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The [4+2] Cycloaddition of Donor-Acceptor Cyclobutanes and Nitrosoarenes

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The Yb(OTf)₃ catalyzed [4+2] cycloaddition between donor-acceptor cyclobutanes and nitrosoarenes is disclosed. This method facilitates the synthesis of tetrahydro-1,2-oxazines in good to excellent yields as single diastereomers. Except for a
10 few electron-deficient nitrosoarenes, excellent regioselectivity was observed throughout these studies.

Cycloaddition chemistry remains a premier method for the synthesis of diverse structural architectures and functionalities.[1] In particular, exploitation of ring strain to facilitate cycloaddition
15 reactions is a well-appreciated strategy in modern organic synthesis.[2] In this regard, the strained carbocyclic donor-acceptor (DA) cyclopropanes have been extensively studied due to their unique reactivity profile and their value as synthetic building blocks has been demonstrated by the preparation of highly
20 functionalized carbo- and heterocyclic products via cycloaddition reactions.[3] While this area continues to mature, the reactivity of the homologous DA cyclobutanes have only recently garnered significant attention. In recent years, a number of reactive partners have been found to undergo cycloadditions with DA
25 cyclobutanes[4] and cyclobutanones,[5] and further exploration will create a greater understanding of these fascinating systems.

Nitrosoarenes have been utilized in a variety of transformations,[6] such as dienophiles in hetero Diels-Alder (HDA) cycloadditions,[7] and enophiles in nitroso-ene reactions.[8]
30 Some intriguing reports describe the nitroso functional group's dichotomous capacity to act as either nitrogen or oxygen transfer reagents in nitroso-aldol chemistry, which can be controlled by judicious selection of catalyst.[9] Surprisingly, nitrosoarenes have not yet seen application in cycloaddition chemistry with either
35 DA cyclopropanes or cyclobutanes or with cyclobutanones.[10] Herein we report the first example of a [4+2] cycloaddition of DA cyclobutanes and nitrosoarenes to give tetrahydro-1,2-oxazines.[11] The tetrahydro-1,2-oxazine core structure can be found in numerous natural products[12] and are known to undergo
40 reductive cleavage of the N-O bond to give synthetically useful

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45 †Electronic Supplementary Information (ESI) available: [Full experimental procedures; ¹H and ¹³C NMR spectra of new compounds, 2D NMR correlations of key compounds and crystalographic data of **3b** and **3k**]. See DOI: 10.1039/b000000x/

motifs, which were utilized in the total synthesis of several
50 natural products.[13]

Investigations into the reactivity of nitrosoarenes and DA cyclobutanes began with the examination of the reaction between cyclobutane **1a** and nitrosobenzene **2a** (Table 1).

While a variety of Lewis acids were found to catalyse the
55 reaction, maximum yields were obtained with Yb(OTf)₃. Additionally, the product yield was dramatically increased (entries 1, 6 and 8) by decreasing the catalyst loading from 10 to 2 mol %. The reaction could be effected with catalyst loadings as low as 0.5 mol % but in lower yield (entry 9).[14] Among the two
60 possible regioisomers (**3a** and **4a**, Table 1), the product observed was always **3a**, and no noticeable amount of **4a** was obtained, irrespective of the Lewis acid used. Thereby demonstrating that the nitrogen of the nitroso functional group was acting as a nucleophile rather than oxygen.[15]

65 **Table 1** Catalyst Screening
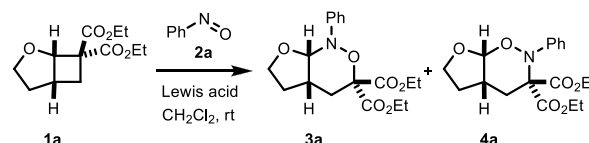
Entry	Lewis acid	Mol %	**3a**:**4a**[a]	Yield (%)[b]
1	Yb(OTf)₃	10	>20:1	60
2	Sc(OTf)₃	10	>20:1	55
3	La(OTf)₃	10	>20:1	22
4	Zn(OTf)₂	10	>20:1	61
5	Pr(OTf)₃	10	>20:1	63
6	Yb(OTf)₃	5	>20:1	72
7	Sc(OTf)₃	5	>20:1	61
8	Yb(OTf)₃	2	>20:1	92
9	Yb(OTf)₃	0.5	>20:1	80

[a]Based on ¹H NMR, [b]Isolated yield

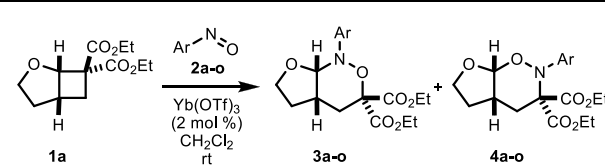70 With optimal conditions in hand, the scope of the reaction was examined (Table 2). It was discovered that nitrosoarenes with

halogen substituents are excellent reaction partners regardless of the position on the aryl ring (entries 2-7).[16] Substrates with moderately deactivating carbonyl (entries 8 and 9) or ethoxycarbonyl (entry 10) substituents were also resulted in good yields. The electron-deficient nitrosoarenes afforded moderate yields (entries 11 and 12); however, another isomer (Figure 2) was also formed up to 25% of the overall isolated yield. Nitrosoarene with weekly electron donating methyl substituent resulted in a substantially decreased yield (entry 13). Upon incorporations of a strongly electron donating group no reaction was observed (entries 14 and 15), likely due to the sequestration of the ytterbium catalyst by the electron-rich nitrosoarene.

Table 2 Reaction Scope

| Entry	Nitrosoarene	Product	Yield (%)[b]
1	Ar = C_6H_5	**3a**	92
2	Ar = 4-C_6H_4Br	**3b**	89
3	Ar = 4-C_6H_4Cl	**3c**	93
4	Ar = 3-C_6H_4Br	**3d**	87
5	Ar = 3-C_6H_4Cl	**3e**	95
6	Ar = 2,4-$C_6H_3Br_2$	**3f**	47
7	Ar = 3,4-$C_6H_3Cl_2$	**3g**	91
8	Ar = 4-$C_6H_4C(O)Me$	**3h**	69
9	Ar = 3-$C_6H_4C(O)Me$	**3i**	87
10	Ar = 4-$C_6H_4CO_2Et$	**3j**	76
11	Ar = 4-C_6H_4CN	**3k, 4k** (3:1)[a]	61
12	Ar = 4-$C_6H_4NO_2$	**3l, 4l** (4:1)[a]	59
13	Ar = 4-$C_6H_4CH_3$	**3m**	29
14	Ar = 4-$C_6H_4OCH_3$	-	no reaction[c]
15	Ar = 4- $C_6H_4N(CH_3)_2$	-	no reaction[c]

[a]Ratio of **3:4** of isolated overall yield, [b]Isolated yield, [c]Yb(OTf)$_3$ 2 mol % or 10 mol %
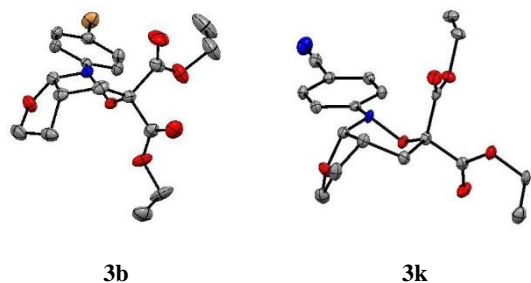
Figure 1 X-ray Crystal Structures of **3b** and **3k**

Fortuitously, X-ray quality crystals of compounds **3b** (entry 2, Table 2) and **3k** (entry 11, Table 2) were obtained and the ORTEP structures are depicted in Figure 1. These crystal structures unambiguously establish both the regiochemistry of the cyclization and the relative configuration at the ring fusion.[17]

Extensive 2D NMR analysis was used to support the structural assignments of the isomers formed with electron deficient nitrosoarenes (entries 11 and 12, Table 2). The major isomer in each case was found to have nOe and ^{1}H-^{15}N HMBC interactions that were consistent with those observed for **3b** and **3k** (Figure 2). The minor isomer, showed nOe interactions suggesting a *cis* ring fusion, and ^{1}H-^{15}N HMBC data indicated that it is a regioisomer, rather than a diasteriomer was formed. Similar nOe and ^{1}H-^{15}N HMBC correlations were observed for **3l** and **4l** also.[18] This lack of selectivity could be due to delocalization of the nitrogen lone pair of electrons into the aromatic ring, leading to competition between nitrogen and oxygen for dominant nucleophilicity.
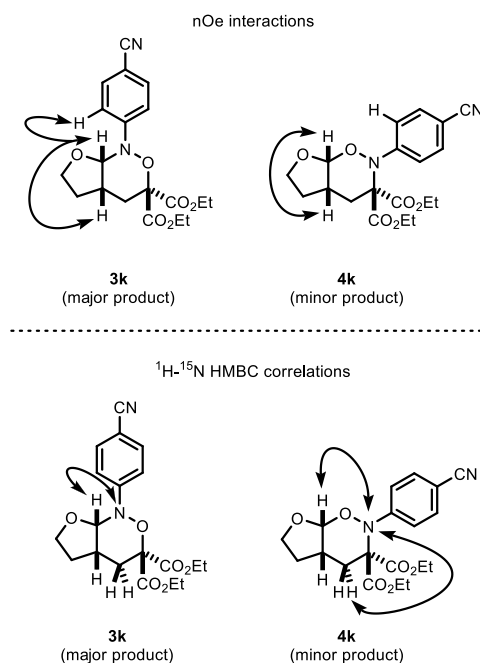
Figure 2 Key nOe and ^{1}H-^{15}N HMBC Correlations for Structural Assignment of **3k** and **4k**

In summary, we have reported the first example of a [4+2] cycloaddition between DA cyclobutanes and nitrosoarenes. The regiochemistry and relative stereochemistry of **3b** and **3k** have been unambiguously assigned by single crystal X-ray diffraction. The reaction proceeds well with electron neutral and deficient nitrosoarenes to form tetrahydro-1,2-oxazines. Optimization of reaction conditions for electron rich nitrosoarenes and expansion of the substrate scope to additional DA cyclobutanes are currently under investigation and a full account will be reported in due course.

Notes and references

Typical Procedure for Cycloaddition: To a mixture of nitrosoarene (0.30 mmol) and Yb(OTf)$_3$ (4 mg, 2 mol %) in anhydrous CH$_2$Cl$_2$ (3 mL) at room temperature, was added the cyclobutane (0.36 mmol) under argon atmosphere. 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).

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15 Atomic charges derived from the electrostatic potentials for the nitrosobenzene were in agreement with the results observed. CHelpG charges (a.u.); nitrogen (-0.228) and oxygen (-0.163). Geometry: B3LYP/6-31G*; Density: B3LYP/6-311++G(3df,3pd)

16 The low yield of the **3f** could be due to the sterics of bromine at 2-position. Investigation of the reaction scope in detail will be reported in the following full paper.

17 The regiochemistry and relative stereochemistry of the other products were assigned by analogy.

18 See supplementary information for details.