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Thermodynamic Control of Diastereoselectivity in the Formal Nucleophilic Substitution of Bromocyclopropanes

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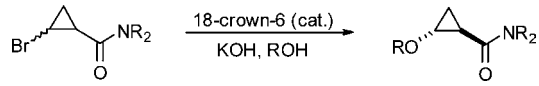
ABSTRACT



A new, general, and chemoselective protocol for the formal nucleophilic substitution of 2-bromocyclopropylcarboxamides is described. A wide range of alcohols and phenols can be employed as pronucleophiles in this transformation, providing expeditious access to trans-cyclopropanol ethers. A new mode of the selectivity control through a thermodynamic equilibrium is realized, alternative to the previously described steric and directing modes.

Stereochemically defined and densely substituted cyclopropanes are readily available from the corresponding cyclopropenes via a number of highly diastereoselective additions of various entities across the strained double bond.[1,2] At the same time, only a limited number of cyclopropenes can boast a long shelf life, while most of the others are relatively short-living species and require special handling. Trying to circumvent this problem, we recently developed a process[3] that allows us to generate reactive cyclopropene intermediates **2** in situ from a stable bromocyclopropane precursor **1** in the presence of *t*-BuOK and catalytic 18-crown-6.[4] Subsequent nucleophilic attack of **2** by an alkoxide provided stereodefined cyclopropanol derivatives **3** in good yield (Scheme 1, eq 1). It was shown that the diastereoselectivity of the latter step could be efficiently controlled by either steric or directing effect.[3]

While all of the previously reported examples involved relatively stable, isolable 3,3-disubstituted cyclopropene intermediates,[4] the main goal of the present study was to make this methodology applicable to more reactive, nonisolable monosubstituted cyclopropenes.[5] Our initial experiment demonstrated that treatment of disubstituted cyclopropane **4a** (used as a mixture of *trans*- and *cis*-isomers, 2:1) with excess *t*-BuOK provided *tert*-butyl ether **6aa** in good yield (Scheme 1, eq 2).[3] Much to our surprise, the diastereoselectivity of the addition was opposite to that observed before with all amide-containing substrates. Thus, instead of the expected *cis*-selectivity, resulting from directing control, the *trans*-diastereomer was obtained predominantly.[6] We rationalized that this selectivity is governed by a thermodynamically driven isomerization, involving deprotonation of the

(1) For reviews, see: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221. (c) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364. (d) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719.

(2) For recent contributions, see: (a) Tarwade, V.; Liu, X.; Yan, N.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382. (b) Sherrill, W. M.; Rubin, M. *J. Am. Chem. Soc.* **2008**, *130*, 13804. (c) Alnasleh, B. K.; Sherrill, W. M.; Rubin, M. *Org. Lett.* **2008**, *10*, 3231. (d) Levin, A.; Marek, I. *Chem. Commun.* **2008**, 4300. (e) Yan, N.; Liu, X.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 563. (f) Trofimov, A.; Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Org. Chem.* **2007**, *72*, 8910. (g) Simaan, S.; Marek, I. *Org. Lett.* **2007**, *9*, 2569.

(3) Alnasleh, B. K.; Sherrill, W. M.; Rubina, M.; Banning, J.; Rubin, M. *J. Am. Chem. Soc.* **2009**, *131*, 6906.

(4) For preparative synthesis of cyclopropenes via this route, see: Sherrill, W. M.; Kim, R.; Rubin, M. *Synthesis* **2009**, 1477.

(5) There is a single precedent of formal substitution (Nu = MeO) of 2-bromocyclopropanecarboxylic acid derivative, which provided marginal yield and poor diastereoselectivity. See: Taylor, E. C.; Hu, B. *Synth. Commun.* **1996**, *26*, 1041.

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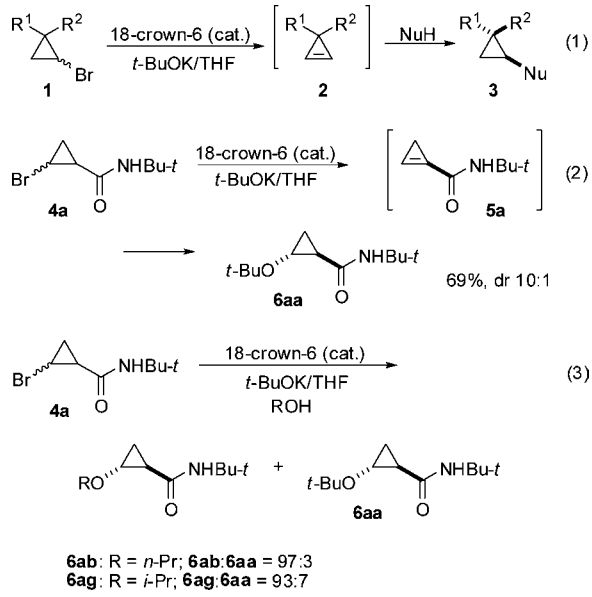
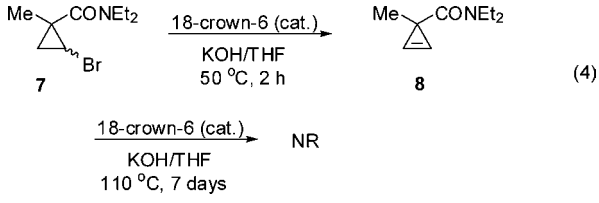
Scheme 1

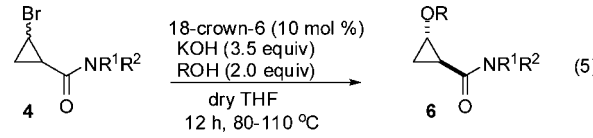


acidic C−H in α-position to the amide function. We found this result very exciting, since it opened the possibility for exploiting a new mode of selectivity control. However, when this reaction was performed in the presence of external nucleophile source (ROH), a competing addition of two nucleophiles across the conjugated double bond of monosubstituted cyclopropene intermediate **5a** was observed (Scheme 1, eq 3), producing notable amounts of unwanted *tert*-butoxide adduct **6aa**. Apparently, nucelophilicity of even such bulky base as *tert*-butoxide was significant enough to cause addition across the extremely activated strained double bond. To address this issue, we tested a series of alternative, non-nucleophilic bases in this reaction; however, most of them (such as NaH, LDA, and LiHMDS) were unable to generate cyclopropene intermediate **5a**. After substantial experimentation, we discovered that the use of powedered KOH allowed for smooth 1,2-elimination, with no subsequent addition of the hydroxide ion to the cyclopropene double bond (eq 4). Indeed, even after prolonged heating at 110



°C, cyclopropene **8**,[4] generated from bromocyclopropane **7** in the presence of KOH and 18-crown-6, did not show any traces of addition or decomposition (eq 4). Although such extremely low nucleophilicity of hydroxide species in the described transformation is puzzling, it was a long sought-after solution that allowed for combining the 1,2-elimination reaction and addition of an alkoxide, generated in situ from an appropriate alcohol pronucleophile, in a sequential chemoselective transformation (eq 5, Table 1).

Table 1. Formal Nucleophilic Substitution of Bromocyclopropanes with Alkoxides[a]



no.	R^1, R^2	RO	product	yield, %[b]	dr[c]
1	*t*-Bu, H	*n*-PrO	**6ab**	71	9:1
2	*t*-Bu, H	$MeOCH_2CH_2O$	**6ac**	97	8:1
3	Et, Et	$MeOCH_2CH_2O$	**6bc**	87	16:1
4	*t*-Bu, H	$CH_2{=}CH(CH_2)_3O$	**6ad**	85	7:1
5	morph[d]	$CH_2{=}CH(CH_2)_3O$	**6cd**	84	12:1
6	*t*-Bu, H	*m*-$NO_2C_6H_4CH_2O$	**6ae**	81	8:1
7	Et, Et	*m*-$NO_2C_6H_4CH_2O$	**6be**	93	7:1
8	Et, Et	$C_6H_4CH_2O$	**6bf**	87[e]	6:1
9	*t*-Bu, H	*i*-PrO	**6ag**	71	9:1
10	*t*-Bu, H	$HC{\equiv}C\text{-}CMe_2O$	**6ah**	59	10:1
11	*t*-Bu, H	Ph_3CO	**6ai**	50	25:1
12	*t*-Bu, H	PhO	**6aj**	79	6:1
13	*t*-Bu, H	*p*-$MeOC_6H_4O$	**6ak**	75	7:1
14	*t*-Bu, H	*p*-BrC_6H_4O	**6al**	86	8:1
15	*t*-Bu, H	*p*-IC_6H_4O	**6am**	80	10:1
16	*t*-Bu, H	*p*-$PhCOC_6H_4O$	**6an**	90	10:1
17	*t*-Bu, H	*p*-NCC_6H_4O	**6ao**	74	10:1

[a] Reactions performed in 0.5 mmol scale unless specified otherwise. [b] Isolated yields of diasteriomeric mixtures. [c] dr (trans:cis) determined by GC or ^{1}H NMR analysis of crude reaction mixtures. [d] morph = morpholine derivative, $R^1R^2 = (CH_2CH_2)_2O$. [e] Reaction performed in 8 mmol scale.

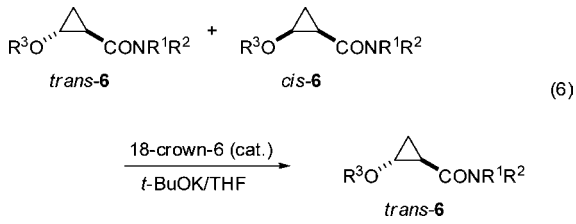
Thus, the reaction of bromocyclopropane **4a** with KOH in the presence of *n*-propanol and catalytic amounts of 18-crown-6 proceeded smoothly affording *trans*-*n*-propoxide adduct **6ab** in good yield and high diastereoselectivity (eq 5, Table 1, entry 1). Other primary alkoxides, possessing functional groups, such as a methyl ether or an isolated C=C double bond, were transferred very efficiently, providing the corresponding cyclopropanol ethers **6ac**, **6bc**, **6ad**, and **6cd** in high yields (entries 2−5).[7] *meta*-Nitrobenzyl-protected cyclopropanols **6ae** and **6be** were also obtained in very good yieds from the corresponding benzyl alcohol (entries 6−7). The reaction with benzyl alcohol was easily scaled up to 8 mmol scale: product **6bf** was obtained after vacuum distillation in 87% yield (entry 8). The reaction of **6a** with secondary propanol also proceeded uneventfully, providing isopropyl ether **6ag** in good yield (entry 9). Much less nucleophilic alkoxides generated from bulky tertiary propargyl alcohol were also efficiently intercepted with cyclo-

(6) For *trans*-selective formal nucleophilic substitution of 2-bromocyclopropanecarboxylate with tert-butoxide, see: Wiberg, K. B.; Barnes, R. K.; Albin, J. *J. Am. Chem. Soc.* **1957**, *79*, 4994.

(7) Starting 2-bromocyclopropanecarboxamides are readily available from the known 2,2-dibromocyclopropanecarbonyl chloride via reaction with the corresponding amine, followed by partial reduction of halogen with *i*-PrMgBr. See Supporting Information for details.

propene intermediate, affording product **6ah**, albeit in a somewhat lower yield (entries 10). Remarkably, no addition of the acetylide species generated from terminal alkyne was observed under the described reaction conditions.[8] Finally, an extremely sterically hindered trityl ether **6ai** was prepared successfully by the reaction of **6a** with triphenylmethanol (entry 11).

Table 2. *t*-BuOK-Assisted Epimerization Leading to Improvement of Diastereomeric Ratios[a]



	dr before treatment	dr after treatment	material balance, %
6ab	9:1	39:1	100
6ac	8:1	19:1	97
6ad	7:1	19:1	95
6ag	9:1	16:1	96
6aj	6:1	>50:1	96
6al	8:1	46:1	100
6ao	10:1	42:1	96
6bf	6:1	>50:1	100

[a] Material balance and diastereomeric ratios were determined by quantitative GC analysis of crude reaction mixtures using *n*-decane as the internal standard.

Having met succes with addition of alkoxides, we attempted to extend this methodology to addition of aryloxide species. We have previously shown that, in contrast to alkoxides, softer phenoxides did not react as nucleophilic components in the formal substitution reaction of bromocyclopropanes of type **1**, mediated by *t*-BuOK (eq 1, Nu = ArO).[3,9] We rationalized that the aptitude toward addition of these nucleophiles to the soft conjugated double bond of cyclopropene intermediate **5** should be significantly higher. To our delight, these expectations were realized to full extent. Thus, the reaction between phenol and cyclopropylbromide **1a** provided phenyl ether **6aj** in good isolated yield and diastereoselectivity (entry 12). Other aryloxides also reacted smoothly producing the corresponding aryl cyclopropyl ethers (**6ak**, **6al**, **6am**, **6an**, **6ao**) in high yields (entires 13−17). Regardless of the nucleophile source, all these additions provided *trans*-cyclopropylethers as major products (Table 1). However, in some cases, relatively low basicity of the non-nucleophlic hydroxide led to incomplete epimerization of the minor *cis*-isomer of product **6** into the thermodynamically more favorable *trans*-isomer (Table 1, entries 8, 12). Neither addition of excess KOH to the reaction mixture nor extension of the reaction time improved the selectivity of this reaction. To address this issue, isolated mixtures of products were treated with *t*-BuOK, which allowed for significant improvement of the diastereomeric ratios for all tested compounds without notable decomposition (Table 2, eq 6).

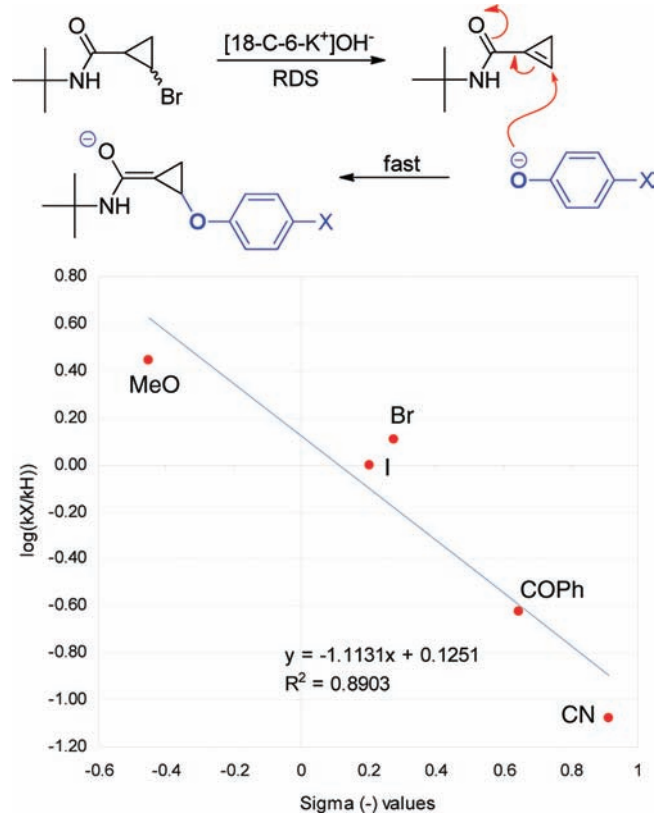


Figure 1. Swain−Lupton LFER Studies for Formal Nucleophilic Substitution of Bromocyclopropane **4a** with Aryloxides.[10]

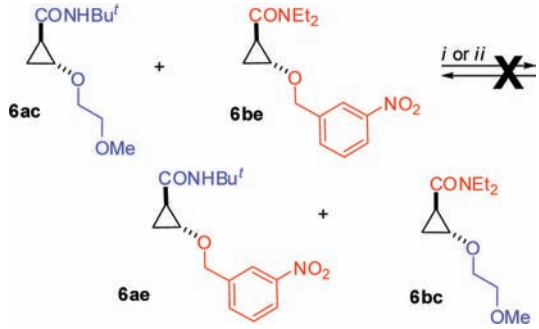
It also deserves noting that formal substitution with phenoxides proceeded much slower and required higher temperatures to achieve complete conversion, as compared to analogous reactions with alkoxides. This difference can be explained in terms of increased acidity of phenols, which readily produce phenoxides and water by a stoichiometric reaction with KOH. Although small amounts of moisture do not adversely affect this transformation, formation of the hydroxide-phenoxide "buffer" lowers the effective basisity of the system. This, in turn, results in significant deceleration of the dehydrobromination step, which is a rate-determining

(8) For direct transition metal-catalyzed addition of terminal alkynes across the double bond of cyclopropenes, see: Yin, J.; Chisholm, J. D. *Chem. Commun.* **2006**, 632.

(9) For preparation of cyclopropyl ethers via alkylation of alcohols and phenols with *c*-C_3H_5Br, see: (a) Chandru, H.; Sharada, A. C.; Bettadaiah, B. K.; Ananda, K., C. S.; Rangappa, K. S.; Jayashree, K. *Bioorg. Med. Chem.* **2007**, *15*, 7696. (b) Corbett, J. W.; Rauckhorst, M. R.; Qian, F.; Hoffman, R. L.; Knauer, C. S.; Fitzgerald, L. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6250–6256. (c) Chiu, G.; Li, S.; Connolly, P. J.; Pulito, V.; Liu, J.; Middleton, S. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3930. (d) van Tilburg, E. W.; van der Klein, P. A. M.; von Frijtag Drabbe Kuenzel, J. K.; de Groote, M.; Stannek, C.; Lorenzen, A.; Ijzerman, A. P. *J. Med. Chem.* **2001**, *44*, 2966.

step in this reaction.[11] The Swain−Lupton LFER parameters obtained from a series of competing parallel reactions reveal a profound negative ρ-value, indicating the diminution of the negative charge in the anionic phenoxide reagent as a result of addition to an electrophilic double bond (Figure 1).

Scheme 2. Crossover Experiments Demonstrating Irreversible Addition of Alkoxide Species[a]



[a] Conditions *i*: **6ac** (50 μmol), **6be** (50 μmol), 18-crown-6 ((5 μmol), KOH (175 μmol), THF (500 μL), 85 °C, 48 h. Conditions *ii*: The same, but KOH was replaced with *t*-BuOK (175 μmol).

We also questioned whether thermodynamic control of the diastereoselectivity is realized via epimerization of the tertiary carbon atom adjacent to the amide functionality, or via a reversible nucleophilic addition of an alkoxide or aryloxide species. To clarify the mechanism, we performed a crossover experiment employng a pair of 2-alkoxycyclopropane carboxamides **6ac** and **6be**, bearing different alkoxide and amide groups. A mixture of these compounds was subjected to the typical reaction conditions in the presence of either KOH or t-BuOK as a base. In both cases no formation of crossover products **6ae** and **6bc** was detected by GC analysis of crude reaction mixtures (Scheme 2). These results strongly support irreversibility of the nucleophilic addition step which, in turn, suggests that thermodynamic control of the diastereoselectivity in this reaction is exclusively realized via a base-assited epimerization of the α-CH group.

In conclusion, we have developed an efficient formal substitution of 2-bromocyclopropanecarboxamides with both hard and soft oxygen-based nucleophiles (alkoxides and aryloxides) in the presence of powdered potassium hydroxide and catalytic amounts of 18-crown-6. The reaction is tolerant to steric hindrance and electronic properties of the nucleophile and predominantly produces *trans*-products via a thermodynamically driven base-assisted epimerization. This new mode of the diastereoselectivity control is complementary to the previously reported *cis*-selective addition governed by a directing effect of an amide function. Further development of this methodology to employ *S*-, *N*-, and *C*-based nucleophiles is currently underway in our laboratories.

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

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(10) σ(−)-Values used are derived from Swain−Lupton parameters adopted from: (a) Swain, C. G.; Lupton, E. C., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4328. (b) Williams, S. G.; Norrington, F. E. *J. Am. Chem. Soc.* **1976**, *98*, 508.

(11) This was confirmed by the fact that the overall kinetic rate of the transformation did not depend on electronic properties of the phenoxide species.