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Direct Intramolecular Conjugate Addition of Simple Alkenes to α,β-Unsaturated Carbonyls Catalyzed by $Cu(OTf)_2$

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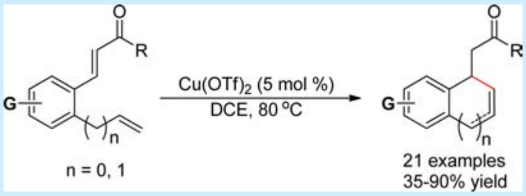
Supporting Information

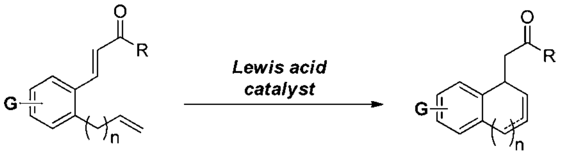
ABSTRACT: An unprecedented intramolecular conjugate addition of simple alkenes to α,β-unsaturated carbonyl compounds has been developed. A simple Lewis acid such as $Cu(OTf)_2$ was found to effectively catalyze the reaction, and six- and five-membered cyclic products were obtained in moderate to high yields.



As a fundamental C−C bond forming reaction, conjugate addition to α,β-unsaturated carbonyl compounds has been extensively explored and the employed carbon nucleophiles vary with an extensive range.[1] Due to the low nucleophilicity as well as uncontrolled side reactions, simple alkenes have seldom been explored in conjugate addition reactions. Typical methods to introduce a vinyl group onto α,β-unsaturated carbonyl compounds require stoichiometric vinyl organometallic reagents,[2] such as alkenylalanes,[2b−g] organosiloxanes,[2j,k] alkenylboronic acid,[2l−p] etc. In 2008, Jamison[3] and Ogoshi[4] independently reported the addition of an unactivated alkene to enones under the catalysis of Ni(0). Yi has advanced ruthenium catalysts[5,6] for this reaction to synthesize tetrasubstituted olefins. In an early work, Snider and co-workers reported that a stoichiometric amount of a Lewis acid catalyzed the addition of alkenes to α,β-enones.[7] In 2013, Okamoto and Ohe described an acid-catalyzed addition of simple alkenes to β-silyl substituted enones.[8] Very recently, we developed an anionic ligand strategy to facilitate β-proton elimination by suppressing cationic olefin polymerization, thus enabling the β-vinylation of enones with a variety of simple alkenes.[9]

Despite these advances in intermolecular additions, examples of intramolecular addition of alkenes to enones, a versatile strategy to access carboncycles, are scarce. Recently, Toste and Bergman[10] documented a rare example of a formal intramolecular addition of alkenes to enones, wherein stoichiometric $CpCo(NO)_2$ was employed to mediate the addition. As a continuation to our recent efforts on carbocation based functionalization of olefins, we have explored the direct intramolecular addition of alkenes to enones. In this regard, a simple Lewis acids such as $Cu(OTf)_2$ was found to be a viable catalyst for the intramolecular alkene addition, providing a facile route for the synthesis of six- and five-membered carbocycles[5,6,11] (Scheme 1).

Scheme 1. Intramolecular Conjugate Addition of *Alkenes to Enones*



The *ortho*-allylic chalcone **1a** was chosen as a model substrate (Table 1). Different metal triflates have been found to promote the reactions (Table 1, entries 1−5) to give cyclic product **2a** with the double bond being conjugated with the phenyl ring. The use of other Lewis acids as well as a strong Brønsted acid such as TfOH led to inferior results (Table 1, entries 6−9). $Cu(OTf)_2$ was eventually identified as the optimal catalyst, delivering **2a** with a 90% yield in 4 h (Table 1, entry 5). Other copper salts failed to catalyze this reaction (Table 1, entries 10−13). In further optimization, different solvents were screened (Table 1, entries 14−18). The reaction worked favorably in chlorinated solvents, such as chloroform, dichloroethane, and chlorobenzene (Table 1, entries 5, 17, and 18), while other solvents were ineffective (Table 1, entries 14−16). The reaction became quite sluggish under lower temperature (Table 1, entries 19 and 20). Under higher temperature, most of the starting material decomposed and no desired product was observed (Table 1, entry 21). The addition of anionic ligand **L1**, the one that showed dramatic performance in the intermolecular addition,[9] led to no improvement (Table 1, entry 22). It seems the intramolecular setting suppresses most of the carbocationic side pathways in this case.

With the optimum reaction conditions, we next surveyed the scope of the conjugate addition of α,β-unsaturated ketones (Table 2) . A variety of *ortho*-allylic chalcones bearing either electron-withdrawing or -donating groups could proceed smoothly under the conditions (Table 2, entries 1−8), although the electron-donating group substituted chalcones led to lower

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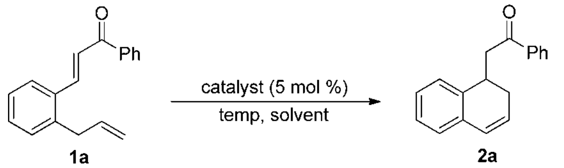
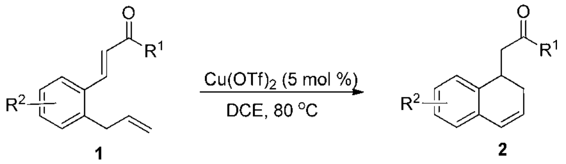
Table 1. Screening of the Reaction Conditions for the Intramolecular Conjugate Addition[a]

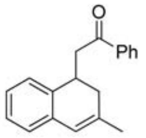
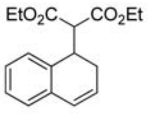


entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]
1	Sc(OTf)$_3$	DCE	80	10	10
2	In(OTf)$_3$	DCE	80	10	35
3	AgOTf	DCE	80	24	73
4	Bi(OTf)$_3$	DCE	80	4	67
5	Cu(OTf)$_2$	DCE	80	4	90
6	BF$_3$·Et$_2$O	DCE	80	4	–[d]
7	TfOH[c]	DCE	80	4	–[d]
8	FeCl$_3$	DCE	80	24	<5
9	InBr$_3$	DCE	80	24	<5
10	CuCl$_2$	DCE	80	24	<5
11	CuBr$_2$	DCE	80	24	<5
12	CuCl	DCE	80	24	<5
13	CuBr	DCE	80	24	<5
14	Cu(OTf)$_2$	THF	80	24	<5
15	Cu(OTf)$_2$	MeOH	80	24	<5
16	Cu(OTf)$_2$	toluene	80	24	<5
17	Cu(OTf)$_2$	CHCl$_3$	80	24	60
18	Cu(OTf)$_2$	C$_6$H$_5$Cl	80	24	69
19	Cu(OTf)$_2$	DCE	60	>48	trace
20	Cu(OTf)$_2$	DCE	40	>48	N.R.
21	Cu(OTf)$_2$	DCE	100	2	–[d]
22[e]	Cu(OTf)$_2$/**L1**	DCE	80	18	15

[a] The general reaction was carried out on a 0.1 mmol scale in 1 mL of solvent, and the catalyst load was 0.005 mmol. [b] Isolated yield. [c] At room temperature, TfOH gave a 41% yield. [d] Most of the substrate was decomposed. [e] **L1**: (*S*)-BINOL-phosphoric acid (0.005 mmol). DCE: dichloroethane. THF: tetrahydrofuran. Tf: trifluoromethanesulfonyl. N.R. = no reaction.

Table 2. Intramolecular Conjugate Addition of *ortho*-Allylic Chalcone 1[a]



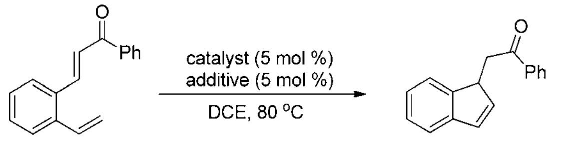
entry	R$_1$	R$_2$	product	time (h)	yield (%)[b]
1	Ph	H	**2a**	5	90
2	4-ClC$_6$H$_4$	H	**2b**	5	77
3	4-FC$_6$H$_4$	H	**2c**	4	70
4	4-NO$_2$C$_6$H$_4$	H	**2d**	5	72
5	4-CH$_3$C$_6$H$_4$	H	**2e**	10	75
6	4-CH$_3$OC$_6$H$_4$	H	**2f**	24	51
7	3-ClC$_6$H$_4$	H	**2g**	10	71
8	3-CH$_3$OC$_6$H$_4$	H	**2h**	10	44
9	Ph	5-Cl	**2i**	5	80 (79)[c]
10	Ph	5-F	**2j**	10	72
11	Ph	4-CH$_3$	**2k**	10	59
12[d]			 Ph **2l**	1	82
13			 EtO$_2$C CO$_2$Et **2m**	10	51
14	2-thiophenyl	H	**2n**	24	71
15	2-pyridinyl	H	**2o**	24	N.R.

[a] The general reaction was carried out on a 0.1 mmol scale in 1 mL of solvent, and the catalyst load was 0.005 mmol. [b] Isolated yield. [c] The reaction was carried out on a 1.0 mmol scale. [d] At 60 °C.

yields (Table 2, entries 6, 8). Meanwhile, 5′-chloro, 5′-fluoro, and 4′-methyl substituted on the allylphenyl moiety were also well tolerated to give the desired adducts with good yields (Table 2, entries 9−11). Moreover, (2-methyl)-allylic chalcone was also a good substrate to give **2l** in 82% yield at 60 °C. At a higher temperature, the reaction gave 2-methylnapthalene via elimination of the phenyl ketone moiety.[12] Michael acceptors other than enones have also been examined. While the switch of the keto moiety to nitro or dinitrile led to no reactions, the reaction of an alkenyl diester proceeded to give the corresponding cyclized adduct in 51% yield (Table 2, entry13). These results suggested that carbonyl binding with Cu(II) may be a critical determinant for the reaction to occur. To expand the scope of substrates, we changed the R$_1$ groups to heterocycles next. Fortunately, **2n** with a thiophene cycle was obtained under the standard conditions by prolonging the reaction time to 24 h (Table 2, entry 14). However, the reaction failed with a pyridine group (Table 2, entry15), indicating an adverse effect of pyridine coordination with Cu(II).

The cyclization of vinyl chalcones (styrenes) was next investigated. The reaction is expected to deliver indene-type products. Indenes are versatile structural units in organic synthesis.[13] This type of compounds can also serve as ligands for transition metals, and the synthesis of substituted indenes is hence of significant interest. In pursuing the direct intramolecular vinylaiton of enones, we were quite delighted to find out that the reaction under the same conditions utilized for allyl chalcones gave indene product **4a** in 47% yield (Table 3, entry 1). The reaction was much faster than that with an allyl chalcone, requiring only 2 h for complete conversion. However, serious polymerization of starting styrenes was clearly observed, which accounted for the low isolated yield. Efforts were then put forward to suppress this polymerization side pathway. Examination of other Lewis acids led to either inferior results or completely no activity (Table 3, entries 2, 3). Extensive screening of additives such as PCy$_3$, pyridine, and bipyridine as well as the employment of **L1** failed to provide obvious improvement (Table 3, entries 4−7). Further optimizations of reaction conditions including catalyst loading, solvent, and

Table 3. Screening of the Reaction Conditions for the Intramolecular Conjugate Addition[a]



3a **4a**

entry	catalyst	additive	temp (°C)	*t* (h)	yield (%)[b]
1	$Cu(OTf)_2$	–	80	2	47
2	$Sc(OTf)_3$	–	80	24	23
3	$Bi(OTf)_3$	–	80	24	17
4	$Cu(OTf)_2$	PCy_3	80	42	38
5	$Cu(OTf)_2$	pyridine	80	42	NR
6	$Cu(OTf)_2$	bipyridine	80	42	10
7	$Cu(OTf)_2$	**L1**	80	42	25

[a] The general reaction was carried out on a 0.1 mmol scale in 1 mL of solvent, and the catalyst load was 0.005 mmol. [b] Isolated yield.

reaction temperature were disappointingly in vain. In this context, it seemed that the substituted styrene is inherently active with a tendency to undergo polymerization under acidic conditions. Nevertheless, as the desired indene products were easily separated from the polymerized side products, we deemed the current protocol to be of synthetic potential and the scope of the reaction was hence explored.

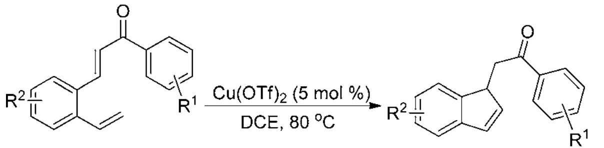
We synthesized a series of substituted 2-vinyl chalcones and tested them in the cyclization reactions. Chalcones bearing either electron-withdrawing or -donating groups are equally applicable to give indenes with moderate yields (Table 4, **4a**). Changing the *α*,*β*-unsaturated ketone to an alkenyl diester gave the corresponding product **4h** in 48% yield. At the same time, substrates of 5′-methyl and 5′-chloro substituted on the styrene moiety were synthesized. Though both were tolerated to give the desired adducts (Table 4, **4i** and **4j**), the reaction with electron-withdrawing substituted styrene proceeded more cleanly with less polymerization (Table 4, **4j**). A pyridine-containing substrate did not work under the conditions (Table 4, **4k**). Interestingly, when styrene **3g**, as an inseparable mixture of *Z* and *E* geometric isomers, was subjected to the reaction, only the *E* configuration could react to give the product **4g** in 50% yield and the remaining *Z*-isomer could be quantitatively recovered as an essentially pure regioisomer (Scheme 2). In this instance, the double bond was arranged in a tetrasubstituted geometry in the cyclized adduct **4g**.

The intramolecular addition to imine has also been examined. In this regard, $Bi(OTf)_3$ was found to be more active than $Cu(OTf)_2$ and the reaction occurred smoothly to give vinyl amine **6** in 74% yield at room temperature (Scheme 3). This represents a rare example of direct intramolecular alkenyl addition to *N*-sulfonyl aldimines.[14]

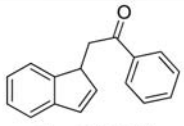
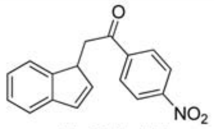
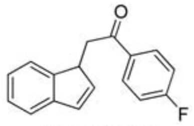
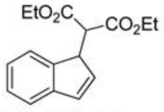
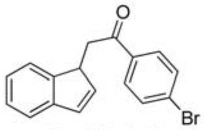
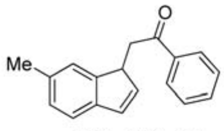
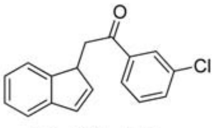
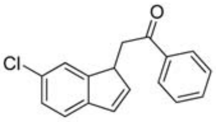
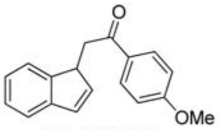
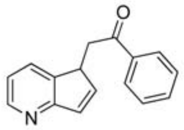
Mechanistically, the reactions were proposed to occur via the carbocation intermediates (Scheme 4). In this scenario, the carbonyl oxygen atom first coordinated to the Lewis acid catalyst $Cu(OTf)_2$. Then the carbocation intermediate was generated by the addition of the alkene to the *β*-carbon atom of the activated enone. The intermediate **A** underwent deprotonation to afford the *δ*, *ε*-unsaturated ketone **2a**.[15]

In summary, we have developed a novel catalytic method for the intramolecular conjugate addition of simple alkenes to *α*,*β*-unsaturated carbonyl compounds catalyzed by $Cu(OTf)_2$. Six- and five-membered cyclic products were obtained in moderate

Table 4. Intramolecular Conjugate Addition of *ortho*-Vinyl Chalcone 3[a,b]

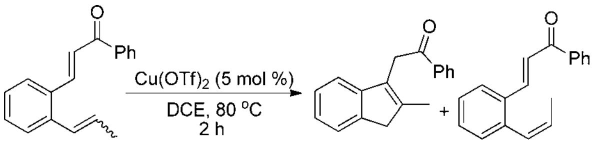


3 **4**

entry	product	entry	product
4a	 2h, 47% yield	**4f**	 4 h, 38% yield
4b	 2h, 44% yield	**4h**	 2 h, 48% yield
4c	 2h, 43% yield	**4i**	 0.5 h, 23% yield
4d	 2 h, 49% yield	**4j**	 3 h , 53% yield
4e	 2 h, 35% yield	**4k**	 24 h,N.R.

[a] The general reaction was carried out on a 0.1 mmol scale in 1 mL solvent, and the catalyst load was 0.005 mmol. [b] Isolated yield.

Scheme 2. Intramolecular Conjugate Addition of 3g

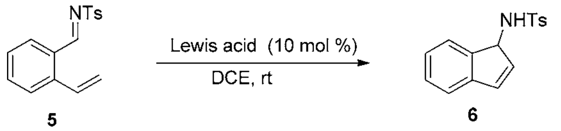


3g
E-/*Z*- mixture

4g
50% yield

(*Z*)-**3g**
48% yield

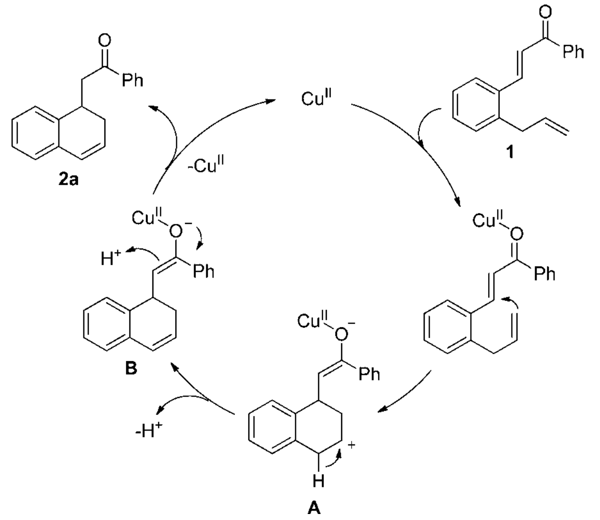
Scheme 3. Intramolecular Addition of Sulfonamide 5



5 **6**

$Cu(OTf)_2$ 3 h, 47% yield
$Cu(OTf)_2$ (80 °C) 1 h, 60% yield
$Bi(OTf)_3$ 20 min, 74% yield

Scheme 4. Proposed Mechanism



to high yields. This method was efficient in the synthesis of γ,δ-unsaturated or δ,ε-unsaturated carbonyl compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthesis and characterization data, procedures, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Alternatively, the reaction may undergo 6π-electrocyclization of an in situ dearomatized triene intermediate (*ortho*-quinodimethane). This mechanism is applicable to allyl chalcone but not vinyl chalcones.