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Enantioselective Insertion of a Carbenoid Carbon into a C−C Bond To Expand Cyclobutanols to Cyclopentanols

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Supporting Information

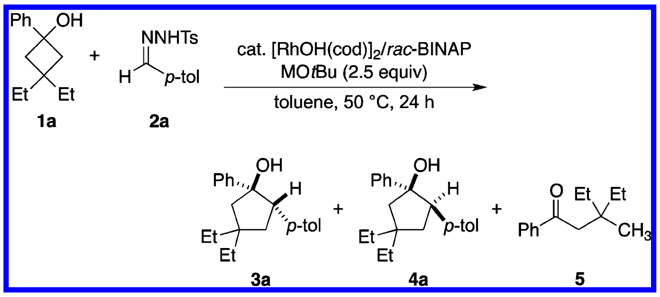
ABSTRACT: When a carbenoid species generated from a tosylhydrazone is reacted with a cyclobutanol in the presence of a chiral rhodium catalyst, a C−C single bond of the cyclobutanol is cleaved, and the carbenoid carbon is inserted therein to furnish a ring-expanded cyclopentanol in an enantioselective manner.

Straightforward methods to construct carbon frameworks with fewer steps are increasingly important. This goal has largely driven the recent rise of new chemistry to activate nonpolar C−H[1] and C−C[2] σ-bonds. It would significantly streamline a synthetic pathway if a C−C single bond is cleaved and an unsaturated organic compound is inserted therein to directly extend the carbon skeleton with two C−C single bonds newly formed. There have appeared in the past decade such examples that incorporate alkenes,[3] alkynes,[4] and carbon monoxide[5,6] in inter- and intramolecular fashions. They may be called as "cut-and-sew" protocols.[2a] We now report a new reaction which expands cyclobutanols to cyclopentanols with control of stereochemistry through insertion of a carbenoid carbon[7] into a C−C single bond[8] of the four-membered ring.[9,10]

We took the *N*-tosylhydrazone **2a** as the carbenoid precursor and reacted it with cyclobutanol **1a** in the presence of an alkali metal tertiary butoxide and catalytic amounts of $[RhOH(cod)]_2$ and *rac*-BINAP. A diastereomeric mixture of cyclopentanols **3a** and **4a**[11] was obtained along with ring-opened product **5** (Table 1). When NaO*t*Bu was used as the base to generate a carbenoid species from **2a**, the cyclopentanol **3a** in which the hydroxy and *p*-tolyl substituents were *trans* was produced in preference to the other diastereomer **4a** (86:14) in 82% yield and **5** was formed only in 9% (entry 2).[12]

A possible reaction mechanism is illustrated in Scheme 1. The substrate **1** is transferred onto rhodium(I) to generate rhodium alkoxide **A**. The four-membered ring is opened by β-carbon elimination, giving γ-keto alkylrhodium intermediate **B** (Step 1). The diazo compound, generated from **2** and the base NaO*t*Bu, reacts with **B** to furnish (alkyl)(carbene)rhodium complex **C**.[13] The alkyl group migrates onto the carbenoid carbon to form **D** (Step 2),[7d,e] which further undergoes intramolecular addition to the carbonyl group in a five-*exo* mode (Step 3). A diastereoselectivity arises during Step 3 upon differentiation of the π-faces of the carbonyl group. The resulting cyclopentoxyrhodium **E** is protonated with **1** to furnish the products **3** and **4** with regeneration of **A**.

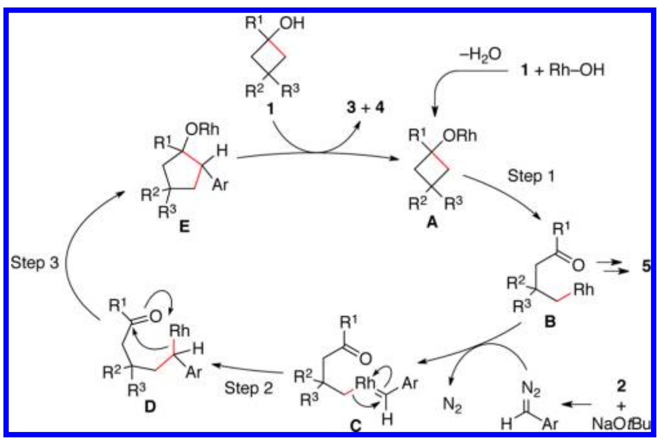
Table 1. Rhodium-Catalyzed Reaction of Cyclobutanol 1a with *N*-Tosylhydrazone 2a[a]



entry	MO*t*Bu	yield, %[b] 3a + 4a	3a:4a[c]	yield, %[b] 5
1	LiO*t*Bu	59	81:19	32
2	NaO*t*Bu	82	86:14	9
3	KO*t*Bu	31	85:15	56

[a] **1a** (25 μmol), **2a** (37.5 μmol), MO*t*Bu (62.5 μmol), $[RhOH(cod)]_2$ (5.0 mol %), *rac*-BINAP (11.0 mol %). [b] NMR yield. [c] Estimated by GC.

Scheme 1. Possible Reaction Mechanism



Induction of enantioselectivity in the ring-expanded products by chiral ligands on rhodium was also investigated (Table 2). (*R*)-BINAP favored the production of the diastereomer **3a** over **4a** and induced moderate enantioselectivities with the both diastereomers (entry 1). Although biphenyl-type ligands, e.g., (*R*)-SEGPHOS (**L1**) and (*R*)-DIFLUORPHOS exhibited

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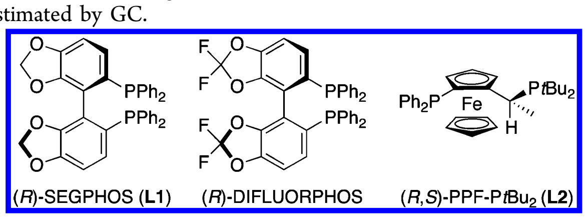
Table 2. Enantioselective Syntheses of Cyclopentanols via Carbene Insertion[a]

		yield, %[b]		% ee
entry	chiral ligand	3a + 4a	3a:4a[c]	3a/4a
1	(*R*)-BINAP	76	86:14	80/65
2	(*R*)-SEGPHOS (**L1**)	86	84:16	95/93
3	(*R*)-DIFLUORPHOS	84	84:16	96/90
4	(*R*,*S*)-PPF-P*t*Bu$_2$ (**L2**)	89	12:88	96/99

[a]**1a** (25 μmol), **2a** (37.5 μmol), NaO*t*Bu (62.5 μmol), $[RhOH(cod)]_2$ (5.0 mol %), chiral ligand (11.0 mol %), toluene, 50 °C. [b]NMR yield. [c]Estimated by GC.



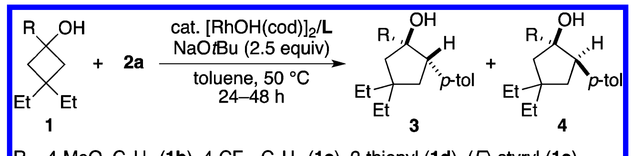
similar diastereoselectivities favoring **3a**, the enantioselectivities observed for the both diastereomers were considerably higher (entries 2 and 3). On the other hand, **L2** having a ferrocene backbone exhibited an opposite preference for **4a** versus **3a** (**3a**:**4a** = 12:88), and in particular, 99% ee was attained with the major diastereomer **4a** (entry 4).

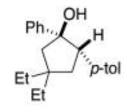
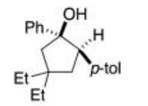
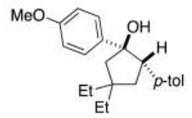
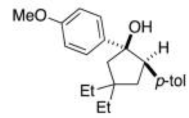
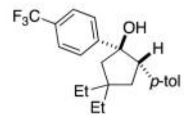
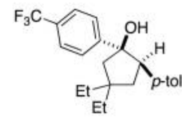
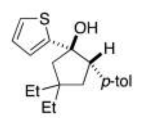
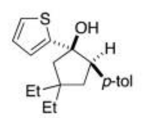
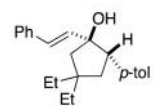
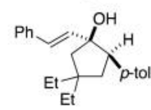
Various cyclobutanols **1** were subjected to the reaction with **2a** under the two different conditions using **L1** and **L2** (Table 3). Those bearing 4-methoxyphenyl, 4-trifluoromethylphenyl, thienyl, and styryl groups successfully participated in the ring-expansion reaction (entries 3–10).[14] When the ligand **L1** was used, the diastereomers **3** were preferentially produced with good enantioselectivities over 94% ee. On the other hand, the ligand **L2** furnished the other diastereomers **4** in preference to **3** with excellent enantioselectivities ranging 95–99% ee. However, cyclobutanols having a phenyl group at the 3-position gave indanols rather than cyclopentanols as the major product.[10b,c] The reactions of cyclobutanols having one or no alkyl (or aryl) substituent at the 3-position also failed, probably due to a competitive process of β-hydride elimination.[15]

The use of *N*-tosylhydrazones derived from various aryl aldehydes was also examined in the reaction with **1a** (Table 4). Methoxy, fluoro, and chloro substituents were all tolerated at the 4-position of the aryl group, giving the corresponding products in good yields with high enantioselectivities (entries 3–8). The results of Table 4 show an analogous stereochemical dichotomy depending on the employed ligand (**L1** or **L2**) to those of Table 3. On the other hand, *N*-tosylhydrazones derived from aliphatic aldehydes failed to give the desired cyclopentanols, presumably because of the instability of alkyl substituted carbenoid intermediates. The reaction with *N*-tosylhydrazones derived from ketones was also sluggish due to the lower reactivity of sterically hindered carbenoid species and formed **5** predominantly.

In the case of symmetrical cyclobutanol *cis*-**1f** having a tertiary carbon with two different substituents at the 3-position, the mechanistic pathway contains three steps, each of which creates a new chiral center. The ring-opening step (Step 1 in Scheme 1) makes the all-carbon tertiary center at the 3-position chiral. The second chiral center is created upon intramolecular migratory insertion of a ring-opened alkyl group onto the neighboring prochiral carbenoid carbon (Step 2). The third chiral center is created upon cyclization by intramolecular

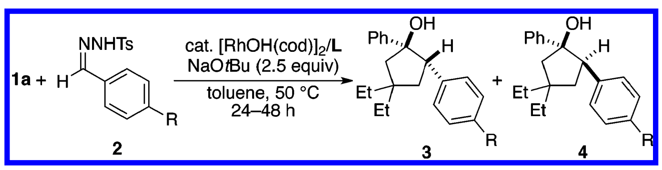
Table 3. Reaction of Various Cyclobutanols 1 with 2a[a]



entry	1	L	3[b]		4[b]	
						
1	**1a**	**L1**	**3a**	60%, 97% ee	**4a**	12%, 95% ee
2		**L2**		15%, 97% ee		71%, 99% ee
						
3	**1b**	**L1**	**3b**	59%, 95% ee	**4b**	10%, 93% ee
4		**L2**		6%, 97% ee		77%, 99% ee
						
5	**1c**	**L1**	**3c**	67%, 99% ee	**4c**	11%, 93% ee
6		**L2**		9%, 94% ee		59%, 99% ee
						
7	**1d**	**L1**	**3d**	47%, 94% ee	**4d**	9%, 92% ee
8		**L2**		17%, 97% ee		52%, 99% ee
						
9	**1e**	**L1**	**3e**	60%, 96% ee	**4e**	10%, 93% ee
10		**L2**		23%, 96% ee		52%, 95% ee

[a]**1** (0.2 mmol), **2a** (0.3 mmol), NaO*t*Bu (0.5 mmol), $[RhOH(cod)]_2$ (5.0 mol %), **L1** or **L2** (11.0 mol %). [b]Isolated yield.

Table 4. Reactions of Various Hydrazones 2 with 1a[a]



entry	2	L	3[b]		4[b]	
1[c]	R = H (**2b**)	**L1**	**3f**	59%, 96% ee	**4f**	15%, 94% ee
2		**L2**		12%, 97% ee		68%, 99% ee
3	R = OMe (**2c**)	**L1**	**3g**	66%, 97% ee	**4g**	9%, 95% ee
4		**L2**		9%, 96% ee		65%, 99% ee
5	R = F (**2d**)	**L1**	**3h**	42%, 96% ee	**4h**	3%, 95% ee
6		**L2**		15%, 97% ee		79%, 99% ee
7[d]	R = Cl (**2e**)	**L1**	**3i**	63%, 96% ee	**4i**	11%, 93% ee
8		**L2**		9%, 97% ee		70%, 99% ee

[a]**1a** (0.2 mmol), **2** (0.3 mmol), NaO*t*Bu (0.5 mmol), $[RhOH(cod)]_2$ (5.0 mol %), **L1** or **L2** (11.0 mol %). [b]Isolated yield. [c]NaOMe was used. [d]*N*-Benzenesulfonylhydrazone was used.

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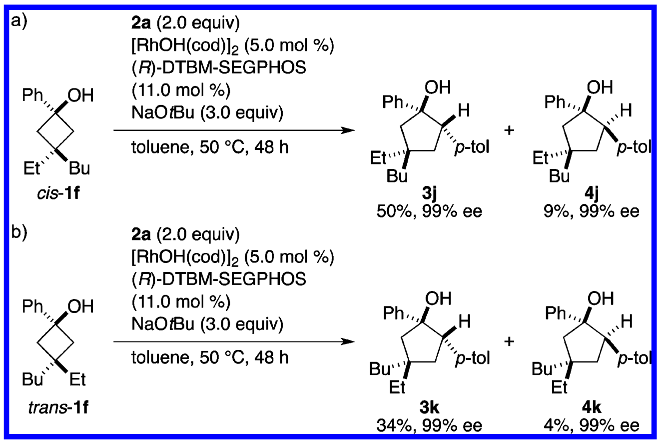
nucleophilic addition to the carbonyl group (Step 3). When **L1** was used as the ligand, a mixture of all four possible diastereomers **3j**, **3k**, **4j**, and **4k** (ca. 69:12:15:4) was formed.[16] In contrast, the use of (*R*)-DTBM-SEGPHOS gave only **3j** (50%) and **4j** (9%),[17] although the starting cyclobutanol *cis*-**1f** was not fully converted (Scheme 2a).[18] Of particular note was that an excellent enantioselectivity of 99% ee was observed for the both diastereomers. This stereochemical outcome is explained by assuming the following scenario. In Step 1, the chiral ligand (*R*)-DTBM-SEGPHOS directs exclusive cleavage of one of the enantiotopic C−C bonds.[10d] In Step 2, the chiral phosphine ligand and the existing tertiary chiral center induce a moderate stereoselectivity (ca. 85:15) to bring about two diastereomers.[19] In Step 3, the chiral ligand rather than the existing two chiral centers dominates differentiation of the two faces of the carbonyl group with almost complete selectivity. As a result, only the two diastereomers are formed both with 99% ee.

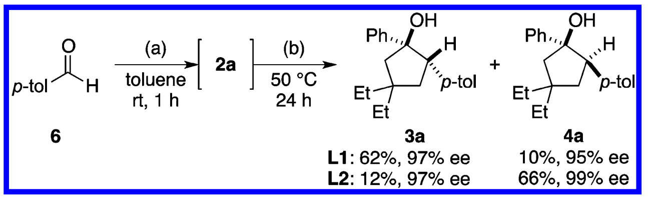
Scheme 2. Reactions of *cis*- and *trans*-3-Butyl-3-ethyl-1-phenylcyclobutanols 1f



The other diastereomer *trans*-**1f** was also subjected to the reaction with **2a** using (*R*)-DTBM-SEGPHOS as the chiral ligand. Only the two diastereomers **3k** and **4k** were produced again, and their enantioselectivities were both 99% ee (Scheme 2b).[18] The same scenario with that assumed for *cis*-**1f** accounts for this result as well, and thus only the two diastereomers **3k** and **4k** are formed both with 99% ee from *trans*-**1f**.

We finally tried to synthesize cyclopentanols in one pot starting from *p*-tolualdehyde **6** (Scheme 3). Initially, a mixture of **6** and tosylhydrazide in toluene was stirred at room temperature for 1 h. Then, the cyclobutanol **1a**, [RhOH(cod)]$_2$, chiral ligand (**L1** or **L2**), and NaO*t*Bu were added to the reaction mixture, which was further stirred at 50 °C for 24 h. Chromatographic purification furnished the cyclopentanols **3a** and **4a**. Their yields and enantioselectivities were comparable to those obtained with the isolated **2a**.

Scheme 3. One-Pot Synthesis Starting from *p*-Tolualdehyde 6



^{a}**6** (0.32 mmol), $TsNHNH_2$ (0.32 mmol); ^{b}**1a** (0.2 mmol), [RhOH(cod)]$_2$ (5.0 mol %), **L1** or **L2** (11.0 mol %), NaO*t*Bu (0.52 mmol).

In summary, cyclobutanols are expanded to cyclopentanols by insertion of a carbenoid carbon with control of stereochemistries. Up to three chiral centers can be created in a stereoselective way by the single reaction involving C−C bond cleavage.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews: (a) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (b) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (d) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (e) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (f) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (g) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (h) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (i) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (j) Yu, J.-Q.; Shi, Z.-J. In *Topics in Current Chemistry*, Vol. *292*; Springer-Verlag: Berlin, 2010. (k) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (l) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (m) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654.

(2) For recent reviews: (a) Dong, G. *Synlett* **2013**, 1. (b) Ruhland, K. *Eur. J. Org. Chem.* **2012**, 2683. (c) Korotvička, A.; Nečas, D.; Kotora, M. *Curr. Org. Chem.* **2012**, *16*, 1170. (d) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (e) Assa, C. *Synthesis* **2011**, 3389.

(3) For selected examples: (a) Liu, L.; Ishida, N.; Murakami, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2485. (b) Souillart, L.; Parker, E.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 3001. (c) Xu, T.; Ko, H. M.; Savage, N. A.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 20005. (d) Dreis, A. M.; Douglas, C. J. *J. Am. Chem. Soc.* **2009**, *131*, 412. (e) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874. (f) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594. See also references cited therein.

(4) For selected examples: (a) Chen, P.; Xu, X.; Dong, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1674. (b) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428. (c) Müller, C.; Lachicotte, R. J.; Jones, W. D. *Organometallics* **2002**, *21*, 1975. See also references cited therein.

(5) (a) Matsuda, T.; Tsuboi, T.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12596. (b) Eisch, J. J.; Piotrowski, A. M.; Han, K. I.; Krüger, C.; Tsay, Y. H. *Organometallics* **1985**, *4*, 224.

(6) Insertion of both carbon monoxide and an alkyne: (a) Shaw, M. H.; Melikhova, E. Y.; Kloer, D. P.; Whittingham, W. G.; Bower, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 4992. (b) Kondo, T.; Kaneko, Y.; Taguchi, Y.; Nakamura, A.; Okada, T.; Shiotsuki, M.; Ura, Y.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **2002**, *124*, 6824.

(7) Reviews for carbene insertion into metal−carbon bonds: (a) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486. (b) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560. (c) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236. For recent examples of carbene insertion into a rhodium−carbon bond: (d) Tsoi, Y.-T.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2011**, *13*, 5370. (e) Walters, A. J. C.; Troeppner, O.; Ivanović-Burmazović, I.; Tejel, C.; del Río, M. P.; Reek, J. N. H.; de Bruin, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 5157. See also references cited therein.

(8) Asymmetric insertion reactions of diazo compounds into carbonyl compounds: (a) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 8834. (b) Gao, L.; Kang, B. C.; Ryu, D. H. *J. Am. Chem. Soc.*, **2013**, *135*, 14556, and references cited therein.

(9) A related ring-expansion reaction of benzocyclobutenols has recently appeared: Xia, Y.; Liu, Z.; Liu, Z.; Ge, R.; Ye, F.; Hossain, M.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2014**, *136*, 3013.

(10) Selected examples of catalytic transformation of cyclobutanols and benzocycobutenols: (a) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862. (b) Shigeno, M.; Yamamoto, T.; Murakami, M. *Chem.—Eur. J.* **2009**, *15*, 12929. (c) Seiser, T.; Roth, O. A.; Cramer, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6320. (d) Seiser, T.; Cramer, N. *J. Am. Chem. Soc.* **2010**, *132*, 5340. (e) Ishida, N.; Sawano, S.; Masuda, Y.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17502. (f) Ziadi, A.; Correa, A.; Martin, R. *Chem. Commun.* **2013**, *49*, 4286. (g) Ishida, N.; Sawano, S.; Murakami, M. *Nat. Commun.* **2014**, *5*, 3111. See also references cited therein.

(11) See SI for structural determination.

(12) See SI for the detailed optimization of the reaction conditions.

(13) Generation of rhodium carbene complexes from diazo compounds: (a) Vigalok, A.; Milstein, D. *Organometallics* **2000**, *19*, 2061. (b) Cohen, R.; Rybtchinski, B.; Gandelman, M.; Rozenberg, H.; Martin, J. M. L.; Milstein, D. *J. Am. Chem. Soc.* **2003**, *125*, 6532.

(14) An attempted reaction of 1-butyl-3,3-diethylcyclobutanol gave the desired products in low yields and the starting cyclobutanol was mostly recovered. This is probably due to slower ring-opening of the 1-alkylcyclobutanol.

(15) The reaction of 3-phenyloxetan-3-ol afforded the products in <10% yield and the starting oxetanol was mostly recovered. Likewise, N-protected 3-pehnylazetidin-3-ols failed to give the desired products.

(16) The reaction of *cis*-**1f** using **L2** as the ligand afforded a mixture of all four diastereomers (**3j**:**3k**:**4j**:**4k** = 5:4:53:38).

(17) The absolute stereochemistries were assigned by analogy with the results reported in ref 10d. See SI for details.

(18) The ring-opened product was isolated in 5−7% yield.

(19) Stereoselective insertion of trimethylsilyldiazomethane into Pt−halogen and Pt−carbon bonds: (a) Bergamini, P.; Costa, E.; Orpen, A. G.; Pringle, P. G.; Smith, M. B. *Organometallics* **1995**, *14*, 3178. (b) McCrindle, R.; McAlees, A. J. *Organometallics* **1993**, *12*, 2445. See also references cited therein.