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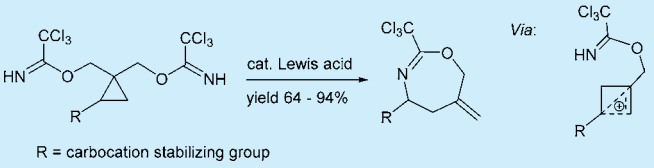
Tetrahydro-1,3-oxazepines via Intramolecular Amination of Cyclopropylmethyl Cation

Marija Skvorcova, Liene Grigorjeva, and Aigars Jirgensons*

Latvian Institute of Organic Synthesis, Riga LV-1006, Latvia

Supporting Information

ABSTRACT: An efficient synthesis of tetrahydro-1,3-oxazepines was developed involving the regioselective intramolecular amination of cyclopropylmethyl cation. The cation was generated by the abstraction of one imidate group in bis-imidate bearing a carbocation-stabilizing substituent. Using 1,1,2,3-tetrasubstituted cyclopropane substrates, highly diastereoselective intramolecular amination to *trans*-tetrahydro-1,3-oxazepines was achieved. The resulting tetrahydro-1,3-oxazepines were transformed to the homoallylamine derivatives in high yields.



Structural investigations of cyclopropylmethyl cation **1** have shown that it exists as an equilibrating mixture of $\pi\sigma$-delocalized bisected cyclopropylmethyl cation **1A** and non-classical bicyclobutonium ion **1B** (Figure 1).[1,2] The carbocation

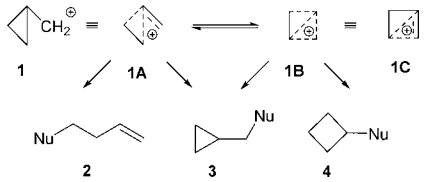


Figure 1. Regioselectivity in cyclopropylmethyl cation reaction with nucleophiles.

1 is often represented as **1C** which is a hybrid of the proposed discrete structures **1A** and **1B**. The reaction of cyclopropylmethyl cation **1C** with nucleophiles can occur at any of the three possible sites bearing partial positive charge leading to homoallyl,[3] cyclopropylmethyl,[2a,3a,j,4] or cyclobutyl[4,5] derivatives **2**−**4**. Several regioselective reactions of cyclopropylmethyl cation **1** with nucleophiles have been reported as a useful approach to products based on structures **2**−**4**.[3−5]

Although not systematically studied, the available experimental data suggest that regioselectivity of intramolecular cyclization is mainly controlled by the geometric constraints and/or effects of cyclopropane substituents. A carbocation stabilizing group can be used to direct the addition of nucleophile to cyclopropylmethyl cation **1C** presumably via inducing electron distribution in favor of the classical carbocation.

Few studies have been reported for amination reactions of cyclopropylmethylcarbocation.[3j,l,5e] The reason for that could be the limited range of amine nucleophiles compatible with acidic conditions typically used to initiate the reaction. Previously, we[6] as well as others[7] have demonstrated that bis-imidates are convenient systems for amination of carbocations. In bis-imidates, one of the imidates serves as the leaving group when activated with an acid catalyst while the other acts as an *N*-nucleophile. Following this approach, it was explored whether carbenium ion **6C** derived from readily available bis-imidate **5** can be regioselectively aminated depending on the cyclopropane substituent (Table 1).

Initial studies showed that substrate **5a** containing phenyl substituent selectively forms homoallyl carbocation amination product **7a** when exposed to Lewis acid catalyst (Table 1, entry 1). Screening of catalysts revealed that relatively weak Lewis acids such as $Cu(OTf)_2$ and $(CuOTf)_2{\cdot}C_6H_6$ were the optimal catalysts for the reaction. Stronger Lewis acids or acids containing nucleophilic counterions led to decomposition of product **7** (see the Supporting Information for details). Further, the substrate scope with respect to the cyclopropane substituent was explored. Bis-imidates **5** bearing aryl substituent with electron donating groups (entries 2, 3, and 5) afforded tetrahydro-1,3-oxazepines in excellent yields. Amination of bis-imidates **5** having electron-poor aryl groups (entries 4 and 15) gave satisfying results only for substrate **5d** (entry 4). Bis-imidates **5** bearing electron-rich heteroaryl substituents also provided the expected product **7** (entries 6 and 9−11). The reaction was not limited only to aryl carbocation stabilizing groups. Substrates bearing vinyl substituent (entries 7 and 8) gave high product yield. Bis-imidates **5b** containing groups with lower carbocation stabilizing ability such as ethyl (entry 13) or alkynyl (entry 14) led to the formation of a product mixture. However, if the alkyl group contained a silyl group as a β-cation-stabilizing substituent, the amination product was obtained in good yield (entry 12).

Tetrahydro-1,3-oxazepine derivatives **7** are masked unsaturated amino alcohols which are valuable multifunctional

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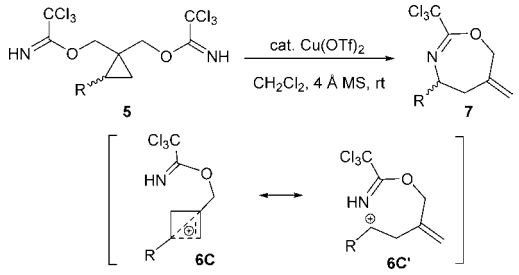
Table 1. Substrate Scope for the Cyclization of Bis-imidates 5 to Tetrahydro-1,3-oxazepines 7[a]



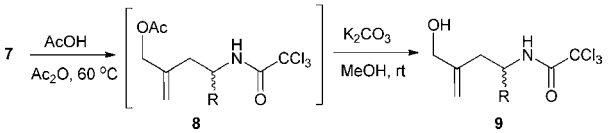
entry	R	product, yield (%)
1	Ph	**7a**, 85
2	4-$MeOC_6H_4$	**7b**, 96
3	4-$Me_2NC_6H_4$	**7c**, 87
4	4-FC_6H_4	**7d**, 83
5	1-naphthyl	**7e**, 90
6	3-(*N*-tosyl)indolyl	**7f**, 94
7	(*E*)-$C_6H_5CH{=}CH$	**7g**, 96
8	vinyl	**7h**, 91
9	2-thienyl	**7i**, 89
10[b]	2-(*N*-methyl)pyrrolyl	**7j**, 64
11[c]	3-furyl	**7l**, 79
12	$Ph(Me)_2SiCH_2$	**7k**, 81
13[d]	Et	
14[d]	$C_6H_5C{\equiv}C$	
15[d]	3,5-(di-Cl)-C_6H_3	

[a]Bis-imidate (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol), CH_2Cl_2 (5 mL). Yields are isolated yields. Please see the Supporting Information for details. [b]$Cu(OTf)_2$ (0.005 mmol). [c]$(CuOTf)_2{\cdot}C_6H_6$ (0.05 mmol). [d]Mixture of products.

intermediates. However, there is a limited number of methods available to access this type of amino alcohol.[8] In order to demonstrate the utility of tetrahydro-1,3-oxazepines **7**, several examples were transformed to amino alcohol derivatives **9** (Table 2). The one-pot, two-step procedure involved cleavage of cyclic imidate function with acetic acid followed by methanolysis of the intermediate **8**.

The cyclization studies with enantioenriched bis-imidate *S*-**5a** showed that tetrahydro-1,3-oxazepine **7a** forms with considerable degree of racemization (Scheme 1).

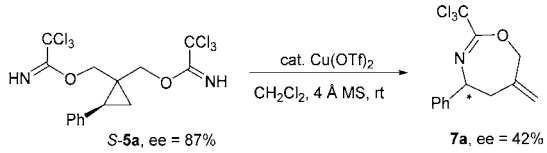
Table 2. Transformation of Tetrahydro-1,3-oxazepines 7 to Amino Alcohols 9[a]



entry	R	product, yield (%)
1	Ph	**9a**, 94
2	4-$MeOC_6H_4$	**9b**, 96
3	2-thienyl	**9i**, 91
4	vinyl	**9h**, 89
5	$Ph(Me)_2SiCH_2$	**9k**, 89

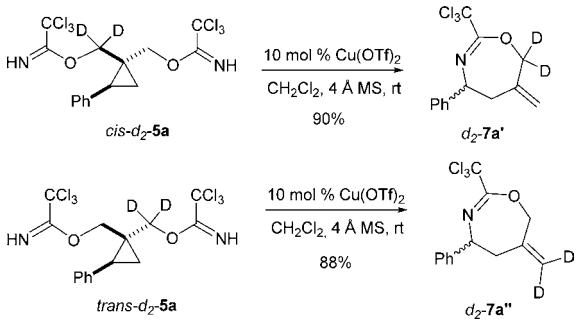
[a]Key: (1) tetrahydro-1,3-oxazepine (1.0 mmol), Ac_2O (1 mL), AcOH (1 mL); (2) K_2CO_3 (3.0 mmol), MeOH (2 mL). Yields are isolated yields. Please see the Supporting Information for details.

Scheme 1. Chirality Transfer in the Cyclization of Enanatioenriched Substrate *S*-5a



To determine if the racemization is associated with unselective abstraction of the imidate group, substrates *cis*-d_2-**5a** and *trans*-d_2-**5a** with deuterium labeling at the methylene position were prepared (Scheme 2). In both substrates, the

Scheme 2. Selective Abstraction of *trans*-Imidate Function in Deuterium-Labeled Bis-imidate 5a



imidate group *trans* to the phenyl group was selectively abstracted to give the corresponding deuterium labeled regioisomers d_2-*rac*-**7a′** and d_2-*rac*-**7a″**, respectively (only one isomer in each case was detected by ^1H NMR). The exclusive *trans*-imidate elimination would be difficult to explain by the accessibility of the sterically less hindered imidate group to the catalyst. More likely, these results point to specific stereoelectronic requirement for the leaving group to facilitate the formation of cyclopropylmethyl cation/homolallyl cation.

Having established that abstraction of the imidate is selective, the partial loss of enantioselectivity in the product **7a** formation obviously stems from the availability of both faces of carbocation **6C**/**6C′**. Nevertheless, the chirality was preserved to some extent which is difficult to explain. This could be related to a partial nature of nonclassical carbocation intermediate since the planar homoallyl cation would lead to complete racemization.

Diastereoselective amination of carbocation **6C**/**6C′** bearing an additional substituent was explored (Scheme 3). Bis-imidate **11** was prepared from readily accessible stereochemically defined dicarboxylic acid derivative **10**.[9] Amination of bis-imidate **11** gave *trans*-substituted tetrahydro-1,3-oxazepine **12** as the only detectable isomer. Configuration of the reaction product **12** was determined by X-ray analysis of the derivatization product−diol **13**.

In summary, we have demonstrated that a cyclopropylmethyl cation generated by the abstraction of one imidate group in bis-imidates undergoes regioselective intramolecular amination. A homoallylamine derivative was formed selectively if cyclopropane contained a carbocation stabilizing substituent. The resulting tetrahydro-1,3-oxazepines were transformed to unsaturated amino alcohol derivatives. It was demonstrated that highly diastereoselective cyclization to *trans*-substituted tetrahydrooxazepine could be achieved starting from 1,1,2,3-tetrasubstituted cyclopropane substrates.

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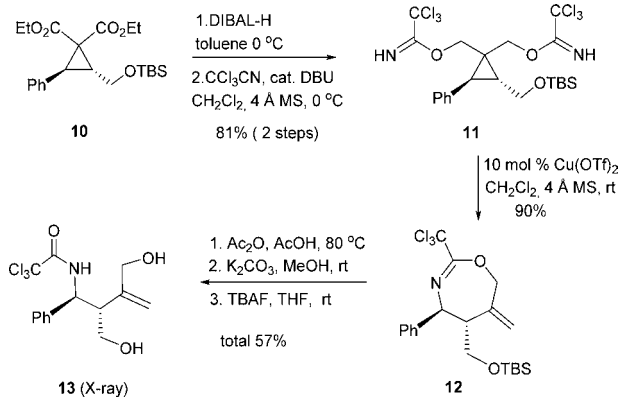
Scheme 3. Diastereoselective Cyclization of Bis-imidate 11 to Oxazepine 12 and Derivatization to Amino Alcohol 13



■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01014.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: aigars@osi.lv.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent investigations on the structure of cyclopropylmethyl cation, see: (a) Franco, M.; Rosenbach, N.; Ferreira, G. B.; Guerra, A. C. O.; Kover, W. B.; Turci, C. C.; Mota, C. J. A. *J. Am. Chem. Soc.* **2008**, *130*, 1592. (b) Olah, G. A.; Prakash, G. K. S.; Rasul, G. *J. Am. Chem. Soc.* **2008**, *130*, 9168. (c) Kling, D. P.; Machado, E. S. A.; Chagas, H. C.; dos Santos, A. P. A.; Rosenbach, N., Jr.; Walkimar Carneiro, J.; Mota, C. J. A. *Chem. Commun.* **2013**, *49*, 4480.

(2) For representative seminal investigations on cyclopropylmethyl cation, see: (a) Mazur, R. H.; White, W. N.; Semenow, D. A.; Lee, C. C.; Silver, M. S.; Roberts, J. D. *J. Am. Chem. Soc.* **1959**, *81*, 4390. (b) Olah, G. A.; Jeuell, C. L.; Kelly, D. P.; Porter, R. D. *J. Am. Chem. Soc.* **1972**, *94*, 146. (c) Staral, J. S.; Yavari, I.; Roberts, J. D.; Prakash, G. K. S.; Donovan, D. J.; Olah, G. A. *J. Am. Chem. Soc.* **1978**, *100*, 8016.

(3) (a) Sarel, S.; Yovell, J.; Sarel-Imber, M. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 577. (b) Poulter, C. D.; Winstein, S. *J. Am. Chem. Soc.* **1970**, *92*, 4282. (c) Kanemoto, S.; Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1987**, *28*, 663. (d) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2001**, *3*, 2717. (e) Yadav, V. K.; Balamurugan, R. *Chem. Commun.* **2002**, 514. (f) Yadav, V. K.; Vijaya Kumar, N. *J. Am. Chem. Soc.* **2004**, *126*, 8652. (g) Honda, M.; Yamamoto, Y.; Tsuchida, H.; Segi, M.; Nakajima, T. *Tetrahedron Lett.* **2005**, *46*, 6465. (h) Honda, M.; Mita, T.; Nishizawa, T.; Sano, T.; Segi, M.; Nakajima, T. *Tetrahedron Lett.* **2006**, *47*, 5751. (i) Zanirato, V.; Pollini, G. P.; De Risi, C.; Valente, F.; Melloni, A.; Fusi, S.; Barbetti, J.; Olivucci, M. *Tetrahedron* **2007**, *63*, 4975. (j) Rao, W.; Chan, P. W. H. *Chem.—Eur. J.* **2008**, *14*, 10486. (k) Mothe, S. R.; Kothandaraman, P.; Rao, W.; Chan, P. W. H. *J. Org. Chem.* **2011**, *76*, 2521. (l) Kothandaraman, P.; Huang, C.; Susanti, D.; Rao, W.; Chan, P. W. H. *Chem.—Eur. J.* **2011**, *17*, 10081. (m) Kranz, D. P.; Chiha, S.; Meier zu Greffen, A.; Neudörfl, J.-M.; Schmalz, H.-G. *Org. Lett.* **2012**, *14*, 3692.

(4) Caserio, M. C.; Graham, W. H.; Roberts, J. D. *Tetrahedron* **1960**, *11*, 171.

(5) (a) Wilt, J. W.; Roberts, D. D. *J. Org. Chem.* **1962**, *27*, 3430. (b) Kanemoto, S.; Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1987**, *28*, 6313. (c) Hardouin, C.; Taran, F.; Doris, E. *J. Org. Chem.* **2001**, *66*, 4450. (d) Bernard, A. M.; Cadoni, E.; Frongia, A.; Piras, P. P.; Secci, F. *Org. Lett.* **2002**, *4*, 2565. (e) Shi, M.; Tian, G.-Q. *Tetrahedron Lett.* **2006**, *47*, 8059. (f) Bernard, A. M.; Frongia, A.; Guillot, R.; Piras, P. P.; Secci, F.; Spiga, M. *Org. Lett.* **2007**, *9*, 541. (g) Chen, A.; Lin, R.; Liu, Q.; Jiao, N. *Chem. Commun.* **2009**, 6842.

(6) (a) Grigorjeva, L.; Jirgensons, A. *Eur. J. Org. Chem.* **2011**, *2011*, 2421. (b) Klimovica, K.; Grigorjeva, L.; Maleckis, A.; Popelis, J.; Jirgensons, A. *Synlett* **2011**, *22*, 2849. (c) Grigorjeva, L.; Maleckis, A.; Klimovica, K.; Skvorcova, M.; Ivdra, N.; Leitis, G.; Jirgensons, A. *Chem. Heterocycl. Compd.* **2012**, *48*, 919. (d) Jirgensons, A.; Grigorjeva, L.; Maleckis, A.; Klimovica, K. *Synlett* **2013**, *24*, 2345. (e) Grigorjeva, L.; Kinens, A.; Jirgensons, A. *J. Org. Chem.* **2015**, *80*, 920.

(7) (a) Link, J. T.; Gallant, M.; Danishefsky, S. J.; Huber, S. *J. Am. Chem. Soc.* **1993**, *115*, 3782. (b) Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552. (c) Rondot, C.; Retailleau, P.; Zhu, J. *Org. Lett.* **2007**, *9*, 247. (d) Ramstadius, C.; Hekmat, O.; Eriksson, L.; Stålbrand, H.; Cumpstey, I. *Tetrahedron: Asymmetry* **2009**, *20*, 795.

(8) (a) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778. (b) Van der Louw, J.; van der Baan, J. L.; Stichter, H.; Out, G. J. J.; de Kanter, F. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron* **1992**, *48*, 9877. (c) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1896. (d) Brown, R. C. D.; Fisher, M. L.; Brown, L. J. *Org. Biomol. Chem.* **2003**, *1*, 2699. (e) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 6330. (f) Shintani, R.; Park, S.; Duan, W.-L.; Hayashi, T. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 5901. (g) Rajender, A.; Rao, J. P.; Rao, B. V. *Tetrahedron Asymmetry* **2011**, *22*, 1306. (h) Hickin, J. A.; Ahmed, A.; Fucke, K.; Ashcroft, M.; Jones, K. *Chem. Commun.* **2014**, *50*, 1238.

(9) Marcoux, D.; Charette, A. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 10155.

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Org. Lett. 2015, 17, 2902−2904