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A Highly Site-, Regio-, and Stereoselective Lewis Acid Catalyzed Formal [3+3] Cycloaddition of Methylenecyclopropane-1,1-Diesters with C,N-Diarylnitrones

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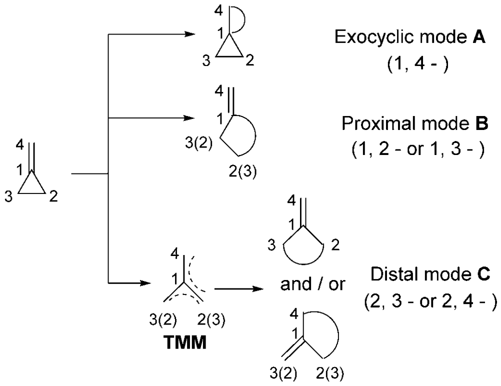
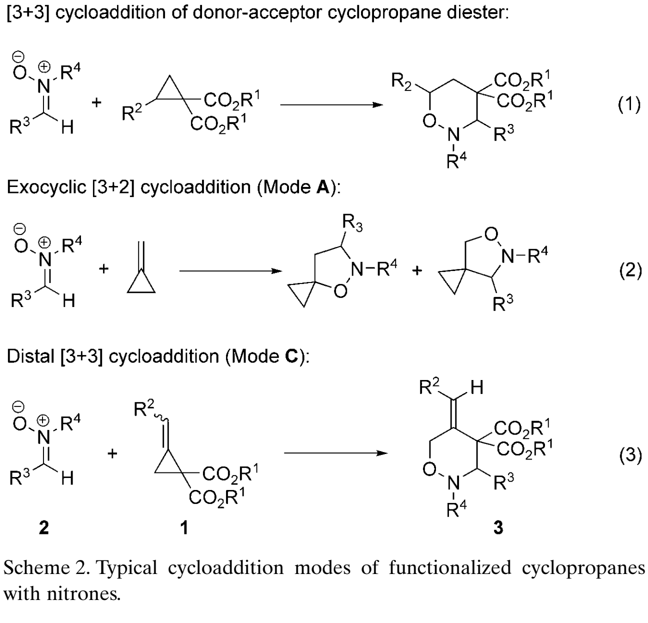
Dedicated to Professor Zhengming Li

Cycloaddition is one of the most powerful tools for the construction of carbo- and heterocyclic skeletons, due to its high efficiency and atom economy.[1] Methylenecyclopropanes (MCPs) are useful building blocks in organic synthesis because they are readily available[2] and display good reactivity.[3] Cycloadditions of MCPs have shown much utility in a variety of synthetic applications.[3] There are three typical modes of cycloaddition of MCPs (Scheme 1): a) the exocyclic mode (mode **A**)[4] in which the exocyclic carbon–carbon double bond formally serves as a dienophile, b) proximal ring opening of a cyclopropane bond (mode **B**),[5] and c) ring-opening at the C–C bond that is distal to the alkene (mode **C**),[6] wherein a trimethylenemethane (TMM)[1a,7] or a metallacyclobutane[8] transition state may be involved. Most of these cycloadditions proceed under thermal conditions or by catalysis using transition metals. Lewis acids, such as lanthanide triflates,[9] are usually effective in promoting the carbocation-related reactions under mild conditions. Recently, Lewis acid-promoted proximal[10] and distal[11] cycloadditions of MCPs have been studied and have attracted considerable attention.



Scheme 1. Typical cycloaddition modes of methylenecyclopropanes.

Nitrone is one of the most useful dipoles in 1,3-dipolar cycloadditions.[1a] The groups of Brandi and de Meijere have studied the 1,3-dipolar cycloaddition of MCPs with nitrones for many years.[3] However, all of these cycloadditions are of the exocyclic [3+2] variety [Scheme 2, Eq. (2)]. In our investigation of cycloadditions of functionalized MCPs, we have



Scheme 2. Typical cycloaddition modes of functionalized cyclopropanes with nitrones.

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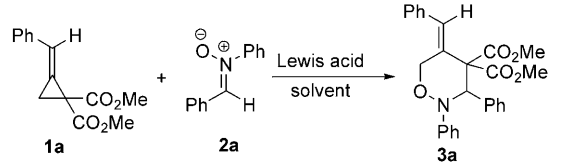
introduced electron-withdrawing groups (EWGs) at C2- or C3-positions of the cyclopropane ring, in an effort to change the electronic character of the TMM transition state and thus achieve fine-tuning of its reactivity and regioselectivity.[11] The groups of Lautens[11a,b] and Monti[11c] have reported Lewis acid-catalyzed distal [3+2] cycloaddition of systems substituted with one EWG. Young and Kerr[12] have reported a [3+3] cycloaddition of donor–acceptor (D–A) cyclopropane diesters with nitrones, catalyzed by $Yb(OTf)_3$ [Scheme 2, Eq. (1)]. Inspired by these results, we envisioned that the geminal installation of two EWGs at the C2 position of the cyclopropane ring might further activate the C2–C3 bond toward cycloaddition. By formation of a complex between the two carbonyl groups and the Lewis acid, a discrete dipolar TMM transition state may be generated, in which the carbanion can be well-stabilized by the two EWGs and the carbocation can be stabilized by conjugation with the neighboring carbon–carbon double bond. Thus, the mode of cycloaddition of MCP-1,1-diesters with nitrones might be changed from exocyclic [3+2] cycloaddition to the distal [3+3] variety. A high regioselectivity might also be anticipated. To our delight, in the $Yb(OTf)_3$-promoted reactions of MCP-diesters **1** with C,N-diarylnitrones **2**, exclusively distal [3+3] cycloaddition products **3** were obtained [Scheme 2, Eq. (3)]. To our knowledge, this is the first Lewis acid-promoted distal [3+3] cycloaddition of MCPs with 1,3-dipoles (Scheme 1, mode **C**).

The first experiment was carried out using MCP-1,1-diester **1a** and C,N-diarylnitrone **2a** in CH_2Cl_2 at 40 °C, catalyzed by $Yb(OTf)_3$ (20 mol %). After 41.5 h, **3a** was obtained, together with 15 % of recovered **1a** (Table 1, entry 1). Solvent screening showed that both the conversion of substrate **1a** and the reaction rate were highest for the reaction in THF (Table 1, entry 4). Several Lewis acids were also tested and, of these, $Yb(OTf)_3$ afforded better results than either $Sc(OTf)_3$ or $Mg(ClO_4)_2{\cdot}6H_2O$ (Table 1, entries 4, 8, and 9). Decreasing the amount of $Yb(OTf)_3$ resulted in decreased conversion of MCP **1a** even with prolonged reaction time or at higher temperature (Table 1, entries 6 and 7).

Table 1. Optimization of conditions for the cycloaddition of MCP-1,1-diester **1a** with C,N-diarylnitrone **2a** in the presence of Lewis acids.[a]



Entry	Lewis acid	Solvent	T [°C]	t [h]	Conv. of **1a** [%][b]
1	$Yb(OTf)_3$	CH_2Cl_2	40	41.5	85
2	$Yb(OTf)_3$	DCE	40–50	29	69
3	$Yb(OTf)_3$	toluene	40–50	20	83
4	$Yb(OTf)_3$	THF	40–50	9.5	>96
5	$Yb(OTf)_3$	$CHCl_3$	40–50	28.5	69
6	$Yb(OTf)_3$	THF	40–50	32.5	68[c]
7	$Yb(OTf)_3$	THF	66	10.5	83[c]
8	$Sc(OTf)_3$	THF	40-50	16.5	64
9	$Mg(ClO_4)_2{\cdot}6H_2O$	THF	40–50	23.5	29

[a] Reaction conditions, unless otherwise stated: **2a** (0.60 mmol), **1a** (0.20 mmol), Lewis acid (20 mol %), solvent (7.0 mL), N_2 atmosphere. [b] Determined by ^1H NMR spectroscopy after purification by column chromatography. [c] $Yb(OTf)_3$ (10 mol %) was used.

The structure of **3a** (exclusively as the *Z* isomer) was established by ^1H and ^{13}C NMR spectroscopy and single-crystal X-ray diffraction (Figure 1).[13] The resulting tetrahydro-1,2-oxazine skeleton is known in many bioactive natural products, and is a valuable intermediate for target molecules.[14]

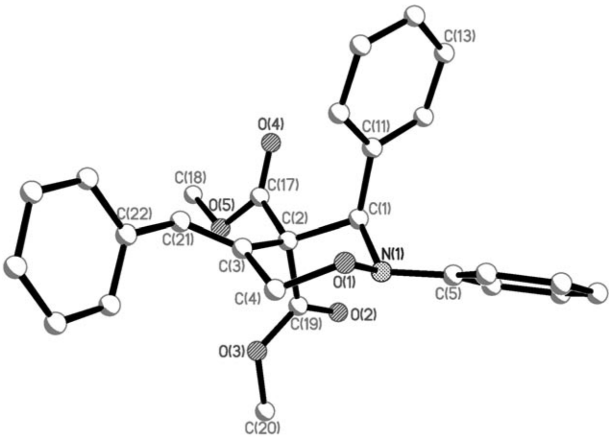
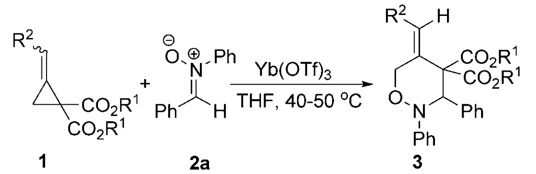


Figure 1. X-ray crystal structure of **3a**.

A wide range of electronically and structurally diverse MCPs **1** can also be employed in this reaction (Table 2). The reactions of C,N-diarylnitrone **2a** with MCP-1,1-diesters **1f**–**i** (as a mixture of two isomers) all gave exclusively the *Z*-

Table 2. Reactions of C,N-diarylnitrone **2a** with various MCP-1,1-diesters **1**.[a]



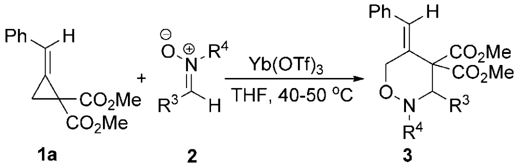
Entry	1	R^1	R^2	t [h]	Product 3	Yield [%][b]
1	**1a**	Me	C_6H_5	9.5	**3a**	98
2	**1b**	Me	p-$MeOC_6H_4$	21	**3b**	83
3	**1c**	Me	p-$CH_3C_6H_4$	5	**3c**	93
4	**1d**	Me	p-BrC_6H_4	70	**3d**	51
5	**1e**	Me	p-ClC_6H_4	21.5	**3e**	78
6	**1f**[c]	Me	Bn	45.5	**3f**	55[d]
7	**1g**[c]	Me	$Ph(CH_2)_2$	39.5	**3g**	94[d]
8	**1h**[c]	Me	$Ph(CH_2)_3$	33	**3h**	89[d]
9	**1i**[c]	Me	n-C_7H_{15}	51	**3i**	64
10	**1j**	Me	1-naphthyl	36	**3j**	66
11	**1k**	Et	Ph	14	**3k**	98

[a] Reaction conditions, unless otherwise stated: **2a** (0.60 mmol), **1a** (0.20 mmol), $Yb(OTf)_3$ (20 mol %), THF (7.0 mL) at 40-50 °C, N_2 atmosphere. [b] Yields isolated by column chromatography on silica gel. [c] Mixture of two isomers; for *E*/*Z* ratios, see the Supporting Information. [d] $Yb(OTf)_3$ (30 mol %) was used.

isomers of **3f**–**i**, in moderate-to-excellent yields (Table 2, entries 6–9).

Further studies revealed that the cycloadditions of a variety of C,N-diarylnitrones **2** with MCP **1a** also proceeded smoothly to give the corresponding products **3l**–**t** in 61–98 % yields as single isomers (Table 3, entries 1–9). It should be mentioned that reactions of C,N-dialkyl nitrones with MCP **1a** did not give positive results, probably due to the intrinsic instability of such nitrones to Lewis acids.

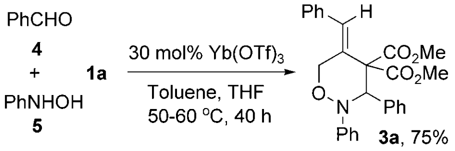
Table 3. Reactions of MCP-1,1-diester **1a** with several C,N-diarylnitrones **2**.[a]



Entry	**2**	R^3	R^4	*t* [h]	Product **3**	Yield [%][b]
1	**2b**	C_6H_5	*m*-ClC_6H_4	11	**3l**	85
2	**2c**	C_6H_5	*p*-ClC_6H_4	13	**3m**	90
3	**2d**	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	5.5	**3n**	94
4	**2e**	*m*-$MeOC_6H_4$	*p*-ClC_6H_4	15	**3o**	98
5	**2f**	p-$MeOC_6H_4$	*p*-BrC_6H_4	5.5	**3p**	93
6	**2g**	p-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	23	**3q**	68[c,d]
7	**2h**	p-IC_6H_4	*p*-ClC_6H_4	45.5	**3r**	66[c]
8	**2i**	C_6H_5	CH_3	72	**3s**	61[d]
9	**2j**	2-furyl	*m*-ClC_6H_4	25.5	**3t**	81
10	**2i**	C_6H_5	CH_3	53[e]	**3u**	56[c]

[a] The reaction conditions are as outlined in Table 2. For details of procedure and analysis, see the Supporting Information. [b] Yields isolated by column chromatography on silica gel. [c] $Yb(OTf)_3$ (30 mol %) was used. [d] Reaction was carried out at 66 °C. [e] Scaled-up reaction with **1c** (27 mmol).

A three-component one-pot adaptation of this cycloaddition, using aldehyde **4**, hydroxylamine **5**, and MCP-1,1-diester **1a** was also developed, and afforded **3a** in 75 % yield (Scheme 3).



Scheme 3. Three-component one-pot formal [3+3] cycloaddition.

The N–O bond cleavage of compound **3a** has been attempted, to allow for synthetic elaboration of the tetrahydro-1,2-oxazine derivatives. However, when treated with either zinc in acetic acid or SmI_2 in THF, compound **3a** underwent decomposition.[15]

In summary, we have disclosed a new type of Lewis acid-promoted distal [3+3] cycloaddition of MCP-1,1-diesters and C,N-diarylnitrones, with high site-, regio- and stereoselectivity. A three-component one-pot version of this cycloaddition was also developed. Further efforts on extensive study and application of this cycloaddition are in progress.

Experimental Section

General procedure for the [3+3] Cycloaddition of methylenecyclopropanes (MCPs) with C,N-diarylnitrones: $Yb(OTf)_3$ (25 mg, 0.04 mmol, 20 mol %), MCP **1** (0.20 mmol), C,N-diarylnitrone **2** (0.60 mmol) and dry THF (7 mL) were stirred at 40–50 °C under a nitrogen atmosphere for the time indicated in Tables 2 and 3. After completion of the reaction (as monitored by TLC), the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: ethyl acetate/petroleum ether) to afford **3**. **3a**: Yield 98 %, single Z-isomer, white solid; m.p. 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.43 (t, $J=7.2$ Hz, 2H), 7.38–7.25 (m, 5H), 7.23–7.10 (m, 5H), 7.05 (s, 1H), 6.70–6.83 (m, 3H), 5.67 (s, 1H), 5.18 (d, $J=13.2$ Hz, 1H), 4.91 (d, $J=13.2$ Hz, 1H), 3.93 (s, 3H), 3.55 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=170.0$, 167.3, 148.6, 136.1, 135.1, 131.6, 130.5, 130.2, 129.1, 128.5, 128.1, 127.6, 127.4, 122.5, 116.8, 71.7 ,70.1 ,64.5, 53.6, 52.5 ppm; IR (KBr): $\tilde{\nu}=3062$, 3028, 2952, 2934, 1752, 1727, 1599, 1489, 1433, 1255, 1221, 1025, 759, 695 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{25}NO_5Na$ $[M+Na]^+$: 466.1625; Found: 466.1624.

Typical Procedure for the Three-Component Reaction: $Yb(OTf)_3$ (30 mol %) was added to a solution of the benzaldehyde **4** (1.32 mmol) and hydroxylamine **5** (1.20 mmol) in dry toluene (5 mL) containing activated 4 Å molecular sieves. The solution was stirred under a nitrogen atmosphere for 3.5 h at room temperature, after which the MCP **1a** (0.4 mmol) dissolved in dry THF (5 mL) was added, and the mixture was heated to 50–60 °C for 40 h. Upon disappearance of the MCP **1a**, the reaction mixture was filtered and the filtrate was evaporated in vacuo. Pure product **3a** (133 mg, 75 %) was obtained after column chromatography on silica gel (eluent: EtOAc in petroleum ether).

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Keywords: cycloaddition · Lewis acids · nitrones · selectivity · small ring systems

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[15] Two experiments were carried out to investigate N−O bond cleavage of **3a**: a) Reaction of **3a** with Zn/AcOH at room temperature for 8 h led to the decomposition of **3a**; b) With SmI_2/THF, at room temperature overnight, no reaction occurred; heating the mixture at reflux for 5 h led to the decomposition of **3a**. Similar difficulties have also been reported by Kerr and co-workers.[14j,14l] Seemingly, substituents on the tetrahydro-1,2-oxazine skeleton affect N−O bond cleavage.

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