

Catalyst-Controlled Chemoselective All-Alkene [2 + 2 + 2] and [2 + 2] Cyclizations of Enamides with Electron-Deficient Alkenes

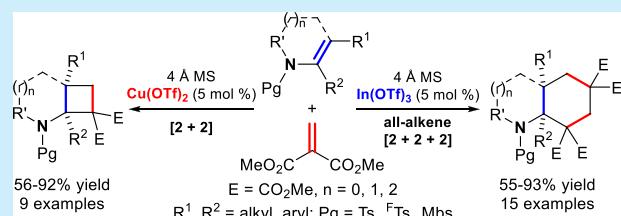
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Supporting Information

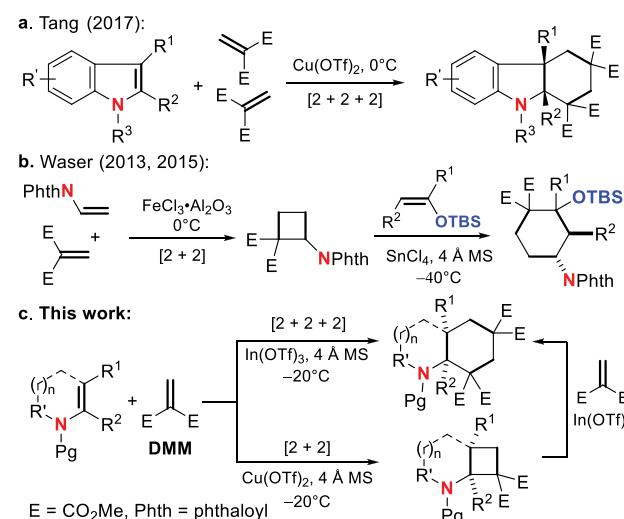
ABSTRACT: In the presence of 4 Å MS, both all-alkene [2 + 2 + 2] and [2 + 2] cyclizations of dimethyl methylenemalonate (DMM) with *N*-sulfonyl enamides were selectively achieved under $\text{In}(\text{OTf})_3$ and $\text{Cu}(\text{OTf})_2$ catalysis, respectively. $\text{In}(\text{OTf})_3$ -catalyzed [4 + 2] cyclization of the sulfonylamidocyclobutanes with another molecule of DMM or other electron-deficient alkenes was also reported.



Cycloadditions, as exemplified by the venerable Diels–Alder reaction, are among the most widely used and efficient methods for construction of cyclic compounds from simple π -systems in organic synthesis.¹ Since the pioneering discovery of thermal and transition-metal-catalyzed cyclo-trimerization of acetylene to benzene,² transition-metal-catalyzed [2 + 2 + 2] cycloaddition reactions have been extensively investigated for the preparation of structurally diverse carbo- and heterocyclic six-membered rings.³ Similar to the popularity of alkynes in transition-metal-catalyzed [2 + 2 + 2] cycloadditions, alkenes are also widely employed π -components in these cyclization processes.^{3g} More importantly, the use of alkenes could deliver the cycloadducts with a high degree of stereochemical complexity,^{4,5} whereas alkyne cyclotrimerization typically generates planar benzenoids. Notably, all-alkene [2 + 2 + 2] cycloaddition could theoretically give cyclohexanes with six continuous stereocenters, which are very attractive yet challenging.⁵ In sharp contrast to olefin linear trimerization,⁶ reports on all-alkene [2 + 2 + 2] cycloadditions are relatively rare, and very few examples using ene–allenes⁵ or conformationally restricted bis-alkenes⁷ have been disclosed.

Inspired by our recent discovery of a copper-catalyzed formal [2 + 2 + 2] cycloaddition reaction of indoles with two molecules of dimethyl methylenemalonate (DMM),^{4f} we wondered if all-alkene [2 + 2 + 2] cycloaddition reaction of DMM with other electron-rich alkenes that replace indoles, such as enamides, can be realized (a, Scheme 1). This seems to be challenging since under Lewis acid catalysis (1) DMM has been found to readily undergo formal [2 + 2] cycloaddition reaction with *N*-vinyl phthalimide^{8,9} and (2) the generated aminocyclobutane further reacted with electron-rich alkenes such as enol ethers to produce the cyclohexane derivatives (b, Scheme 1).¹⁰ Surprisingly, we recently found that, by the use of *N*-sulfonyl enamides, both all-alkene [2 + 2 + 2] and [2 + 2]

Scheme 1. Catalyst-Controlled Cycloaddition Reactions of Enamine Derivatives with DMM



cycloaddition reactions of DMM could be selectively controlled by different Lewis acid catalysts. The resulting donor–acceptor (D–A) cyclobutanes readily react with another molecule of DMM to generate the cyclohexanes (c, Scheme 1), indicative of the rare nucleophilicity of strained D–A cycloalkanes.¹¹ Taking advantage of the subtle reactivity difference, three-component [2 + 2 + 2] annulation of sulfonyl enamides with DMM and less activated alkenes was realized.

Initially, the cyclic enamide *N*-tosyl-2,3-dihydropyrrole (**1a**) was attempted to react with DMM at $-20\text{ }^\circ\text{C}$ in dichloromethane in the presence of 10 mol % of $\text{Cu}(\text{OTf})_2$,^{4f} affording

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the desired cyclohexane **2a** in 39% yield (Table 1, entry 1). Encouraged by this result, a wide range of Lewis acids were

Table 1. Optimization of the [2 + 2 + 2] Cyclization

entry	catalyst	time (h)	yield ^{a,b} (%)
1	Cu(OTf) ₂	8	39
2	Cu(NTf ₂) ₂	8	54
3	Cu(ClO ₄) ₂ ·6H ₂ O	8	49
4	FeCl ₃	8	52
5	InCl ₃	8	trace
6	Ni(OTf) ₂	8	trace
7	Yb(OTf) ₃	8	trace
8	Fe(OTf) ₃	8	16
9	In(OTf) ₃	4	78
10	Sc(OTf) ₃	8	63
11 ^c	In(OTf) ₃	4	92
12 ^{e,f}	In(OTf) ₃	4	95
13 ^{e,e}	In(OTf) ₃	4	93
14 ^{e,f}	In(OTf) ₃	4	71
15 ^{e,g}	In(OTf) ₃	4	89

^aReaction conditions: **1a** (0.2 mmol), DMM (0.6 mmol), catalyst (0.02 mmol) in DCM (2.0 mL), -20 °C. ^bYield determined by the ¹H NMR spectrum of the crude mixture with tetrachloroethane (TTCE) as an internal standard. ^cWith 4 Å MS (50 mg). ^dCatalyst (5 mol %). ^eCatalyst (2 mol %). ^fPerformed at -40 °C. ^gRun at 0 °C.

then investigated, and the results were summarized in Table 1. Other copper salts such as Cu(NTf₂)₂ and Cu(ClO₄)₂·6H₂O showed slightly better catalytic activities (Table 1, entries 2 and 3). As the use of metal chlorides such as FeCl₃ and InCl₃ resulted in no improvement (Table 1, entries 4 and 5), we then turned to well-established metal triflates as catalysts. While nickel and ytterbium triflates were found to be inactive (Table 1, entries 6 and 7) and a lower yield of **2a** was observed with iron triflate (Table 1, entry 8), both indium and scandium triflates led to the formation of **2a** in improved yields (Table 1, entries 9 and 10), and the reaction catalyzed by In(OTf)₃ was completed in a shorter time. Notably, the addition of 4 Å MS to the reaction mixture improved the yield to 92% (Table 1, entry 11), whereas the reactions were unaffected when the reduced catalyst loadings were employed (Table 1, entries 12 and 13). The temperature is important since the yields of **2a** dropped down at the higher or lower reaction temperatures (Table 1, entries 14 and 15). Overall, no diastereomer was observed under the reaction conditions studied.

Under the optimal conditions, a variety of sulfonyl enamides were then examined for the all-alkene [2 + 2 + 2] annulation with DMM. As shown in Figure 1, 2,3-dihydropyrrole protected by the slightly stronger electron-withdrawing *N*-*p*-fluorotosyl group (^FTs, **1b**) was less reactive than **1a**, providing **2b** in 84% isolated yield at rt. Thus, *N*-tosylated 2,3-dihydropyrroles with various 4-alkyl substituents, such as methyl (**1c**), *n*-propyl (**1d**), benzyl (**1e**), allyl (**1f**), and propargyl (**1g**), were studied, and good to excellent yields of the corresponding octahydroindoles (**2c–g**) were obtained albeit for a prolonged time. The pendant multiple bonds in **2c** and **2g** may allow for further elaboration. In addition, 4,5-

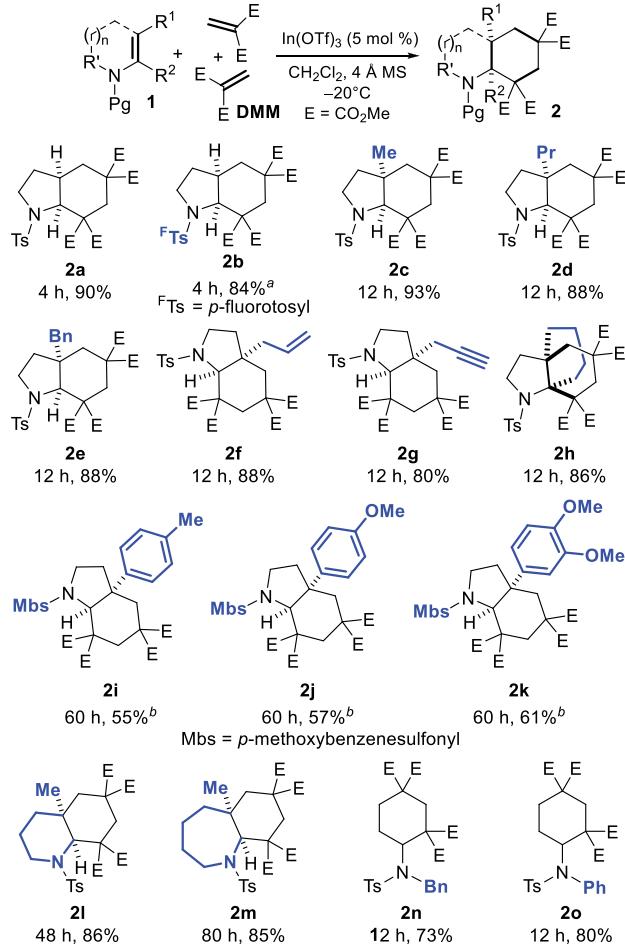


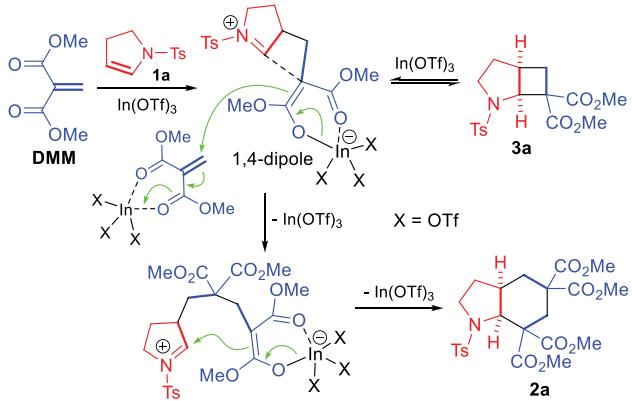
Figure 1. Scope for the [2 + 2 + 2] cyclization: **1** (0.3 mmol), DMM (0.9 mmol), In(OTf)₃ (5 mol %), and 4 Å MS (75 mg) in DCM (3.0 mL), -20 °C. Isolated yield. (a) Run at rt. (b) Run on 0.2 mmol scale (1).

annulated *N*-tosyl-2,3-dihydropyrrole **1h** worked well, giving the tricyclic product **2h** in 86% yield that resembles the core structure of the hasubanan and acutumine alkaloids.¹² To compensate for the reduced reactivity of the double bond caused by the conjugate effect of aryls, the less electron-withdrawing *p*-methoxybenznesulfonyl group (Mbs)¹³ was chosen for 4-aryl-2,3-dihydropyrroles, and the arylated octahydroindoles **2i–k** were isolated in acceptable yields, although a longer reaction time was needed. In addition, this cyclization was applicable for the larger cyclic enamides (**1l** and **1m**) and acyclic ones bearing *N*-alkyl (**1n**) or *N*-aryl (**1o**) substituents.

Lewis acid catalyzed formal [4 + 2] cycloaddition reactions of D–A cyclobutanes with unsaturated molecules have been extensively studied by several groups.^{10,14} Generally, the unsaturated components such as aldehydes, imines, indoles, and enol ethers act as the nucleophile to trigger the cyclization.^{11a,14b} However, in the current reaction, electron-deficient DMM is unlikely to serve as a nucleophile to initiate the annulation with the putative D–A aminocyclobutanes or the zwitterionic 1,4-dipoles formed from the first molecule of DMM and sulfonyl enamides. Instead, possibly due to the strong donating ability of the sulfonylamido group,¹⁵ the cyclobutane ring is prone to open upon interacting with Lewis acid and the nucleophilic attack of the zwitterionic 1,4-dipole

intermediates on DMM may initiate the annulation (**Scheme 2**), similar to that proposed in the [4 + 2] cyclization of D-A.

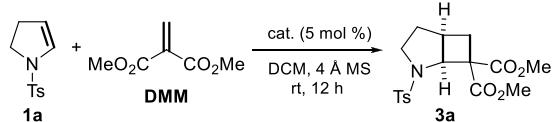
Scheme 2. Proposed Pathway for [2 + 2 + 2] Cyclization



cyclobutanes by *N*-heterocyclic carbene catalysis.^{11b} In this regard, sulfonylamidocyclobutanes are in great demand for exploring their possible [4 + 2] annulation with DMM.

The initial trial for the $\text{In}(\text{OTf})_3$ -catalyzed reaction performed at -78°C was not successful (**Table 2**, entry 1).

Table 2. Optimization of the [2 + 2] Cyclization



entry	catalyst	yield ^{a,b} (%)
1 ^c	$\text{In}(\text{OTf})_3$	no reaction
2	$\text{Yb}(\text{OTf})_3$	trace
3	InCl_3	trace
4	FeCl_3	(50) ^d
5	$\text{Cu}(\text{ClO}_4)_2 \bullet 6\text{H}_2\text{O}$	(60) ^d
6	$\text{Ni}(\text{OTf})_2$	69
7	$\text{Fe}(\text{OTf})_3$	45
8	$\text{Cu}(\text{OTf})_2$	82
9 ^e	$\text{Cu}(\text{OTf})_2$	90
10 ^{e,f}	$\text{Cu}(\text{OTf})_2$	90

^aReaction conditions: **1a** (0.2 mmol), DMM (0.5 mmol), catalyst (0.01 mmol), and 4 Å MS (20 mg) in DCM (2.0 mL), rt. ^bYield determined by the ¹H NMR spectrum of the crude mixture with TTCE as an internal standard. ^cRun at -78°C . ^dProduct **2a**. ^eRun at -20°C , 24 h. ^fDMM (0.3 mmol).

Several attempts with reported Lewis catalysts such as $\text{Yb}(\text{OTf})_3$ ^{9d} and InCl_3 ^{10b} afforded only a trace amount of **3a** (**Table 1**, entries 2 and 3), whereas those with FeCl_3 ⁸ and $\text{Cu}(\text{ClO}_4)_2 \bullet 6\text{H}_2\text{O}$ ^{4g,9g} produced cyclohexane **2a** in moderate yields (**Table 2**, entries 4 and 5). Pleasingly, in the presence of 4 Å MS, nickel triflate that proved to be inactive in the all-alkene [2 + 2 + 2] cycloaddition showed a promising reactivity for the [2 + 2] annulation, which afforded **3a** in 69% yield (**Table 2**, entry 6). Encouraged by this finding, both $\text{Fe}(\text{OTf})_3$ and $\text{Cu}(\text{OTf})_2$ were then studied, of which the latter exhibited a superior result, thereby giving **3a** in 82% yield (**Table 2**, entries 7 and 8). Cooling the reaction at -20°C further improved the product yield to 90%, although a longer time took for the completion of the reaction (**Table 2**, entry 9).

Notably, the product yield remained constant when 1.5 equiv of DMM was employed (**Table 2**, entry 10).

Like the $\text{In}(\text{OTf})_3$ -catalyzed all-alkene [2 + 2 + 2] annulation, the $\text{Cu}(\text{OTf})_2$ -catalyzed [2 + 2] cyclization showed the similar tolerance for different functionalities. As depicted in **Figure 2**, aminocyclobutanes bearing *N*-*p*-fluorotosyl (3b),

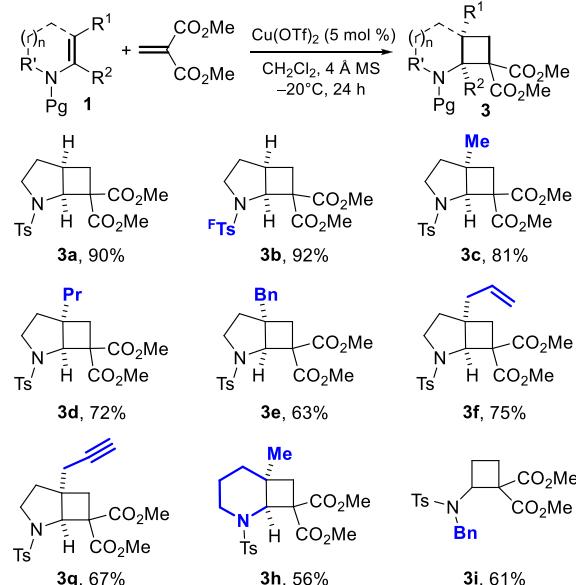


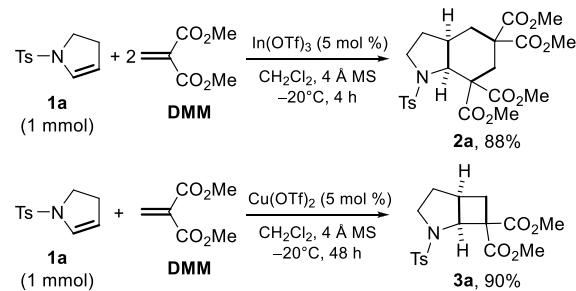
Figure 2. Scope for the [2 + 2] cyclization: **1** (0.2 mmol), DMM (0.3 mmol), $\text{Cu}(\text{OTf})_2$ (5 mol %), and 4 Å MS (20 mg) in DCM (2.0 mL), -20°C , 24 h. Isolated yield.

saturated and unsaturated alkyls (**3c-g**), six-membered azacyclic (**3h**), and acyclic (**3i**) topologies were prepared in good to excellent yields. Unfortunately, 3-aryl-substituted 2,3-dihydropyrroles were not reactive under the copper triflate catalysis.

Both the [2 + 2 + 2] and [2 + 2] cyclizations are highly diastereoselective since only the *cis*-annulated diastereomers were observed for **2a-m** and **3a-h**. The relative stereochemistry of **2j**, **2m**, and **3e** was unambiguously confirmed by single-crystal X-ray analysis. Additionally, both annulation reactions could be run on a 1 mmol scale without notable loss of the yields (**Scheme 3**).

With **3a** in hand, the reaction of **3a** with DMM catalyzed by indium triflate in the presence of 4 Å MS was then investigated. As expected, **2a** was isolated in 77% yield (**Scheme 4**), thereby supporting the proposed reaction pathway shown in **Scheme 2**. Interestingly, under either

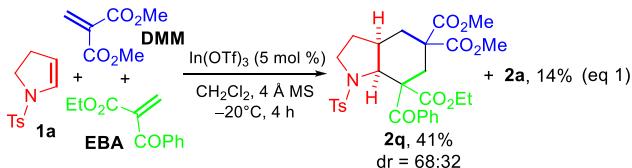
Scheme 3. [2 + 2 + 2] and [2 + 2] Cyclization at 1 mmol Scale



Scheme 4. In(OTf)₃-Catalyzed [4 + 2] Cyclization of 3a with Electron-Deficient Alkenes



In(OTf)₃ or Cu(OTf)₂ catalysis, both di-*tert*-butyl methylenemalonate (DBM) and ethyl 2-benzoyl acrylate (EBA) were unreactive with enamide 1a. However, both were successfully inserted into cyclobutane 3a catalyzed by In(OTf)₃, yielding octahydroindoles 2p and 2q in 74% and 76% yields, respectively (**Scheme 4**). Moreover, a three-component reaction of 1a with DMM and EBA under the same conditions produced 2q in 41% yield along with 14% yield of 2a (**eq 1**), demonstrating the viability of the Lewis acid-catalyzed one-pot [2 + 2 + 2] cycloaddition reaction with three different alkenes.



In summary, catalyst-controlled stereoselective [2 + 2 + 2] and [2 + 2] cycloaddition reactions of *N*-sulfonyl enamides and dimethyl methylenemalonate have been developed for the first time, providing convenient and practical synthetic methods for the valuable aminated cyclohexanes and cyclobutanes from the same starting substrates. The amino-cyclobutanes resulting from the Cu(OTf)₂-catalyzed [2 + 2] annulation could readily undergo the In(OTf)₃-catalyzed [4 + 2] cyclization with another molecule of electron-deficient alkenes, including dimethyl methylenemalonate itself, to produce the aminocyclohexanes, demonstrating the unprecedented nucleophilicity of the donor–acceptor cyclobutanes for triggering the annulation under Lewis acid catalysis. Moreover, relying on the subtle reactivity change, the all-alkene [2 + 2 + 2] cycloaddition reaction of one sulfonyl enamide with dimethyl methylenemalonate and less activated alkenes has been also exemplified.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.9b00209](https://doi.org/10.1021/acs.orglett.9b00209).

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1890561–1890563 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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