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Chiral Lewis Acid Catalyzed Asymmetric Cycloadditions of Disubstituted Ketenes for the Synthesis of β-Lactones and δ-Lactones

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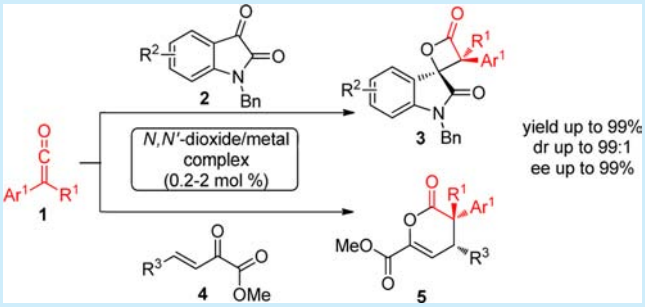
Supporting Information

ABSTRACT: Highly diastereo- and enantioselective [2 + 2]- and [4 + 2]-cycloadditions of disubstituted ketenes were realized by chiral Lewis acid catalysis. A series of arylalkylketenes underwent the reaction smoothly with isatins and β,γ-unsaturated α-ketoesters, providing optically active β-lactones and δ-lactones with vicinal chiral centers in excellent yields (up to 99%) and enantioselectivities (up to 99% ee), as well as exclusively high diastereoselectivities under 0.2−2 mol % catalyst loading.



Introduced by Staudinger a century ago,[1] ketenes have been developed into excellent precursors for diverse asymmetric reactions due to their unique chemical reactivity.[2] For example, [2 + 2]- and [4 + 2]-cycloadditions of ketenes with carbonyl compounds and α,β-unsaturated carbonyl compounds provided a simple and powerful means of accessing chiral β-lactones and δ-lactones.[3,4] Wynberg's group pioneered an asymmetric synthesis of the β-lactone from unsubstituted ketene;[4a,b] after that, extensive studies have been focused on developing more general and robust catalytic systems.[4] In comparison to mono- and unsubstituted ketenes, disubstituted ketenes are more stable, less reactive, and more sterically hindered in asymmetric cycloadditions. Recently, the Ye group reported NHC (N-heterocyclic carbene) promoted asymmetric cycloaddition of disubstituted ketenes with isatins and β,γ-unsaturated ketones; although high enantioselectivity was achieved, the reaction suffered moderate diastereoselectivity and tedious operation in some cases.[4i,q] Smith reinforced the same strategy to [4 + 2]-cycloaddition with β,γ-unsaturated α-ketoesters; however, the outcomes were unsatisfactory for the isomerization of the products in the presence of Cs_2CO_3.[4r] Therefore, such cycloaddition reactions that generate vicinal chiral centers, including quaternary stereocenters remain challenging with regard to high enantioselectivity, diastereoselectivity, and mild reaction conditions.[5]

Among the catalysts used for the cycloaddition reactions of ketenes, chiral Lewis bases predominated, for example, cinchona alkaloids,[4a−d] planar-chiral DMAP derivatives,[4g] NHCs,[4h−k] and phosphines.[4l], A key zwitterionic enolate intermediate was generated from the nucleophilic attack to ketene, which was also responsible for the side reaction−dimerization of ketenes.[6] Alternatively, the work of Evans[4f] showed that chiral Lewis acids could activate LUMO of the carbonyl substrates and promote the cycloadditions in a concerted way, resulting in the desired products with high stereoselectivity and yield. Here we describe asymmetric [2 + 2]- and [4 + 2]-cycloadditions of disubstituted ketenes using modular chiral *N*,*N*′-dioxide−metal complex catalysts. Feasible modification of the central metals and chiral ligands benefits efficient generation of optically active β-lactones and δ-lactones from isatins and β,γ-unsaturated α-ketoesters, respectively. The notable features of this catalytic system are facile procedure, mild reaction conditions, and applicability to a wide variety of substrates with high yield and enantioselectivity, as well as excellent diastereoselectivity, even if the catalyst loading is decreased to 0.5 mol %.

Initially, the *N*-methyl protected isatin **2aa** was chosen to react with phenylethylketene **1a** in the presence of our established *N*,*N*′-dioxide/metal complex.[7] [2 + 2]-Cycloaddition with **L1**−$Cu(OTf)_2$ failed to give the desired β-lactones (Table 1, entry 1). The complexes of **L1** with $Sc(OTf)_3$ and $Y(OTf)_3$ promoted the reaction smoothly, affording the β-lactone **3aa** in high diastereoselectivity and moderate yield and ee value (Table 1, entries 2 and 3). $Sc(OTf)_3$ catalyzed cycloaddition much more selectively than $Y(OTf)_3$. We found that *N*,*N*′-dioxide **L3** bearing L-ramipril and 2,6-diisopropylaniline moieties afforded a higher ratio of diastereo- and enantiomers as well as improved yield within 8 h (99:1 dr, 75% ee, and 50% yield; Table 1, entry 5; also see the Supporting Information for a complete list of chiral ligands screened). To our delight, the cycloaddition of *N*-benzylisatin **2a** and ketene **1a** was found to be extremely stereoselective, and the corresponding adduct **3a** was obtained in 76% yield, 99:1 dr, and 96% ee (Table 1, entry 6). A dramatic improvement in the yield was realized, when molecular sieves

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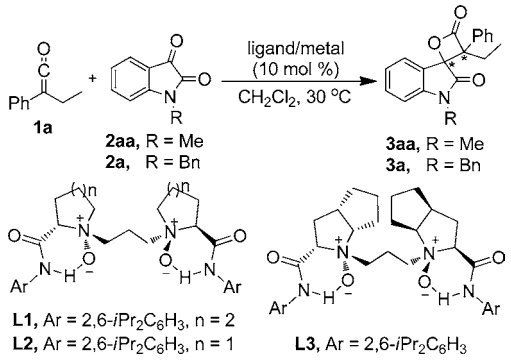
Table 1. Optimization of the Reaction Conditions[a]



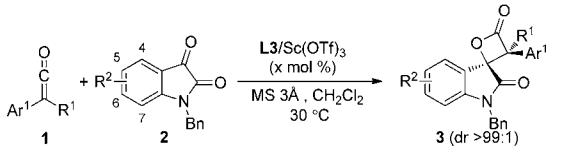
entry	ligand	metal	time (h)	yield[b] (h)	dr[c]	ee[c] (%)
1	**L1**	$Cu(OTf)_2$	12	nr		
2	**L1**	$Y(OTf)_3$	12	29	90:10	30
3	**L1**	$Sc(OTf)_3$	12	30	97:3	60
4	**L2**	$Sc(OTf)_3$	12	30	66:34	20
5	**L3**	$Sc(OTf)_3$	8	50	99:1	75
6[d]	**L3**	$Sc(OTf)_3$	8	76	99:1	96
7[d,e]	**L3**	$Sc(OTf)_3$	8	96	99:1	96
8[f]	**L3**	$Sc(OTf)_3$	8	96	99:1	95

[a]Unless otherwise noted, all reactions were performed with **1a** (0.15 mmol), **2aa** (0.1 mmol), ligand (10 mol %), and metal salt (10 mol %) in CH_2Cl_2 (0.5 mL) at 30 °C. [b]Isolated yield, nr = no reaction. [c]Determined by chiral HPLC analysis. [d]**2a** (0.1 mmol) was used. [e]MS 3 Å (10.0 mg) was added. [f]**L3**–$Sc(OTf)_3$ (0.5 mol %), **1a** (0.3 mmol), **2a** (0.2 mmol), and MS 3 Å (20.0 mg) in CH_2Cl_2 (0.1 mL) at 30 °C. Tf = trifluoromethanesulfonyl, MS = molecular sieves.

(3 Å) were used as additive (96% yield; Table 1, entry 7); therefore, the reaction could be conveniently run at a catalyst loading as low as 0.5 mol % (Table 1, entry 8).

The optimal conditions for the asymmetric [2 + 2]-cycloaddition were found to be generally applicable to disubstituted ketenes and substituted isatins. The generality and functional group tolerance of this reaction are listed in Table 2. Phenylalkylketenes with methyl, *n*-propyl, and *n*-butyl groups worked with a slight loss of ee value (Table 2, entries 1–4). The substituent on the aryl group of ketenes had little or no effect on stereoselectivity (Table 2, entries 5–12). Electron-withdrawing substituents such as fluorine and chlorine were tolerated but tended to decrease reaction rates; therefore, the catalyst loading was increased to 1–2 mol %. Notably, 2-naphthylethyl-substituted ketene gave an excellent result (95% yield, 97% ee) in the reaction (Table 2, entry 13). We then investigated the reaction performance with respect to the isatin substrates (Table 2 entries 14–22). The position of substituents on the isatins had an obvious effect on both enantioselectivity and reactivity (Table 2, entries 14–17). Isatin derivatives substituted at the C5 and C6 positions were subjected to cycloaddition, giving a lower level of enantioselectivity than isatins with substituents at the C7 positions (Table 2, entries 14, 15 vs entry 17). The enantioselectivity of C7-substituted isatins, except for the 7-CF_3 group, were almost identical (97–98% ee, Table 2, entries 17–22). The absolute configuration of *β*-lactone **3s** was unambiguously determined to be (*S*,*S*) by X-ray diffraction analysis.[8] It should be noted that extremely high diastereoselectivity was obtained for all cases (dr >99:1, determined by NMR and HPLC analysis), and the reaction showed inversion diastereo-preference compared with the previous report using NHCs as the catalyst.[4i]

Table 2. Substrate Scope of the Asymmetric Cycloaddition of Ketenes 1 and Isatins 2[a]



entry	Ar^1, R^1	R^2	*x* (mol %)	yield[b] (%)	ee (%) (config)[c]
1	Ph, Et	H	0.5	96 (**3a**)	95 (*S*,*S*)
2	Ph, Me	H	0.5	91 (**3b**)	90 (*S*,*S*)
3	Ph, *n*-Pr	H	0.5	95 (**3c**)	88 (*S*,*S*)
4	Ph, *n*-Bu	H	2	97 (**3d**)	91 (*S*,*S*)
5	2-FC_6H_4, Et	H	1	90 (**3e**)	96 (*S*,*S*)
6	3-FC_6H_4, Et	H	1	91 (**3f**)	95 (*S*,*S*)
7	4-FC_6H_4, Et	H	2	95 (**3g**)	96 (*S*,*S*)
8	2-$MeOC_6H_4$, Et	H	1	77 (**3h**)	86 (*S*,*S*)
9	3-$MeOC_6H_4$, Et	H	0.5	96 (**3i**)	97 (–)
10	4-$MeOC_6H_4$, Et	H	0.2	87 (**3j**)	96 (–)
11	4-MeC_6H_4, Et	H	1	91 (**3k**)	98 (–)
12	4-ClC_6H_4, Et	H	2	99 (**3l**)	96 (*S*,*S*)
13	2-naphthyl, Et	H	0.5	95 (**3m**)	97 (–)
14	Ph, Et	5-F	2	95 (**3n**)	85 (–)
15	Ph, Et	6-F	0.5	80 (**3o**)	96 (–)
16	Ph, Et	6-Br	2	90 (**3p**)	80 (–)
17	Ph, Et	7-F	0.5	90 (**3q**)	98 (*S*,*S*)
18	Ph, Et	7-Cl	0.5	84 (**3r**)	97 (*S*,*S*)
19	Ph, Et	7-Br	0.5	96 (**3s**)	97 (*S*,*S*)
20	Ph, Et	7-Me	1	79 (**3t**)	98 (*S*,*S*)
21	Ph, Et	7-F_3C	0.5	98 (**3u**)	89 (–)
22	Ph, Et	7-F_3CO	0.5	80 (**3v**)	96 (*S*,*S*)

[a]Unless otherwise noted, the reactions were performed with **1** (0.30 mmol), **2** (0.20 mmol), **L3**/$Sc(OTf)_3$ (0.2–2 mol %, 1:1), MS 3 Å (20 mg), and CH_2Cl_2 (0.1 mL) at 30 °C for 8–48 h (for details, see the Supporting Information). [b]Yield of isolated product. [c]Determined by chiral HPLC. The absolute configurations of the products **3a**–**h**,**l**,**q**,**r**,**t**,**v** were determined by comparing the circular-dichroism spectra with those of **3s**.

Furthermore, we were encouraged to investigate the [4 + 2]-cycloaddition between *β*,*γ*-unsaturated *α*-ketoesters and disubstituted ketenes. The optimization of the catalysts showed that optically active *δ*-lactones were easily access with the *N*,*N*′-dioxide **L1**–$Y(OTf)_3$ complex (see the Supporting Information for a complete list of optimization of the reaction conditions). For instance, *δ*-lactone **5a** bearing vicinal quaternary and tertiary carbon centers could be given with 98% yield and 95% ee in the presence of 0.5 mol % of the catalyst within 6 h (Table 3, entry 1). The procedures also enabled the enantioselective synthesis of *δ*-lactones with different substituents. Ketenes with methyl or *n*-propyl substituent worked well to produce the desired *δ*-lactone in excellent yield and enantioselectivity (Table 3, entries 1–3).

The electronic property of substituents at the aryl group of ketenes had a slight impact on the enantioselectivity (Table 3, entries 4–7). Moreover, asymmetric cycloadditions also converted a variety of *β*,*γ*-unsaturated *α*-ketoesters into *δ*-lactones with high yields, excellent diastereoselectivities, and ee values (95–99% ee), regardless of the electronic properties of the substituents on the aromatic ring of ketoesters (Table 3, entries 8–12). Remarkably, the condensed-ring and hetero-aromatic *β*,*γ*-unsaturated *α*-ketoesters were also found to be

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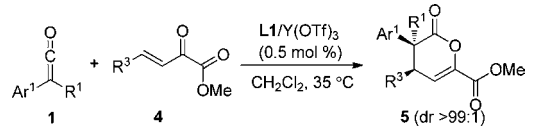
Table 3. Substrate Scope of the Asymmetric Cycloaddition of Ketene 1 and β,γ-Unsaturated α-Ketoesters 4[a]



entry	Ar^1, R^1	R^3	t [h]	yield [%][b]	ee [%] (config)[c]
1	Ph, Et	Ph	6	98 (**5a**)	95 (*S,S*)
2	Ph, Me	Ph	11	90 (**5b**)	95 (*S,S*)
3	Ph, nPr	Ph	11	93 (**5c**)	96 (*S,S*)
4	Ph, Et	4-ClC_6H_4	15	89 (**5d**)	98 (*S,S*)
5	Ph, Et	4-MeC_6H_4	15	89 (**5e**)	97 (*S,S*)
6	Ph, Et	4-$MeOC_6H_4$	15	88 (**5f**)	94 (−)
7	Ph, Et	2-naphthyl	15	99 (**5g**)	95 (*S,S*)
8	Ph, Et	3-$MeOC_6H_4$	7	86 (**5h**)	99 (−)
9	Ph, Et	4-BrC_6H_4	7	84 (**5i**)	96 (*S,S*)
10	Ph, Et	4-NCC_6H_4	8	67 (**5j**)	95 (*S,S*)
11	Ph, Et	4- $F_3CC_6H_4$	8	73(**5k**)	94 (*S,S*)
12	Ph, Et	4-PhC_6H_4	10	94 (**5l**)	99 (*S,S*)
13	Ph, Et	2-naphthyl	10	82(**5m**)	95 (−)
14	Ph, Et	2-thienyl	8	97 (**5n**)	98 (*S,R*)
15	Ph, Et	2-furyl	10	91 (**5o**)	97 (*S,R*)
16	Ph, Et		7	96 (**5p**)	99 (−)
17	Ph, Et		12	75 (**5q**)	98 (−)

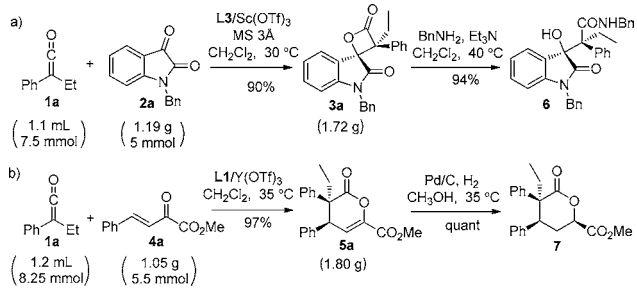
[a]Unless otherwise noted, the reactions were performed with **1** (0.30 mmol), **4** (0.20 mmol), **L1**/$Y(OTf)_3$ (0.5 mol %, 1:1), and CH_2Cl_2 (0.2 mL) at 35 °C. [b]Yield of isolated product. [c]Determined by chiral HPLC. The absolute configurations of the products **5a−e,g,j−l,n,o** were determined by comparing their circular-dichroism spectra with those of **5i**.

excellent substrates for the reaction, affording the desired products with good outcomes (82−95% yield, 95−98% ee, Table 3, entries 13−16). Additionally, ketoester with a cinnamyl group gave a high yield and excellent ee value (Table 3, entry 17). The relative absolute configuration of the major *cis*-diastereoisomer of δ-lactone **5i** was unambiguously confirmed as (3*S*,4*S*) by X-ray diffraction analysis,[8] with the configuration of the others assigned by analogy via CD spectra. In the presence of *N,N′*-dioxide **L1**−$Y(OTf)_3$ complex catalyst, *cis*-isomers formed exclusively and none of the isomeric dihydropyranones arose in the cases surveyed. Thus, this system overcomes the isomerization process of the initially formed cycloadducts that occurs in an NHC/Cs_2CO_3 catalytic system.[4r]

To test the synthetic value of the reactions, we performed a gram-scale transformation (Scheme 1). Both β-lactone **3a** and δ-lactone **5a** could be obtained in satisfactory results. The product **3a** could be efficiently converted into 3-hydroxyindolinone **6** containing two quaternary carbon centers through ring-opening using benzylamine. Hydrogenation of the δ-lactone **5a** gave the corresponding tetrahydropyranone **7** in complete conversion with extremely high diastereoselectivity and maintained enantioselectivity (see the Supporting Information for the proposed catalytic model).

In conclusion, we have described highly diastereo- and enantioselective [2 + 2]- and [4 + 2]-cycloadditions of

Scheme 1. Applications of the Catalytic Asymmetric Cycloaddition



disubstituted ketenes promoted by chiral Lewis acids. The complexes of chiral *N,N′*-dioxides enabled efficient construction of β-lactones and δ-lactones from isatins and β,γ-unsaturated α-ketoesters, respectively. Excellent yields (up to 99%), diastereoselectivities (dr up to 99:1), and enantioselectivities (ee up to 99%) were achieved in the presence of 0.2−2 mol % of the catalyst. Particular advantages of the catalytic system also include broad substrate scope, facile procedure, and mild reaction conditions. The unfavorable results in previous reports were well addressed. Further application of the catalyst in other reactions is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral and analytical data for the products, and CIF. 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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