Highly Stereoselective Prins Cyclization of Silylmethyl-Substituted Cyclopropyl Carbinols to 2,4,6-Trisubstituted Tetrahydropyrans

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Highly Stereoselective Prins Cyclization of Silylmethyl-Substituted Cyclopropyl Carbinols to 2,4,6-Trisubstituted Tetrahydropyrans

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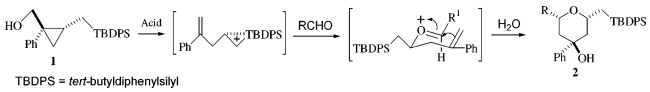
Prins cyclization is a versatile method for the construction of a tetrahydropyran ring.[1] The tetrahydropyran ring is featured in a variety of biologically active natural products, marine toxins, and pheromones.[2] Cyclopropane is a versatile intermediate for the synthesis of a wide range of molecular skeletons, including carbocycles and heterocycles.[3] Cyclopropyl carbinol will give cyclopropyl carbinyl cation on treatment with an acid. This cation will undergo either ring expansion to a cyclobutyl cation[4] or ring cleavage to a homoallyl cation[5] to relieve ring strain. We considered promoting the ring-cleavage pathway through stabilization of the homoallyl cation by a silylmethyl function[6,7] and wished to trap the cation by a carbonyl function. The subsequent intramolecular nucleophilic capture of the so-formed oxonium ion by the in situ formed olefin will generate a multiply substituted tetrahydropyran ring as outlined in Scheme 1. The scope of the Prins reaction will thus stand amply expanded. In the present communication, we present an account of our results.

The results are collected in Table 1. Butyraldehyde reacted with **1**[8] in the presence of 10 equiv of trifluoroacetic acid (TFA) in CH_2Cl_2 at −30 °C to furnish **3** in 72% yield as a single isomer (entry 1). The reaction introduced three stereogenic centers in the product. The high stereoselectivity observed throughout is possibly due to the bulky silylmethyl group that occupied the equatorial position in the six-membered cyclic transition state and the stereoelectronically controlled nucleophilic capture of the aryl-substituted cation from the axial direction (Scheme 1).[9] Among the several Lewis acids that were used, $BF_3{\cdot}OEt_2$ was found to be the most effective. However, it provided a 2:1 mixture of **4a** and **4b** in 78% combined yield (entry 2). The intermediate benzylic cation formed from the final ring closure had met with exclusive deprotonation. The 2,6-cis-stereoselectivity was ascertained from nOe measurements. Aromatic aldehydes containing electron-donating and electron-attracting substituents and α,β-unsaturated aldehydes also reacted well to furnish the expected products in good yields.

We were naturally tempted to gauge the efficacy of the above protocol for the construction of tetrahydropyran ring, and thus we attempted reactions of **1** with ketones as well.[10] The reactions proceeded smoothly to generate the desired products in good yields (Table 2). $BF_3{\cdot}OEt_2$ (2 equiv) was found to be the most effective Lewis acid for the reaction as several other Lewis acids including TFA were found to be either less effective or not effective at all.[11] The [6.6] spiro species **11a** and **11b** were formed as a 3:2 mixture in a combined 75% yield (entry 2).[12] The reaction with unsymmetrical 2-pentanone furnished **12a** and **12b** as a 3:2 mixture in a combined 60% yield. The exclusive 2,6-cis-stereoselectivity observed in **12a**/**12b** is indeed remarkable (entry 3). It will be useful in the synthetic planning of molecules that are rich in multiple stereocenters.

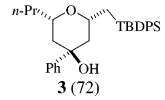
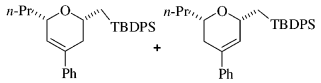
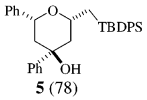
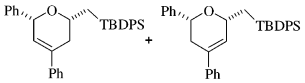
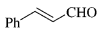
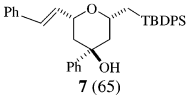
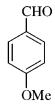
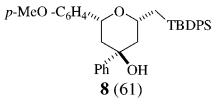
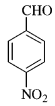
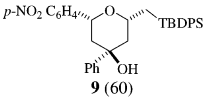
To assess the contribution of the phenyl group to the final ring closure and to further expand the scope of the present methodology for tetrahydropyran ring construction, we studied **13a** and **13b** (Scheme 2). that were prepared conveniently by a rhodium-catalyzed addition of the carbene generated from α-diazocyclohexanone to allyl−*tert*-butyldiphenylisilane, followed by reduction of the carbonyl function with $LiAlH_4$. Optimization studies demonstrated $BF_3{\cdot}OEt_2$ to outsmart several other Lewis acids that we attempted; **13a** reacted with 1.5 equiv of benzaldehyde and gave **14a** as a single isomer in 70% yield. The reaction had proceeded with high selectivity, and four new stereogenic centers were generated in one shot. The cis stereochemistry of the ring junction and the relative stereochemistry of the other substituents in **14a** were determined from nOe measurements, *J* values, and further chemical transformation.[13] The isomeric **13b** gave a 1:3 mixture of the above **14a** and the fluoro-**14b** under similar reaction conditions. The formation of

Scheme 1



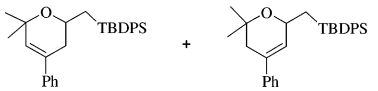
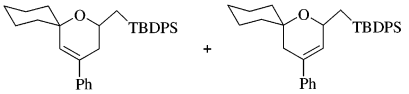
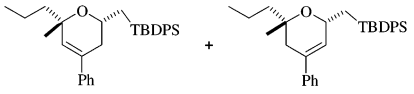
TBDPS = *tert*-butyldiphenylsilyl

Table 1. Prins Cyclization of **1** with Aldehydes

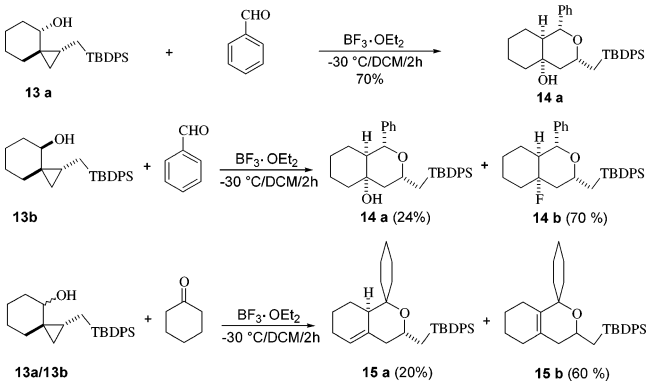
Entry	Acid	Aldehyde	Product (Yield %)
1	TFA		 **3** (72)
2	$BF_3{\cdot}OEt_2$		 **4a** (52) **4b** (26)
3	TFA		 **5** (78)
4	$BF_3{\cdot}OEt_2$		 **6a** (48) **6b** (32)
5	TFA		 **7** (65)
6	TFA		 **8** (61)
7	TFA		 **9** (60)

10.1021/ja048000c CCC: $27.50

Table 2. Reaction of **1** with Ketones in the Presence of $BF_3{\cdot}OEt_2$

Entry	Ketone	Products (yield)
1		 **10 a** (38) **10 b** (27)
2		 **11 a** (45) **11 b** (30)
3		 **12 a** (36) **12 b** (24)

Scheme 2



14b is surprising. The inversion of configuration of the alcohol stereocenter is apparently the cause of the formation of **14b** as the major product. However, its incidence on product distribution **14a**/**14b** and, particularly, the formation of **14b** is not clear. We have established from a separate reaction under identical conditions that **14b** was not derived from **14a**. Both **13a** and **13b** reacted with cyclohexanone to furnish an almost identical 1:3 mixture of products **15a** and **15b**. The carbocation formed from ring closure had met with exclusive elimination and isomerization.

In conclusion, we have developed the first Prins cyclization of a silicon-stabilized homoallyl cation formed from a cyclopropyl carbinol that was vicinally substituted by a silylmethyl function. The reaction was applied to the synthesis of 2,4,6-trisubstituted tetrahydropyran rings in good to excellent yields.[14,15]

Acknowledgment. This work is dedicated to Professor K. K. Balasubramanian on the occasion of his 65th birthday. We thank DST for funding. N.V.K. thanks CSIR for JRF.

Supporting Information Available: Experimental details and characterization data for all the compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Heathcock, C. H. Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, pp 527−561. (b) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022. (c) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092. (d) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; King, C. D.; Simpson, T. J.; Smith, R. W.; Willis, C. L. *Chem. Commun*. **2001**, 835. (e) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **2001**, *123*, 8420. (f) Lopez, F.; Castedo, L.; Mascarenas, J. L. *J. Am. Chem. Soc*. **2002**, *124*, 4218. (g) Barry, C. St. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett*. **2003**, *5*, 2429 (h) Aubele, D. L.; Lee, C. A.; Floreancig, P. E. *Org. Lett*. **2003**, *5*, 4521. (i) Cho, Y. S.; Karupaiyan, K.; Kang, H. J.; Pae, A. N.; Cha, J. H.; Koh, H. Y.; Chang, M. H. *Chem. Commun*. **2003**, 2346. (j) Hart, D. J.; Bennett, C. E. *Org. Lett*. **2003**, *5*, 1499. (k) Miranda, P. O.; Diaz, D. D.; Padron, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979.

(2) (a) *Polyether Antibiotics*; Westly, J. W., Ed.; Dekker: New York, 1983; Vols. I and II (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1. For examples of polysubstituted tetrahydropyrans, see: (a) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 10211. (b) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836. (c) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 1993.

(3) (a) Reissig, H.-U. *Small Ring Compounds in Organic Synthesis III*, *Topics in Current Chemistry*. de Meijere, A. Ed,; Springer-Verlag: Berlin, Heidelberg, Germany, 1991; Vol. 144, p 73. (b) Salaun, J. R. Y. *Small Ring Compounds in Organic Syntheis III*; de Meijere, A. Ed.; Topics in Current Chemistry, 144; Springer-Verlag: Berlin, Heidelberg, Germany, 1991; p 1. (c) Hudlicky, H.; Reed, J. W. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Heathcock, C. H., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, p 899. (d) Reissig, H.-U.; Zimmer, R. *Chem. Rev*. **2003**, *103*, 1151.

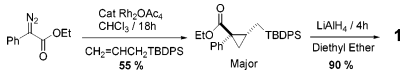
(4) (a) Kanemoto, S.; Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1987**, *28*, 6313. (b) Hardouin, C.; Taran, F.; Doris, E. *J. Org. Chem.* **2001**, *66*, 4450.

(5) (a) Sarel, S.; Yovell, J.; Sarel-Imber, M. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 577. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Huldicky, T. *Chem. Rev*. **1989**, *89*, 165.

(6) (a) Yadav, V. K.; Balamurugan, R. *Org. Lett*. **2001**, *3*, 2717. (b) Yadav, V. K.; Balamurugan, R. *Chem. Commun.* **2002**, 514. (c) Yadav, V. K.; Sriramurthy, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2669.

(7) For discussions on silyl-stabilized β-carbocations, see: (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976; p 81. (b) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.

(8) The reactant **1** was prepared from carbene addition to the requisite allyl silane followed by reduction as shown below.



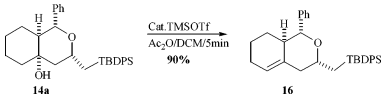
(9) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc*. **2002**, *124*, 4960.

(10) (a) Herrinton, P. M.; Hopkins, M. H,; Mishra, P.; Brown, M. J.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 3711. (b) Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Mishra, P.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5365. (c) Patterson, B.; Rychnovsky, S. D. *Synlett* **2004**, *3*, 543.

(11) We obtained only the cyclopropane ring opened product on use of TFA.

(12) For alternative preparations of oxygen spirocycles, see: (a) Paquette, L. A.; Tae, J. *J. Org. Chem*. **1996**, *61*, 7860. (b) Rychnovsky, S. D.; Takaoka, L. R. *Angew. Chem., Int. Ed*. **2003**, *42*, 818.

(13) Attempted acetylation of the alcohol **14a** using TMSOTf and Ac_2O led to elimination to form only one trisubstituted olefin shown below. This is possibly a consequence of exclusive 1,2-trans-elimination.



(14) Typical procedure for the TFA-assisted Prins cyclization of **1** with butyraldehyde: A solution of cyclopropyl carbinol **1** (76 mg, 0.19 mmol) and butyraldehyde (21 mg, 0.29 mmol) in CH_2Cl_2 (2 mL) was cooled to −30 °C and mixed with TFA (0.146 mL, 1.9 mmol). The reaction was quenched with aqueous $NaHCO_3$ when it was complete by TLC (1.5 h), and it was stirred vigorously for 10 min. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layer was dried, filtered, and concentrated. The crude material was dissolved in methanol (2 mL), mixed with K_2CO_3 (50 mg, 0.35 mmol), and stirred for 10 h at 25 °C. Methanol was removed, and the residue was dissolved in water (2 mL) and Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layer was dried, filtered, and concentrated. The crude material was purified by radial chromatography to obtain **3** (65 mg, 72%).

(15) Typical procedure for the $BF_3{\cdot}OEt_2$-assisted Prins cyclization of **1** with butyraldehyde or acetone: The stirred solution of cyclopropyl carbinol **1** (76 mg, 0.19 mmol) and butyraldehyde (21 mg, 0.29 mmol) or acetone (22 mg, 0.38 mmol) in CH_2Cl_2 (2 mL) at − 30 °C (−30 °C to 25 °C in the case of acetone) was treated dropwise with $BF_3{\cdot}OEt_2$ (54 mg, 0.38 mmol) under nitrogen. After the completion of the reaction (1.5 h for butyraldehyde and 4.5 h for acetone), it was quenched with aqueous $NaHCO_3$. The mixture was extracted with Et_2O (2 × 10 mL), and the combined organic extract was washed with water and brine, dried, filtered, and concentrated. The crude material was purified by radial chromatography for the products **4a**/**4b** = 2:1, 67.3 mg, 78%; **10a**/**10b** = 4:3, 54.3 mg, 65%.

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