ORGANIC LETTERS

2010
Vol. 12, No. 12
2679−2681

A Facile Method for the Synthesis of Highly Substituted Six-Membered Rings: Mukaiyama−Aldol−Prins Cascade Reaction

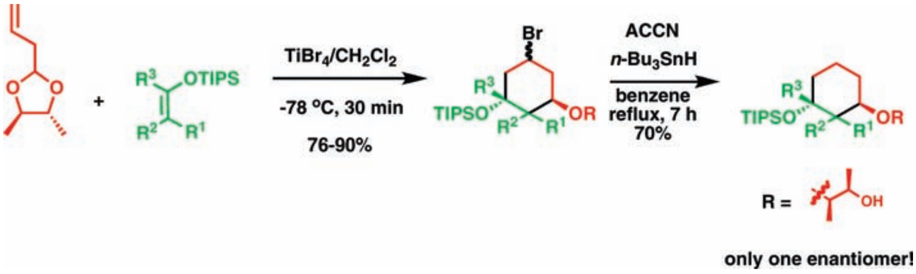
Hao Li and Teck-Peng Loh*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371

teckpeng@ntu.edu.sg

Received April 23, 2010

ABSTRACT



A highly efficient cascade reaction has been developed using cheap commercially available or easily accessible starting materials. It has the ability to construct highly functionalized six-membered ring with three to four stereogenic centers in high yields.

Cascade reactions are useful synthetic transformations as they allow expedient and efficient construction of complex structures.[1] Among the many cascade reactions, the development of a new cascade reaction to create highly functionalized ring systems with the generation of multiple stereogenic centers in a one-pot manner is highly sought-after.[2] Recently, our group has reported an efficient method for the synthesis of highly functionalized five-membered rings in high yields with excellent regio-, diastereo-, and enantioselectivities using cascade Mukaiyama−Aldol−Prins reaction (Scheme 1, path a).[3] We envisage that by tuning the stability of the carbocation formed via variation of the acetal olefinic substituents, a six-membered ring (Scheme 1, path b) can be obtained instead of the five-membered ring. Therefore, if nonsubstituted acetal is utilized, a six-membered ring could be formed through path b.[4] Herein, we report a novel cascade

---

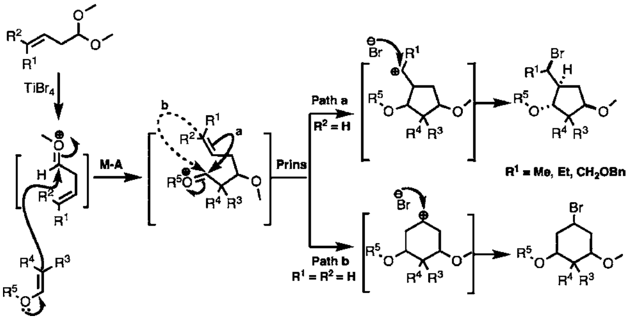
(1) For reviews of cascade reactions, see: (a) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Tietze, L. F.; Brasche. G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: New York, 2006. (d) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131. For selected examples of cascade reactions, see: (e) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233. (f) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962. (g) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (h) Casas, J.; Engqvist, M.; Ibrahem, I. B.; Kaynak, B.; Cordova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343. (i) Yang, J. W.; Hechavarria, M.; Fonseca, T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (j) Huang, Y. A.; Larsen, M. C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (k) Wang, Y.; Liu, X. F.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (l) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986. (m) Xie, H. X.; Zu, L. S.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886. (n) Zu, L. S.; Wang, J.; Li, H.; Xie, H. X.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (o) Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256. (p) Wu, B. F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (q) Vicario, J. L.; Reboredo, S.; Badia, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168. (r) Wang, J.; Li, H.; Xie, H. X.; Zu, L. S.; Shen, X.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9050. (s) Reyes, E.; Jiang, H.; Milelli, A.; Elsner, P.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 9202. (t) Cabrera, S.; Alema, J.; Bolze, P.; Bertelsen, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 121.

(2) (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Organic Synthesis I*; Wiley-VCH: New York, 1996. (b) Nicolaou, K. C.; Snyder, S. A. *Classics in Organic Synthesis II*; Wiley-VCH: New York, 2003.

(3) Li, H.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 7194.

10.1021/ol100937r

Scheme 1. Our Proposed Hypothesis

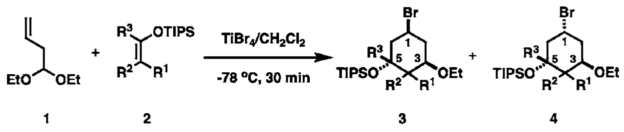


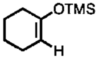
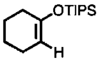
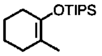
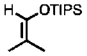
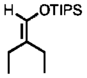
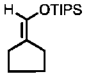
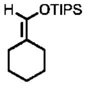
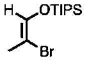
reaction involving the Mukaiyama−Aldol−Prins (MAP) cascade reaction to create highly functionalized six-membered ring systems with the generation of up to four new stereogenic centers in a one-pot manner. This method provides a fast access to a wide variety of cyclohexane skeletons which are important building blocks in the synthesis of complex molecules.

Initially, cyclohexenyloxytrimethylsilane reacted with the commercially available 4,4-diethoxybut-1-ene[5] in the presence of $TiBr_4$.[6] Unfortunately, only the Mukaiyama−Aldol product was obtained (Table 1, entry 1). Replacing the trimethylsilyl (TMS) group with the more robust triisopropylsilyl (TIPS) group gave the desired product, albeit in low yield (Table 1, entry 2). Fortunately, the yield of the product could be increased dramatically when *β*-disubstituted silyl enol ethers were used (Table 1, entries 3−8). The desired product was obtained as a single isomer at C_{3-5} but with moderate diastereoselectivity at C_1 (ca. 2:1 diastereomeric mixture). These results suggested that the substituent at the *β* position of the silyl enol ether plays an important role in the cascade process. Especially noteworthy is that *β*-substituted brominated silyl enol ether reacts with acetal **1** to afford the desired product in good yield (Table 1, entry 8). This reaction further expanded the scope of this method. Since the bromine can easily be removed or functionalized, other cyclohexane building blocks could potentially be obtained.

Next, we investigated the asymmetric version of this reaction using optically pure cyclic acetal **5**.[7] The results are summarized in Table 2. In all cases, the desired products were obtained in good yields. Similar to the nonasymmetric version, the two diastereomers were obtained and easily separated by column chromatography. It is important to note

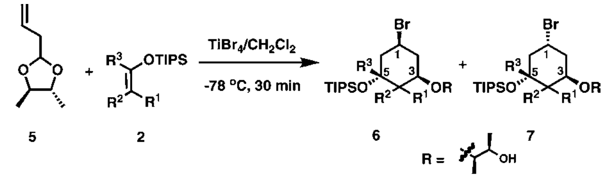
Table 1. Mukaiyama−Aldol−Prins Reaction To Form Six-Membered Ring[a,b]

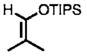
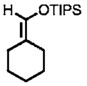
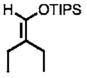
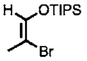
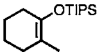


entry	silyl enol ether	yield (%)[c]	dr[d] **3:4**
1		70[e]	-
2		20	-
3		81	66:34
4		86	63:37
5		84	70:30
6		84	65:35
7		92	79:21
8	 Z / E=85:15	75	75:25[f]

[a] Mukaiyama−Aldol−Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal, and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b] Nonsubstituted acetal was purchased from Sigma-Aldrich. [c] Isolated yield. [d] Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses. [e] Only Mukaiyama−Aldol reaction product was obtained in 70% yield. [f] Four isomers, but isolated yield is determined by the major set of two isomers.

Table 2. MAP Cascade Reactions Using Chiral Acetal[a]



entry	silyl enol ether	yield (%)[b]	dr[c] **6:7** (enantioselectivity)
1		80	65:35 (>99:1) / (>99:1)
2		90	62:38 (>99:1) / (>99:1)
3		89	57:43 (>99:1) / (>99:1)
4	 *E* / *Z*=85:15	76	60:40 (>99:1) / (>99:1)
5		85	75:25[d] (>99:1) / (>99:1)

[a] Mukaiyama−Aldol−Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal, and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b] Isolated yield. [c] Diastereomeric ratios were determined by ^1H and ^{13}C NMR analyses. [d] Four isomers, but isolated yield is based on the major set of two isomers.

that both of the diastereomers were obtained as a single isomer (>99:1) as determined by ^{1}H and ^{13}C NMR. The relative and absolute stereochemistry of the major product of one of the compounds was confirmed by the X-ray crystallography (Figure 1, refer to the Supporting Information). Removal of the bromine atom in both diastereomers led to identical diastereomers (Scheme 2).

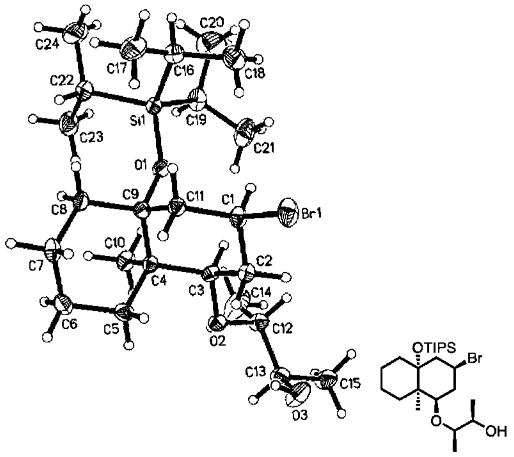
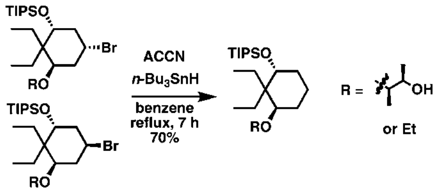


Figure 1. X-ray crystal structure of the major isomer of product in Table 2, entry 5.

In summary, we have developed a highly efficient cascade reaction using cheap commercially or easily accessible starting materials to construct a highly functionalized six-membered ring with three to four stereogenic centers in high yields. When chiral acetal **5** was employed, the desired cyclohexane derivatives could be obtained as a single isomer after removal of the bromine. We are in the process of applying this strategy to the synthesis of natural products.

Scheme 2. Confirmation of the Relative and Absolute Stereochemistry of the Minor Product in Table 1, Entry 5, and Table 2, Entry 3



Acknowledgment. We gratefully acknowledge the Nanyang Technological University and Singapore Ministry of Education Research Fund Tier 2 (No. T206B1221) for the financial support of this research and Dr. Y.-X. Li (Nanyang Technological University) for X-ray support.

Supporting Information Available: Additional experimental procedures, chromatograms, cif file of crystallographic data and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100937R

---

(4) (a) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491. (b) Liu, F.; Loh, T. P. *Org. Lett.* **2007**, *9*, 2063. (c) Hu, X. H.; Liu, F.; Loh, T. P. *Org. Lett.* **2009**, *11*, 1741.

(5) Sigma-Aldrich product no. 307246.

(6) Balme, G.; Gore, J. *J. Org. Chem.* **1983**, *48*, 3336.

(7) Zhao, Y. J.; Chng, S. S.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 492.