Lewis Acid Mediated (3 + 2) Cycloadditions of Donor-Acceptor Cyclopropanes with Heterocumulenes

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Abstract
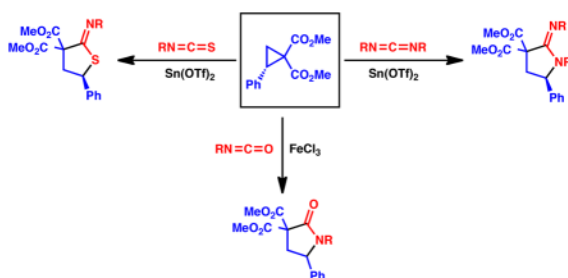
Isocyanates, isothiocyanates, and carbodiimides are effective substrates in (3 + 2) cycloadditions with donor–acceptor cyclopropanes for the synthesis of five-membered heterocycles. These reactions exhibit a broad substrate scope, high yields, and well-defined chemoselectivity. Discussed herein are the implications of Lewis acid choice on the stereochemical outcome and the reaction mechanism.

Donor-acceptor cyclopropanes are a useful class of building blocks for organic synthesis.[1] Indeed, (3 + 2) cycloadditions of donor-acceptor cyclopropanes have proven to be a powerful strategy for the direct synthesis of 5-membered carbo- and heterocycles, and such methodologies have been applied toward natural product syntheses.[2] Given our own interest in this field,[2e] we sought to examine heterocumulenes as potential dipolarophiles in stereoselective (3 + 2) cycloadditions to enable access to five-membered heterocycles. At the outset of this project, isocyanates[3a,b] and isothiocyanates[3c,d] had previously been shown to be reactive with alkoxy-substituted donor-acceptor cyclopropanes in only low to moderate yields, and stereocontrol of these reactions has relied on existing stereocenters remote to the site of reactivity. Based on the work of Johnson and others, we envisioned that the use of aryl substituents as the donor component would allow for an enantiospecific process by means of nucleophilic attack at the chiral benzylic center.[4,5] The products formed could serve as useful building blocks toward optically active natural products and pharmaceutically relevant heterocyclic compounds.

We began by examining the reactivity of allyl isothiocyanate with aryl-substituted cyclopropanes (**1**). We found that a stoichiometric amount of tin(II) triflate enabled full

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conversion of the starting materials to thioimidates (**2**, Scheme 1). Notably, the chemoselectivity of this reaction is complementary with respect to the previous studies in which alkoxy-substituted donor-acceptor cyclopropanes are converted to thioamides.[3,6]

We found that a variety of substituted aryl groups were tolerated in this reaction. Thioimidates with electron-rich aryl substituents (**2b**, **2c**, **2m**) were obtained with the shortest reaction times. Reactions leading to products with *ortho* or electron withdrawing arene substituents (**2d**, **2h**, **2i**) were the slowest. Cyclopropanes were not limited to those with aryl substituents; a vinyl group could also be used as an electron-donating substituent, offering 5-vinylthioimidate **2j** in quantitative yield. In addition, cyclohexyl isothiocyanate was also compatible under these conditions, providing thioimidates **2k** and **2l** in 91% and 99% yield respectively.

Under tin(II) triflate mediated conditions, we found aryl isothiocyanates to be poorly reactive; however, concurrent with our studies, Li and coworkers disclosed an iron(III) chloride mediated (3 + 2) cycloaddition of aryl isothiocyanates with donor-acceptor cyclopropanes to form thiolactams (*e.g.* **4**) rather than thioimidates (*e.g.* **5**, Scheme 2a).[7] We suspected that the products reported by Li may have been misassigned, and decided to investigate this further. Upon comparison of the ^{13}C NMR spectra of our products (*e.g.* **2a**–**2m**) to those reported by Li, we found similar shifts in the carbonyl range for both sets of spectra. In both cases, three signals are typically observed near 160 ppm: two correspond to the ester functionalities, and the third is consistent with a thioimidate; by contrast, a thioamide C=S ^{13}C NMR signal is expected at approximately 200 ppm.[8] Furthermore, our IR spectra consistently exhibited C=N stretches near 1650 cm^{-1}, and C=S signals were not observed.[9] Although no IR spectra were included in Li's report, we reacted cyclopropane **3** with phenyl isothiocyanate under similar conditions to those reported by Li and obtained a compound with NMR spectra matching those reported (Scheme 2b). The product IR spectrum contained a C=N stretch at 1638 cm^{-1} and no C=S peak was observed. Finally, we found that the 5-mesityl substituted thioimidate (**2h**, Scheme 1) was crystalline and its structure was confirmed by single crystal X-ray diffraction (Scheme 2c).[10a] Combined, the IR, ^{13}C NMR and X-ray crystallography data support our assignment of both the Li group's and our products as thioimidates and not thioamides.

We then turned our attention to carbodiimide dipolarophiles and we observed that under tin(II) triflate mediated reaction conditions, the use of diisopropyl carbodiimide resulted in complete conversion of cyclopropane **3** to amidine **6a** in only 80 minutes, and required only 1.1 equivalents of the dipolarophile.[10b] Electron rich 5-*para*-methoxyphenyl amidine **6b** was formed almost quantitatively in less than 10 minutes (Scheme 3). Primary amidines (**6e** and **6f**) could also be accessed using bis(trimethylsilyl)carbodiimide. Notably, (3 + 2) reactions were possible with cyclopropanes that are unreactive with isothiocyanates. For instance, a sterically congested 5,5-disubstituted amidine **6g** could be generated in 58% yield. In addition, while aryl isothiocyanates were poorly reactive in the presence of tin(II) triflate, use of diphenylcarbodiimide resulted in the formation of the corresponding amidine (**6h**) in 79% yield. Overall, the shorter reaction times indicate that carbodiimides are considerably more reactive dipolarophiles than comparable isothiocyanates in these reactions.

We also examined isocyanates in (3 + 2) cycloadditions, however, they suffered from poor reactivity under tin mediated reaction conditions. Microwave heating resulted in shorter reaction times but an array of side products. Fortunately, we were able to obtain lactams in moderate yields using iron(III) chloride (Scheme 4).[11] A variety of *N*-alkyl substituted lactams could be prepared, including isopropyl (**7a**), benzyl (**7b** and **7c**), allyl (**7d**), and *n*-butyl (**7e**). In addition, a secondary lactam (**7f**) could be synthesized using trimethylsilylisocyanate as a dipolarophile. In general, these isocyanate reactions were

considerably lower yielding than those with carbodiimides and isothiocyanates, nevertheless, they provide a meaningful entry into the important lactam series.

Finally, we sought to establish whether stereochemical information from the starting material is transferred to the product under the reaction conditions. We prepared enantioenriched cyclopropane (*S*)-**3** according to literature methods and subjected it to our standard reaction conditions (Scheme 5).[12] Although treatment of this substrate with an isocyanate in the presence of iron(III) chloride resulted in complete racemization of the benzylic stereocenter (Scheme 5a),[13] we observed transfer of chirality in the case of tin(II) triflate mediated (3 + 2) cycloadditions (Schemes 5b and 5c). Notably substrates that required longer reaction times resulted in increased erosion of optical activity.[14] We were able to confirm the absolute stereochemistry of the HBr salt of (*R*)-**6a** by single crystal X-ray diffraction, which revealed an inversion of configuration at the benzylic stereocenter through the course of the reaction (Figure 1).

We propose that the mechanism of the isothiocyanate and carbodiimide reactions with tin(II) triflate involves a stereospecific intimate-ion pair mechanism analogous to that invoked by Johnson and coworkers for (3 + 2) cycloadditions of aldehydes and donor-acceptor cyclopropanes developed in their laboratories (Scheme 6).[4c,d,16] Our observations including stereochemical inversion at the benzylic position, along with the greater reactivity of electron-rich dipolarophiles and of cyclopropanes with electron-rich aromatic substitutuents are all consistent with this mechanistic hypothesis.

In conclusion, we have disclosed an effective method for formation of pyrrolidinones, thioimidates and amidines from donor-acceptor cyclopropanes. Our data suggest that with comparable substituents, carbodiimides are more reactive than isothiocyanates, which are in turn more reactive than isocyanates. We have also disclosed a new mode of reactivity for isothiocyanates with donor-acceptor cyclopropanes. Furthermore, while iron(III) chloride caused racemization of the cyclopropane and formed racemic cycloadducts, tin(II) triflate mediated (3 + 2) reactions with isothiocyanates and carbodiimides were shown to proceed through an enantiospecific pathway, with inversion of configuration. Efforts to develop conditions catalytic in Lewis acid, as well as conditions for the enantioselective reactions of isocyanates with donor-acceptor cyclopropanes are currently underway. Applications of these methods for a range of purposes are also being investigated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

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5. Additional examples of stereoselective cycloadditions of donor-acceptor cyclopropanes can be found in the review articles in ref 1.

6. Chemoselectivity comparable to that observed in our studies has been shown in a palladium-catalyzed (3 + 2) cycloaddition of isothiocyanates with aziridines. Baeg J-O, Bensimon C, Alper H. J Am Chem Soc. 1995; 117:4700–4701.

7. Wang H, Yang W, Liu H, Wang W, Li H. Org Biomol Chem. 2012; 10:5032–5035. [PubMed: 22647999]

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9. A thioamide C=S IR stretch is expected as a strong band near 1140–1190 cm^{-1}.[8]

10. (a) The assignment of *Z*-stereochemistry for thioimidate **2h** was established via single crystal X-ray diffraction, and other thioimidates in Table 1 were assigned by analogy. (b) The assignment of *E*-stereochemistry for amidine **6a** is based on the crystal structure of its HBr salt (see below), and other amidines in Table 2 were assigned by analogy.

11. Two methods were used to setup reactions with dry iron(III) chloride: (a) iron(III) chloride stored in a nitrogen-filled glovebox and dispensed into a flame-dried flask or (b) iron(III) chloride stored on a benchtop was dispensed into an oven-dried vial, and used in conjunction with 4 Å molecular sieves. Although (b) is more operationally convenient, method (a) appears to result in shorter reaction times and higher yields.

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13. Treatment of cyclopropane (***R***)-**3** with iron(III) chloride, in the absence of a dipolarophile, results in racemization of the material.

14. Prolonged exposure of cyclopropane (***R***)-**3** to Sn(OTf)$_2$ results in racemization. See ref 4c.

15. Methyl and phenyl hydrogen atoms and the bromide counterion are omitted for clarity.

16. Related mechanistic investigations were originally performed on cyclopropane nitrone cycloadditions: Karadeolian A, Kerr MA. J Org Chem. 2007; 72:10251–10253. [PubMed: 17999536] Sapeta K, Kerr MA. J Org Chem. 2007; 72:8597–8599. [PubMed: 17919002] Wanapun D, Van Gorp KA, Mosey NJ, Kerr MA, Woo TK. Can J Chem. 2005; 83:1752–1767.
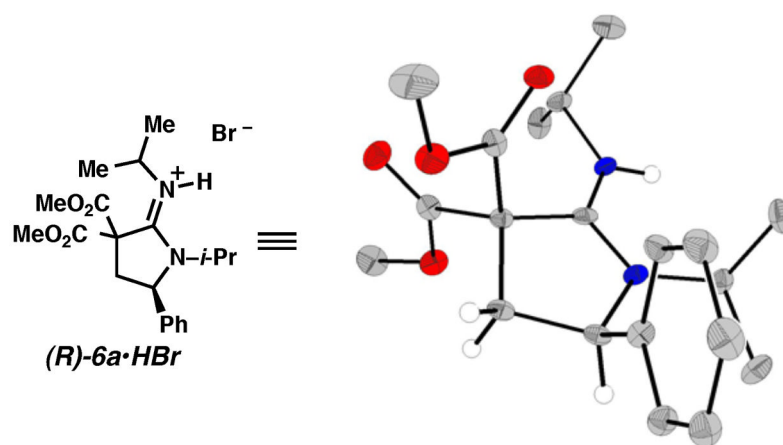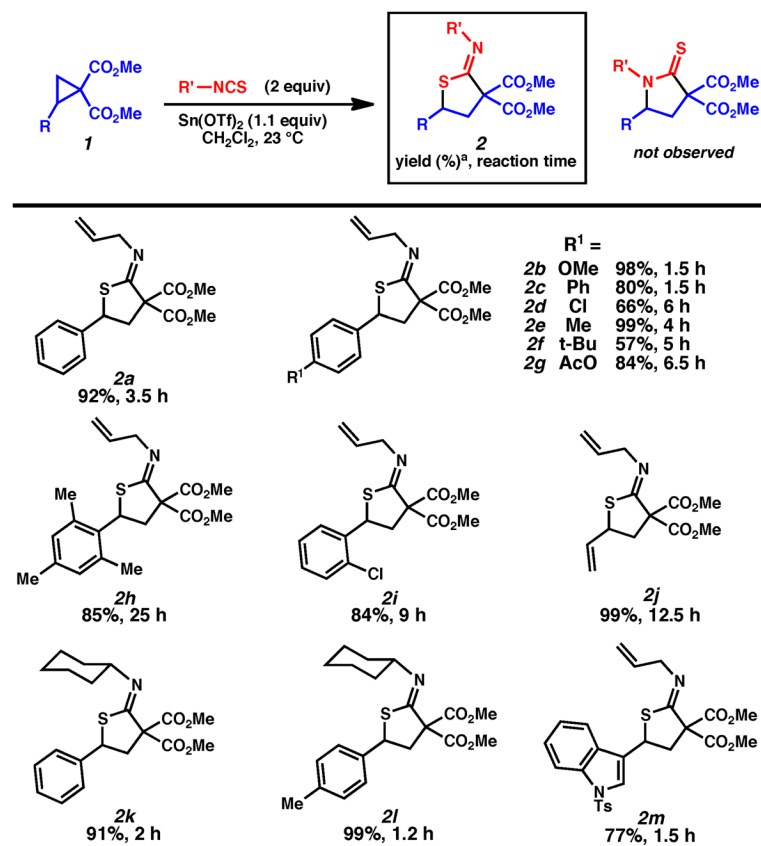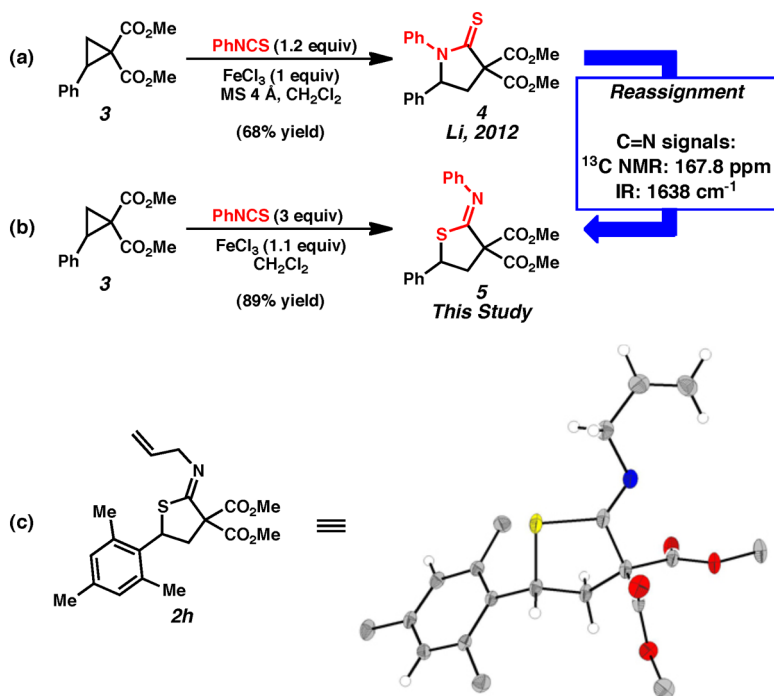
Figure 1.
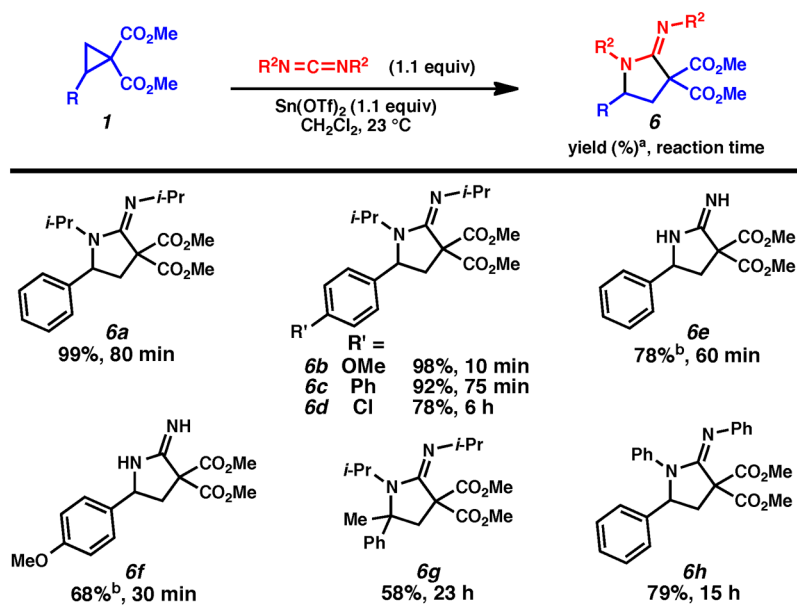Determination of Absolute Configuration.[15]

Scheme 1.
Substrate Scope of Isothiocyanate (3 + 2) Cycloaddition.
Conditions: cyclopropane **1** (0.4 mmol), isothiocyanate (0.8 mmol), $Sn(OTf)_2$ (0.44 mmol), CH_2Cl_2 (1.3 mL). [a] Isolated yields.
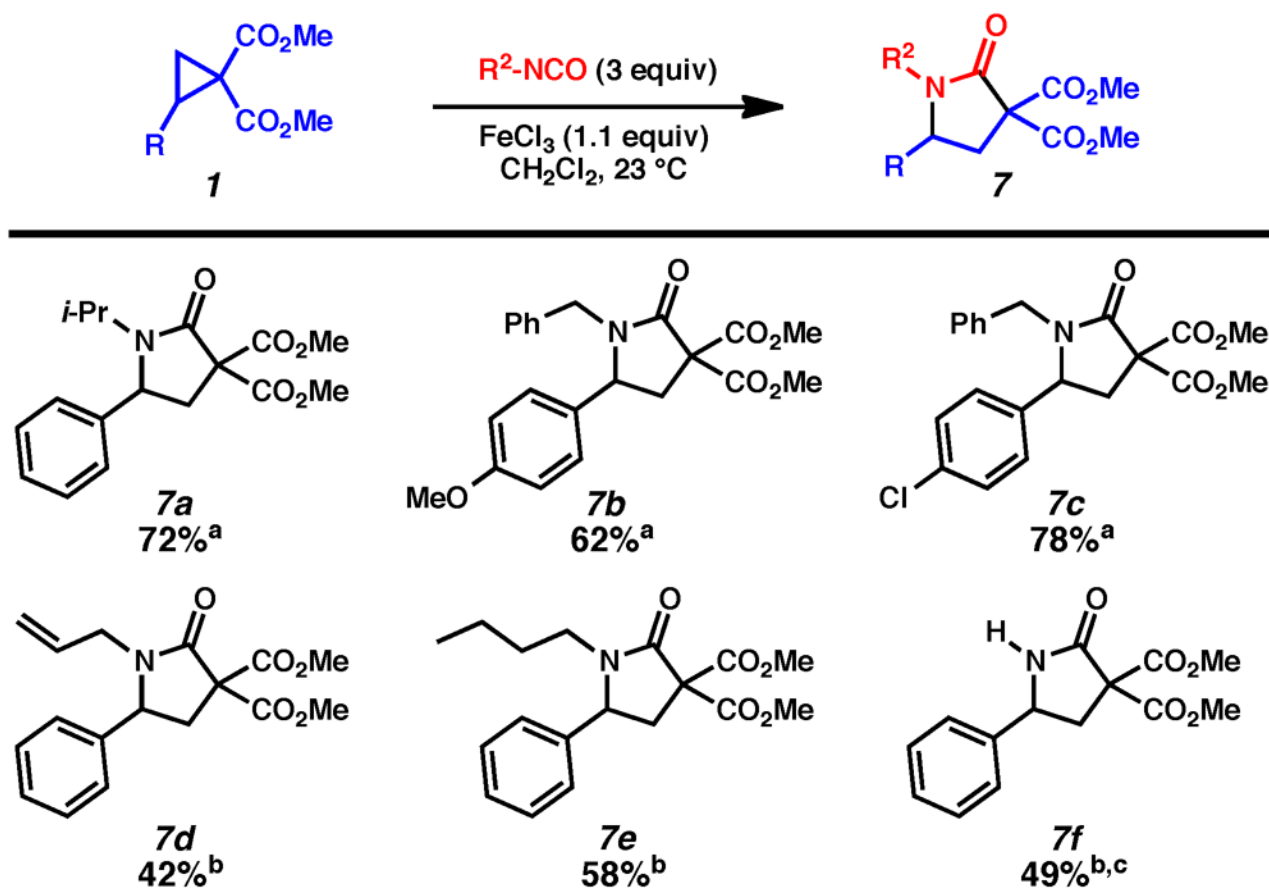
Scheme 2.
Structural Reassignment of Li's Arylisothiocyanate (3 + 2) Products.
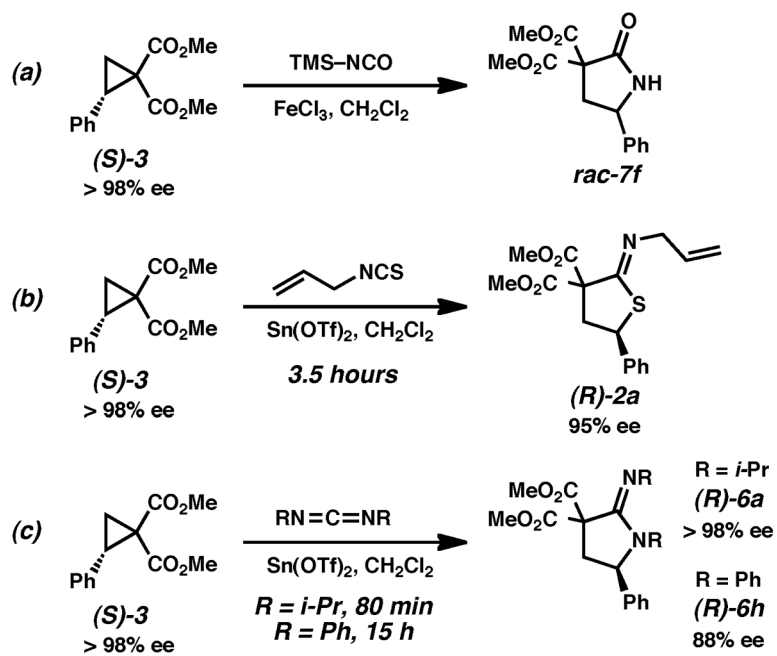
Scheme 3.
Substrate Scope of Carbodiimide (3 + 2) Cycloaddition.
Conditions: cyclopropane **1** (0.4 mmol), carbodiimide (0.44 equiv), tin(II) triflate (0.44 mmol), CH$_2$Cl$_2$ (1.3 mL). [a] Isolated yields. [b] Bis(trimethylsilyl)carbodiimide is used as the dipolarophile.
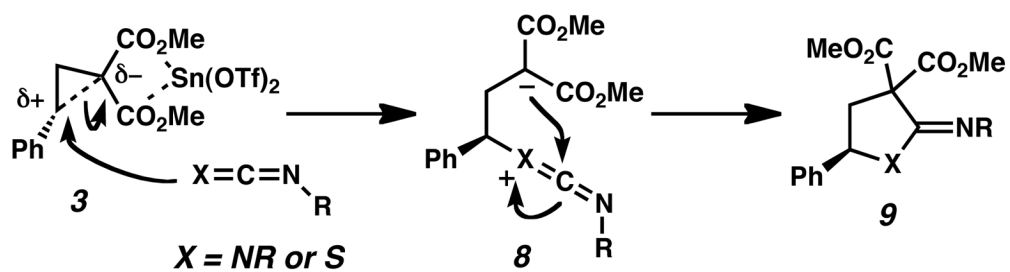
Scheme 4.
Isocyanate (3 + 2) Cycloaddition Substrate Scope.

Conditions: [a] Cyclopropane **1** (0.4 mmol), $FeCl_3$ (glovebox, 0.44 mmol), isocyanate (1.2 mmol), CH_2Cl_2 (1.3 mL) or [b] cyclopropane (0.4 mmol), $FeCl_3$ (benchtop, 0.44 mmol), isocyanate (1.2 mmol), MS 4 Å (50 mg), CH_2Cl_2 (1.3 mL). [c] Trimethylsilylisocyanate was used.

Scheme 6.
Proposed Mechanism for (3 + 2) Cycloaddition.