e, f]			**4a**	81	90
3			**4b**	97	91
4[f]			**4c**	71	>85
5			**4d**	86	97
6			**4e**	77	95
7			**4f**	75	95
8[g]			**5**	77 (5:1 *dr*)	99
9[h]			**4g**	72	95
10[h]			**4h**	60	98
11			**4i**	99	97
12[e]			**4i**	54	90
13			**4j**	99	93

[a] Conditions: 0.1 mmol **1**, 2.5 mol % $[Rh(OH)(cod)]_2$, 6.0 mol % **L8**, toluene (0.25 M), 110 °C, 12 h. [b] Isolated product. [c] *ee*'s were determined by HPLC with a chiral stationary phase. [d] 15 equiv of H_2O, dioxane. [e] *ent*-**L8**. [f] 1.5 equiv of Cs_2CO_3, 120 °C, xylene. [g] **L5**. [h] **L7**.

Scheme 2. Synthesis of (*S*)-4-Ethyl-4-methyl-octane (**7**)[a]

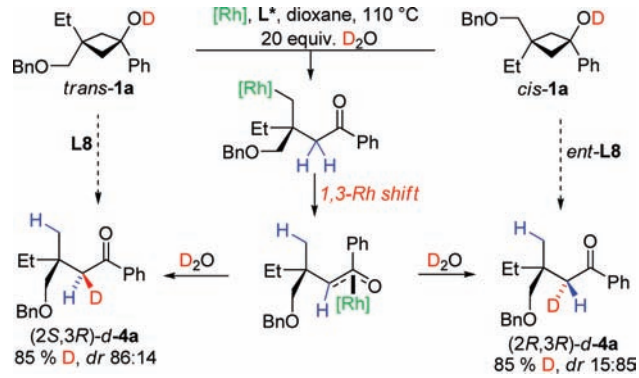


[a] Conditions: (a) 2.5 mol % $[Rh(OH)(cod)]_2$, 6 mol % **L8**, toluene, 110 °C, 4 h, then $BF_3 \cdot Et_2O$, propane-1,3-dithiol, 23 °C, 12 h; (b) Raney-nickel, MeOH, 23 °C, 2 h.

rhodium stage (**3**) (Scheme 3). Instead, we observed a 85% incorporation of one deuterium atom α to the carbonyl group, suggesting that a more stable rhodium enolate is formed *via* a 1,3-rhodium shift.[7c,12] The subsequent deuteration quench proceeded with a diastereomeric ratio of 86:14 in favor of the depicted (2*S*,3*R*) isomer *d*-**4a**. Subjecting *cis*-**1a** to the identical reaction conditions using *ent*-**L8** as ligand gave diastereomer (2*R*,3*R*)-*d*-**4a** with a *dr* of 15:85, indicating a remarkably selective catalyst controlled protonation.[13]

In summary, we demonstrated a rhodium-catalyzed C−C bond cleavage/protonation sequence providing an entry to acyclic methyl substituted quaternary stereogenic centers in excellent enantioselectivities. Its utility was demonstrated by a synthesis of (*S*)-4-ethyl-4-methyl-octane, the simplest hydrocarbon with a quaternary stereogenic center. Further ongoing research in this direction is directed to the development of methods for the activation of C−C bonds enabling novel and useful transformations.

Scheme 3. A 1,3-Rh Shift Leads to Diastereoselective Deuteration



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

References

(1) For recent reviews see: (a) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (c) Kakiuchi, F. *Top. Organomet. Chem.* **2008**, *24*, 1.
(2) For recent reviews see: (a) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 871. (b) Murakami, M.; Ito, Y. *Top. Organomet. Chem.* **1999**, *3*, 97. (c) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759. (d) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610. (e) Satoh, T.; Miura, M. *Top. Organomet. Chem.* **2005**, *14*, 1.
(3) (a) Wender, P. A.; Haustedt, L. O.; Lim, J.; Love, J. A.; Travis, J. W.; Yoon, J.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 6302. (b) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594. (c) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874. (d) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303. (e) Reddy, V. J.; Douglas, C. J. *Org. Lett.* **2010**, *12*, 952.
(4) (a) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 3124. (b) Zhao, P.; Hartwig, J. F. *Organometallics* **2008**, *27*, 4749.
(5) Seiser, T.; Cramer, N. *Org. Biomol. Chem.* **2009**, *7*, 2835.
(6) (a) Seiser, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 9294. (b) Seiser, T.; Roth, O. A.; Cramer, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6320. (c) Seiser, T.; Cramer, N. *Chem.—Eur. J.* **2010**, *16*, 3383.
(7) Palladium-catalyzed: (a) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *Chem. Commun.* **2002**, 50. (b) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862. Rhodium-catalyzed: (c) Matsuda, T.; Shigeno, M.; Makino, M.; Murakami, M. *Org. Lett.* **2006**, *8*, 3379. (d) Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12086. (e) Shigeno, M.; Yamamoto, T.; Murakami, M. *Chem.—Eur. J.* **2009**, *47*, 12929.
(8) (a) Douglas, J. C.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (b) Trost, B. M.; Jiang, D. C. *Synthesis* **2006**, 369. (c) *Quaternary Stereocenters*; Christoffers, J., Baro, A., Eds.; Wiley: Weinheim, 2005.
(9) (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.
(10) The absolute configuration of compounds **4** were assigned in analogy to the reported cleavage site. See refs 6a and 6b.
(11) (a) Hoeve, W. T.; Wynberg, H. *J. Org. Chem.* **1980**, *45*, 2754. (b) Fujita, T.; Obata, K.; Kuwahara, S.; Miura, N.; Nakahashi, A.; Monde, K.; Decatur, J.; Harada, N. *Tetrahedron Lett.* **2007**, *48*, 4219. (c) Grimme, S.; Mück-Lichtenfeld, C. *Chirality* **2008**, *20*, 1009.
(12) No deuterium was incorporated subjecting **4a** to identical conditions.
(13) For examples of enantioselective protonation of Rh-enolates, see: (a) Laure Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719.

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