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Formal Nucleophilic Substitution of Bromocyclopropanes with Amides en route to Conformationally Constrained β-Amino Acid Derivatives

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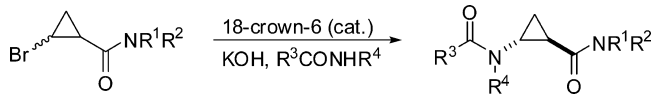
ABSTRACT



A chemo- and diastereoselective protocol for the formal nucleophilic substitution of 2-bromocyclopropylcarboxamides with secondary amides is described. This method allows for convergent and highly selective synthesis of trans-β-aminocyclopropane carboxylic acid derivatives.

Designing small molecules that bind to therapeutically important biological targets with high affinity and selectivity is one of the major goals of contemporary bioorganic and medicinal chemistry. In this respect, cyclopropane-based peptide mimics are attractive and versatile targets due to their innate rigidity, unusual geometry, compact size, and metabolic stability.[1] Natural and synthetic analogs of α-aminocyclopropanecarboxylic acid (α-ACC) are ubiquitous; they have been extensively explored and find a widespread application in medicinal, chemical and agricultural research.[2] β-ACC derivatives[3] are emerging as important tools for investigation of conformational preferences in peptides,[1,4] key elements of muliple natural products,[5] organocatalysts[6] and prospective drug candidates.[1,7]

We have recently reported an efficient and selective approach to functionalized cyclopropyl ethers via a formal inter- and intramolecular substitution in bromocyclopropanes with oxygen-based nucleophiles.[8,9] This method allows for installation of nucleophilic entities in the three-membered ring via the strain-driven addition to the cyclopropene double bond,[10] while bypassing the isolation of the cyclopropene species, which permits employment of even the most unstable strained olefins (eq 1).

(1) See, for example: (a) Benfield, A. P.; Teresk, M. G.; Plake, H. R.; DeLorbe, J. E.; Millspaugh, L. E.; Martin, S. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 6830. (b) DeLorbe, J. E.; Clements, J. H.; Teresk, M. G.; Benfield, A. P.; Plake, H. R.; Millspaugh, L. E.; Martin, S. F. *J. Am. Chem. Soc.* **2009**, *131*, 16758.

(2) For leading reviews, see: (a) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511. (b) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1.

(3) See, for recent examples: (a) Urman, S.; Gaus, K.; Yang, Y.; Strijowski, U.; Sewald, N.; De Pol, S.; Reiser, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 3976. (b) Koglin, N.; Zorn, C.; Beumer, R.; Cabrele, C.; Bubert, C.; Sewald, N.; Reiser, O.; Beck-Sickinger, A. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 202. See also: (c) Beumer, R.; Bubert, C.; Carbele, C.; Vielhauer, O.; Pietzsch, M.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 8960, and references cited therein.

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(5) For reviews, see: (a) *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985. (b) Hoekstra, W. J. Chemistry and Biology of β-Amino Acids. *Curr. Med. Chem.* **1999**, *6*, 905. (c) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117.

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

(9) Banning, J. E.; Prosser, A. R.; Rubin, M. *Org. Lett.* **2010**, *12*, 1488.

(10) For our recent reports on preparative synthesis of isolable cyclopropenes, see: (a) Sherrill, W. M.; Kim, R.; Rubin, M. *Synthesis* **2009**, 1477. (b) Kim, R.; Sherrill, W. M.; Rubin, M. *Tetrahedron* **2010**, *66*, 4947.

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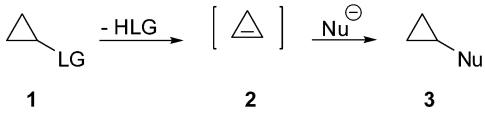
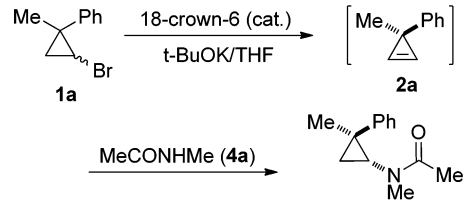


(1)

1 2 3

As a part of an ongoing program aimed at expanding the range of nucleophilic entities pertinent to this transformation, we herein report a method for incorporation of a nitrogen moiety in the three-membered ring, which allows for direct access to β-ACC derivatives. While diastereoselective transfer of transition metal carbenoids generated from diazocompounds to enamines remains a challenging task,[11] β-ACC cores are usually accessed via Michael-initiated ring closure reactions[12] or [2 + 1]-cyclopropanation of acrylates with α-nitrodiazoacetates,[13] followed by appropriate functional group transformations. At the same time, approaches that allow direct and efficient installation of amine function in a pre-existing three-membered ring remain scarce.[14,15] Several previously reported attempts on the addition of such nucleophiles to cyclopropenes resulted in cleavage of the small ring.[16]

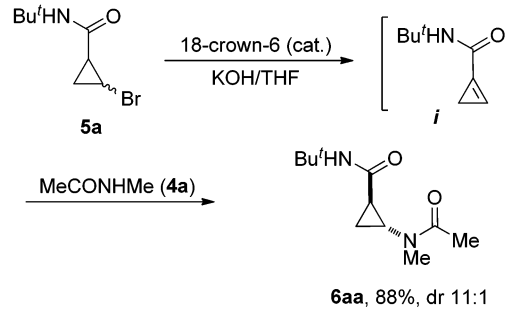
We started by probing a series of different amines as *N*-pronucleophiles; however, our attempts to induce addition of diethylamine, diphenylamine, *N*-ethylaniline, *N*-tosylbutylamine, and phthalimide met with no success.[17] In contrast, nucleophilic attack by *N*-methylacetamide (NMA, **4a**) on the generated in situ but isolable 3-methyl-3-phenylcyclopropene (**2a**) afforded *trans*-cyclopropylamine derivative **3aa** in good yield and high diastereoselectivity, which was controlled by steric factors (eq 2).[8,18] Encouraged by these results, we tested 1,2-elimination of bromocyclopropane **5a** under conditions used previously for addition of O-nucleophiles.[9] As it was shown previously, dehydrohalogenation of **5a** produces a highly unstable conjugate cyclopropene ***i***, which decomposes rapidly unless intercepted with a nucleophile.[19] To our delight, trapping of ***i*** with NMA proceeded efficiently affording high yield of *trans*-diamide **6aa** (eq 3).



1a 2a

3aa, 85%, dr 13:1

(2)



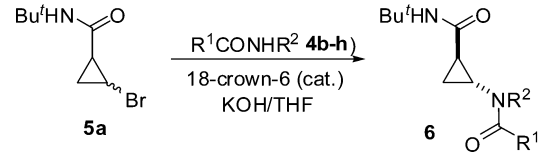
5a *i*

6aa, 88%, dr 11:1

(3)

Further screening of various *N*-alkyl alkylcarboxamides against bromocyclopropylcarboxamide **5a** revealed an adverse steric effect. Thus, introduction of a primary alkyl substituent in both *N*- and *C*-termini of an amide **4b** resulted in a notable yield drop (Table 1, entry 2). Pronucleophiles bearing a secondary alkyl substituent at either terminus (**2c**,**d**) provided poor yields (entries 3,4), whereas *t*-Bu-substituted

Table 1. Steric Effect in the Formal Substitution of Bromocyclopropane **5a** with Secondary Amides



5a 6

(4)

no.	R^1	R^2	NuH	product[a]	yield, %[b]	dr[c]
1	Me	Me	**4a**	**6aa**	88	11:1
2	*n*-Pr	*n*-Bu	**4b**	**6ab**	51	25:1
3	*n*-Pr	*i*-Pr	**4c**	**6ac**	28[d]	25:1
4	*i*-Pr	*n*-Bu	**4d**	**6ad**	31[d]	17:1
5	*n*-Bu	*t*-Bu	**4e**	**6ae**	NR	–
6	*t*-Bu	*n*-Bu	**4f**	**6af**	NR	–
7	Ph	Me	**4g**	**6ag**	75	>25:1
8	Ph	*n*-Bu	**4h**	**6ah**	72	>25:1

[a] Reactions performed in 0.5 mmol. [b] Isolated yields of diastereomeric mixtures unless specified otherwise. [c] dr (*trans*:*cis*) determined by GC or ^{1}H NMR analysis of crude reaction mixtures. [d] NMR yields determined by analysis of a crude reaction mixture. Bromocyclopropane **5a** was consumed completely.

(11) For discussion, see: (a) Miller, J. A.; Hennessy, E. J.; Marshall, W. J.; Scialdone, M. A.; Nguyen, S. T. *J. Org. Chem.* **2003**, *68*, 7884. For development of diastereoselective protocols, see: (b) Sladojevich, F.; Trabocchi, A.; Guarna, A. *Org. Biomol. Chem.* **2008**, *6*, 332. (c) Denton, J. R.; Davies, H. M. L. *Org. Lett.* **2009**, *11*, 787. (d) Bonge, H. T.; Pintea, B.; Hansen, T. *Org. Biomol. Chem.* **2008**, *6*, 3670.

(12) See for example: (a) Inokuma, T.; Sakamoto, S.; Takemoto, Y. *Synlett* **2009**, 1627. (b) Fan, R.; Ye, Y.; Li, W.; Wang, L. *Adv. Synth. Catal.* **2008**, *350*, 2488. (c) Zhang, J.; Hu, Z.; Dong, L.; Xuan, Y.; Lou, C.-L.; Yan, M. *Tetrahedron: Asymmetry* **2009**, *20*, 355. (d) Lv, J.; Zhang, J.; Lin, Z.; Wang, Y. *Chem.—Eur. J.* **2009**, *15*, 972.

(13) See for example Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8460.

(14) For ring-retentive nucleophilic addition of amines to cyclopropenes, see: (a) Gritsenko, E. I.; Khaliullin, R. R.; Plemenkov, V. V.; Faizullin, E. M. *Zh. Obshch. Khim.* **1988**, *58*, 2733. (b) Franck-Neumann, M.; Miesch, M.; Kempf, H. *Tetrahedron* **1988**, *44*, 2933. For nucleophilic displacement of halogen in cyclopropyl halides with *N*-heterocycles, amides, and sulfamides, see: (c) Kang, S. Y.; Lee, S.-H.; Seo, H. J.; Jung, M. E.; Ahn, K.; Kim, J.; Lee, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2385. (d) Basle, E.; Jean, M.; Gouault, N.; Renault, J.; Uriac, P. *Tetrahedron Lett.* **2007**, *48*, 8138. (e) Liang, G.-B.; Qian, X.; Feng, D.; Biftu, T.; Eiermann, G.; He, H.; Leiting, B.; Lyons, K.; Petrov, A.; Sinha-Roy, R.; Zhang, B.; Wu, J.; Zhang, X.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1903.

(15) For ring retentive installation of phosphorous-based nucleophilic moiety into pre-existing three-membered cycle, see: Alnasleh, B. K.; Sherrill, W. M.; Rubin, M. *Org. Lett.* **2008**, *10*, 3231.

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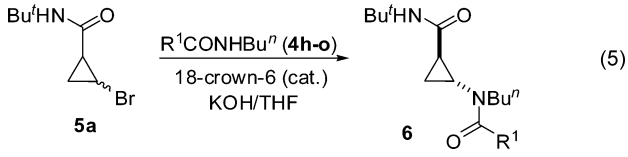
(17) It is believed that a fine balance between acidity and nucleofilicity of the pronucleophile is essential for the successful transformation. See ref 9 for discussion.

pronucleophiles **4e**,**f** gave no reaction (entries 5,6). We rationalized that the effective nucleophilicity of the sterically hindered amide species can be enhanced by varying their electronic properties. To test this idea, we substituted an alkyl group at the *C*-terminus of the pronucleophile with a phenyl ring. Gratifyingly, the reaction between bromocyclopropane **5a** and benzamide **4g** afforded good yield of diamide **6ag**. Likewise, *N*-butyl amide **4h** produced **6ah** with comparably high yield and excellent diastereoselectivity (Table 1, entries 7, 8). Next, we tested **5a** with a series of differently substituted *N*-butyl benzamides **4i**-**o** to further explore the effect of electronic factors on the reactivity (Table 2).

Table 2. Electronic Effect in the Formal Substitution of Bromocyclopropane **5a** with Secondary Amides



(5)

no.	R^1	NuH	product[a]	yield, %[b]	dr[c]
1	Ph	**4h**	**6ah**	72	>25:1
2	*p*-MeOC$_6$H$_4$	**4i**	**6ai**	NR	–
3	*o*-ClC$_6$H$_4$	**4j**	**6aj**	80[d]	>25:1
4	*p*-ClC$_6$H$_4$	**4k**	**6ak**	81	>25:1
5	*p*-CNC$_6$H$_4$	**4l**	**6al**	80	>25:1
6	*p*-NO$_2$C$_6$H$_4$	**4m**	**6am**	80	>25:1
7	*p*-CF$_3$C$_6$H$_4$	**4n**	**6an**	85	>25:1[e]
8	3,5-(CF$_3$)$_2$C$_6$H$_3$	**4o**	**6ao**	87	>25:1[e]

[a] Typical reaction conditions: bromocyclopopane **5a** (0.5 mmol), amide **4** (1.0 mmol), powdered KOH (1.75 mmol), 18-crown-6 (0.05 mmol), THF (5 mL) - stirred at 85 °C for 12 h. [b] Isolated yields of *trans*-diamide. [c] dr (*trans*:*cis*) determined by GC or ^{1}H NMR analysis of crude reaction mixtures. The notation >25:1 is used when no minor diastereomer was detected. [d] NMR yields determined by analysis of a crude reaction mixture. [e] dr (*trans*:*cis*) determined by ^{19}F NMR analysis of crude reaction mixtures.

Interestingly, introduction of an electron-donating *p*-MeO group completely shut down the reaction (Table 2, entry 2). On the other hand, incorporation of an electron-withdrawing groups in the *ortho*- (entry 3) or *para*- (entries 4−7) position of the aromatic ring in the benzamide pronucleophile allowed for improved reactivity. The best results were achieved with *p*-CF$_3$-(entry 7) and 3,5-bis(CF$_3$)-substituted aryl groups (entry 8). It should be mentioned that no diamide product was observed in the reaction with primary amide (*p*-CF$_3$C$_6$H$_4$CONH$_2$) despite complete consumption of the bromocyclopropane **5a**.[20]

We envisioned that the described methodology can be efficiently applied toward convergent synthesis of conformationaly constrained *trans*-cyclopropyl amino acid derivatives, with the possibility for a three-dimensional diversification (Scheme 1). Thus, readily available acyl chloride **7** can be converted into an array of amides **5** by varying primary or secondary amines **8**. At the same time, a variety of pronucleophiles **4** can be obtained from primary amines **10** and different carboxylic acids **9**. Amides **4** derived from linear aliphatic and electron-defficient benzoic acids **9** usually provide highest yields in this transformation (Tables 1 and 2, Scheme 1). Notably, installation of the CF$_3$-groups in the benzamide derivatives **4n**,**o** significantly facilitated isolation and purification of the corresponding products **6an** and **6ao** due to their improved solubility in organic solvents compared to other *N*-butyl benzamide derivatives (**6ah**, **6aj**−**am**, Table 2). The presence of fluorine-containing groups also allowed for accurate assessment of the selectivity by ^{19}F NMR, as severe line broadening in proton spectra resulting from slow conformational rotation made ^{1}H NMR data inapplicable for the analysis. Accordingly, CF$_3$-substituted benzamides were used for more detailed investigations of the scope and limitation of this reaction. It was found that *p*-CF$_3$-substituted benzamides possessing primary *N*-alkyl groups rendered efficient nucleophilic addition to give *n*-octyl- (**6ap**), benzyl- (**6aq**), and 2-phenethyl benzamides (**6ar**) in high yields and perfect diastereoselectivites (Scheme 1). At the same time, nucleophilic addition of a more sterically hindered *N*-cyclohexyl 4-(trifluoromethyl)benzamide (**2s**) proceeded sluggishly, resulting in marginal yield of the corresponding diamide **6as** (Scheme 1). In contrast, amides **4o**, **4t**−**w** derived from 3,5-bis(trifluoromethyl)benzoic acid reacted with bromocyclopropane **5a** much more readily. Superior product yields were obtained not only for the less sterically hindered derivative **6aw**, but also for more challenging bulky products **6at**, **6av**, **6au**, bearing secondary *N*-alkyl substituents. However, very bulky *N*-*tert*-butylamide **4y** (R^1 = 3,5-(CF$_3$)$_2$C$_6$H$_3$, R^2 = *t*-Bu) did not provide any product in the reaction with **5a**.

The scope of the cyclopropylcarboxamides **5** was also investigated. Bromocyclopropylcarboxamide derivatives of morpholine (**5b**), piperidine (**5c**), and cyclohexylamine (**4d**), afforded diamides **6bo**, **6bw**, **6cw**, **6cx**, and **6dt** in good to high yields (Scheme 1). Weinreb amide **5e** was also tested in this reaction; however, the corresponding product **6ex** was obtained in 31% yield only, presumably, due to a decreased stability of the intermediate cyclopropene species (Scheme 1).

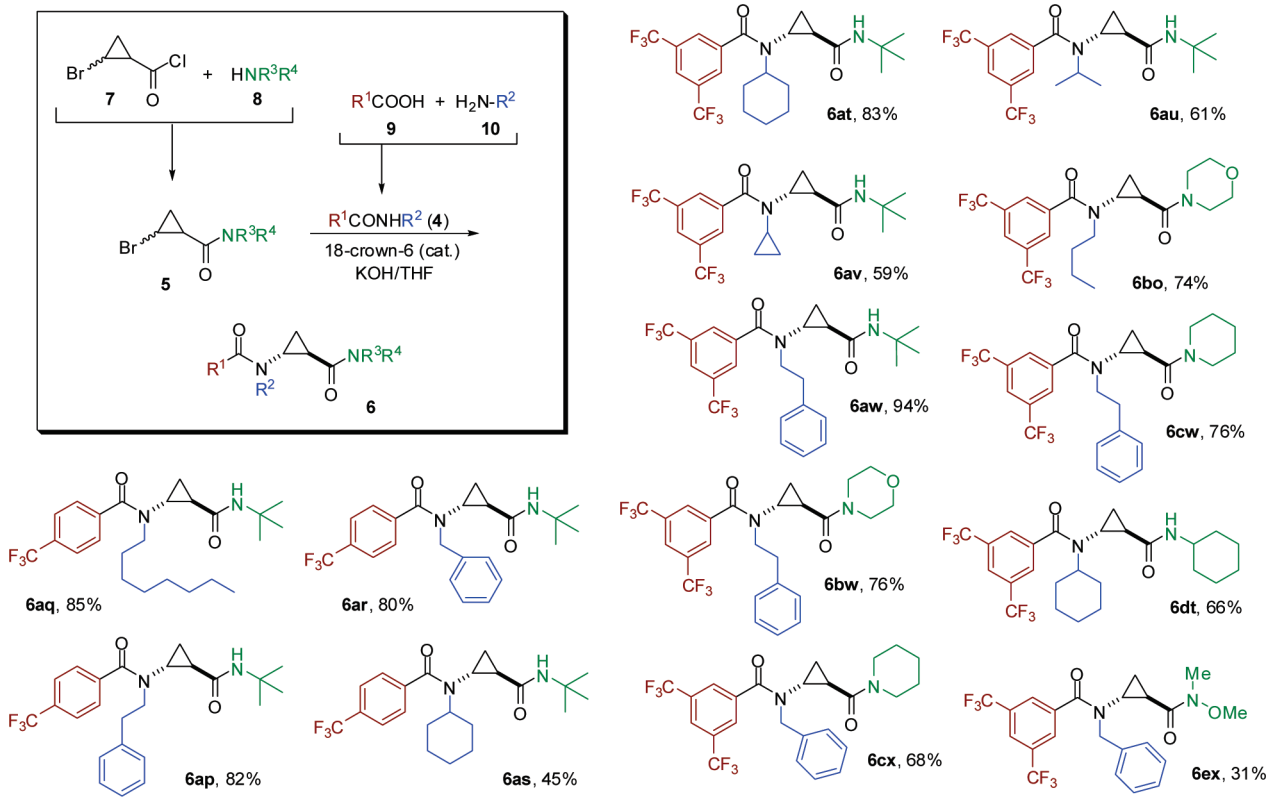
Similarly to the previously reported formal nucleophilic substitution reaction with alkoxides and phenoxides,[9] the diastereoselectivity in the described transformation was governed by a base-assisted epimerization. However, additional treatment of the reaction mixture with *t*-BuOK was unnecessary in this case,[9] as the thermodynamically more favored *trans*-diastereomer was produced exclusively under the standard reaction conditions. It should be mentioned that accurate assignment of the product configuration by ^{1}H NMR based on the analysis of $^3J_{HH}$ coupling constants of the cyclopropyl proton signals was impeded by severe broadening of the corresponding resonance lines. Careful optimiza-

(18) We have also previously demonstrated a single example of a formal nucleophilic substitution of **1a** with pyrrole. Studies on incorporation of other heterocyclic moieties in the three-membered ring via this approach are currently underway and will be reported in due course.

(19) Although never observed directly, intermediate i was proved in the reaction of **5a** with phenoxides. See ref 9.

(20) We failed to detect any cyclopropane-containing products in this reaction.

Scheme 1. Convergent Approach to Conformationally Constrained *trans*-Cyclopropyl Amino Acid Derivatives



tion of the sample temperature provided acceptable resolution for measuring the coupling constants in **6ab** in DMSO-d_6. As an additional evidence, *trans*-configuration of diamide **6bw** was unambigously assigned by X-ray crystallography (Figure 1). These data were used to assign the structures of all other products by analogy.

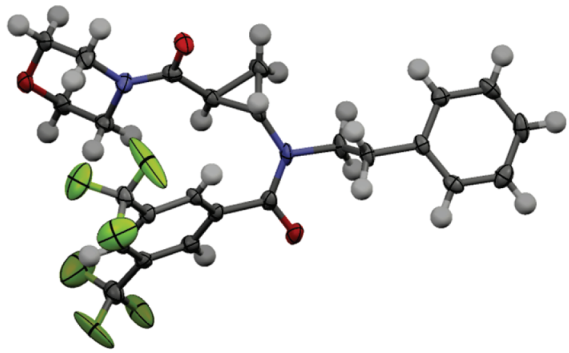


Figure 1. ORTEP drawing of diamide **6bw** showing 50% probability amplitude displacements ellipsoids.

In conclusion, we have developed an efficient and highly diastereoselective formal substitution of 2-bromocyclopropane carboxamides with secondary amides leading to conformationally constrained *trans*-cyclopropyl β-amino acid derivatives. Strong influence of the steric and electronic factors on the efficiency of the formal substitution reaction has been demonstrated. The *trans*-selectivity in this reaction is effectively controlled by a base-assisted epimerization. Development of a nonracemic version of this reaction and work on further transformations of β-diamides 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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