ORGANIC
LETTERS

2013
Vol. 15, No. 23
6010–6013

Dual Control of the Selectivity in the Formal Nucleophilic Substitution of Bromocyclopropanes en Route to Densely Functionalized, Chirally Rich Cyclopropyl Derivatives

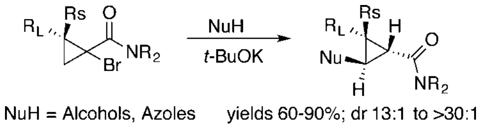
Pavel Ryabchuk,[†] Andrew Edwards,[†] Nikolay Gerasimchuk,[‡] Marina Rubina,[†] and Michael Rubin*,[†]

Department of Chemistry, University of Kansas 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, United States, and Department of Chemistry, Missouri State University, 456 Temple Hall, Springfield, Missouri 65897, United States

mrubin@ku.edu

Received October 9, 2013

ABSTRACT



Densely substituted cyclopropanol and cyclopropylazole derivatives with three stereogenic carbons in the small cycle are obtained via a highly diastereoselective formal nucleophilic substitution of bromocyclopropanes. The chiral center at C-2 in bromocyclopropane dictates the configuration of the other two stereocenters that are successively installed via a sterically controlled addition of a nucleophile, followed by a thermodynamically driven epimerization of the resulting enolate intermediate.

Densely functionalized, chirally rich cyclopropanes have been the focus of rapidly growing interest, as both advanced synthons[1−3] and important pharmacophores,[4] as evident from the vast number of emerging publications. Despite impressive achievements in the development of powerful methods for di- and trisubstituted cyclopropanes, and use thereof in the synthesis of complex biologically relevant targets,[5] there is still a significant demand for complementary approaches to analogs with denser substitution patterns and an expanded functional group scope.

In our continuing efforts to develop the diastereoselective formal nucleophilic substitution reaction of halocyclopropanes with heteroatom nucleophiles,[6] we aimed at expanding the scope of this reaction to include multisubstituted substrates. We have shown previously that 1,2-dehydrohalogenation of 1,2-di- and 1,2,2-trisubstitued cyclopropylbromides produces achiral cyclopropenes **1** and **2**, which upon *in situ* addition of a nucleophile furnish heterosubstituted cyclopropanes (modes 1 and 2, Scheme 1). Three alternative means of controlling the diastereoselectivity of addition have been demonstrated: a thermodynamically driven epimerization (mode 1), and a steric or directing effect of the substituents in the cyclopropene (mode 2, Scheme 1).[6] In both these modes, the generation of cyclopropene intermediates **1** and **2** was

---

[†] University of Kansas.

[‡] Missouri State University.

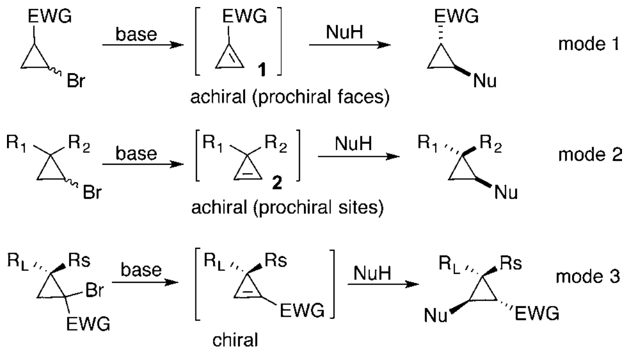
(1) (a) Xu, H.; Qu, J.-P.; Liao, S.; Xiong, H.; Tang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4004. (b) Volkova, Y. A.; Budynina, E. M.; Kaplun, A. E.; Ivanova, O. A.; Chagarovskiy, A. O.; Skvortsov, D. A.; Rybakov, V. B.; Trushkov, I. V.; Melnikov, M. Y. *Chem.—Eur. J.* **2013**, *19*, 6586. (c) Ladd, C. L.; Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 1350. (d) Wenz, D. R.; Read de Alaniz, J. *Org. Lett.* **2013**, *15*, 3250.

(2) (a) Haubenreisser, S.; Hensenne, P.; Schröder, S.; Niggemann, M. *Org. Lett.* **2013**, *15*, 2262. (b) Truong, P. M.; Mandler, M. D.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2013**, *15*, 3278. (c) Kaschel, J.; Schneider, T. F.; Schrimer, P.; Maass, C.; Stalke, D.; Werz, D. B. *Eur. J. Org. Chem.* **2013**, 4539. (d) Fisher, L. A.; Smith, N. J.; Fox, J. M. *J. Org. Chem.* **2013**, *78*, 3342.

(3) For most recent reviews, see: (a) Mack, D. J.; Njardarson, J. T. *ACS Catal.* **2013**, *3*, 272. (b) Jiao, L.; Yu, Z.-X. *J. Org. Chem.* **2013**, *78*, 6842. (c) Wang, Z. *Synlett* **2012**, *23*, 2311. (d) Tang, P.; Qin, Y. *Synthesis* **2012**, *44*, 2969.

10.1021/ol4027792

Scheme 1



Scheme 2. "Dual-Control" Strategy

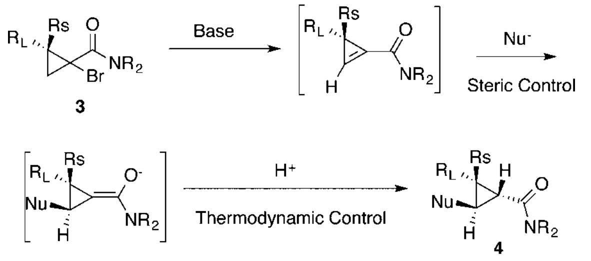
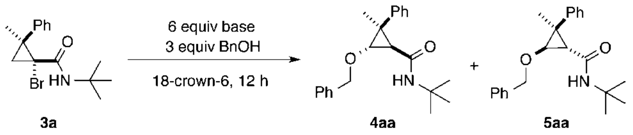


Table 1. Optimization of Reaction Conditions for the Bromocyclopropane **3a**[a]



no.	base	*t*, °C	solvent	18-c-6, %	yield, %[b]	dr[c]
1	t-BuOK	60	THF	10	49	14:1
2	t-BuOK	80	THF	10	62	11:1
3	t-BuOK	90	THF	10	61	8:1
4	KOH	80	THF	10	37[e]	22:1
5	KOH[d]	80	THF	10	37[e]	19:1
6	t-BuOK	80	toluene	10	28	2:1
7	t-BuOK	80	DCM	10	–	–
8	t-BuOK	80	DMA	10	59	27:1
9	t-BuOK	80	NMP	10	76	32:1
10	t-BuOK	80	CH$_3$CN	10	35	19:1
11	t-BuOK	80	DMSO	10	71	36:1
12	**t-BuOK**	**40**	**DMSO**	**10**	**80**	**46:1**
13	t-BuOK	25	DMSO	10	20[e]	50:1

[a] Optimization reactions performed in 0.03 mmol scale. [b] GC yields of major diastereomer **4aa**. [c] dr (**4aa**:**5aa**) was determined by quantitative GC of crude reaction mixtures. [d] Reaction time = 1 week. [e] Incomplete conversion.

accompanied by a complete loss of the inherent chiral information and its subsequent reinstallation during the nucleophilic attack at either the prochiral face (mode 1) or prochiral site (mode 2). Thus, nonracemic products could be obtained only via a diastereoselective addition of an enantiomerically pure nucleophilic reagent.[6a]

Extension of this methodology beyond trisubstituted substrates amplifies the challenge of controlling the stereoselectivity of addition. Indeed, both modes 1 and 2 required control of a single center only, since the two forming chiral centers were linked to each other. The new mode 3 (Scheme 1) realized in this work utilizes tetrasubstituted substrates, in which installation of two stereogenic centers is asynchronized and is controlled by both means (Scheme 2).

We envisioned that α-bromocyclopropylcarboxamides **3** easily available in optically active form[7] would provide convenient probes for this transformation, because the chirality of the β-quaternary center in these substrates would be preserved during the dehydrohalogenation/addition sequence, which would allow for carrying over the asymmetric information from the substrate to the product. We began by testing a model reaction of bromocyclopropane **3a** using benzyl alcohol as a pronucleophile, under the standard reaction conditions employed previously for the addition of alkoxides.[6c] This reaction provided cyclopropyl ether **4aa** as a major diastereomer (dr = 14:1), albeit in 49% yield only (Table 1, entry 1). The stereoselectivity of the addition followed the predicted pattern: the generated *in situ* cyclopropene underwent addition of the nucleophile from the least hindered face, while the subsequent thermodynamically driven epimerization at the α-carbon of the amide set the third stereocenter. The minor stereoisomer **5aa** was isolated, and its realtive configuration was established by NMR experiments.[8] It was thus confirmed that the observed diastereoselectivity

---

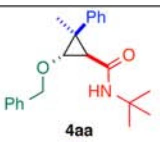
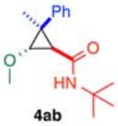
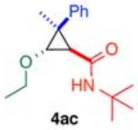
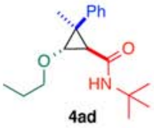
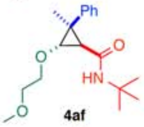
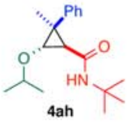
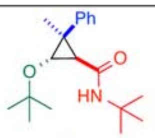
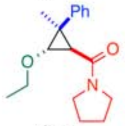
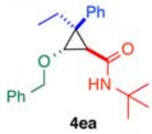
(4) For most recent examples, see: (a) Wang, Y.; Liu, J.; Dransfield, P. J.; Zhu, L.; Wang, Z.; Du, X.; Jiao, X.; Su, Y.; Li, A.; Brown, S. P.; Kasparian, A.; Vimolratana, M.; Yu, M.; Pattarapong, V.; Houze, J. B.; Swaminath, G.; Tran, T.; Nguyen, K.; Guo, Q.; Zhang, J.; Zhuang, R.; Li, F.; Miao, L.; Bartberger, M. D.; Correl, T. L.; Chow, D.; Wong, S.; Luo, J.; Lin, D. C-H.; Medina, J. C. *ACS Med. Chem. Lett.* **2013**, *4*, 551. (b) Blass, B. *ACS Med. Chem. Lett.* **2013**, *4*, 379. (c) Hayashi, R.; Miyazaki, M.; Osada, S.; Kawasaki, H.; Fujita, I.; Hamasaki, Y.; Kodama, H. *Bioorg. Med. Chem.* **2013**, *21*, 668. (d) Risgaard, R.; Nielsen, S. D.; Hansen, K. B.; Jensen, C. M.; Nielsen, B.; Traynelis, S. F.; Clausen, R. P. *J. Med. Chem.* **2013**, *56*, 4071. (e) Kawamura, S.; Unno, Y.; List, A.; Mizuno, A.; Tanaka, M.; Sasaki, T.; Arisawa, M.; Asai, A.; Groll, M.; Shuto, S. *J. Med. Chem.* **2013**, *56*, 3689. (f) Chen, H.; et al. *J. Med. Chem.* **2013**, *56*, 685. (g) Zhang, H.-K.; Yu, L.-F.; Eaton, J. B.; Whieaker, P.; Onajole, O. K.; Hanania, T.; Brunner, D.; Lukas, R. J.; Kozikowski, A. P. *J. Med. Chem.* **2013**, *56*, 5495. (h) Mizono, A.; Miura, S.; Watanabe, M.; Ito, Y.; Yamada, S.; Odagami, T.; Kogami, Y.; Arisawa, M.; Shuto, S. *Org. Lett.* **2013**, *15*, 1686.

(5) For most recent reviews, see: (a) Gagnon, A.; Duplessis, M.; Fader, L. *Org. Prep. Proc. Int.* **2010**, *42*, 1. (b) Chen, D. Y.-K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631. (c) Cha, J. K.; Kulinkovich, O. G. *Org. React.* **2012**, *77*, 1.

(6) (a) Alnasleh, B. K.; Sherrill, W. M.; Rubina, M.; Banning, J.; Rubin, M. *J. Am. Chem. Soc.* **2009**, *131*, 6906. (b) Banning, J. E.; Prosser, A. R.; Rubin, M. *Org. Lett.* **2010**, *12*, 1488. (c) Banning, J. E.; Prosser, A. R.; Alnasleh, B. K.; Smarker, J.; Rubina, M.; Rubin, M. *J. Org. Chem.* **2011**, *76*, 3968. (d) Ryabchuk, P.; Rubina, M.; Xu, J.; Rubin, M. *Org. Lett.* **2012**, *14*, 1752. (e) Banning, J. E.; Gentillon, J.; Ryabchuk, P. G.; Prosser, A. R.; Rogers, A.; Edwards, A.; Holtzen, A.; Babkov, I.; Rubina, M.; Rubin, M. *J. Org. Chem.* **2013**, *78*, 7601. (f) Prosser, A. R.; Banning, J. E.; Rubina, M.; Rubin, M. *Org. Lett.* **2010**, *12*, 3986.

(7) Homochiral bromocyclopropylcarboxamides were obtained with > 99% ee via an efficient chiral resolution protocol developed in our laboratories. A detailed account on the synthesis and optical resolution of α-bromocyclopropylcarboxamides **3** will be reported in due course.

Table 2. Synthesis of Tetrasubstituted Cyclopropanes via the "Dual-Control" Strategy[a,b]

no.	product	yield, % (conds.)	dr
1	 **4aa**	49 (A)	11:1
2		68 (B)	>30:1
3	 **4ab**	63 (A)	13:1
4		60 (B)	>30:1
5	 **4ac**	63 (A)	7:1
6		67 (B)	>30:1
7	 **4ad**	80 (A)	9:1
8		66 (B)	>30:1
9	 **4ae**	79 (B)	>30:1
10	 **4af**	79 (B)	>30:1
11	 **4ag**	92 (B)	>30:1
12	 **4ah**	60 (A)	10:1
13		decomp. (B)	-
14		decomp. (A)	-
15		decomp. (B)	-
16	 **4bb**	63 (A)	13:1
17		decomp. (B)	-
18	 **4cc**	73 (B)	>30:1
19	 **4ai**	69 (B)	>30:1
20	 **4aj**	78 (B)	>30:1
21	 **4df**	91 (B)	25:1
22[c,d]	 **4ea**	68 (B)	14:1

[a] Reactions performed in 0.2 mmol scale; isolated yields are listed. Values of dr are measured by GC or NMR analysis of crude reaction mixtures. [b] Conditions **A**: bromocyclopropane **3** (0.2 mmol), pronucleophile (0.6 mmol), *t*-BuOK (1.2 mmol), THF (10 mL), 18-crown-6 (0.02 mmol), stirred at 80 °C for 12 h. Conditions **B**: bromocyclopropane **3** (0.2 mmol), pronucleophile (0.6 mmol), *t*-BuOK (1.2 mmol), DMSO (5 mL), 18-crown-6 (0.02 mmol), stirred at 40 °C for 12 h. [c] Reaction was run on a 0.45 mmol scale. [d] After stirring at 40 °C for 12 h, the reaction mixture was heated to 80 °C and stirred for an additional 30 min until complete conversion.

is a result of the facial differentiation at the nucleophilic attack step, whereas the last stereocenter is set with perfect diastereoselectivity via a thermodynamically driven epimerization, which occurs very rapidly in the presence of *t*-BuOK.[6c] Increasing the temperature to 80 °C (Conditions **A**) allowed for an improved yield of **4aa**, however, at the expense of diastereoselectivity (entry 2). A further temperature increase caused notable deterioration of the *dr* with no yield improvement (entry 3). Reaction with a weaker base KOH did not proceed to completion, even after prolonged stirring at higher temperatures, despite providing excellent diastereoselectivities. Poor conversions achieved with KOH were attributed to the fact that dehydrohalogenation of **3** requires higher effective basicity of the medium as compared to β-bromocyclopropylcarboxamides, in which deprotonation occurs at the more acidic α-carbon. Other alkaline bases such as lithium, sodium, magnesium hydroxides, and *tert*-butoxides gave no reaction. Solvent screening revealed that polar, aprotic solvents, such as DMSO and NMP, were superior media for this transformation (entries 11 and 14). Accordingly, DMSO was chosen as the medium due to being a safer alternative.[9] A quick temperature optimization in DMSO showed that the best yield and *dr*'s are achieved at 40 °C (entry 15, Conditions **B**).

---

(8) See Supporting Information for details.

Having optimized the reaction conditions, we moved on to examine the scope of this reaction. Screening a series of alcohols against a few bromocyclopropylcarboxamides **3** revealed that the sterics of the nucleophiles had a significant effect on their reactivity. Thus, all primary alcohols, including those bearing functional groups, reacted uneventfully under conditions **A** and **B** (entries 1−11, Table 2). Conditions **B** consistently allowed for higher diastereoselectivities, although in a few cases provided lower yields due to partial loss of product upon extraction from DMSO (entries 1−8, Table 2). The reaction with a secondary alcohol proceeded much more sluggishly in DMSO and led to substantial decomposition; however, a reasonable yield of **4ac** was obtained under alternative conditions **A** in THF (entries 12−13). Attempts to add tertiary alcohols met with no success (entries 14−15). The sensitivity of the reaction to sterics can be further seen by comparing the reactivity of bromocyclopropanes **3a** and **3e**, possessing a methyl and an ethyl group, respectively, at the β-quaternary center (entries 2 and 22). In spite of providing the same isolated yield as **3a**, homologue **3e** reacted very sluggishly at 40 °C and required higher temperature to achieve full conversion, which led to a lower, although still respectable, diastereoselectivity.

A brief survey of substituents on the carboxamide group showed that tertiary and bulky secondary amides are compatible with both conditions **A** and **B**, while sterically less hindered secondary amides, such as **3b**, react in DMSO with notable decomposition (entries 16−17). We were also pleased to find that azoles underwent facile addition to provide substituted hetarylcyclopropanes **4ai** and **4aj** (entires 19−20, Table 2). The 2*r*-1*c*-3*t*-configuration of the obtained tetrasubstituted cyclopropanes was unambigously confirmed by NOE experiments and single crystal X-ray crystallography (Figure 1).[8]

To showcase the efficient transfer of the chiral information from the starting material to the product, homochiral bromocyclopropane **3d*** derived from (1*R*,2*S*)-1-bromo-2-methyl-2-(*p*-tolyl)cyclopropane-1-carboxylic acid[7] was cleanly converted into benzyl cyclopropyl ether **4da*** in excellent isolated yield and diastereoselectivity (Scheme 3).

Scheme 3. Addition of Benzyl Alcohol to Homochiral Bromocyclopropane **3d***

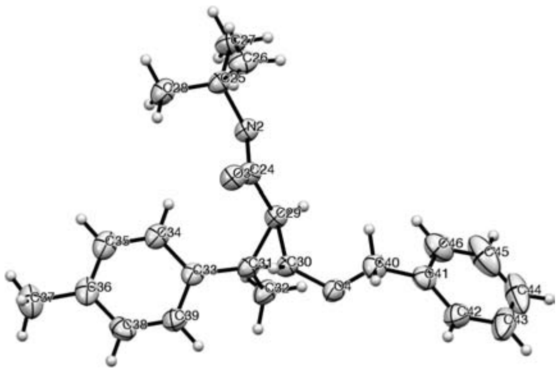


Figure 1. ORTEP drawing of homochiral cyclopropane **4da*** showing 50% probability amplitude displacement ellipsoids.

In conclusion, a "dual-control" strategy was successfully employed for a highly diastereoselective addition of nucleophilic species to *in situ* generated cyclopropenes. This reaction afforded tetrasubstituted donor−acceptor cyclopropanes with all three asymmetric carbons in the strained ring. The chiral integrity of the starting material is translated to the product via a sequential installation of two stereogenic centers efficiently controlled by steric and thermodynamic effects.

Acknowledgment. We thank the University of Kansas and USDA (Award 2011-10006-30362) for financial support. We also thank NSF-MRI (Award CHE-0923449) used for purchasing an X-ray diffractometer.

Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(9) NMP is currently under evaluation in the European Union as a substance of very high concern: Jouyban, A.; Fakhree, M. A. A.; Shayanfar, A. *J. Pharm. Pharmaceut. Sci.* **2010**, *13*, 524.

The authors declare no competing financial interest.