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Boronate Urea Activation of Nitrocyclopropane Carboxylates

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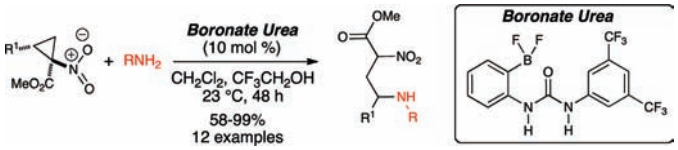
ABSTRACT



Boronate ureas operate as catalysts for the activation of nitrocyclopropane carboxylates in nucleophilic ring-opening reactions. A variety of amines were found to open the urea-activated nitrocyclopropane carboxylates, generating highly useful nitro ester building blocks in good yields. Standard manipulations allow access to a wide range of valuable compounds from the ring-opened products with direct applications in bioactive target synthesis.

Hydrogen bond donors (HBDs) operate as impressive catalysts for the activation of electrophiles.[1] Suitable ureas, for example, effectively enhance the reactivity of β-nitrostyrenes and α,β-unsaturated imides toward the 1,4-addition of nucleophiles (**1**).[2] The activation of imines and carbonyl compounds for 1,2-nucleophilic addition reactions provides additional evidence of the power of urea catalysis (**2**).[3] While the collection of reactions catalyzed through hydrogen bonding with ureas has grown tremendously in the past ten years, the realization of the full potential of urea catalysis requires the continued development of catalysts with improved activity and the exploration of new activation modes. A research program in our laboratory is geared toward the design of enhanced urea catalysts, along with the study of their application toward the development of unique reactivity patterns for the synthesis of bioactive target molecules. Herein we report our initial success with boronate urea catalyzed activation of strained rings (**3**).

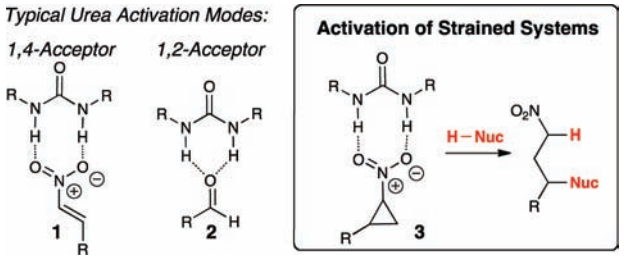


Figure 1. Proposed urea activation of strained systems.

Recently, we reported that fluoroboronate urea catalysts offer improved reactivity over conventional urea catalysts in the conjugate addition reactions of indoles to nitroalkenes, possibly due to enhanced acidity of the N–H protons resulting from internal coordination of the urea carbonyl to the strategically placed boron.[4–6] We were interested in taking advantage of these enhanced HBDs in

(1) For recent reviews, see: (a) Pihko, P. M. *Hydrogen Bonding in Organic Synthesis*, 1st ed.; Wiley-VCH: Weinheim, 2009. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.

(2) (a) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (b) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576. (c) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032.

(3) (a) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (b) Kavanagh, S. A.; Piccinini, A.; Fleming, E. M.; Connon, S. J. *Org. Biomol. Chem.* **2008**, *6*, 1339. (c) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.

(4) So, S. S; Burkett, J. A.; Mattson, A. E. *Org. Lett.* **2011**, *13*, 716.

(5) For pioneering work using boronate ureas in anion recognition, see: (a) Hughes, M. P.; Shang, M. Y.; Smith, B. D. *J. Org. Chem.* **1996**, *61*, 4510. (b) Hughes, M. P.; Smith, B. D. *J. Org. Chem.* **1997**, *62*, 4492.

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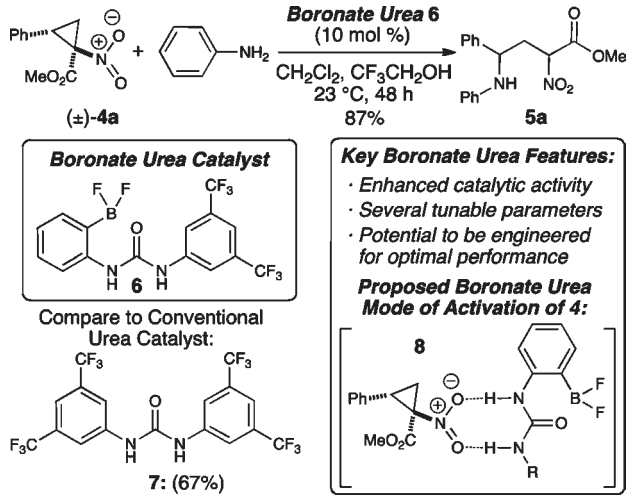
Scheme 1



new bond-forming processes and set out to develop boronate urea catalyzed ring-opening reactions of nitrocyclopropanes (**3**).[7] Investigations exploring reactions of activated cyclopropanes typically focus on the reactivity of 1,1-diestercyclopropanes.[8,9] Reactions of nitrocyclopropanes are significantly less studied and warrant further development due to the value of products containing the nitro group, as it can be easily converted into useful nitrogen functionalities often found in bioactive targets.[10] Indeed, the highly useful nature of the products obtained from the ring-opening of nitrocyclopropanes was the basis of our initial attraction to this area. We envisioned taking advantage of boronate ureas (**6**) for the activation of nitrocyclopropane carboxylates (**4**) toward attack by an amine nucleophile to access γ-amino α-nitro ester products (**5**), valuable building blocks for the construction of drug targets. In the few existing reports of nucleophilic ring-opening reactions of nitrocyclopropane carboxylates, typically metal catalysts and/or elevated reaction temperatures are required to generate high yields of product; no organocatalytic variant has been reported. The most efficient Lewis acid catalyst was found to be nickel perchlorate, while many other Lewis acids caused undesired rearrangement of the nitrocyclopropane to the isoxazoline *N*-oxide.[10e] Prior work taking advantage of urea activation of nitroalkenes for conjugate addition reactions did provide a starting point for the support of our studies, yet at the onset of our investigations it remained unclear if a HBD would operate as a strong enough catalyst to activate a nitrocyclopropane for ring-opening.[11] To the best of our knowledge, this is the first study dedicated toward ring-opening reactions of activated cyclopropanes using a HBD catalyst.

Studies commenced with the treatment of racemic nitrocyclopropane carboxylate **4a** with a catalytic amount of boronate urea **6** in the presence of aniline (Scheme 1). Gratifyingly, **5a** was isolated in 87% yield as a 1:1 mixture of diastereomers after 48 h at 23 °C in methylene chloride. In addition to enhanced activity, boronate ureas are readily prepared from commercially available materials and benefit from several tunable parameters (e.g., Lewis acid, ligand) that can be easily altered to facilitate the engineering of a catalyst with optimal performance for a particular reaction.[4,12,13] A direct comparison of boronate urea **6** to conventional urea **7** demonstrated the benefit of internal Lewis acid activation on the activity of the catalyst (87% vs 67% yields). On the basis of literature precedent involving urea activation of nitroalkenes, it is proposed that the catalyst may operate through hydrogen bond association of **6** with the nitro group of **4a** to generate intermediate **8**, a species in which the cyclopropane is activated for attack.[2,14]

With the initial bond-forming process established, the limits of the reaction with respect to the nitrogen nucleophile were put to the test (Table 1). The reaction was found to be tolerant of anilines containing both electron-donating and electron-withdrawing substituents. 4-Methoxyaniline as a nucleophile gave rise to 90% **5b** with 10 mol % **6** (entry 2). The less electron rich 4-bromoaniline rendered the reaction more sluggish, affording 58% **5c** after 48 h (entry 3). Nitrogen heterocycles were found to be well tolerated as nucleophiles in the reaction system. The addition of morpholine to **4a** yielded 95% **5d**. Nucleophilic addition of piperidine was more challenging, although a 78% yield of desired product **5e** was obtained (entry 5). Indoline operated well in the ring-opening of **4a** to afford 99% **5f** (entry 6). Phenylhydrazine was also well tolerated in the reaction, affording a near-quantitative yield of **5g**

(6) For additional recent, interesting examples of alternate strategies to access hydrogen bond donors with enhanced activity see: (a) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110. (b) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464.

(7) For a review on nitrocyclopropanes see: Averina, E. B.; Yashin, N. V.; Kuznetsova, T. S.; Zefirov, N. S. *Russ. Chem. Rev.* **2009**, *78*, 887.

(8) For reviews on the reactivity of activated cyclopropanes, see: (a) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (b) Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (c) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (d) Reissig, H. U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (e) Burrit, A.; Coron, J. M.; Steel, P. J. *Trends Org. Chem* **1993**, *4*, 517. (f) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (g) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

(9) For recent examples of Lewis acid catalyzed reactions of 1,1-diestercyclopropanes see: (a) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196. (b) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689. (c) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (d) Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 4561.

(10) For reports of ring-opening reactions of nitrocyclopropanes see: (a) Vettiger, T.; Seebach, D. *Liebigs Ann. Chem* **1990**, 195. (b) Seebach, D.; Haener, R.; Vettiger, T. *Helv. Chim. Acta* **1987**, *70*, 1507. (c) Wurz, R. P.; Charette, A. *Org. Lett.* **2005**, *7*, 2313. (d) Budynina, E. M.; Ivanova, O. A.; Averina, E. B.; Kuznetsova, T. S.; Sefirov, N. S. *Tetrahedron Lett.* **2006**, *47*, 647. (e) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809. (f) Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6838.

(11) For intramolecular H-bond activation of cyclopropanes see: Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 4180.

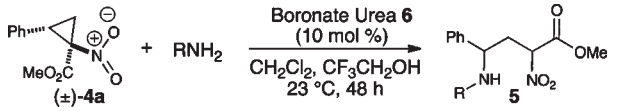
(12) For early work demonstrating that diaryl ureas with trifluoromethyl substituents have enhanced activity, see: (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (b) Wittkopp, A.; Schreiner, P. R. *Chem.—Eur. J.* **2003**, *9*, 407.

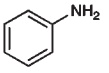
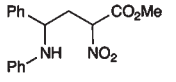
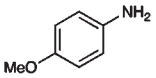
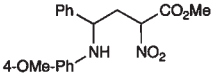
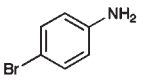
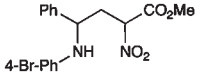
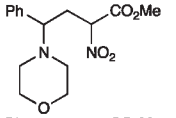
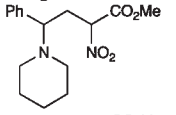
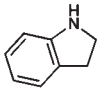
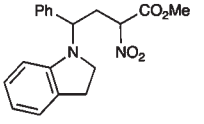
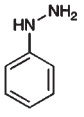
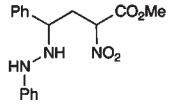
(13) A variety of ureas were surveyed as catalysts in this process. See Supporting Information for more on the catalyst structure.

(14) Participation of the ester in the activation of intermediate **8** has not been ruled out at this time.

after 48 h (entry 7). Under these optimized conditions we were unable to observe any successful ring-opening of nitrocyclopropanes with primary amines, such as benzyl amine. It is noteworthy to mention that the rearrangement of **4** to the corresponding isoxazoline *N*-oxide, a problem encountered under many types of Lewis acidic conditions (BF_3OEt_2, $AlCl_3$, and others), was not observed in any reaction catalyzed by a urea.[10e,15]

Table 1. Substrate Scope with Nitrogen Nucleophile[a]

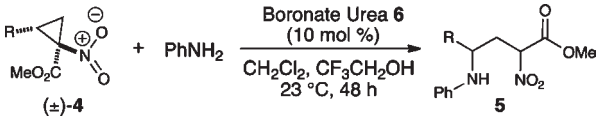


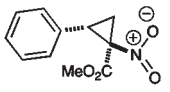
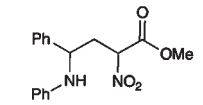
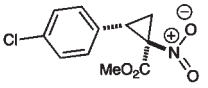
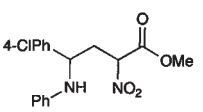
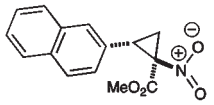
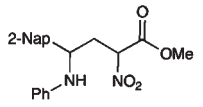
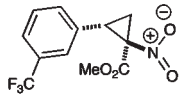
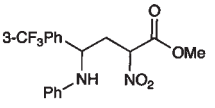
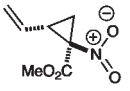
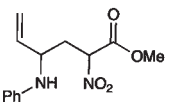
entry	amine	product[b]		yield (%)[c]
1			**5a**	87
2			**5b**	90
3			**5c**	58
4			**5d**	95
5			**5e**	78
6[d]			**5f**	99
7			**5g**	99

[a] Reactions performed using 1.5 equiv of amine at a concentration of 0.5 M. Control experiments result in a 12% yield of product in the absence of the urea catalyst. See Supporting Information for detailed experimental procedures. [b] Isolated as a 1:1 mixture of diastereomers unless otherwise noted. [c] Isolated yield. [d] dr = 1:1.3.

Next we explored the generality of the reaction with respect to the nitrocyclopropane carboxylate (Table 2). Product **5h**, isolated after the ring-opening of *p*-Cl styrene-derived nitrocyclopropane with aniline, was produced in high yield (77%, entry 2). The naphthyl-derived nitrocyclopropane operated well in the addition reaction, affording a near-quantitative yield of **5i** (entry 3). Installation of a *m*-CF_3 group on the phenyl ring was also fairly well tolerated in the reaction, generating a 59% yield of **5j** (entry 4). In addition to aromatic rings, alkenes were found to be viable substituents at the point of substitution on the cyclopropane. Nucleophilic addition of aniline to the nitrocyclopropane derived from 1,3-butadiene gave rise to 76% **5k** (entry 5). Nitrocyclopropanes prepared from electron-rich aromatic rings were not examined in this study, as their rearrangement to the isoxazoline *N*-oxide occurred upon purification by column chromatography on silica gel.

Table 2. Substrate Scope with Nitrocyclopropane Carboxylate[a]



entry	(±)-4	product[b]		yield (%)[c]
1			**5a**	87
2			**5h**	77
3			**5i**	99
4			**5j**	59
5			**5k**	76

[a] Reactions performed using 1.5 equiv of aniline at a concentration of 0.5 M. See Supporting Information for detailed experimental procedures. [b] Isolated as a 1:1 mixture of diastereomers. [c] Isolated yield.

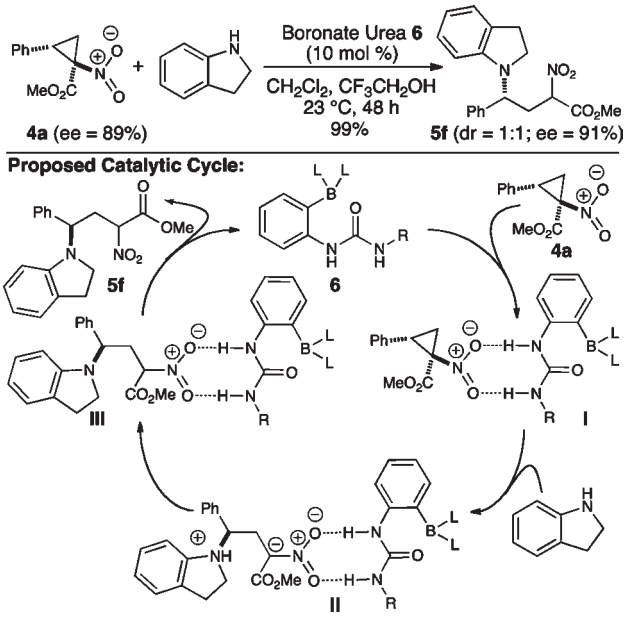
Pleased with the wide range of products accessible from boronate urea catalyzed ring-opening of nitrocyclopropanes, we became curious about the stereochemical outcome of the ring-opening of an enantioenriched nitrocyclopropane (Scheme 2). The exposure of enantioenriched **4a** (89% ee) to indoline in otherwise optimized conditions gave rise to 99% **5f** as a 1:1 mixture of diastereomers with complete inversion of stereochemistry (91% ee for each of the products).[10e,16] Taking this result in combination with previous reports of urea-catalyzed processes, a plausible catalytic pathway can be proposed. Initial coordination of **6** with **4a** affords the activated nitrocyclopropane intermediate **I**.[14] Nucleophilic attack by the amine causes ring-opening, giving rise to **II** through an S_N2-type reaction pathway, consistent with the observation that the product has inverted stereochemistry with respect to the starting material. This cycle is in contrast to

(15) For rearrangements of nitrocyclopropanes to isoxazoline *N*-oxides see: Bianchi, L.; Dell'Erba, C.; Gasparrini, F.; Novi, M.; Petrillo, G.; Sancassan, F.; Tavani, C. *ARKIVOC* **2002**, *xi*, 142.

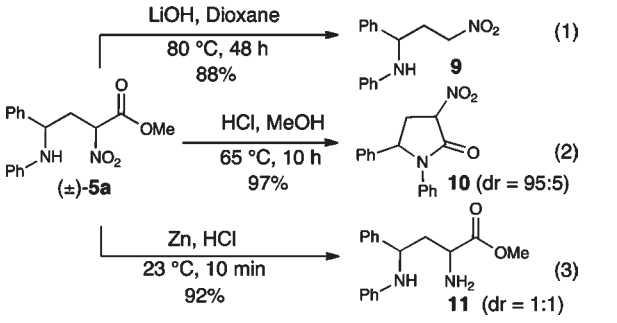
(16) For detailed experimental procedures, including evidence for stereocenter inversion, see the Supporting Information.

an alternate S_N1-like pathway that would likely give rise to a racemic mixture of **5f**, in which ring-opening of the nitrocyclopropane occurs prior to nucleophilic attack. After proton transfer to form **III** the product is released with simultaneous reintroduction of the urea into the catalytic cycle.

Scheme 2. Ring-Opening of an Enantioenriched Nitrocyclopropane and Proposed Catalytic Cycle



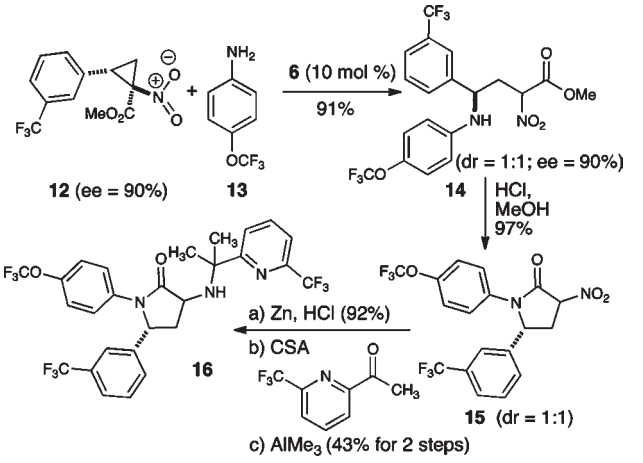
Scheme 3. Utility of Nitroester Products



A few exemplary manipulations readily carried out on **5a** demonstrate some of the utility of the γ-amino α-nitro ester products prepared from the boronate urea catalyzed ring-opening of nitrocyclopropanes (Scheme 3). Decarboxylation was effected in excellent yield with lithium hydroxide in dioxanes, giving rise to amine **9** (88%, eq 1). Straightforward subjection of **5a** to 1 M HCl in MeOH afforded the lactam **10** in 97% yield as a single diastereomer, and our NMR spectroscopic studies suggest a *trans* orientation between the nitro group and phenyl ring (eq 2). Chemoselective reduction of the nitro group was achieved upon subjection of **5a** to Zn and HCl to yield α-aminoester **11** (92%, eq 3).

The application of the activation of nitrocyclopropanes toward the synthesis of **16**, a CB-1 receptor inverse agonist recently patented by Eli Lilly, demonstrates potential applications of boronate urea catalysis in drug discovery (Scheme 4).[17] The addition of 4-(trifluoromethoxy)aniline (**13**) to enantioenriched nitrocyclopropane **12** in the presence of 10 mol % **6** gave rise to nitroester **14** as a 1:1 mixture of diastereomers in 91% yield with 90% ee for each of the products. Lactamization of **14** using HCl in methanol enabled isolation of **15** in 97% yield. The aminolactam was accessed in 92% yield upon reduction of **15** with Zn and HCl. Condensation of amine with 1-(6-(trifluoromethyl)pyridin-2-yl)ethanone followed by addition of trimethylaluminum gave rise to the desired drug candidate **16** in good yield (43% in two steps).

Scheme 4. Application to Synthesis of Drug Target **16**



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Supporting Information Available. Experimental procedures and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(17) Hu, J. U.S. Patent 0028520 A1, February 3, 2011.