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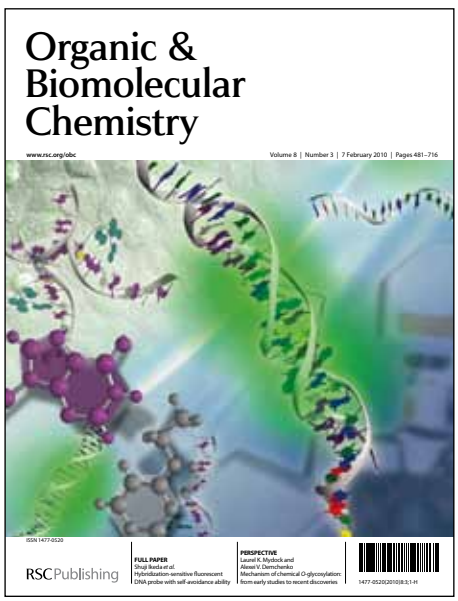

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ARTICLE TYPE

Urea Catalyzed Construction of Oxazinanes

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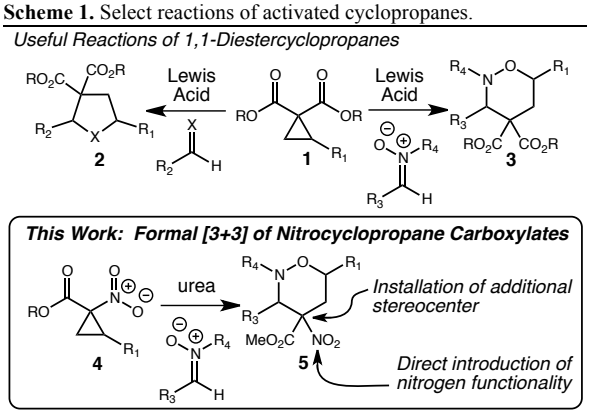
Highly functionalized oxazinanes are efficiently prepared through urea-catalyzed formal [3+3] cycloaddition reactions of nitrones and nitrocyclopropane carboxylates. The reaction system is general with respect to both the nitrocyclopropane carboxylates and nitrones enabling the preparation of a large family of oxazinanes, typically in high yield. This method affords access to enantioenriched oxazinane products through chirality transfer from enantioenriched nitrocyclopropane carboxylates.

Formal cycloaddition reactions of donor acceptor cyclopropanes have emerged as useful methods to access biologically important heterocycles.[1] More specifically, the activation of 1,1-diestercyclopropanes (**1**) under Lewis acidic conditions is a powerful strategy to effect formal [3+2] cycloaddition reactions with partners such as imines and aldehydes to give rise to pyrrolidines (**2**, X = N) and tetrahydrofurans (**2**, X = O, Scheme 1).[2] Similarly, formal [3+3] cycloadditions of **1** with nitrones are efficiently catalyzed in the presence of Lewis acids to yield oxazinanes (**3**).[3] It is surprising that reactions of nitrocyclopropane carboxylates (**4**), another interesting family of activated cyclopropanes, remain significantly less studied than 1,1-diestercyclopropanes.[4] Only a few reports exist on nucleophilic ring-opening reactions of nitrocyclopropane carboxylates[5,6] and to the best of our knowledge there are no previous publications exploring formal cycloaddition reactions of species like **4**.

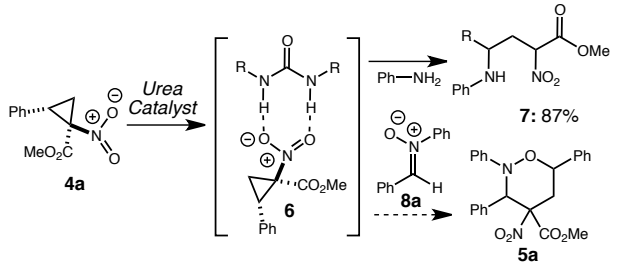
Scheme 1. Select reactions of activated cyclopropanes.



The development of cycloaddition methodology of nitrocyclopropane carboxylates (**4**) presents the opportunity for compelling investigations for at least two reasons: (1) the incorporation of the nitro group, an easily manipulated functionality for bioactive target synthesis, into the product and (2) the rapid buildup of molecular complexity via the direct installation of several stereocenters, including an additional stereocenter when compared to similar reactions of 1,1-diestercyclopropanes. Intrigued by the promise of developing a new process to access highly-functionalized building blocks in a single step, we became curious to identify conditions in which nitrocyclopropane **4** would react in a formal [3+3] cycloaddition reaction with a nitrone to generate highly functionalized oxazinane **5**.

The starting point for our studies on formal cycloaddition chemistry of nitrocyclopropane carboxylates was inspired by the recent discovery in our laboratory that ureas[7] are able to catalyze ring-opening reactions of nitrocyclopropane carboxylates (**4**) in the presence of strong nitrogen nucleophiles (Scheme 2).[6] While the urea-catalyzed conversion of **4a** to **7** did provide encouraging evidence to pursue our investigations, we were also aware this methodology was limited to strong nucleophiles. At the beginning of our studies we were uncertain if ureas would be effective catalysts to activate nitrocyclopropane carboxylates for reactions with less nucleophilic species, such as nitrones, imines and aldehydes, envisioned for participation in cycloaddition-type chemistry. Our work in this area was initiated with testing the reaction of **4a** and **8a** to give rise to **5a** (Scheme 2).

Scheme 2. Urea activation of nitrocyclopropane carboxylates.



Gratifyingly, optimization of the reaction conditions enabled the identification of a protocol affording access to **5a** in high yield as a 2:1 mixture of diastereomers from **4a** and **8a** in the

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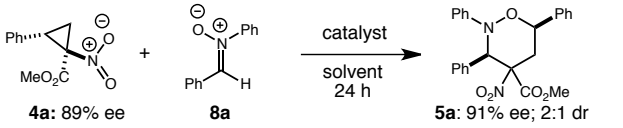
presence of 15 mol % urea catalyst **9a** (Table 1).[8] The success of the reaction was dependent on solvent and reaction temperature. Early testing with dichloromethane provided **5a** in low yield (35%, entry 1). Select higher boiling solvents, like toluene and chloroform, provided improvements in yield (91% and 79%, entries 2 and 3). The best set of reaction conditions were identified as toluene at 80 °C with a urea loading of 15 mol % giving rise to 91% of **5a** after 24 h (entry 5). Notably, difluoroboronate urea **9a** is a highly active dual HBD catalyst for the activation of nitrocyclopropane carboxylates, potentially a result of enhanced urea polarization due to internal coordination of the urea carbonyl to the strategically placed boron.[6,9,10,11] The difluoroboronate substituent is key as the related boronate urea pinacol ester (**9c**) afforded low yields of **5a** (27%). Conventional urea **9b** gave rise to good yields of product while conventional thiourea **9d** yielded just 9% of the desired oxazinane **5a**. Thiourea decomposition at elevated temperatures is proposed to be the reason for the poor performance of catalyst **9d**.[12]

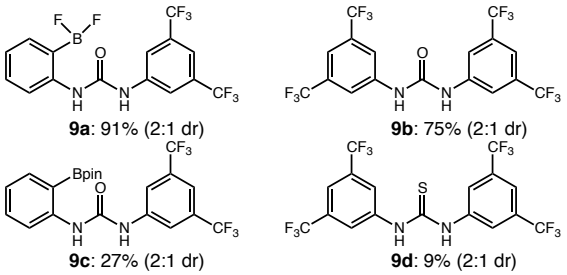
Table 1. Urea-catalyzed formal [3+3] cyloaddition optimization.



4a: 89% ee **8a** **5a**: 91% ee; 2:1 dr

entry[a]	mol % **9a**	solvent	temp. (°C)	**5a** yield[b]
1	20 mol %	dichloromethane	35	35
2	20 mol %	toluene	100	91
3	20 mol %	chloroform	50	79
4	20 mol %	acetonitrile	50	36
5	15 mol %	toluene	80	91
6	10 mol %	toluene	80	74

Select urea catalysts explored and yields under the optimized conditions in entry 5:



[a]Reactions performed using 1.5 equivalents of nitrone at a concentration of 0.5 M. Control experiments for entry 5 result in a 13% yield of **5a** in the absence of the catalyst. See Supporting Information for detailed experimental procedures. [b]Percent isolated yield as a 2:1 mixture of diastereomers.

Chirality transfer was observed from an enantioenriched nitrocyclopropane carboxylate. Specifically, the subjection of enantioenriched **4a** to the optimized reaction conditions gave rise to **5a** as a 2:1 mixture of enantioenriched (91% ee) diastereomers. The assignment of the relative stereochemistry of **5a'** and **5a''** was achieved through x-ray crystallographic analysis of crystals collected from a racemic mixture (Figure 1).[8] The major diastereomer **5a'** was found to have the two aromatic rings and the nitro group *cis* while **5a''** was epimeric at the carbon bearing the nitro group.

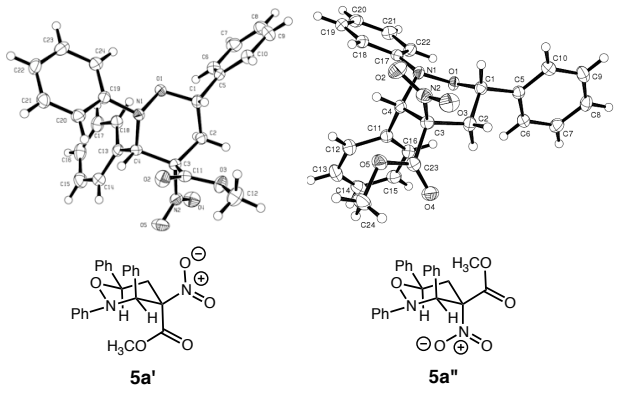
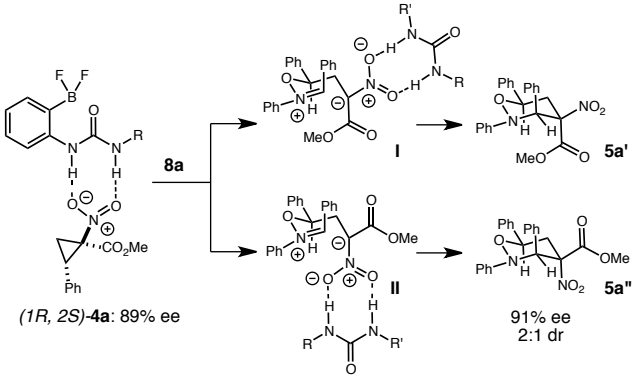


Figure 1. ORTEP representations of oxazinanes **5a'** and **5a''**. Drawn with 50% probability displacement ellipsoids.

The identification of the two diastereomers isolated in combination with the observed chirality transfer, led us to a plausible stepwise reaction pathway for the transformation (Scheme 3).[13] After initial activation of the nitrocyclopropane carboxylate with the urea catalyst, the nitrone undergoes nucleophilic addition with inversion of configuration giving rise to species **I** and **II**. Evidence for inversion of configuration was collected by establishing the absolute configuration of the major enantiomer of the oxazinane **5k**.[8] The stereochemical outcome of the reaction may result from the cyclization of **I** and **II** through chair-like transition states.

Scheme 3. Plausible stepwise reaction pathway.



A variety of substituted phenyl rings on the nitrocyclopropane were found to be well tolerated in the transformation giving rise to high yields of the corresponding oxazinane products (Table 2). Nitrocyclopropane carboxylates derived from *p*-chlorostyrene and *p*-bromostyrene afforded good yields of **5b** and **5c** (67% and 73%, respectively, entries 2 and 3). A near quantitative yield of oxazinane **5d** was isolated when a naphthalene-derived nitrocyclopropane was incorporated into the process (entry 4). Steric hindrance resulting from substitution in the *ortho* position of the phenyl did not prevent the bond-forming event, although in select cases lower yields were observed. For example, the nitrocyclopropanes derived from *o*-methylstyrene gave rise to a

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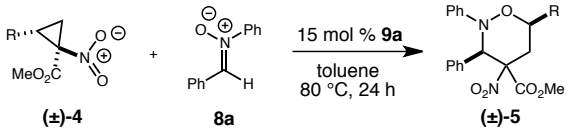
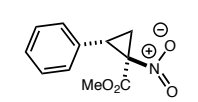
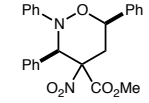
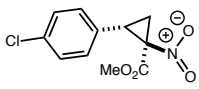
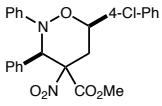
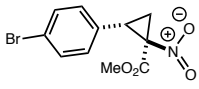
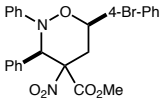
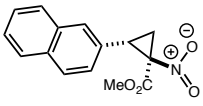
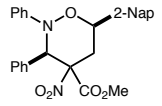
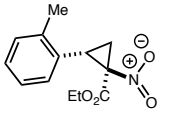
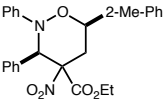
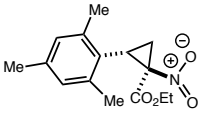
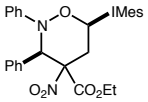
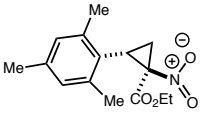
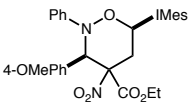
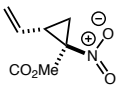
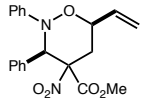
modest yield of **5e** (41%, entry 5). Even 2,4,6-trimethylphenyl substituted nitrocyclopropane **4f** participated in the cycloaddition reaction giving rise to **5f** in 47% yield (entry 6). A good yield of oxazinane **5g** was observed when the more nucleophilic nitrone derived from *p*-anisaldehyde was employed in the reaction (76%, entry 7). Alkenyl substitutents on the nitrocyclopropane did not prevent the reaction; however, lower yields were isolated. For example, formal [3+3] cycloaddition of **4g** and **8a** afforded **5h** in 25% yield (entry 8). The methodology is currently limited from the incorporation of electron-rich nitrocyclopropane carboxylates because these substrates are unstable and difficult to isolate as they easily rearrange to the isoxazoline *N*-oxide.[5e,14]

Table 2. Substrate scope of nitrocyclopropane carboxylates.

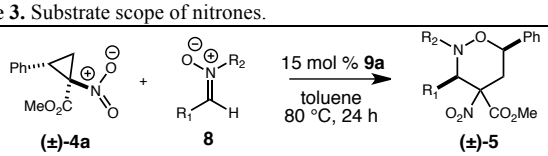


(±)-4 8a (±)-5

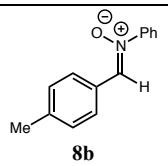
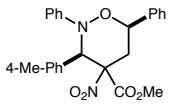
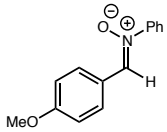
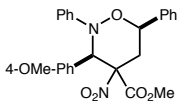
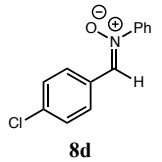
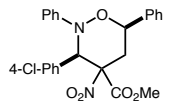
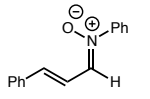
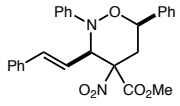
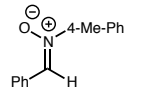
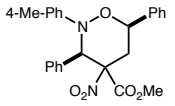
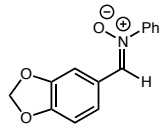
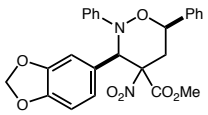
entry[a]	(±)-4	5	yield (%)[b]
1	 **4a**	 **5a**	91
2	 **4b**	 **5b**	67
3	 **4c**	 **5c**	73
4	 **4d**	 **5d**	99
5[c]	 **4e**	 **5e**	41
6[c]	 **4f**	 **5f**	47
7[c,d]	 **4f**	 **5g** (3:1 dr)	76
8	 **4g**	 **5h**	25

[a]Reactions performed using 1.5 equiv of nitrone at a concentration of 0.5 M in toluene at 80 °C for 24 h. See Supporting Information for detailed experimental procedures. [b]Isolated yield as a 2:1 mixture of diastereomers unless otherwise noted. [c]The ethyl ester derivative of the nitrocyclopropanes was used. [d]The nitrone derived from *p*-anisaldehyde was used.

Table 3. Substrate scope of nitrones.



(±)-4a 8 (±)-5

entry[a]	8	5	yield (%)[b]
1	 **8b**	 **5i** (3:1 dr)	99
2	 **8c**	 **5j** (4:1 dr)	91
3	 **8d**	 **5k**	87
4	 **8e**	 **5l**	93
5	 **8f**	 **5m** (3:1 dr)	56
6	 **8g**	 **5n**	47

[a]Reactions performed using 1.5 equiv of nitrone at a concentration of 0.5 M in toluene at 80 °C for 24 h. See Supporting Information for detailed experimental procedures. [b]Isolated yield as a 2:1 mixture of diastereomers unless otherwise noted.

The reaction of a variety of nitrones (**8**) with **4a** led to the formation of variously substituted oxazinanes **5i-n**, typically in good yield (Table 3). The nitrone derived from *p*-tolualdehyde, afforded a quantitative yield of oxazinane **5i** with 15 mol % of catalyst **9a** (entry 1). Oxazinane **5j** was isolated in excellent yield from the nitrone containing an electron-donating methoxy substituent (entry 2). An electron-withdrawing substituent on the nitrone derived from *p*-chlorobenzaldehyde was also well tolerated in the formal cycloaddition reaction, affording 87% of oxazinane **5k** (entry 3). The nitrone **8e** derived from

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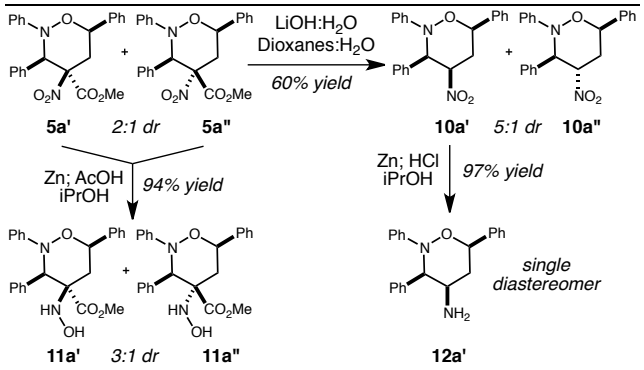
cinnamaldehyde also performed well affording 93% of oxazinane **5l** (entry 4). The *N*-*p*-tolyl substituted as well as a piperonal derived nitrones were tolerated in the reaction giving rise to oxazinanes **5m** and **5n** in 56% and 47% yields, respectively (entries 5 and 6). In its present state, the reaction precludes use of nitrones derived from aliphatic aldehydes and *N*-alkyl substituents. In our attempts to incorporate nitrones from both acetaldehyde and isobutyraldehyde into the cycloaddition reaction we observed only decomposition of nitrone and nitrocyclopropane: no cycloaddition adducts were observed.

The highly functionalized oxazinane products present opportunities as building blocks in the synthesis of more complex nitrogen-containing target molecules. Decarboxylation of a 2:1 mixture of **5a** was achieved in good yield in the presence of lithium hydroxide to give rise to **10a** as a 5:1 diastereomers.[8] Chirality transfer from **5a** was observed enabling the preparation of **10a'** and **10a''** as an enantioenriched (95% ee) mixture of diastereomers.[8] Subjecting **5a** (2:1 dr) to mild reduction conditions selectively reduced the nitro group providing hydroxylamine **11a** in excellent yield as a 3:1 mixture of diastereomers. Treating **10a'** with similar conditions selectively reduced the nitro group to the corresponding amine in 97% yield (Scheme 4).

Scheme 4. Transformations of oxazinane **5a**.



Conclusions

In summary, ureas operate as catalysts for the preparation of highly substituted oxazinanes produced from the reaction of nitrones with nitrocyclopropane carboxylates. This is the first report of nitrocyclopropane carboxylates participating in formal [3+3] cycloaddition reactions. The oxazinane products can be isolated in high enantiomeric access via chirality transfer of an enantioenriched nitrocyclopropane. The urea-activation of nitrocyclopropane carboxylates fits into a larger on-going research program in our laboratory focused on interesting reactivity patterns accessed via hydrogen bond donor catalysis.

Notes and references

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† Electronic Supplementary Information (ESI) available: detailed experimental procedures and characterization data are included in the supporting information. See DOI: 10.1039/b000000x/

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