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Synthesis of Tetrahydro-1,2-oxazines and Pyrrolidines via Cycloadditions of Donor-Acceptor Cyclobutanes and Nitrosoarenes

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FULL PAPER

Synthesis of Tetrahydro-1,2-oxazines and Pyrrolidines *via* Cycloadditions of Donor-Acceptor Cyclobutanes and Nitrosoarenes

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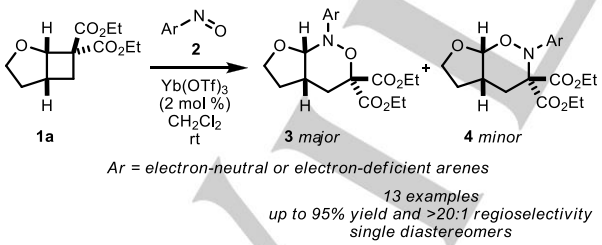
During efforts to expand the scope of Lewis acid catalyzed [4+2] cycloaddition between donor-acceptor cyclobutanes and nitrosoarenes, an unexpected formation of pyrrolidine products was discovered when 50 mol % of MgI_2 was used as a Lewis acid. It was also observed that the electronics of the nitrosoarene and judicious selection of the Lewis acid catalyst have a profound effect on the regioselectivity of the reaction.

Introduction

Cycloaddition chemistry is an excellent method to construct highly complex structures from simple starting materials. [1] In particular, 1,3-dipolar cycloadditions using a variety of dipolarophiles have been extensively studied and well documented. [2] Interestingly, generation of 1,4-dipolar intermediates by exploitation of ring strain in carbocycles is a clever approach in modern organic synthesis.[3] In this regard, reactivity of donor-acceptor (DA) cyclobutanes has recently garnered significant attention, and a number of reactive partners have been found to undergo cycloadditions with DA cyclobutanes[4] and cyclobutanones.[5]

Recently, we reported the first examples of [4+2] cycloadditions between DA cyclobutanes and nitrosoarenes (Scheme 1).[6] The reactions proceed well with electron-neutral and electron-deficient nitrosoarenes to form tetrahydro-1,2-oxazines with excellent regioselectivity; however, no reaction was observed with electron-rich nitrosoarenes under the reported conditions.



Scheme 1. Previous work with DA cyclobutanes and nitrosoarenes.

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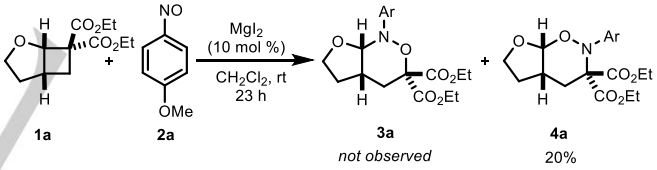
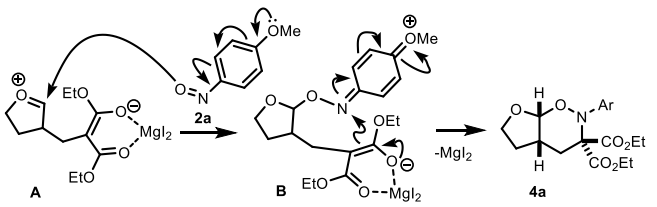
Results & Discussion

In an attempt to extend the reaction scope to include electron-rich substrates, we employed 1-methoxy-4-nitrosobenzene **2a** as a model substrate. After a thorough screening of Lewis acids under a variety of conditions, MgI_2 was found to be functional for this reaction, however producing low yields of product (Scheme 2).[7] Interestingly the regioisomer isolated under these conditions was acetal **4a** and not the aminal **3a** as expected (compare schemes 1 and 2).



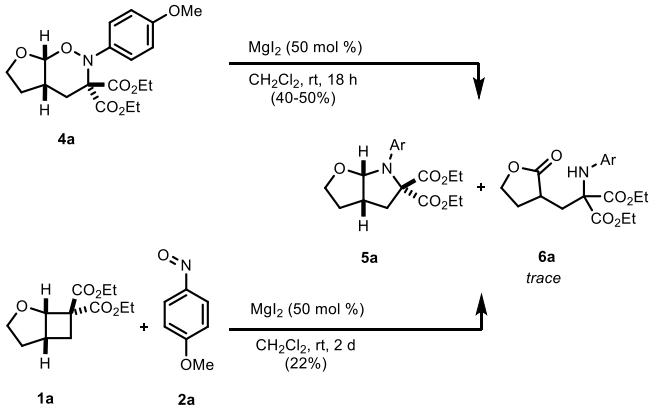
Scheme 2. Reaction of DA cyclobutane **1a** with **2a** under MgI_2 catalysis.



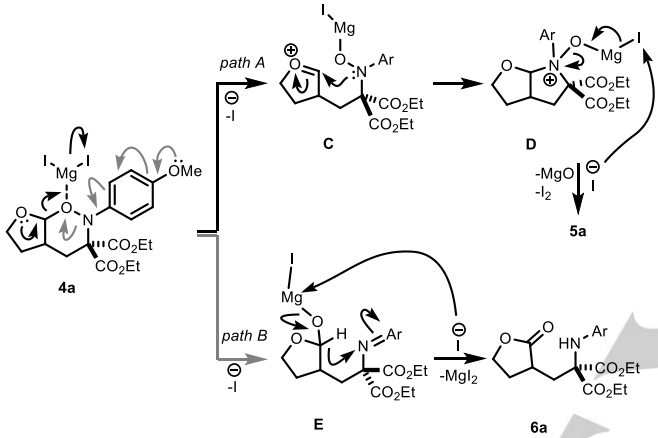
Scheme 3. Proposed mechanism for the formation of **4a**.

This reversal in regioselectivity could be rationalized by the proposed mechanism (Scheme 3). The electron donating methoxy group on the aryl ring enhances the nucleophilicity of the nitroso oxygen, causing the oxygen to act as the nucleophile instead of nitrogen. Nucleophilic addition of the oxygen of the nitroso on the oxocarbenium ion **A** followed by cyclization *via* intermediate **B** would yield **4a.**

During the optimization of this reaction an interesting observation was made.[8] When the reaction was left to stir for 2 days at room temperature or when **4a** was treated with 50 mol % MgI_2 at room temperature overnight, pyrrolidine **5a** was formed with trace amounts of lactone **6a** (Scheme 4).



Scheme 4. Formation of pyrrolidine **5a**.



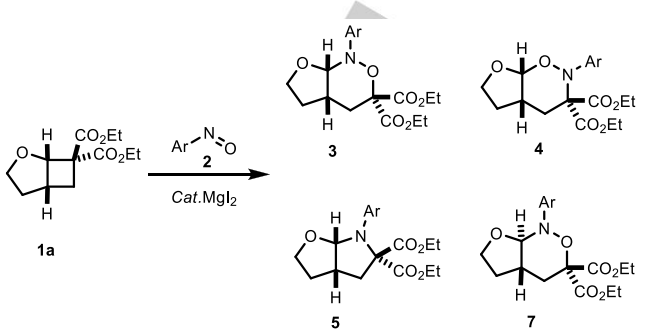
Scheme 5. Proposed mechanism for the formation of **5a** and **6a**.

A postulated mechanism to explain this unique redox transformation is depicted in Scheme 5. Coordination of MgI_2 to the oxygen of tetrahydro-1,2-oxazine **4a** polarizes both the C-O and N-O bonds indicated. Cleavage of the C-O bond (*Path A*) generates an oxocarbenium ion **C**, which then undergoes nucleophilic attack by the pendant nitrogen, forming pyrrolidinium intermediate **D**. Finally, the initially displaced iodide reacts with the Mg side chain on the nitrogen, resulting in N-O bond reduction, and concomitantly producing I_2, MgO, and pyrrolidine **5a**. Lactone **6a** can be formed via N-O bond cleavage of **4a** (*Path B*) leading to intermediate **E** followed by internal hydride migration.

Based on the proposed mechanism it is clear that stoichiometric MgI_2 was necessary for complete conversion of **4a** to **5a**, but disappointingly the yields were further lowered with considerable decomposition of cyclobutane under such conditions.

With these interesting results we proceeded to investigate if other nitrosoarenes would follow a similar reaction manifold under MgI_2 promoted conditions. Thus, the reaction of electron-rich nitrosoarene **2b** (which did not react under 10 or 20 mol % MgI_2 loadings) directly yielded pyrrolidine **5b** (entry 2, Table 1), and isolation of the anticipated tetrahydro-1,2-oxazine **4b** was not possible.

Table 1. Scope of the MgI_2 promoted cycloaddition.



Entry	Nitrosoarene	Product	MgI_2 (mol %)	Yield (%)[b]
1	**2a** Ar = 4-C_6H_4OMe	**5a**	50	26
2	**2b** Ar = 4-$C_6H_4N(CH_3)_2$	**5b**	50	22
3	**2c** Ar = 4-C_6H_4CN	**4c, 7c** (2:1)[a]	10	35
4	**2d** Ar = C_6H_5	**3d**	10	56
5	**2e** Ar = 2-pyridine	**4e**	50	28
6	**2f** Ar = *N*-BOC-5-nitrosoindole	**4f**	10	19

[a] Ratio of **4**:**7** of isolated overall yields. [b] Isolated yields.

Interestingly, the substrate **2c**, which afforded aminal **3c** as the major product under $Yb(OTf)_3$ catalysis (Scheme 1), resulted in reversal of regioselectivity albeit in low yield (entry 3, Table 1). Also, the isolated aminal **7c** was the *trans*-diastereomer (confirmed by single-crystal X-ray diffraction),[9] rather than *cis* (**3c**, Scheme 1).[10] Nitrosobenzene **2d**, which is electronically sandwiched between **2a** and **2c**, produced aminal **3d** as the exclusive product. The hetero-nitrosoarenes 2-nitrosopyridine **2e** and BOC protected 5-nitrosoindole **2f**, which did not react under $Yb(OTf)_3$ conditions, provided exclusive acetal products (**4e** and **4f** respectively) in low yields (entries 5 and 6, Table 1).

Next other cyclobutanes were explored under both $Yb(OTf)_3$ and MgI_2 reaction conditions (Table 2). The DA cyclobutane **1b** gave a moderate yield with nitrosobenzene **2d** under $Yb(OTf)_3$ catalysis, while electron-rich nitrosoarenes **2a** and **2b** resulted in low yields of exclusive pyrrolidine products **9a** and **9b** respectively (entries 2 and 3, Table 2). Crystals of **9a** were obtained and the X-ray structure unambiguously establishes the pyrrolidine product (Figure 1).[11]

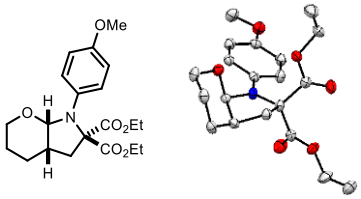
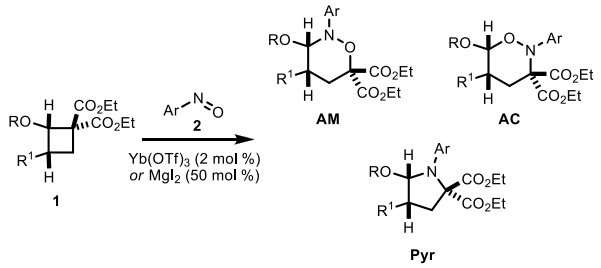
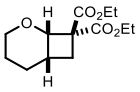
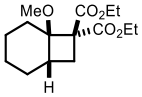
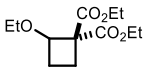


Figure 1. ORTEP structure of **9a**.

Table 2. Reaction scope of DA cyclobutanes in the cycloaddition.

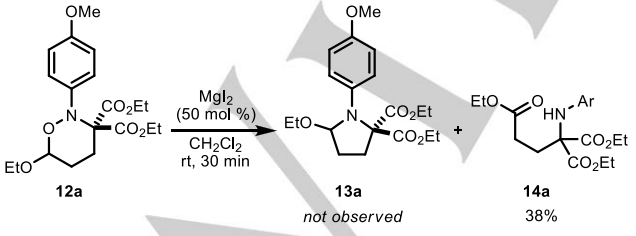


Entry	Cyclobutane	Nitrosoarene	Product Yield[a]	
			$Yb(OTf)_3$	MgI_2
1	 **1b**	**2d** Ar = C_6H_5	**AM-8d**, 45%	-
2		**2a** Ar = 4-C_6H_4OMe	-	**Pyr-9a,** 35%
3		**2b** Ar = 4-$C_6H_4N(CH_3)_2$	-	**Pyr-9b**, 18%
4	 **1c**	**2d** Ar = C_6H_5	**AM-10d**, 73%	-
5		**2g** Ar = 4-C_6H_4Cl	**AM-10g**, 70%	-
6	 **1d**	**2d** Ar = C_6H_5	**AM-11d**, 21%	-
7		**2a** Ar = 4-C_6H_4OMe	-	**AC-12a,** 38%

[a] Isolated yield.

The DA cyclobutane **1c** smoothly reacted with nitrosobenzene **2d** and 1-chloro-4-nitrosobenzene **2h** to furnish tetrahydro-1,2-oxazines **10d** and **10g** in good yields (entries 4 and 5, Table 2). Disappointingly the ethoxy substituted DA cyclobutane **1d** gave a poor yield with nitrosobenzene **2d**, while electron-rich nitrosoarene **2a** resulted in a low yield of acetal product **12a** (entry 7, Table 2).

Knowing that the acetal **4a** could be converted into pyrrolidine **5a** via MgI_2 mediated reaction (Scheme 4), **12a** was subjected 50 mol % of MgI_2 in CH_2Cl_2 (Scheme 6). However, the reaction yielded ester **14a** instead of pyrrolidine **13a**.



Scheme 6. Reaction of **12a** under MgI_2 conditions.

Conclusions

In conclusion, we have discovered the formation of unexpected pyrrolidine products in MgI_2 promoted cycloaddition reactions between DA cyclobutanes and electron-rich nitrosoarenes. The scope of $Yb(OTf)_3$ catalyzed [4+2] cycloaddition between DA cyclobutanes and nitrosoarenes is extended to additional DA cyclobutanes. Furthermore a procedure to make pyrrolidines from tetrahydro-1,2-oxazines was reported. The regiochemistry and stereochemistry of the unexpected pyrrolidine product **9a** has been unambiguously assigned by single-crystal X-ray diffraction. Future work includes mechanistic studies to further efficiency of the process.

Experimental Section

General experimental details:

All reactions were run under argon atmosphere unless otherwise indicated. Flasks were oven dried and cooled in a desiccator prior to use. Solvents and reagents were purified by standard methods.[12] Dichloromethane was purified by passing the solvent through an activated alumina column. All other chemicals were of reagent quality and used as obtained from commercial sources unless otherwise noted. The progress of reactions were monitored by thin layer chromatography (TLC) performed on F254 silica gel plates. The plates were visualized by UV light (254 nm) or by staining with ceric ammonium molybdate (CAM).[13] Column chromatography was performed with Silica Flash P60 60 Å silica gel from *SiliCycle*® according to the Still method.[14]

The ^1H and ^{13}C NMR data were obtained on either 400 or 600 MHz spectrometers. All spectra were obtained in deuterated chloroform and were referenced to the residual chloroform at 7.26 ppm for ^1H spectra and the center peak of the triplet at 77.0 ppm for ^{13}C spectra. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; quin, quintet; dt, doublet of triplets; dq, doublet of quartets; m, multiplet; br, broad; app, apparent. Scalar coupling was eliminated from nOe experiments by using acquisition delays of 500 ms. Electron ionization mass spectra were obtained on a Finnigan MAT 8200 spectrometer at an ionizing voltage of 70 eV.

Nitrosoarenes, which are not commercially available, were prepared according to literature methods.[15]

Table 1. Catalyst screening for electron-rich nitrosoarenes.

entry[a]	catalyst	mol %	temperature, time	result[b]
1	$Yb(OTf)_3$	50	rt, 30 min	19 %[c]
2	$Zn(OTf)_2$	10	rt, 20 h	13%[c]
3	$ZnCl_2$	10	rt, 6 h	26%[c]
4	$Zn(NTf_2)_2$	10	rt, 2 h	**4a**-15%
5	$AlCl_3$	10	rt, 23 h	**4a**-9%
6	$AlBr_3$	10	rt, 72 h	no reaction[f]
7	$AlMe_3$	20	rt, 24 h	no reaction[f]
8	$MADNTf_2$	100	rt, 72 h	no reaction[f]
9	Et_2AlCl	20	0 °C, 2 h; rt, 18 h	decomposition[e]
10	$Sc(OTf)_3$	10	rt, 30 min	decomposition[e]
11	CuI	10	rt, 52 h	no reaction[f]
12	$Cu(OTf)_2$	10	rt, 30 min	**4a**-14%
13	$SnCl_2$	10	rt, 46 h	no reaction[f]
14	$SnCl_4$	10	0 °C, 1 h	decomposition[e]
15	$Sn(OTf)_2$	10	rt, 18 h	**4a**-10%

16	Bu_2BOTf	10	0 °C, 2 h; rt, 30 min	decomposition[e]
17	$BF_3{\cdot}OEt_2$	10	0 °C, 4 h; rt, 18 h	decomposition[e]
18	AgOTf	10	rt, 15 min	decomposition[e]
19	AgCl	10	rt, 18 h	decomposition[e]
20	$ZrCl_4$	10	0 °C, 3 h; rt, 18 h	decomposition[e]
21	$TiCl_4$	10	0 °C, 3 h; rt, 18 h	decomposition[e]
22	$In(NTf_2)_3$	10	rt, 30 min	**4a**-20%
23	$In(OTf)_3$	10	rt, 3.5 h	**4a**-13%
24	$MgCl_2$	10	rt, 100 h	no reaction[f]
25	$MgBr_2$	10	rt, 120 h	**4a**-4%
26	$Mg(ClO_4)_2$	10	0 °C, 4 h; rt, 2 h	decomposition[e]
27	MgI_2	10	rt, 23 h	**4a**-20%
28	MgI_2	5	rt, 24 h	**4a**-17%
29	MgI_2	10	0 °C, 40 h	**4a**-30%
30	MgI_2	10	-20 °C, 72 h	**4a**-20%
31	MgI_2	50	0 °C, 15 min	**4a**-26%
32	MgI_2	50	rt, 18 h	**4a**-13%,**5a**-13%[g]
33	MgI_2	50	rt, 48 h	**5a**-22%[g]
34	MgI_2	10	40 °C, 45 min[d]; 100 °C, 30 min[d]	**4a**-9%, **5a**-11%[g]

[a] **Typical reaction conditions**: To a solution of Lewis acid in CH_2Cl_2 (3 mL) at specified temperature, was added nitrosoarene **2a** (0.3 mmol) followed by cyclobutane **1a** (0.36 mmol). Reactions were monitored until nitrosoarene **2a** was consumed by TLC. [b] Isolated yields. [c] 1:1 mixture **4a** and another unknown compound by ^{1}H NMR. [d] Microwave irradiation. [e] Cyclobutane **1a** consumed. [f] Cyclobutane **1a** recovered with some decomposition based on TLC and/or crude NMR. [g]Trace amount of **6a** was also isolated.

General $Yb(OTf)_3$ catalyzed cycloaddition procedure

To a stirred solution of $Yb(OTf)_3$ (4 mg, 0.006 mmol, 2 mol %) in CH_2Cl_2 (3 mL) at room temperature was added nitrosoarene (0.30 mmol, 1.0 equiv) followed by cyclobutane (0.36 mmol, 1.2 equiv). After complete consumption of the nitrosoarene (as indicated by TLC) the reaction mixture was layered directly onto a silica gel column and purified by flash chromatography (0-25% EtOAc/hexanes).

General MgI_2 catalyzed cycloaddition procedure

To a stirred solution of MgI_2 (41.5 mg, 0.15 mmol, 50 mol %) in CH_2Cl_2 (3 mL) at 0 °C was added nitrosoarene (0.30 mmol, 1.0 equiv) followed by cyclobutane (0.36 mmol, 1.2 equiv). After complete consumption of the nitrosoarene (as indicated by TLC) the reaction mixture was layered directly onto a silica gel column and purified by flash chromatography (0-25% EtOAc/hexanes).

Compound 4a: The title compound was prepared according to the general MgI_2 catalyzed cycloaddition procedure at 0 °C for 15 minutes to afford a pale yellow paste (30 mg, 26%); R_f 0.41 (1:1 hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 – 7.26 (m, 2 H), 6.75 – 6.77 (m, 2 H), 5.55 (d, *J* = 5.3 Hz, 1 H), 4.20 – 4.24 (m, 1 H), 4.15 – 4.19 (m, 1 H), 4.07 – 4.13 (m, 2 H), 4.01 – 4.06 (m, 1 H), 3.96 (td, *J* = 8.1, 5.0 Hz, 1 H), 3.76 (s, 3 H), 2.61 – 2.72 (m, 2 H), 2.50 – 2.57 (m, 1 H), 2.01 – 2.09 (m, 1 H), 1.95 (dq, *J* = 12.2, 6.3 Hz, 1 H), 1.14 (t, *J* = 7.0 Hz, 3 H), 1.10 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 168.8, 156.6, 140.7, 122.7, 113.0, 104.5, 74.3, 68.8, 61.9, 61.6, 55.4, 35.1, 32.3, 28.9, 13.8, 13.8; HRMS *m*/*z* 379.1635 (calcd for $C_{19}H_{25}NO_7$, 379.1631).

Compound 5a: To a stirred solution of MgI_2 (44 mg, 0.16 mmol) in 10 mL CH_2Cl_2 at room temperature was added 4a (120 mg, 0.32 mmol). The reaction mixture was stirred for about 18 hours at room temperature (complete consumption of starting material by TLC) then the reaction mixture was layered directly onto a silica gel column and purified by flash chromatography (0-25% EtOAc/hexanes); R_f 0.37 (1:1 hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.90 – 6.94 (m, 2 H), 6.75 – 6.78 (m, 2 H), 5.62 (d, *J* = 5.9 Hz, 1 H), 4.15 – 4.25 (m, 4 H), 3.91 – 4.00 (m, 2 H), 3.74 (s, 3 H), 3.00 – 3.07 (m, 1 H), 2.70 (dd, *J* = 12.9, 8.8 Hz, 1 H), 2.39 (dd, *J* = 13.5, 8.8 Hz, 1 H), 2.00 – 2.08 (m, 1 H), 1.72 (dd, *J* = 12.6, 5.0 Hz, 1 H), 1.21 (t, *J* = 7.3 Hz, 3 H), 1.18 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 169.9, 153.4, 138.3, 117.6, 113.9, 98.6, 74.8, 65.5, 61.8, 61.8, 55.5, 40.6, 40.1, 32.0, 14.0, 14.0; HRMS *m*/*z* 363.1692 (calcd for $C_{19}H_{25}NO_6$, 363.1682).

Compound 6a: The title compound was isolated in trace amount along with **5a** as pale brown oil; R_f 0.24 (70% hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.75 – 6.72 (m, 2 H), 6.65 – 6.62 (m, 2 H), 4.89 (s, 1 H), 4.29 – 4.15 (m, 5 H), 4.06 (ddd, *J* = 11.2, 9.1, 6.2 Hz, 1 H), 3.72 (s, 3 H), 3.09 (dd, *J* = 15.3, 3.5 Hz, 1 H), 2.67 – 2.60 (m, 1 H), 2.44 (dd, *J* = 15.3, 10.0 Hz, 1 H), 2.34 – 2.27 (m, 1 H), 1.78 (qd, *J* = 11.7, 8.8 Hz, 1 H), 1.21 – 1.16 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 169.9, 169.2, 153.3, 137.5, 116.9, 114.7, 67.9, 66.4, 62.5, 62.5, 55.5, 35.2, 33.7, 29.7, 13.9; HRMS *m*/*z* 379.1639 (calcd for $C_{19}H_{25}NO_7$, 379.1631).

Compound 5b: The title compound was prepared according to the general MgI_2 catalyzed cycloaddition procedure at room temperature for 4 hours to afford a yellow colored oil (25 mg, 22%); R_f 0.33 (60% hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.90 – 6.94 (m, 2 H), 6.66 – 6.70 (m, 2 H), 5.62 (d, *J* = 5.9 Hz, 1 H), 4.13 – 4.24 (m, 4 H), 3.91 – 3.98 (m, 2 H), 2.99 – 3.06 (m, 1 H), 2.82 (s, 6 H), 2.68 (dd, *J* = 13.5, 8.8 Hz, 1 H), 2.37 (dd, *J* = 13.2, 8.5 Hz, 1 H), 1.98 – 2.06 (m, 1 H), 1.70 (dd, *J* = 12.6, 4.4 Hz, 1 H), 1.15 – 1.21 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 170.0, 145.3, 136.0, 118.2, 114.3, 98.7, 74.8, 65.4, 61.7, 61.6, 41.7, 40.5, 40.0, 32.2, 14.0, 14.0; HRMS *m*/*z* 376.2044 (calcd for $C_{20}H_{28}N_2O_5$, 376.1998).

Compound 7c:[g] The title compound was prepared along with **4c** according to the general MgI_2 (10 mol %) catalyzed cycloaddition procedure at room temperature for 2 hours to afford a pale brown solid (15 mg, 13%); R_f 0.44 (70% hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 – 7.63 (m, 2 H), 7.54 – 7.59 (m, 2 H), 4.22 – 4.34 (m, 5 H), 4.06 – 4.15 (m, 2 H), 2.98 (dd, *J* = 12.9, 3.5 Hz, 1 H), 2.24 – 2.32 (m, 1 H), 2.19 – 2.24 (m, 1 H), 1.87 (t, *J* = 12.9 Hz, 1 H), 1.70 – 1.79 (m, 1 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 166.2, 151.9, 132.5, 119.4, 119.2, 107.2, 94.5, 84.0, 67.7, 62.6, 62.3, 41.4, 34.1, 27.9, 14.0, 14.0; HRMS *m*/*z* 374.1480 (calcd for $C_{19}H_{22}N_2O_6$, 374.1478).

Compound 4e: The title compound was prepared according to the general MgI_2 catalyzed cycloaddition procedure at room temperature for 2 hours to afford a yellow syrup (30 mg, 28%); R_f 0.34 (70% hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 – 8.04 (m, 1 H), 7.55 – 7.60 (m, 1 H), 7.19 – 7.23 (m, 1 H), 6.75 – 6.79 (m, 1 H), 5.58 (d, *J* = 4.7 Hz, 1 H), 4.22 – 4.32 (m, 2 H), 4.19 (q, *J* = 7.0 Hz, 1 H), 4.10 – 4.17 (m, 1 H), 3.93 (q, *J* = 8.0 Hz, 1 H), 2.68 – 2.77 (m, 2 H), 2.53 – 2.60 (m, 1 H), 1.98 – 2.10 (m, 2 H), 1.22 – 1.27 (m, 3 H), 1.13 – 1.17 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 168.7, 159.3, 145.6, 137.5, 116.7, 109.8, 104.1, 69.9, 69.1, 62.0, 61.6, 36.1, 31.8, 27.6, 13.8, 13.7; HRMS *m*/*z* 350.1470 (calcd for $C_{17}H_{22}N_2O_6$, 350.1478).

Compound 4f: The title compound was prepared according to the general MgI_2 (10 mol %) catalyzed cycloaddition procedure at room temperature for 4 hours to afford a pale yellow oil (28 mg, 19%); R_f 0.29 (70% hexanes /EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.6 Hz, 1 H), 7.52 (d, *J* = 3.5 Hz, 1 H), 7.50 (d, *J* = 2.3 Hz, 1 H), 7.26 (dd, *J* = 9.0, 2.3 Hz, 1 H), 6.47 (d, *J* = 3.5 Hz, 1 H), 5.60 (d, *J* = 5.5 Hz, 1 H), 3.94 – 4.28 (m, 6 H), 2.64 – 2.77 (m, 2 H), 2.51 – 2.62 (m, 1 H), 2.02 – 2.13 (m, 1 H), 1.92 – 2.02 (m, 1 H), 1.65 (s, 9 H), 1.12 (t, *J* = 7.0 Hz, 3 H), 1.04 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 168.9, 142.9, 130.1, 126.1, 118.0, 114.1, 112.9, 107.5, 104.5, 83.4, 74.4, 68.8, 62.0, 61.6, 35.3, 32.6, 29.0, 28.2, 13.8, 13.7; HRMS *m*/*z* 488.2153 (calcd for $C_{25}H_{32}N_2O_8$, 488.2159).

Compound 8d: The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure for 4 hours to afford a pale yellow solid (50 mg, 45%); R_f 0.25 (70% hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 – 7.31 (m, 4 H), 7.00 (t, *J* = 7.0 Hz, 1 H), 4.88 (d, *J* = 2.9 Hz, 1 H), 4.26 – 4.33 (m, 2 H), 4.14 – 4.26 (m, 2 H), 4.04 – 4.10 (m, 1 H), 3.50 (td, *J* = 11.7, 1.8 Hz, 1 H), 2.42 – 2.49 (m, 1 H), 2.22 – 2.35 (m, 2 H), 1.87 – 1.95 (m, 1 H), 1.76 – 1.86 (m, 2 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 1.16 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 166.9, 146.6, 128.5, 122.9, 117.4, 84.4, 67.9, 62.1, 61.8, 29.9, 28.5, 27.5, 20.1, 14.1, 14.0; HRMS *m*/*z* 363.1688 (calcd for $C_{19}H_{25}NO_6$, 363.1682).

Compound 9a:[11] The title compound was prepared according to the general MgI_2 catalyzed cycloaddition procedure at 0 °C for 15 minutes to afford a pale brown solid (40 mg, 35%); R_f 0.26 (70% hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.90 – 6.94 (m, 2 H), 6.72 – 6.77 (m, 2 H), 5.03 (d, *J* = 3.5 Hz, 1 H), 4.15 – 4.25 (m, 4 H), 3.90 – 3.96 (m, 1 H), 3.73 (s, 3 H), 3.44 (td, *J* = 11.3, 2.1 Hz, 1 H), 2.84 (t, *J* = 12.3 Hz, 1 H), 2.43 (dd, *J* = 12.0, 6.8 Hz, 1 H), 2.33 – 2.40 (m, 1 H), 1.85 – 1.94 (m, 1 H), 1.69 – 1.80 (m, 2 H), 1.38 – 1.44 (m, 1 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.16 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 153.3, 137.8, 118.0, 113.8, 90.0, 74.0, 63.9, 61.7, 61.7, 55.5, 38.2, 35.1, 23.7, 20.7, 14.0, 13.9; HRMS *m*/*z* 377.1837 (calcd for $C_{20}H_{27}NO_6$, 377.1838).

Compound 9b: The title compound was prepared according to the general MgI_2 catalyzed cycloaddition procedure at 0 °C for 1 hour, followed by 1 hour at room temperature to afford a yellow oil (22 mg, 19%); R_f 0.43 (50% hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.92 – 6.96 (m, 2 H), 6.65 – 6.68 (m, 2 H), 5.01 (d, *J* = 4.1 Hz, 1 H), 4.15 – 4.21 (m, 4 H), 3.92 (d, *J* = 11.2 Hz, 1 H), 3.42 (td, *J* = 11.0, 2.1 Hz, 1 H), 2.82 (s, 6 H), 2.39 – 2.44 (m, 1 H), 2.33 – 2.39 (m, 1 H), 1.83 – 1.93 (m, 1 H), 1.68 – 1.80 (m, 2 H), 1.37 – 1.43 (m, 1 H), 1.24 – 1.30 (m, 1 H), 1.21 (t, *J* = 7.3 Hz, 3 H), 1.15 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 170.4, 145.5, 135.5, 118.9, 114.3, 90.2, 74.1, 63.8, 61.6, 61.5, 41.8, 38.1, 35.2, 23.8, 20.8, 14.0, 13.9; HRMS *m*/*z* 390.2167 (calcd for $C_{21}H_{30}N_2O_5$, 390.2155).

Compound 10d: The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure for 15 minutes to afford a pale yellow oil (85 mg, 73%); R_f 0.59 (70% hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 - 7.24 (m, 4 H), 6.98 - 7.01 (m, 1 H), 4.11 - 4.22 (m, 4 H), 3.13 (s, 3 H), 2.60 (t, *J* = 12.6 Hz, 1 H), 2.14 (dd, *J* = 12.6, 3.8 Hz, 1 H), 1.95 - 2.00 (m, 1 H), 1.66 - 1.75 (m, 2 H), 1.60 - 1.65 (m, 1 H), 1.43 - 1.48 (m, 2 H), 1.21 - 1.35 (m, 3 H), 1.12 - 1.18 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 167.9, 148.8, 127.6, 123.3, 120.5, 101.4, 76.3, 62.1, 61.0, 48.1, 40.6, 33.8, 29.3, 27.6, 25.5, 22.5, 13.9, 13.7; HRMS *m*/*z* 391.1987 (calcd for $C_{21}H_{29}NO_6$, 391.1995).

Compound 10g: The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure for 45 minutes to afford a pale yellow oil (90 mg, 70%); R_f 0.65 (70% hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (s, 4 H), 4.11 - 4.23 (m, 4 H), 3.10 (s, 3 H), 2.58 (t, *J* = 12.6 Hz, 1 H), 2.12 (dd, *J* = 12.6, 3.8 Hz), 1.93 – 1.99 (m, 1 H), 1.60 - 1.75 (m, 3 H), 1.42 - 1.52 (m, 3 H), 1.26 - 1.36 (m, 1 H), 1.19 - 1.26 (m, 1 H), 1.14 - 1.19 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 167.8, 147.5, 127.6, 122.0, 101.6, 76.4, 62.2, 61.2, 48.0, 40.6, 33.7, 29.3, 27.6, 25.5, 22.5, 14.0, 13.7; HRMS *m*/*z* 425.1607 (calcd for $C_{21}H_{28}ClNO_6$, 425.1605).

Compound 11d: The title compound was prepared according to the general $Yb(OTf)_3$ catalyzed cycloaddition procedure for 15 minutes to afford a yellow oil (29 mg, 21%); R_f 0.40 (70% hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 – 7.24 (m, 4 H), 6.99 – 7.03 (m, 1 H), 5.03 (dd, *J* = 7.9, 3.8 Hz, 1 H), 4.19 – 4.25 (m, 2 H), 4.11 – 4.19 (m, 2 H), 3.94 (dq, *J* = 9.9, 7.1 Hz, 1 H), 3.61 (dq, *J* = 9.9, 7.1 Hz, 1 H), 2.58 (dt, 13.5, 4.7 Hz, 1 H), 2.44 (ddd, 13.4, 12.2, 4.4 Hz, 1 H), 1.97 (dq, *J* = 13.4, 4.2 Hz, 1 H), 1.76 – 1.84 (m, 1 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.18 (t, *J* = 7.0 Hz, 3 H), 1.13 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 168.1, 148.3, 127.7, 123.3, 119.5, 102.5, 74.8, 64.7, 61.9, 61.6, 30.8, 27.0, 15.1, 13.8, 13.7; HRMS *m*/*z* 351.1679 (calcd for $C_{18}H_{25}NO_6$, 351.1682).

Compound 12a: The title compound was prepared according to the general MgI_2 catalyzed cycloaddition procedure at 0 °C for 15 minutes to afford a yellow oil (43 mg, 38%); R_f 0.36 (70% hexanes /EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 – 7.23 (m, 2 H), 6.75 – 6.79 (m, 2 H), 5.00 (dd, *J* = 8.2, 3.5 Hz, 1 H), 4.06 – 4.23 (m, 4 H), 3.83 – 3.90 (m, 1 H), 3.77 (s, 3 H), 3.53 – 3.60 (m, 1 H), 2.57 (dt, *J* = 13.5, 4.7 Hz, 1 H), 2.44 (td, *J* = 12.6, 4.7 Hz, 1 H), 1.95 (dq, *J* = 13.4, 4.2 Hz, 1 H), 1.73 – 1.83 (m, 1 H), 1.17 – 1.22 (m, 6 H), 1.13 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 168.1, 156.4, 141.3, 122.7, 112.8, 102.3, 75.2, 64.6, 61.8, 61.5, 55.4, 27.1, 37.7, 15.1, 13.9, 13.8; HRMS *m*/*z* 381.1778 (calcd for $C_{19}H_{27}NO_7$, 381.1788).

Compound 14a: To a stirred solution of MgI_2 (47 mg, 0.17 mmol) in 6 mL CH_2Cl_2 at room temperature was added **12a** (130 mg, 0.34 mmol). The reaction mixture was stirred for about 30 minutes at room temperature (complete consumption of starting material by TLC) then the reaction mixture was layered directly onto a silica gel column and purified by flash chromatography (0-25% EtOAc/hexanes) to afford a yellow oil (50 mg, 38%); R_f 0.43 (70% hexanes /EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 - 6.75 (m, 2 H), 6.58 - 6.64 (m, 2 H), 4.81 (s, 1 H), 4.16 - 4.26 (m, 4 H), 4.04 (q, *J* = 7.2 Hz, 2 H), 3.73 (s, 3 H), 2.61 - 2.68 (m, 2 H), 2.22 - 2.29 (m, 2 H), 1.19 (t, *J* = 7.0 Hz, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.3, 172.7, 169.6, 153.2, 137.6, 116.9, 114.6, 68.1, 62.4, 60.5, 55.6, 28.7, 27.4, 14.1, 13.9; HRMS *m*/*z* 381.1789 (calcd for $C_{19}H_{27}NO_7$, 381.1788).

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[7] See experimental section for complete list of catalyst screening.

[8] See experimental section for complete optimization study.

[9] CCDC 1061592 contains the crystal data for **7c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.

[10] No conversion to **5c** was observed when **4c** was exposed to 50 mol % MgI_2.

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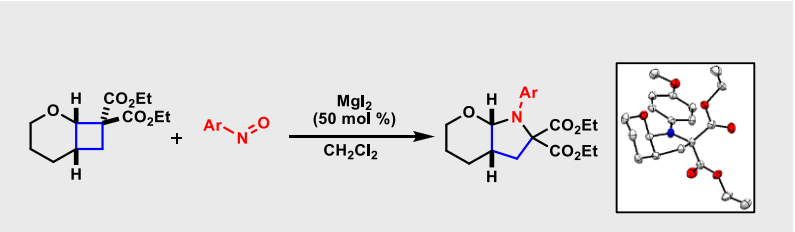

During efforts to expand the scope of Lewis acid catalyzed [4+2] cycloaddition between donor-acceptor cyclobutanes and nitrosoarenes, an unexpected formation of pyrrolidine products was discovered when 50 mol % of MgI_2 was used as a Lewis acid. It was also observed that the electronics of the nitrosoarene and judicious selection of the Lewis acid catalyst have a profound effect on the regioselectivity of the reaction.

Cycloadditions

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Synthesis of Tetrahydro-1,2-oxazines and Pyrrolidines *via* Cycloadditions of Donor-Acceptor Cyclobutanes and Nitrosoarenes

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