Heterocycles

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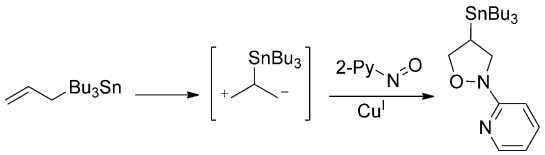
# Stereospecific Formal [3+2] Dipolar Cycloaddition of Cyclopropanes with Nitrosoarenes: An Approach to Isoxazolidines**

*Shyamal Chakrabarty, Indranil Chatterjee, Birgit Wibbeling, Constantin Gabriel Daniliuc, and Armido Studer**

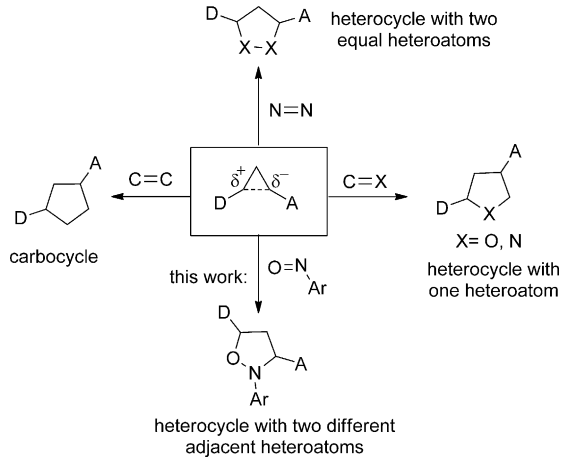
***Abstract:*** *The $MgBr_2$-catalyzed formal [3+2] cycloaddition of donor–acceptor activated cyclopropanes with nitrosoarenes offers a novel approach to various structurally diverse isoxazolidines. The reactions, which are experimentally easy to conduct, occur with complete stereospecificity and perfect control of regioselectivity. Product isoxazolidines can be readily transformed into α-amino lactones by reductive or decarboxylative N–O cleavage and subsequent lactonisation, and the N-aryl bond cleavage is also possible under oxidative conditions.*

Cycloaddition reactions that involve nitroso compounds as 2π components offer an efficient approach to numerous structurally diverse heterocycles, which are commonly used as intermediates for the synthesis of natural products.[1] Cleavage of the labile N–O bond of the corresponding cycloadducts affords synthetically useful amino alcohols. In the past, many research groups have investigated the [4+2] and [2+2] cycloaddition of nitroso compounds with various dienes and alkenes.[2,3] However, the use of nitroso compounds as coupling partners in [3+2] cycloadditions has not been well explored to date. Along these lines, we recently reported the Cu-catalyzed formal [3+2] cycloaddition reaction of allylstannes with 2-nitroso pyridine, in which allylstannes are used as formal 1,3 dipoles (Scheme 1).[4]




***Scheme 1.*** Formal [3+2] cycloaddition of 2-nitroso pyridine with allyl tributyl tin.

Inspired by this work and the continuation of the development of nitrosoarene chemistry,[2i,j,5] and considering the importance of isoxazolidines as valuable heterocycles, we decided to explore other potential 1,3 dipoles in the [3+2] cycloaddition with nitrosoarenes. Donor–acceptor (DA) cyclopropanes have gained much attention to the synthetic community because of their synthetic utility and ease of preparation.[6] In the presence of a Lewis acid (LA), DA-cyclopropanes undergo a ring opening to form a 1,3 dipole equivalent that has been used for [3+*n*] annulation reactions.[7–9] Work by Johnson, Kerr, and other research groups showed that cyclopropanes react with various 2π components, such as aldehydes, imines, nitriles, olefins, and other systems, to afford a variety of carbocycles and heterocycles (Scheme 2).[8,9]




***Scheme 2.*** [3+2] cycloaddition of cyclopropane with different 2π components.

Moreover, the [3+2] cycloaddition with nitrosylchloride was reported to afford isoxazolines.[10] However, the reaction of DA-cyclopropanes with nitrosoarenes is to our knowledge currently unknown.[11] Herein, we wish to present the formal [3+2] cycloaddition reaction of cyclopropanes with nitrosoarenes to give isoxazolidines.

We first investigated the reaction of readily available cyclopropane **1a** (1 equiv) with nitrosobenzene **2a** (1.5 equiv) to afford isoxazolidine **3a** (Table 1). The initial experiment was conducted with $Cu(OTf)_2$ (20 mol%) as LA in $CH_2Cl_2$ at room temperature. Pleasingly, the targeted isoxazolidine **3a** was formed, showing that the concept is working. The structure of **3a** was unambiguously assigned by X-ray analysis (see below). However, the yield of the isolated product was low (25%, Table 1, entry 1). Other Lewis acids that are frequently used for the activation of DA-cyclopropanes, such as $Sc(OTf)_3$, $Sn(OTf)_2$, and $InBr_3$ in either $CH_2Cl_2$ or

[*] S. Chakrabarty, Dr. I. Chatterjee, B. Wibbeling, Dr. C. G. Daniliuc, Prof. Dr. A. Studer
NRW Graduate School of Chemistry, Organisch-Chemisches Institut, Westfälische Wilhelms-Universität
Corrensstraße 40, 48149 Münster (Germany)
E-mail: studer@uni-muenster.de

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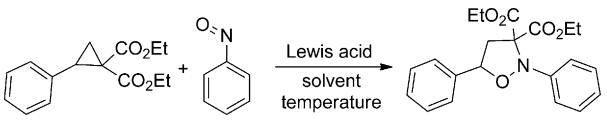
***Table 1:*** Reaction of **1a** with **2a** under different conditions.




**1a** **2a** (1.5 equiv) **3a**

| Entry | Lewis acid | LA [mol%] | *T* [°C] | Solvent | Yield [%] |
|---|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | 20 | 20 | $CH_2Cl_2$ | 25 |
| 2 | $Sc(OTf)_3$ | 20 | 20 | $CH_2Cl_2$ | 10 |
| 3 | $Sn(OTf)_2$ | 15 | 20 | $ClCH_2CH_2Cl$ | 20 |
| 4 | $InBr_3$ | 20 | 20 | $CH_2Cl_2$ | <10 |
| 5 | $FeCl_3$ | 20 | 20 | $ClCH_2CH_2Cl$ | 40 |
| 6 | $MgCl_2$ | 20 | 20 | $CH_2Cl_2$ | 40 |
| 7 | $MgI_2$ | 20 | 20 | $CH_2Cl_2$ | 40 |
| 8 | $MgI_2$ | 20 | 20 | $ClCH_2CH_2Cl$ | 60 |
| 9 | $MgI_2$ | 20 | 90 | $ClCH_2CH_2Cl$ | 20 |
| 10 | $MgBr_2$ | 20 | 20 | $CH_2Cl_2$ | 50 |
| 11 | $MgBr_2$ | 20 | 20 | $ClCH_2CH_2Cl$ | 70 |
| **12** | **$MgBr_2$** | **20** | **90** | **$ClCH_2CH_2Cl$** | **92** |
| 13 | $MgBr_2$ | 10 | 90 | $ClCH_2CH_2Cl$ | 50 |
| 14 | $MgBr_2$ | 20 | 20 | $CCl_4$ | 10 |
| 15 | $MgBr_2$ | 20 | 20 | THF | 40 |

The entry in bold marks optimized reaction conditions.

$ClCH_2CH_2Cl$ provided only 10%, 20%, and trace amounts of **3a**, respectively (Table 1, entries 2–4).

Disappointingly, Lewis acids such as $Mg(ClO_4)_2$, $AlCl_3$, $GaCl_3$, $Cu(SbF_6)_2$, and $Ni(ClO_4)_2{\cdot}6H_2O$ did not deliver any product (not shown). The use of $FeCl_3$ as a catalyst improved the yield to 40%, and a similar result was also obtained with $MgCl_2$ in $CH_2Cl_2$ (Table 1, entries 5 and 6). The product was isolated with the same yield in the $MgI_2$-catalyzed reaction (Table 1, entry 7). A further improvement was achieved with $MgI_2$ upon changing the solvent from $CH_2Cl_2$ to $ClCH_2CH_2Cl$ (60%; Table 1, entry 8). However, increasing the temperature to 90°C resulted in a significantly lower yield (20%; Table 1, entry 9). Switching the catalyst from $MgI_2$ to $MgBr_2$ in $CH_2Cl_2$ at room temperature led to **3a** in 50% yield, which was then further improved to 70% when $ClCH_2CH_2Cl$ was used as a solvent (Table 1, entries 10 and 11). Pleasingly, we found that the yield was further increased to 92% at an elevated temperature (90°C; Table 1, entry 12). Varying the solvent ($CCl_4$ and THF; Table 1, entries 14 and 15) as well as lowering the catalyst loading to 10 mol% (Table 1, entry 13) provided worse results.

Using the optimized reaction conditions (see Table 1, entry 12), the scope and limitations of the [3+2] cycloaddition were studied (Figure 1). Various ester groups at the DA-cyclopropanes were tested with **2a** as the reaction partner. These studies were conducted using racemic cyclopropane derivatives. As expected, the methyl ester gave **3b** in good yield (82%). A slightly lower yield was achieved with the allyl ester (see **3d**), and the bulkier *tert*-butoxycarbonyl cyclopropane gave the corresponding isoxazolidine **3c**, albeit in slightly lower yield (51%). Note that for this substrate the phenyl substituent at the cyclopropane moiety was also substituted by a *p*-tolyl group.

We then explored the compatibility of various donor groups of the DA-cyclopropanes. Aryl-substituted bismethoxycarbonyl cyclopropanes were studied first, investigating electronic effects exerted by substituents at the aryl group. Electron-rich *p*-acetoxy- and *p*-methoxy-substituted arylcyclopropanes gave isoxazolidines **3e** and **3f** in 70% and 75% yield, respectively. However, cycloadditions with substrates that bear aryl substituents with electron-withdrawing groups, such as *p*-cyano and *p*-trifluoromethyl, proceeded less efficiently and **3g** and **3h** were isolated in 45% and 50% yield, respectively. Steric effects seem to be less important, as the reaction with the *ortho*-tolyl cyclopropane gave **3i** in 70% yield. The naphthyl derivative worked well (**3j**) and the furanyl substituent was tolerated, but the product (**3k**) was obtained in a significantly lower yield. Notably, a cyclopropane derived from indane worked very well and **3l** was isolated in 82% yield as a single diastereoisomer.

We next explored the generality of the reaction by switching to non-aromatic donor substituents at the DA-cyclopropane moiety. The vinylcyclopropane derivative gave the isoxazolidine **3n** in high yield (82%); the corresponding

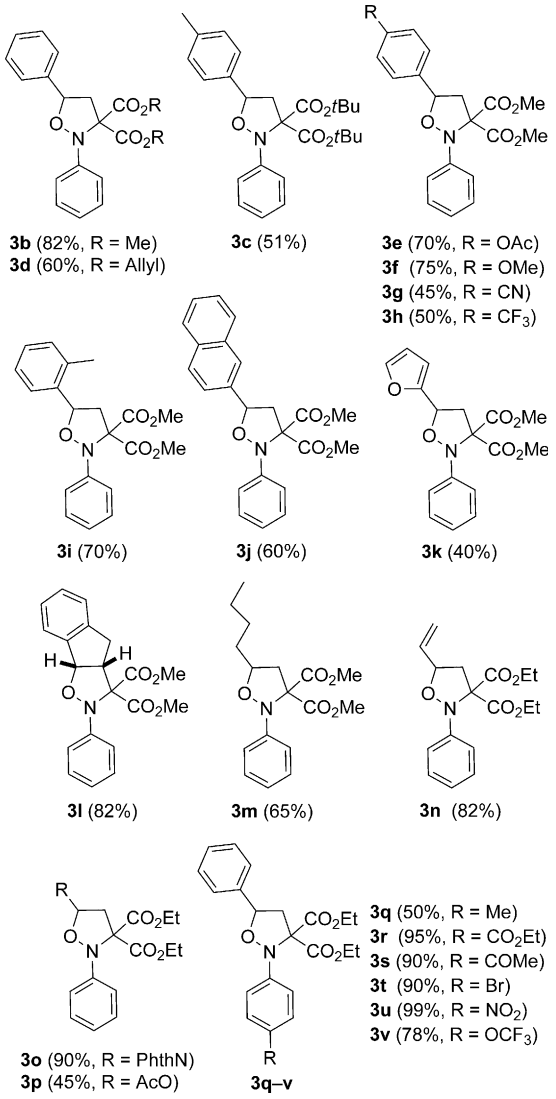


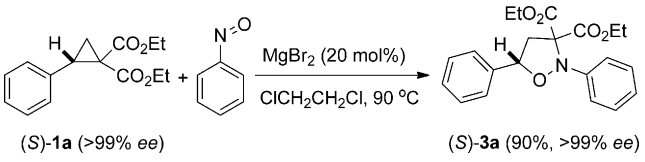

***Figure 1.*** Products of the cycloaddition of various DA-cyclopropanes with various nitrosoarenes.

isomeric 7-membered heterocycle (an 1,2-oxazepane derivative) resulting from reaction at the terminal vinyl position was not identified. Pleasingly, we found that the less activated *n*-butyl derivative gave **3m** in 65% yield, showing that an activating π-donor substituent is not mandatory for this transformation. Also the *N*-phthaloyl-substituted isoxazolidine **3o** could be obtained in very good yield, showing that the method is not restricted to C-substituted DA-cyclopropanes. The structure of **3o** was assigned by X-ray analysis (see the Supporting Information).[12] A lower yield was obtained with the acetoxy-substituted cyclopropane derivative (see **3p**).

The scope of the reaction was further tested with respect to the nitrosoarene component. We found that electron-deficient nitrosoarenes that bear either π or σ acceptors at the para position delivered the corresponding cycloadducts in excellent yield (**3r–u**). Notably, a quantitative yield was obtained using *p*-nitro nitrosobenzene (**3u**). The reaction worked with *p*-nitrosotoluene; however, **3q** was isolated in a lower yield, showing that cycloadditions work far more efficiently with electron-deficient nitrosoarenes. Indeed, with electron-rich congeners such as *o*-methoxy and *p*-methoxy nitrosobenzene (not shown in the figure), the reaction with **1a** under the optimized conditions did not work. However, the cycloaddition occurred smoothly with the *p*-trifluoromethoxy nitrosobenzene and **3v** was isolated in 78% yield.

We next explored the stereospecificity of the [3+2] cycloaddition using the enantiopure phenyl cyclopropane (*S*)-**1a**.[9d] Nitrosobenzene reacted with (*S*)-**1a** with complete stereospecificity, providing (*S*)-**3a** in 90% yield (Scheme 3,

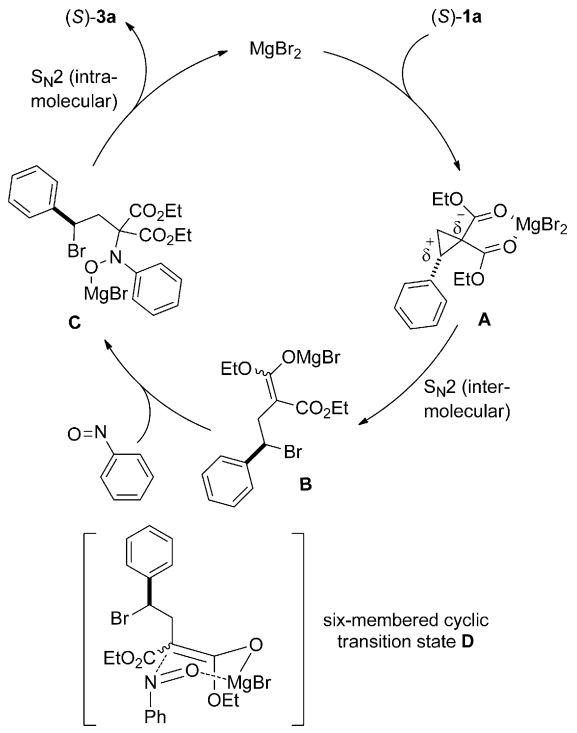



(*S*)-**1a** (>99% *ee*) (*S*)-**3a** (90%, >99% *ee*)

***Scheme 3.*** Testing stereospecificity of the cycloaddition of nitrosobenzene with enantiopure cyclopropane (*S*)-**1a**.

>99% *ee* as found by HPLC, see the Supporting Information). The absolute configuration was unambiguously determined by X-ray analysis.[12] Hence, cycloaddition occurred with net retention at the stereogenic center. This is in contrast to the [3+2] cycloaddition of DA-cyclopropanes with aldehydes, which occurs with excellent stereospecificity but with reversal of stereochemistry.[9d] As an additional example, we reacted enantiopure (*S*)-bismethylester with nitrosobenzene and obtained isoxazolidine (*S*)-**3b** in 70% yield with more than 99% *ee* (see the Supporting Information).

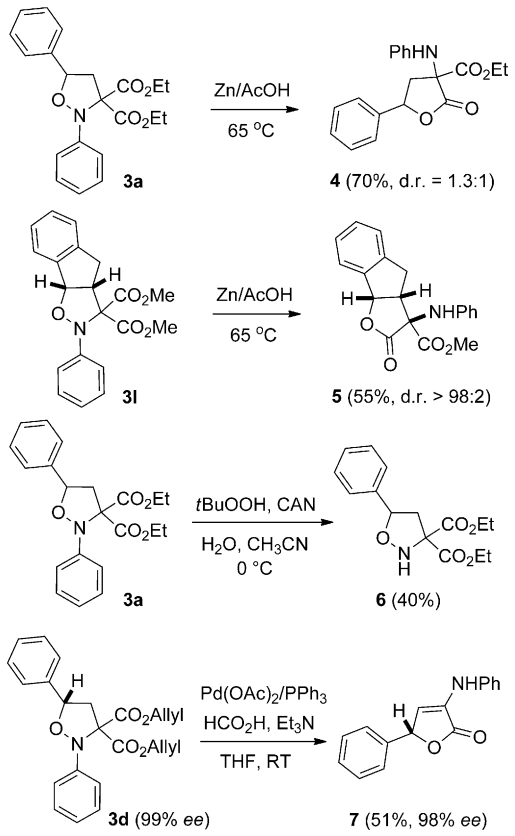
Our suggested mechanism for the cycloaddition reaction is depicted in Scheme 4. The catalyst $MgBr_2$ first interacts with DA-cyclopropane (*S*)-**1a**, providing the activated $MgBr_2$-complexed cyclopropane **A**. The Br anion then opens the cyclopropane ring at the benzylic position in an $S_N2$ reaction, generating enolate **B**, as previously suggested in the literature.[13] Enolate **B** then reacts with the nitrosobenzene, likely via the 6-membered transition state **D**, in which the O atom of the nitroso compound is bound to the oxophilic




***Scheme 4.*** Proposed catalytic cycle.

Mg atom of enolate **B**, to give magnesiated hydroxylamine **C**. The Mg–O interaction in **D** explains the observed regioselectivity of the enolate amination. Note that the regioisomeric isoxazolidine was not identified in the experiment. Intermediate **C** eventually cyclizes through an intramolecular $S_N2$ substitution to close the catalytic cycle, providing (*S*)-**3a** with net retention at the stereogenic center with respect to the starting cyclopropane (*S*)-**1a**. The experimentally observed higher reactivity of the electron-deficient nitrosoarenes can be explained by their intrinsic higher electrophilicity and hence more efficient reaction with enolate **B**. The lower Lewis basicity at the O atom of the electron-deficient nitrosoarenes obviously plays a less important role in the enolate amination.

To document the potential of the isoxazolidines **3** as building blocks in synthesis, we further investigated follow-up chemistry (Scheme 5). Reductive cleavage of the N–O bond was achieved by Zn/AcOH to provide the corresponding 1,3 amino alcohols, which spontaneously undergo cyclization to afford α-amino γ-butyrolactones. Subjecting **3a** to reductive cleavage gave **4** in 70% yield as a 1.3:1 diastereoisomeric mixture. However, complete diastereoselectivity was observed when **3l** was used for the reductive cleavage, and the corresponding α-amino lactone **5** was isolated in 55% yield. The relative configuration was assigned by NMR spectroscopy. The *N*-aryl group in **3a** was successfully cleaved under oxidative conditions[14] to provide **6** in 40% yield of isolated product. It is known that decarboxylation in isoxazolidine 5-carboxylic acids readily occurs by cleavage of the N–O bond.[15] We found that a regioisomer studied herein showed a similar reactivity. Hence, mild Pd-catalyzed deallylation[16] of allyl ester **3d** provided lactone **7** in 51% yield. Very little racemization of the product occurred under the applied




***Scheme 5.*** Follow-up reactions on isoxazolidines **3a**, **3d**, and **3l** (CAN = ceric ammonium nitrate).

conditions. The sequence comprises a deallylation with subsequent decarboxylation to give the corresponding imino alcohol, which in turn undergoes lactonization. Tautomerization of the imine eventually affords **7**.

In conclusion, we have reported an unprecedented formal [3+2] cycloaddition of nitrosoarenes with DA-cyclopropanes as formal 1,3 dipoles to give valuable isoxazolidines with high yields and complete regioselectivity. Further examination of the cycloaddition with an enantiomerically pure cyclopropane gave the product isoxazolidine with complete stereospecificity. The reaction occurred with retention of stereochemistry at the stereogenic center. We have also shown that these isoxazolidine scaffolds can be readily transformed into α-amino lactones by reductive or decarboxylative N–O bond cleavage and subsequent lactonisation, and N-aryl bond cleavage is also possible under oxidative conditions.

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[1] a) S. M. Weinreb, R. R. Staib, *Tetrahedron* **1982**, *38*, 3087; b) D. L. Boger, S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, San Diego, **1987**; c) M. D. Bednarski, J. P. Lyssikatos, *Compr. Org. Synth.* **1991**, *2*, 661; d) L. F. Tietze, G. Kettschau, *Top. Curr. Chem.* **1997**, *189*, 1.

[2] a) J. Streith, A. Defoin, *Synthesis* **1994**, 1107; b) H. Waldmann, *Synthesis* **1994**, 535; c) J. Streith, A. Defoin, *Synlett* **1996**, 189; d) F. P. Vogt, J. M. Miller, *Tetrahedron* **1998**, *54*, 1317; e) X. Ding, Y. Ukaji, S. Fujinami, K. Inomata, *Chem. Lett.* **2003**, *32*, 582; f) H. Yamamoto, N. Momiyama, *Chem. Commun.* **2005**, 3514; g) Y. Yamamoto, H. Yamamoto, *Eur. J. Org. Chem.* **2006**, 2031; h) H. Yamamoto, M. Kawasaki, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595; i) C. K. Jana, A. Studer, *Angew. Chem.* **2007**, *119*, 6662; *Angew. Chem. Int. Ed.* **2007**, *46*, 6542; j) C. K. Jana, S. Grimme, A. Studer, *Chem. Eur. J.* **2009**, *15*, 9078.

[3] a) M. Dochnahl, G. C. Fu, *Angew. Chem.* **2009**, *121*, 2427; *Angew. Chem. Int. Ed.* **2009**, *48*, 2391; b) I. Chatterjee, C. K. Jana, M. Steinmetz, S. Grimme, A. Studer, *Adv. Synth. Catal.* **2010**, *352*, 945; c) S. Chakrabarty, I. Chatterjee, L. Tebben, A. Studer, *Angew. Chem.* **2013**, *125*, 3041; *Angew. Chem. Int. Ed.* **2013**, *52*, 2968.

[4] I. Chatterjee, R. Fröhlich, A. Studer, *Angew. Chem.* **2011**, *123*, 11453; *Angew. Chem. Int. Ed.* **2011**, *50*, 11257.

[5] C. K. Jana, A. Studer, *Chem. Eur. J.* **2008**, *14*, 6326.

[6] For DA-cyclopropane reviews, see: a) H. U. Reissig, *Top. Curr. Chem.* **1988**, *144*, 73; b) H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **1989**, *89*, 165; c) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151; d) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321; e) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117; f) D. Agrawal, V. K. Yadav, *Chem. Commun.* **2008**, 6471; g) F. De Simone, J. Waser, *Synthesis* **2009**, 3353; h) M. Y. Mel'nikov, E. M. Budynina, O. A. Ivanova, I. V. Trushkov, *Mendeleev Commun.* **2011**, *21*, 293; i) A. K. Kumar, *Int. J. Pharm. Pharm. Sci.* **2013**, *5*, 467; j) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804.

[7] [3+1+1] cycloaddition: a) V. S. Korotkov, O. V. Larionov, A. de Meijere, *Synthesis* **2006**, 3542. [3+3] cycloaddition: b) I. S. Young, M. A. Kerr, *Angew. Chem.* **2003**, *115*, 3131; *Angew. Chem. Int. Ed.* **2003**, *42*, 3023; c) I. S. Young, M. A. Kerr, *Org. Lett.* **2004**, *6*, 139; d) M. D. Ganton, M. A. Kerr, *J. Org. Chem.* **2004**, *69*, 8554; e) I. S. Young, J. L. Williams, M. A. Kerr, *Org. Lett.* **2005**, *7*, 953; f) F. Cardona, A. Goti, *Angew. Chem.* **2005**, *117*, 8042; *Angew. Chem. Int. Ed.* **2005**, *44*, 7832; g) Z. Ma, C. P. Jasperse, M. P. Sibi, *J. Am. Chem. Soc.* **2005**, *127*, 5764; h) Y. B. Kang, X. L. Sun, Y. Tang, *Angew. Chem.* **2007**, *119*, 3992; *Angew. Chem. Int. Ed.* **2007**, *46*, 3918; i) K. Sapeta, M. A. Kerr, *J. Org. Chem.* **2007**, *72*, 8597; j) C. Perreault, S. R. Goudreau, L. E. Zimmer, A. B. Charette, *Org. Lett.* **2008**, *10*, 689; k) T. P. Lebold, A. B. Leduc, M. A. Kerr, *Org. Lett.* **2009**, *11*, 3770; l) L. Wu, M. Shi, *Chem. Eur. J.* **2010**, *16*, 1149; m) T. P. Lebold, M. A. Kerr, *Pure Appl. Chem.* **2010**, *82*, 1797; n) O. A. Ivanova, E. M. Budynina, A. O. Chargarovskiy, I. V. Trushkov, M. Ya. Melnikov, *J. Org. Chem.* **2011**, *76*, 8852; o) H. B. Yang, M. Shi, *Org. Biomol. Chem.* **2012**, *10*, 8236; p) E. O. Gorbacheva, A. A. Tabolin, R. A. Novikov, Y. A. Khomutova, Y. V. Nelyubina, Y. V. Tomilov, S. L. Ioffe, *Org. Lett.* **2013**, *15*, 350; q) A. M. Hardman, S. S. So, A. E. Mattson, *Org. Biomol. Chem.* **2013**, *11*, 5793. [4+3] cycloaddition: r) O. A. Ivanova, E. M. Budynina, Y. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Angew. Chem.* **2008**, *120*, 1123; *Angew. Chem. Int. Ed.* **2008**, *47*, 1107; s) Y. Bai, J. Fang, J. Ren, Z. Wang, *Chem. Eur. J.* **2009**, *15*, 8975; t) A. O. Chagarovskiy, E. M. Budynina, O. A. Ivanova, Y. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Tetrahedron* **2009**, *65*, 5385; u) O. A. Ivanova, E. M. Budynina, A. O. Chagarovskiy, A. E. Kaplun, I. V. Trushkov, M. Y. Melnikova, *Adv. Synth. Catal.* **2011**, *353*, 1125. [8+3] cycloaddition: v) R. Tejero, A. Ponce, J. Adrio, J. C. Carretero, *Chem. Commun.* **2013**, *49*, 10406.

[8] For the formation of carbocycles through [3+2] cycloaddition with cyclopropanes, see: a) R. B. Beal, M. A. Dombroski, B. B.

Snider, *J. Org. Chem.* **1986**, *51*, 4391; b) K. Miura, K. Fugami, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1988**, *29*, 5135; c) D. A. Singleton, K. M. Church, M. J. Lucero, *Tetrahedron Lett.* **1990**, *31*, 5551; d) K. Saigo, S. Shimada, T. Shibasaki, M. Hasegawa, *Chem. Lett.* **1990**, 1093; e) M. Komatsu, I. Suehiro, Y. Horiguchi, I. Kuwajima, *Synlett* **1991**, 771; f) Y. Horiguchi, I. Suehiro, A. Sasaki, I. Kuwajima, *Tetrahedron Lett.* **1993**, *34*, 6077; g) Y. Sugita, K. Kawai, H. Hosoya, I. Yokoe, *Heterocycles* **1999**, *51*, 2029; h) Y. Sugita, S. Yamadoi, H. Hosoya, I. Yokoe, *Chem. Pharm. Bull.* **2001**, *49*, 657; i) V. K. Yadav, V. Sriramurthy, *Angew. Chem.* **2004**, *116*, 2723; *Angew. Chem. Int. Ed.* **2004**, *43*, 2669; j) K. Takasu, S. Nagao, M. Ihara, *Adv. Synth. Catal.* **2006**, *348*, 2376; k) J. Fang, J. Ren, Z. Wang, *Tetrahedron Lett.* **2008**, *49*, 6659; l) J. P. Qu, C. Deng, J. Zhou, X.-L. Sun, Y. Tang, *J. Org. Chem.* **2009**, *74*, 7684; m) B. M. Trost, P. J. Morris, *Angew. Chem.* **2011**, *123*, 6291; *Angew. Chem. Int. Ed.* **2011**, *50*, 6167; n) J. P. Qu, Y. Liang, H. Xu, X. L. Sun, Z. X. Yu, Y. Tang, *Chem. Eur. J.* **2012**, *18*, 2196; o) Y. A. Volkova, E. M. Budynina, A. E. Kaplun, O. A. Ivanova, A. O. Chagarovskiy, D. A. Skvortsov, V. B. Rybakov, I. V. Trushkov, M. Y. Melnikov, *Chem. Eur. J.* **2013**, *19*, 6586; p) H. Xiong, H. Xu, S. Liao, Z. Xie, Y. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 7851; q) W. Zhu, J. Fang, Y. Liu, J. Ren, Z. Wang, *Angew. Chem.* **2013**, *125*, 2086; *Angew. Chem. Int. Ed.* **2013**, *52*, 2032.

[9] For selected examples of the formation of heterocycles through [3+2] cycloaddition with cyclopropanes, see: With C=O: a) S. D. R. Christie, R. J. Davoile, M. R. J. Elsegood, R. Fryatt, R. C. F. Jones, G. Pritchard, *Chem. Commun.* **2004**, 2474; b) K. Fuchibe, Y. Aoki, T. Akiyama, *Chem. Lett.* **2005**, *34*, 538; c) P. D. Pohlhaus, J. S. Johnson, *J. Org. Chem.* **2005**, *70*, 1057; d) P. D. Pohlhaus, J. S. Johnson, *J. Am. Chem. Soc.* **2005**, *127*, 16014; e) A. M. Bernard, A. Frongia, P. P. Piras, F. Secci, M. Spiga, *Org. Lett.* **2005**, *7*, 4565; f) A. Gupta, V. K. Yadav, *Tetrahedron Lett.* **2006**, *47*, 8043; g) A. T. Parsons, M. J. Campbell, J. S. Johnson, *Org. Lett.* **2008**, *10*, 2541; h) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, *130*, 8642; i) A. T. Parsons, J. S. Johnson, *J. Am. Chem. Soc.* **2009**, *131*, 3122; j) S. D. R. Christie, J. Cummins, M. R. J. Elsegood, G. Dawson, *Synlett* **2009**, 257; k) M. J. Campbell, J. S. Johnson, A. T. Parsons, P. D. Pohlhaus, S. D. Sanders, *J. Org. Chem.* **2010**, *75*, 6317; l) T. F. Schneider, D. B. Werz, *Org. Lett.* **2011**, *13*, 1848; m) A. G. Smith, M. C. Slade, J. S. Johnson, *Org. Lett.* **2011**, *13*, 1996; n) G. Yang, Y. Shen, K. Li, Y. Sun, Y. Hua, *J. Org. Chem.* **2011**, *76*, 229; o) S. Xing, Y. Li, Z. Li, C. Liu, J. Ren, Z. Wang, *Angew. Chem.* **2011**, *123*, 12813; *Angew. Chem. Int. Ed.* **2011**, *50*, 12605; p) F. Benfatti, F. de Nanteuil, J. Waser, *Org. Lett.* **2012**, *14*, 386; q) F. Benfatti, F. de Nanteuil, J. Waser, *Chem. Eur. J.* **2012**, *18*, 4844; r) S. Haubenreisser, P. Hensenne, S. Schroder, M. Niggemann, *Org. Lett.* **2013**, *15*, 2262; s) Y. Miyake, S. Endo, T. Moriyama, K. Sakata, Y. Nishibayashi, *Angew. Chem.* **2013**, *125*, 1802; *Angew. Chem. Int. Ed.* **2013**, *52*, 1758; t) X. Ma, J. Zhang, Q. Tang, J. Ke, W. Zoub, H. Shao, *Chem. Commun.* **2014**, *50*, 3505. With C=N and C≡N: u) M. Yu, B. L. Pagenkopf, *Org. Lett.* **2001**, *3*, 2563; v) M. Yu, B. L. Pagenkopf, *Org. Lett.* **2003**, *5*, 5099; w) M. Yu, B. L. Pagenkopf, *J. Am. Chem. Soc.* **2003**, *125*, 8122; x) C. A. Carson, M. A. Kerr, *J. Org. Chem.* **2005**, *70*, 8242; y) Y. B. Kang, Y. Tang, X. L. Sun, *Org. Biomol. Chem.* **2006**, *4*, 299; z) N. A. Morra, C. L. Morales, B. Bajtos, X. Wang, H. Jang, J. Wang, M. Yu, B. L. Pagenkopf, *Adv. Synth. Catal.* **2006**, *348*, 2385; aa) S. K. Jackson, A. Karadeolian, A. B. Driega, M. A. Kerr, *J. Am. Chem. Soc.* **2008**, *130*, 4196; ab) A. T. Parsons, A. G. Smith, A. J. Neel, J. S. Johnson, *J. Am. Chem. Soc.* **2010**, *132*, 9688; ac) G. Sathishkannan, K. Srinivasan, *Org. Lett.* **2011**, *13*, 6002; ad) R. Tombe, T. Kurahashi, S. Matsubara, *Org. Lett.* **2013**, *15*, 1791. With N = C=O and N=C=S: ae) K. Yamamoto, T. Ishida, J. Tsuji, *Chem. Lett.* **1987**, 1157; af) V. S. Korotkov, O. V. Larionov, A. de Meijere, *Synthesis* **2006**, 3542; ag) A. F. G. Goldberg, N. R. O. Connor, R. A. Craig, B. M. Stoltz, *Org. Lett.* **2012**, *14*, 5314; ah) H. Wang, W. Yang, H. Liu, W. Wang, H. Li, *Org. Biomol. Chem.* **2012**, *10*, 5032; ai) Y. Sun, G. Yang, Z. Chai, X. Mu, J. Chai, *Org. Biomol. Chem.* **2013**, *11*, 7859. With N=N: aj) V. S. Korotkov, O. V. Larionov, A. Hofmeister, J. Magull, A. de Meijere, *J. Org. Chem.* **2007**, *72*, 7504.

[10] a) F. Cermola, L. Di Gioia, M. L. Graziano, M. R. Iesce, *J. Chem. Res.* **2005**, *10*, 677; b) K. Mizuno, N. Ichinose, T. Tamai, Y. Otsuji, *J. Org. Chem.* **1992**, *57*, 4669.

[11] The [4+2] cycloaddition of DA-cyclobutanes with nitrosoarenes was very recently disclosed: N. Vemula, A. C. Stevens, T. B. Schon, B. L. Pagenkopf, *Chem. Commun.* **2014**, *50*, 1668.

[12] CCDC 981252 ((*S*)-**3a**) and 989899 (**3o**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] a) P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel, E. M. Carreira, *Angew. Chem.* **1999**, *111*, 3379; *Angew. Chem. Int. Ed.* **1999**, *38*, 3186; b) W. Han, M. Lautens, *J. Am. Chem. Soc.* **2002**, *124*, 6312; c) M. E. Scott, W. Han, M. Lautens, *Org. Lett.* **2004**, *6*, 3309.

[14] K. Krohn, J. Vitz, *J. Prakt. Chem.* **2000**, *342*, 825.

[15] S. Yu, H. Ishida, M. E. Juarez-Garcia, J. W. Bode, *Chem. Sci.* **2010**, *1*, 637.

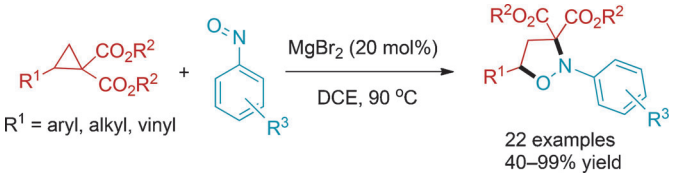
[16] J. Tsuji, M. Nisar, I. Shimizu, *J. Org. Chem.* **1985**, *50*, 3416.

# Communications

## Heterocycles

S. Chakrabarty, I. Chatterjee,
B. Wibbeling, C. G. Daniliuc,
A. Studer* _____ ■■■■–■■■■




Stereospecific Formal [3+2] Dipolar Cycloaddition of Cyclopropanes with Nitrosoarenes: An Approach to Isoxazolidines

**Stereospecific and regioselective**: The $MgBr_2$-catalyzed formal [3+2] cycloaddition of donor–acceptor-activated cyclopropanes with nitrosoarenes offers a novel approach to structurally diverse isoxazolidines. The reactions, which are experimentally easy to conduct, occur with complete stereospecificity and perfect control of regioselectivity.