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Synthesis of Functionalized Tetrahydropyridines by SNCl4-mediated [4+2] Cycloaddition between Donor–Acceptor Cyclobutanes and Nitriles

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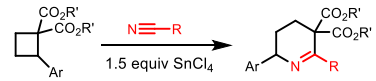
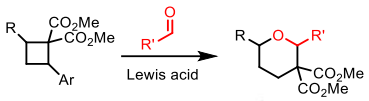
Synthesis of Functionalized Tetrahydropyridines by $SnCl_4$-mediated [4+2] Cycloaddition between Donor–Acceptor Cyclobutanes and Nitriles

David Tong, Jackie Wu, Nathan Bazinski, Donghyun Koo, Naresh Vemula and Brian L. Pagenkopf*

Abstract: *Cycloadditions of strained carbocycles promoted by Lewis acids are powerful methods to construct heterocyclic frameworks. In fact, the formal [3+2] cycloadditions of donor-acceptor (DA) cyclopropanes with nitriles has seen particular success in synthesis. In this work, we report on the first [4+2] cycloaddition of nitriles with DA cyclobutanes via Lewis acid activation. Tetrahydropyridine derivatives were obtained in up to 91% yield from various aryl activated cyclobutane diesters and aliphatic or aromatic nitriles.*



Cycloadditions of donor-acceptor cyclopropanes (DACPs) have emerged as a powerful means to construct heterocycles and carbocycles, and they thus play pivotal roles in natural product syntheses.[1] Cyclobutanes share a similar degree of bond-strain to cyclopropanes,[2] but they largely remained unexplored as reaction partners in cycloaddition chemistry until the last decade.[3] Generalized DA-cyclobutane (DACB) cycloaddition reactions were firstly reported in 2009 by Johnson[4] and by Prichard and Christie[5] with aldehydes as the dipolarophiles (Figure 1). In the following year we disclosed the first alkoxy-activated DACB cycloaddition reactions with aldehydes,[6] and subsequently reported DACB cycloadditions with imines,[7] nitrones,[8] alkynes,[9] and nitrosoarenes.[10]

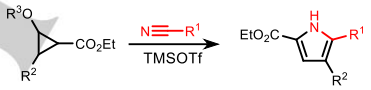


Johnson (2009), R = Ph
Christie, Prichard (2009), R = PhC_2•$Co(CO)_6$
Our previous work (2010), R = OAlkyl

Figure 1. Pioneering contributions to cycloadditions of donor-acceptor cyclobutanes activated by geminal diesters (Ref. [4], [5], [6]).

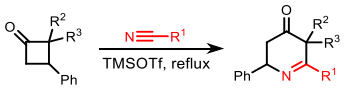
Cycloaddition reactions of cyclopropanes with nitriles have been particularly productive (for example, the pyrrole synthesis in Scheme 1A).[1a,11] Yet, the analogous reaction of cyclobutanes bearing geminal diesters has not been reported to date. In the most relevant example, Matsuo recently reported the cycloaddition between aryl-substituted cyclobutanones and nitriles (Scheme 1, eq B).[12] However, the cyclobutanones were structurally distinct from the cyclopropanes or cyclobutanes with exocyclic ester electron withdrawing functionality (e.g., Figure 1). In this contribution, we describe the formal [4+2]-cycloaddition reactions between nitriles and aryl-activated DACBs via Lewis acid promotion (Scheme 1, eq C). The method reported herein could afford a rich variety of tetrahydropyridine derivatives that are medicinally privileged constituents in many bioactive natural products[13] thanks to the electronic and structural diversity that are tolerated across both the cyclobutane and nitrile components.

Our previous work (2003):



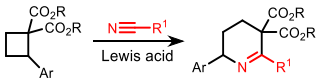
(A)

Matsuo (2018):



(B)

This work:



(C)

Scheme 1: Cyclobutane cycloaddition reactions with nitriles. (Refs [11], [12]).

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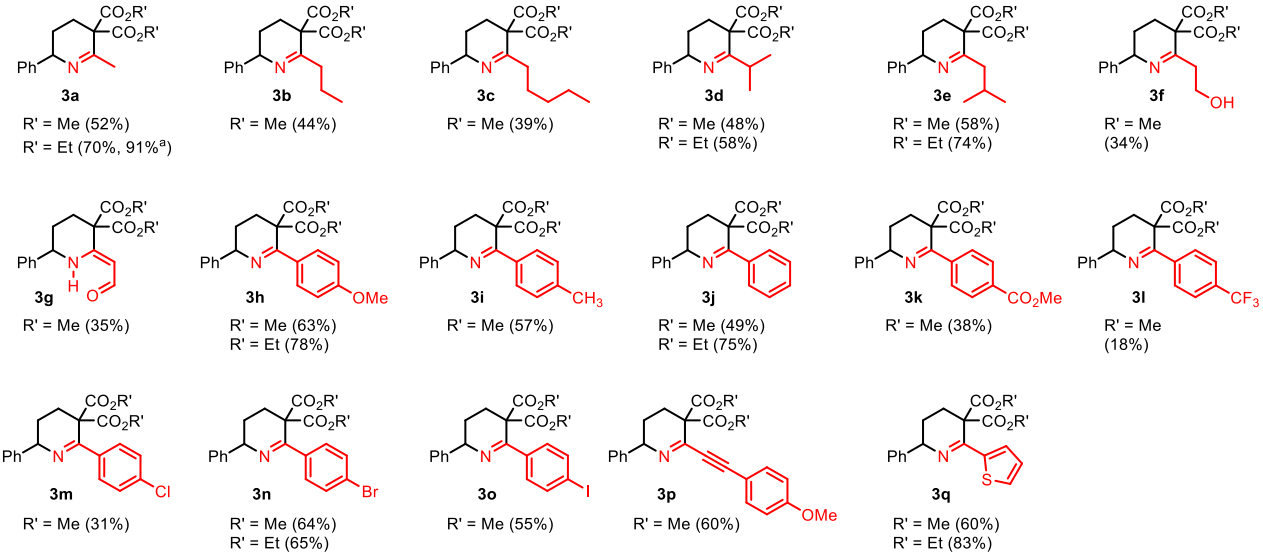
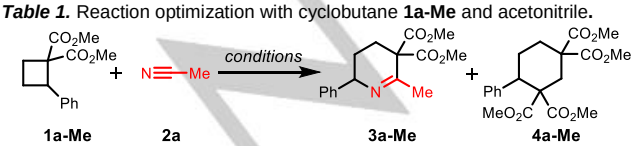


Scheme 2. Cycloaddition of model cyclobutanes **1a-Me** and **1a-Et** with nitriles. [a] Acetonitrile used as solvent. *General procedure*: To a solution of cyclobutane (1.0 equiv, 0.4 mmol) and nitrile (3.0 equiv, 1.2 mmol) in dichloroethane (DCE) at 55 °C was added dropwise $SnCl_4$ (1.5 equiv, 0.6 mmol) in 2 mL DCE.

The cyclobutane **1a-Me** and acetonitrile (**2a**) were chosen as model reaction partners to firstly establish reactivity and optimize conditions for their cycloaddition to give **3a-Me** (Table 1). The Lewis acids $Yb(OTf)_3$ and $Sc(OTf)_3$ that were highly effective in the cycloadditions of aldehydes with aryl4 or alkoxy-activated DACBs6-8 turned out to be inactive or minimally effective (Table 1, entries 1, 2). Neither was TMSOTf successful, although it efficiently catalyzed the analogous cycloaddition between cyclopropanes and nitriles (Scheme 1, eq A; Table 1, entries 3, 4). Other common catalysts often employed in the cycloadditions of donor-acceptor carbocycle were also not productive (entries 5–8). Ultimately, $SnCl_4$ emerged as the most viable catalyst (entries 9–18),[14] and dichloroethane was identified as the most effective solvent. Reaction temperature was critical (entries 16–20) because the formation of the fragmentation / cycloaddition product **4a** became competitive at >55 °C (entry 19).[15] Ultimately, the conditions established for this [4+2] cycloaddition employed super stoichiometric $SnCl_4$ (1.5 equiv) at 55 °C and gave the cycloadduct **3a-Me** in a modest 52% yield. The yield increased to 78% (entry 20) when acetonitrile was used as solvent, which demonstrates that sufficient Lewis acid remained to catalyze the cycloaddition although formation of $SnCl_4$ adducts with nitriles, *i.e.*, $SnCl_4{\cdot}(MeCN)_2$, are known. [16] Similarly, our previously reported DA-cyclopropane cycloadditions catalyzed by Me_3SiOTf were also more efficient when ran in acetonitrile solvent.[11] The preliminary conditions optimized for **1a-Me** were then attempted with other substrates, most of which proved more efficient.

Table 1. Reaction optimization with cyclobutane **1a-Me** and acetonitrile.



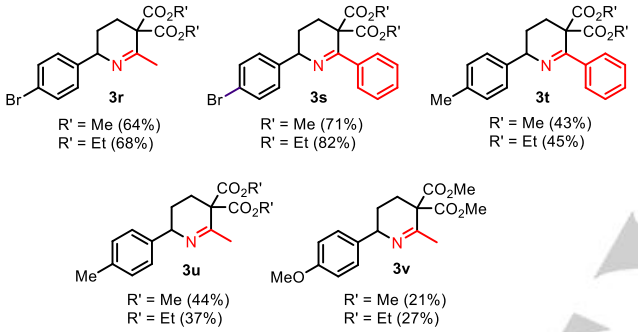
	conditions[a]				
Entry	catalyst (equiv)	Solvent	temp (°C)	Time (h)	yield[b] **3a** (%)
1	$Yb(OTf)_3$ (0.1)	DCM	rt – 55	15	Nr
2	$Sc(OTf)_3$ (0.05)	DCM	55	24	16
3	TMSOTf (0.1)	DCM	rt	18	trace
4[d]	TMSOTf (1.1)	DCM	rt	18	18
5	$Pr(OTf)_3$ (0.05)	DCM	rt – 55	48	nr
6	$Mg(OTf)_2$ (0.1)	DCM	rt – 55	12	nr
7	MgI_2 (0.5)	DCM	rt - 55	12	dec
8	$BF_3{\cdot}OEt_2$ (0.1)	DCM	rt - 55	16	Nr
9	TfOH (0.1)	DCM	rt - 55	4	nr
10	$SnCl_4$ (0.5)	DCM	rt	3	26
11	$SnCl_4$ (1.1)	DCM	rt	3	39
12	$SnCl_4$ (1.5)	DCM	rt	3	43
13	$SnCl_4$ (2.1)	DCM	rt	3	44
14	$SnCl_4$ (1.5)	$MeNO_2$	rt	3	36
15	$SnCl_4$ (1.5)	Toluene	rt	3	37
16	$SnCl_4$ (1.5)	DCE	rt	3	44
17	$SnCl_4$ (1.5)	DCE	0	3	33
18	$SnCl_4$ (1.5)	DCE	55	3	52
19	$SnCl_4$ (1.5)	DCE	85	3	38
20[e]	$SnCl_4$ (1.5)	MeCN	55	3	78

[a] Reactions were run in the indicated solvent on 0.4 mmol scale with MeCN (5.0 equivalents). [b] Isolated yield. [c] No reaction was observed at 0 °C. [d] Reaction was conducted in a microwave reactor. DCM = dichloromethane. DCE = dichloroethane. nr = no reaction. [e] Acetontrile as solvent (0.1 M cyclobutane, 192 equiv of acetonitrile).

It is known that increasing the size of the esters, i.e., methyl to ethyl, decreases reactivity and helps reduce decomposition.6-7 Using the diethyl ester **1a-Et** gratifyingly improved the efficiency of the cycloaddition with acetonitrile to 70% from the 52% yield with **1a-Me** (Scheme 2). By running the reaction in acetonitrile as solvent the yield improved to 91%. Further evaluation of the reaction scope was arbitrarily carried out with either the dimethyl or the diethyl diester variants of the cyclobutane, and the results are summarized in Scheme 2. The [4+2] cycloaddition was accomplished with a broad range of nitriles, and both saturated straight-chain and branched aliphatic nitriles were well tolerated (**3a**–**e**). Reaction in the presence of a free 3-hydroxy group was successful (**3f**), and 3-methoxyacrylonitrile gave the vinylogous formamide **3g** in 35% yield after hydrolysis.

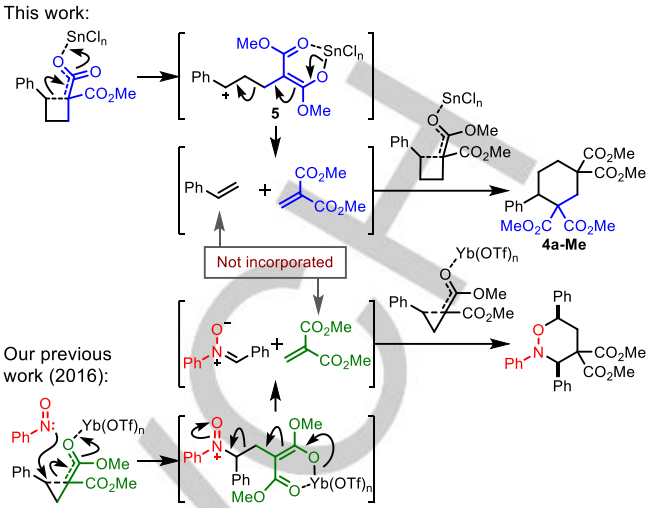
Electronically diverse aromatic nitriles were also evaluated, and as expected, electron rich nitriles such as *para*-methoxy or *para*-methyl benzontrile were more effective (**3h**, **3i**).[17] Electron poor nitriles with electron withdrawing groups such as ester or trifluoromethyl gave lower yields (**3k**, **3l**). Cycloaddition with halogenated arenes were successful (**3m**–**o**). Alkynyl nitriles could also engage when provided sufficient electronic donation (**3p**). 2-Thienyl nitrile also proved to be an efficient partner (**3q**). The electronic trends observed with these aryl nitriles were consistent with a Ritter-type reaction mechanism.

The structure of the cyclobutanes was then varied (Scheme 4). Both acetonitrile (**2a**) and benzonitrile (**2j**) were then used as model nitriles to explore the generality of the reaction with various cyclobutanes. A *para*-bromo substituted aryl cyclobutane gave the cycloadducts with acetonitrile or benzonitrile in 68% and 82% yield, respectively (**3r-Et**, **3s-Et**). The adducts **3m**–**o**, **3r-Et** and **3s-Et** provide a convenient aryl halide for additional synthetic manipulation on both participants.



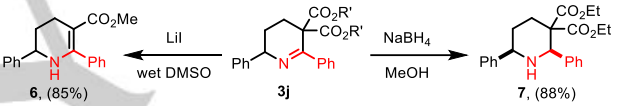
Scheme 3. Scope of cycloaddition with cyclobutanes **1b**-**1d** with acetonitrile and/or benzonitrile.

Formation of the fragmentation-cycloaddition product **4a-Me** (Table 1) increased notably when the aryl donors on the cyclobutane (**3t**–**v**) became increasingly electron rich.[18] Electron rich donors likely favor the formation of a zwitterionic intermediate **5** (Scheme 4) that can undergo E1cB fragmentation to give styrene and methylidene malonate, a process faster than the interception of the relatively stable benzylic cation **5** by the nitrile. The methylidene malonate can then combine with another equivalent of DA-cyclobutane to afford **4a**. This proposed mechanism is consistent with our detailed crossover study on similar products formed in cycloadditions of DA-cyclopropanes.[15]



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

The tetrahydropiperidene adduct **3** readily underwent classic transformations, including dealkoxycarbonylation to the vinylogous carbamate **6** and reduction from the tetrahydropyridine **3j** to the piperidene **7j** (Scheme 5).



Scheme 5. Krapcho dealkoxycarbonylation and reduction of **3j**.

In summary, we have developed a $SnCl_4$-mediated cycloaddition between nitriles and donor-acceptor cyclobutanes that are activated by vicinal aryl donating and geminal-diester electron withdrawing substituents. The resulting reaction favors electron rich donors and nitriles, but is also compatible with a wide range of substituents, particularly on the nitrile. Halogenated substituents on either the cyclobutane or the nitrile are compatible and provide a convenient handle for additional synthetic manipulation. Further studies on asymmetric variants are underway in our laboratory.

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Keywords: cycloaddition • cyclobutane • donor-acceptor systems • nitrogen heterocycles • strained molecules

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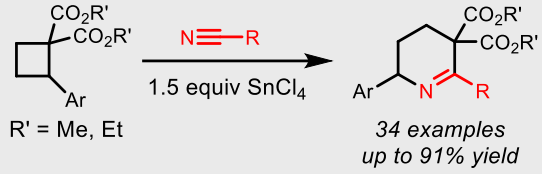

The Lewis-acid promoted cycloadditions of nitriles with donor-acceptor (DA) cyclopropanes have proven to be powerful tools for the construction of heterocyclic frameworks, but the analogous reaction with cyclobutanes has remained elusive. Here we report the first [4+2] cycloaddition of nitriles with DA cyclobutanes by Lewis acid activation to provide useful tetrahydropyridine derivatives.

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