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Formation of Five-Membered Carbocycles by Intramolecular Palladium-Catalyzed Ring Opening of *tert*-Cyclobutanols

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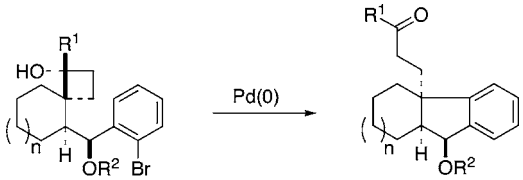
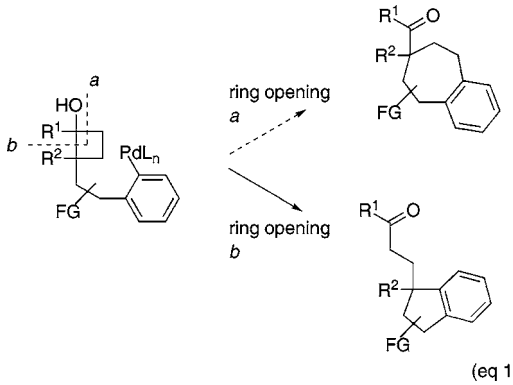
ABSTRACT



n = 0 and 1

We report herein stereoselective formation of a functionalized five-membered carbocycle bearing a quaternary center by intramolecular palladium-catalyzed ring-opening of *o*-bromophenyl-tethered *tert*-cyclobutanols.

Ring opening of small rings is accompanied by release of ring strain. Strain-releasing fragmentation reactions can be induced by various methods and have seen frequent applications in organic chemistry. As cyclopropanes and cyclobutanes possess similar strain energies (27.4 and 26.4 kcal/mol, respectively),[1] both rings show comparable reactivity toward transition metal-mediated ring cleavage.[2] Synthetically useful transition metal-mediated ring-opening reactions of cyclobutanols have recently been developed besides well-known counterparts involving cyclopropanols.[3−5] For example, Uemura and co-workers reported palladium-catalyzed C−C bond cleavage of *tert*-cyclobutanols, whereas β-carbon elimination takes place at a less hindered primary alkyl group.[4] To our knowledge, no intramolecular variant has appeared: we speculated that geometrical factors imposed by an intramolecular process could be relied on to override the typical regioselectivity of β-carbon elimination (ring opening *a*) for the construction of quaternary centers (ring opening *b*) (eq 1). We describe herein stereoselective formation of a functionalized five-membered carbocycle bearing a quaternary center by intramolecular palladium-catalyzed ring opening of *tert*-cyclobutanols.



(eq 1)

Ready access to the requisite cyclobutanones bearing three contiguous stereocenters was found in coupling of 1-(cyclohexenyl)cyclopropan-1-ol trimethylsilyl ether (**1**) and an

(1) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312.

(2) It is interesting to note, however, that there is a marked difference in their reactivity toward electrophiles; this disparity is attributed primarily to bent bonds of cyclopropanes.

(3) For reviews, see: (a) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485. (b) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (c) Muzart, J. *Tetrahedron* **2005**, *61*, 9423.

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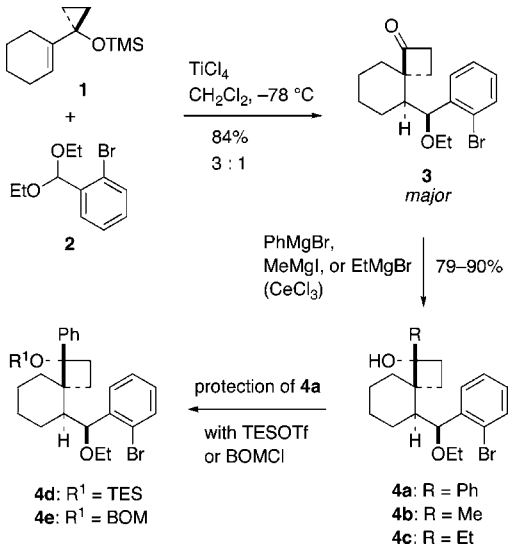
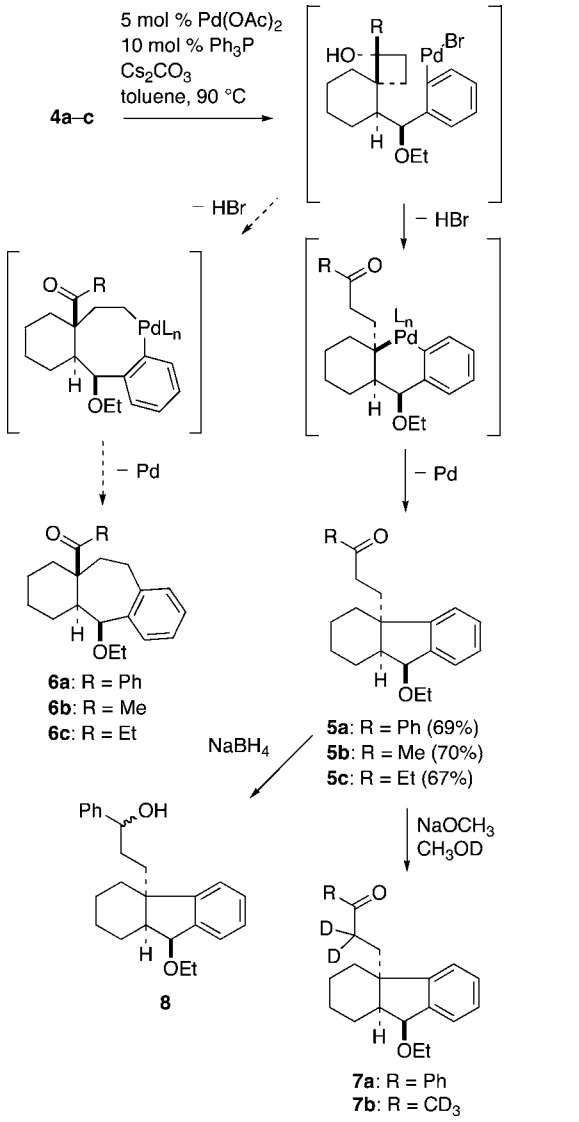
Scheme 1. Coupling of **1** and **2**, Followed by Addition of a Grignard Reagent



acetal in the presence of a Lewis acid (Scheme 1).[6,7] Treatment of a mixture of TMS ether **1** and acetal **2** with $TiCl_4$ at −78 °C afforded spirobutanone **3** in 84% yield and with moderate diastereoselectivity (∼3:1 admixed with trace amounts of the third isomer). The major isomer **3** was separated easily by silica gel chromatography. Addition of the phenyl, methyl, or ethyl Grignard reagent (or the corresponding ceriates) to **3** gave the respective cyclobutanols **4a**−**c** as single isomers in 79−90% yield. Single-crystal X-ray diffraction studies of **4a** and **4c** revealed that addition of the Grignard reagent took place from the more hindered side of the spirocyclobutanone, presumably due to chelation-controlled approach.[8]

We next explored palladium-mediated ring opening of **4a**−**c** (Scheme 2): the intermediacy of a Pd(II)-alcoholate species was precluded due to the unexpected stereochemistry of the *tert*-cyclobutanol moiety, whereas the aforementioned Uemura protocol is likely to proceed via a Pd(II)-alcoholate intermediate.[4] Treatment of **4a** with 5 mol % of $Pd(OAc)_2$ and 10 mol % of Ph_3P in the presence of Cs_2CO_3 in toluene

Scheme 2. Pd-Mediated Annulation of **4a**−**c**



at 90 °C resulted in formation of the five-membered carbocycle **5a** (IR 1684 cm^{-1}) in 69% yield. Similarly, **5b** and **5c** were obtained in 67−70% yield. A priori, the respective 7-membered annulation products **6a**−**c** could not be discounted, especially because both ring systems would also display similar splitting patterns in their ^1H NMR spectra. The unequivocal structural assignment of **5a**−**c** vis-à-vis **6a**−**c** was secured by deuterium labeling studies of **5a**,**b** and also $NaBH_4$ reduction of **5a**, coupled with analysis of the ^1H NMR spectra of the resulting compounds **7a**,**b** and **8**.

A brief screening of several ligands with **4a** and $Pd(OAc)_2$ showed no significant difference between monodentate and bidentate ligands: Ph_3P (69%); dppp (69% + 8% unreacted **4a**); dppe (66% + 15% **4a**); and *rac*-BINAP (64% + 6% **4a**). Comparable yields were obtained with $Pd(PPh_3)_4$, but $Pd_2(dba)_3{\cdot}CHCl_3$ was ineffective regardless of ligands employed. With regard to base, Cs_2CO_3 proved to be superior to K_2CO_3, Ag_2CO_3, or Et_3N. To establish the necessity of

(4) (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc*. **1999**, *121*, 2645. (b) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc*. **1999**, *121*, 11010. (c) Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem*. **2001**, *66*, 1455. (d) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *Chem. Commun*. **2002**, 50. (e) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc*. **2003**, *125*, 8862. (f) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201.

(5) Cf. (a) Murakami, M.; Amii, H.; Shigeto, K.; Ito, Y. *J. Am. Chem. Soc*. **1996**, *118*, 8285. (b) Matsuda, T.; Makino, M.; Murakami, M. *Angew. Chem., Int. Engl*. **2005**, *44*, 4608. (c) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc*. **2006**, *128*, 2166.

(6) (a) Oh, H.-S.; Lee, H. I.; Cha, J. K. *Org. Lett*. **2002**, *4*, 3707. (b) Oh, H.-S.; Cha, J. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2911.

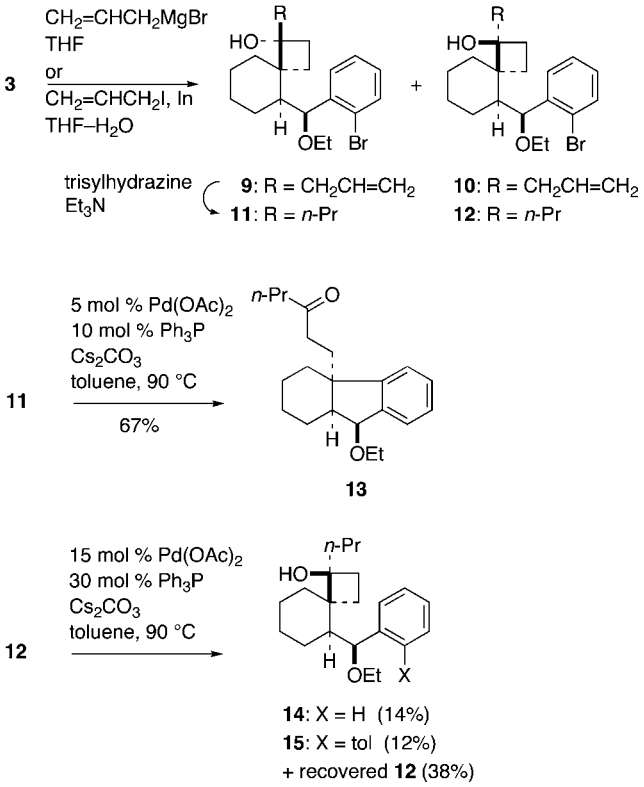
(7) (a) Trost, B. M.; Brandi, A. *J. Am. Chem. Soc*. **1984**, *106*, 5041. (b) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc*. **1988**, *110*, 6556. (c) Trost, B. M.; Chen, D. W. C. *J. Am. Chem. Soc*. **1996**, *118*, 12541. For reviews, see: (d) Trost, B. M. *Top. Curr. Chem*. **1986**, *133*, 3. (e) Salaün, J. *Top. Curr. Chem*. **1988**, *144*, 1.

(8) We thank Dr. Mary Jane Heeg of our Department for single-crystal X-ray analyses. The X-ray data have been deposited with the Cambridge Structural Database: please refer to CSD nos. 239496 (**4a**), 239454 (**4c**), 232508 (**19**), 232507 (**20**), 230187 (**21**), and 232509 (**22**).

the free alcohol, **4d** and **4e** were prepared by standard methods (Scheme 1). When **4d** and **4e** were subjected to identical conditions, no annulation was observed, but the bulk of starting material was recovered unreacted. Thus, base is necessary for not only removal of HBr generated, but also deprotonation of the cyclobutanol.

tert-cyclobutanols epimeric to **4a**−**c** were also prepared to examine the possible involvement of an Uemura-type cyclic palladium alcoholate,[4] although formation of an eight-membered palladium species would seem unfavorable. Addition of allylmagnesium bromide gave a 5:1 separable mixture of **9** and **10** in 73% yield, whereas a 1:1 mixture was obtained in 65% yield by means of an allylindium reagent. After separation, **9** and **10** were reduced by diimide to afford **11** and **12**, respectively, in 90% yield (Scheme 3).

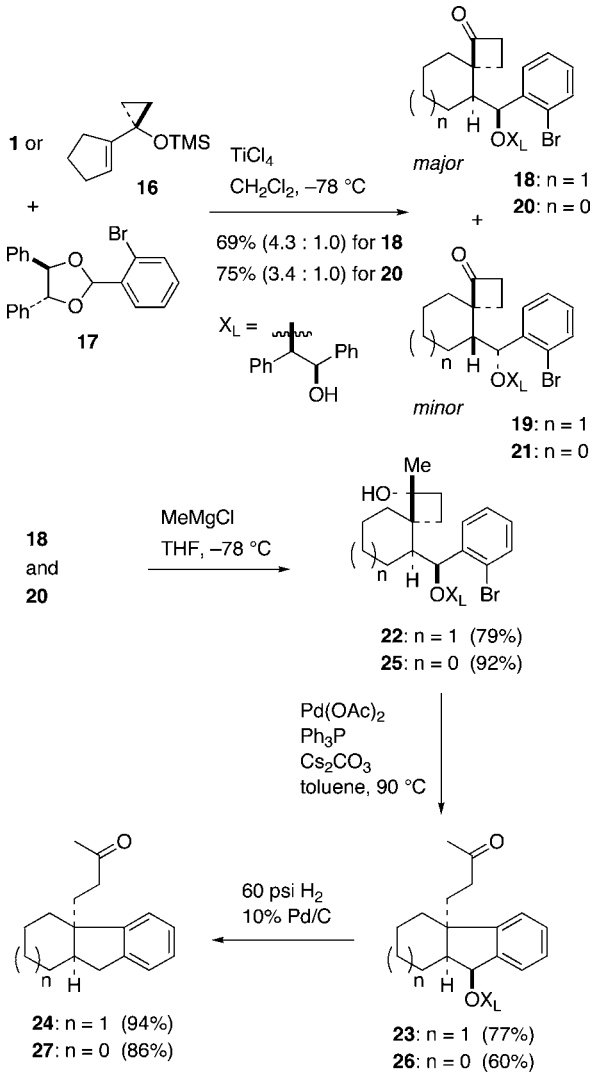
Scheme 3. Comparison of Both Epimers in Pd-Mediated Annulation



As expected, **11** yielded **13** uneventfully under previously developed conditions. However, no annulation product was isolated from the epimer **12**. Instead, **14** and **15** were isolated in low yields along with recovered **12**. Whereas full elucidation of the reaction mechanism awaits further studies, these results suggest that formation of **5a**−**c** and **13** arises from direct electrophilic attack at the cyclobutanol ring by an arylpalladium(II) intermediate derived from oxidative addition of a Pd(0) species to aryl bromide.[9,10] A salient feature is atypical cleavage of the more substituted C−C bond of the cyclobutanol ring, which is probably due to favorable entropy of a five-membered ring formation.

As was the case with related compounds,[6] a straightforward entry to enantioselective synthesis was available by utilizing a nonracemic C_2-symmetric acetal in the coupling reactions of **1** and **16** (Scheme 4). The stereochemistry of

Scheme 4. Enantioselective Pd-Mediated Annulation



the coupling products **18**−**21** was secured by X-ray analysis.[8] The observed, albeit modest, 1,3-diastereofacial selectivity by the chiral C_2-symmetric acetal is consistent with literature precedents.[11] The major isomers **18** and **20** were subjected to stereoselective addition of the methyl Grignard reagent and subsequent annulation to afford **23** and **26**, respectively. For additional characterization, **24** and **27** were

(9) Cf. Siloxycyclopropanes are known to react with arylpalladium cation complexes: (a) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296. (b) Fujimura, T.; Aoki, S.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2809.

(10) For related palladium-catalyzed ring expansion reactions, see: (a) Larock, R. C.; Reddy, C. K. *Org. Lett.* **2000**, *2*, 3325. (b) Larock, R. C.; Reddy, C. K. *J. Org. Chem.* **2002**, *67*, 2027. (c) Wei, L.-M.; Wei, L.-L.; Pan, W.-B.; Wu, M.-J. *Tetrahedron Lett.* **2003**, *44*, 595.

obtained in good yield by hydrogenolysis of **23** and **26**, respectively.

Inasmuch as the stereochemistry of the minor coupling products **19** and **21** was unequivocally established, they were subjected to the identical sequence of transformations to gain additional information on the scope. Addition of methylmagnesium chloride to **19** and **21** gave poor conversion, presumably due to competing enolization, but use of the ceriate agent furnished the corresponding *tert*-cyclobutanols as a ca. 2:1 diastereomeric mixture in 55% and 89% yield, respectively. None of these *tert*-cyclobutanols furnished the annulation products. These control experiments indicate that the *cis*-stereochemical relationship between the two side chains involved is required for the cyclization reaction.[12]

In summary, intramolecular palladium-catalyzed ring opening of *tert*-cyclobutanols has been developed for the stereoselective preparation of functionalized five-membered carbocycles containing a quaternary center. It is interesting to note that palladium(II)-catalyzed cleavage of the tethered *tert*-cyclobutanol occurs at the more hindered C−C bond. Also included are stereochemical requirements for the key annulation reaction. A modified approach to medium-sized carbocycles is currently under investigation.

Acknowledgment. We thank the National Institutes of Health (GM35956) for generous financial support.

Supporting Information Available: Experimental details and spectroscopic data for key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070985Q

(11) See, inter alia: (a) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477. (b) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc*. **1991**, *113*, 8089. (c) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc*. **1992**, *114*, 10998.

(12) Analogous results were also obtained with the minor cyclobutanone product (structure not shown) from the coupling reaction of **1** and **2** (Scheme 1): no annulation products were obtained from a 3:1 inseparable mixture of the two *tert*-cyclobutanols, which were prepared by addition of the methyl Grignard reagent.