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Asymmetric Cycloaddition of β,γ-Unsaturated α-Ketoesters with Electron-Rich Alkenes Catalyzed by a Chiral Er(OTf)$_3$/*N*,*N*′-Dioxide Complex: Highly Enantioselective Synthesis of 3,4-Dihydro-2*H*-pyrans**

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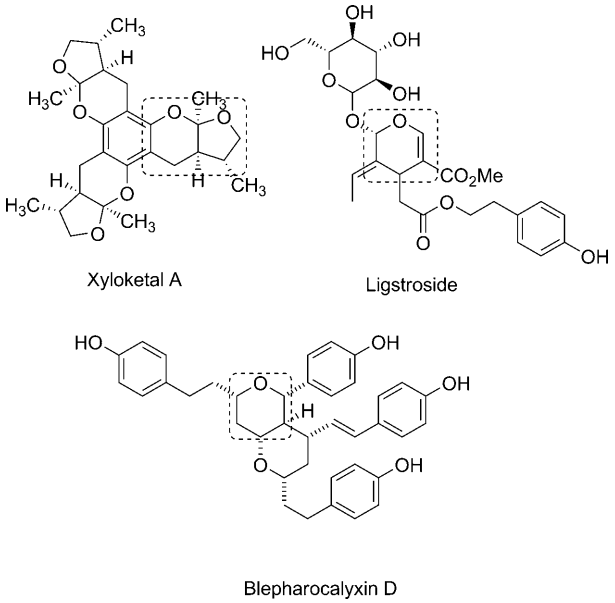
Abstract: The asymmetric inverse-electron-demand hetero-Diels–Alder (HDA) reactions of β,γ-unsaturated α-ketoesters with electron-rich alkenes were investigated, with an *N*,*N*′-dioxide/erbium(III) complex employed as the catalyst. Quantitative conversion of the β,γ-unsaturated α-ketoesters and excellent enantioselectivities (up to >99% *ee*) and diastereoselectivities (up to >99:1 d.r.) were observed for a broad range of substrates by using a 0.5–0.05 mol% catalyst loading under mild reaction conditions. The reaction could be scaled up to the gram scale with the same results. In addition, this was the first application of Er(OTf)$_3$ to the asymmetric inverse-electron-demand HDA reaction and it behaved as an efficient catalyst. Moreover, the synthetic utility of this methodology was demonstrated with the synthesis of key intermediates of some natural products.

Keywords: asymmetric catalysis · cycloaddition · erbium · heterocycles · *N*,*N*′-dioxides

Introduction

The importance of substituted 3,4-dihydro-2*H*-pyrans and related tetrahydropyran derivatives in synthetic chemistry is illustrated by the general occurrence of these motifs in the synthesis of a vast range of natural products and bioactive compounds.[1,2] As examples (Scheme 1), xyloketal A is an interesting lead compound in the treatment of Alzheimer's disease,[2h,i,3] ligstroside, isolated from extra virgin olive, imparts bitterness, pungency, and astringency,[2j,4] and blepharocalyxin D exhibits significant in vitro antiproliferative activity against human fibrosarcoma HT-1080 and murine colon 26-L5 carcinoma cells.[5]

Among the numerous methods for synthesizing the 3,4-dihydro-2*H*-pyrans, the inverse-electron-demand hetero-Diels–Alder (HDA) reactions[6–9] of α,β-unsaturated carbonyl compounds with electron-rich alkenes (dienophiles) have been demonstrated to afford a facile synthesis of these core structures. To the best of our knowledge, only a few effective catalytic systems have been reported. After the early studies,[10–12] Evans et al.[13] and Jørgensen and co-workers[14] respectively reported enantioselective HDA reactions catalyzed by oxazoline/copper(II) complexes with good results at almost the same time. Subsequently, a chiral Schiff base/Cr^{III} complex was applied to the HDA reactions of α,β-unsaturated aldehydes.[8e,f] Recently, two examples catalyzed by oxazoline/copper(II) complexes were presented.[15,16] However, most of the HDA reactions were performed at extremely low temperatures (generally −78 °C) and with relatively high catalyst loadings (generally 2–10 mol%). There-



Scheme 1. Natural and bioactive products containing 3,4-dihydro-2*H*-pyran subunits.

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[**] OTf: Trifluoromethanesulfonate.

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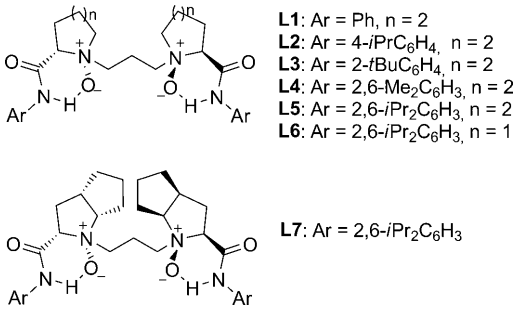
fore, the development of a milder and efficient new catalytic system is still in great demand.

N,*N*′-Dioxide ligands are excellent chiral scaffolds because they can coordinate with various different metals and have been shown to be highly efficient in many asymmetric reactions.[17] Herein, we report the asymmetric inverse-electron-demand HDA reaction of β,γ-unsaturated α-ketoesters **1**, promoted by 0.05–0.5 mol% of an *N*,*N*′-dioxide/$Er(OTf)_3$ complex under mild reaction conditions (generally 0°C), to give the adducts with excellent diastereoselectivities (up to >99:1 d.r.) and enantioselectivities (up to >99% *ee*) for a broad range of β,γ-unsaturated α-ketoesters and alkenes. This was the first application of $Er(OTf)_3$, an important lanthanide metal salt, which features advantages in stability, recovery, and electropositive properties,[18] to the asymmetric inverse-electron-demand HDA reaction.

Results and Discussion

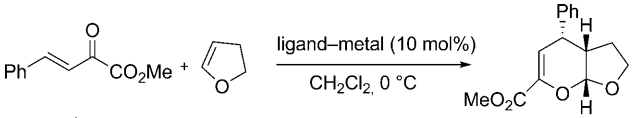
Initially, *N*,*N*′-dioxide **L1** (Scheme 2) was complexed in situ with various metals to catalyze the HDA reaction between β,γ-unsaturated α-ketoester **1a** and 2,3-dihydrofuran (**2**;



Scheme 2. Chiral ligands used in the study.

Table 1, entries 1–11). As shown in Table 1, many metal/**L1** complexes gave poor results in the HDA reaction (Table 1, entries 1–7). $Tb(OTf)_3$, $Yb(OTf)_3$, $Lu(OTf)_3$, $Er(OTf)_3$ which belong to the lanthanide metal salts, gave similar enantioselectivities (20–23% *ee*; Table 1, entries 8–11). However, $Er(OTf)_3$ was more suitable than the others because of its higher yield (>99%) and better diastereoselectivity (95:5 d.r.; Table 1, entry 11 versus entries 8–10). Further optimization of the reaction conditions was then aimed at improving the efficiency of the $Er(OTf)_3$ catalyst with other structures of *N*,*N*′-dioxide ligand (Scheme 2), including changes to both the chiral backbone and the steric hindrance of the aniline moiety (Table 1, entries 12–17). Sterically hindered **L2** enhanced the enantioselectivity, with 38% *ee*, 92:8 d.r., and 87% yield (Table 1, entry 12). To our delight, a remarkable improvement was achieved by employing the more hindered **L3**, and an *ee* value of up to 84% was obtained (Table 1, entry 13). However, *N*,*N*′-dioxide **L4** with two methyl groups substituted at the *ortho* positions of the aniline moieties decreased the enantioselectivity (61% *ee*; Table 1, entry 14). *N*,*N*′-dioxide **L5**, which contained bulkier isopropyl groups, displayed excellent results (>99% yield, >99:1 d.r., 97% *ee*), and an extremely short reaction time was needed (15 min; Table 1, entry 15). The chiral backbone of the *N*,*N*′-dioxide also had a significant impact on the enantioselectivity of the reaction. L-Pipecolic acid derivative *N*,*N*′-dioxide **L5** was superior to L-proline derived **L6** and L-ramipril acid derived **L7** (Table 1, entry 15 versus entries 16 and 17). Therefore, the $Er(OTf)_3$/**L5** complex was chosen as the best catalyst (Table 1, entry 15).

Table 1. Catalytic asymmetric HDA reaction of β,γ-unsaturated α-ketoester **1a** with 2,3-dihydrofuran (**2**) promoted by metal/**L** catalysts.



1a 2 3a

Entry[a]	Metal	L	Yield [%][b]	*endo*/*exo*[c]	*ee* [%][d]
1	$Cu(OTf)_2$	**L1**	trace	n.d.[e]	n.d.[e]
2	$Fe(acac)_2$[f]	**L1**	trace	n.d.[e]	n.d.[e]
3	$Sc(OTf)_3$	**L1**	83	92:8	5
4	$La(OTf)_3$	**L1**	73	90:10	7
5	$Eu(OTf)_3$	**L1**	96	93:7	13
6	$Ho(OTf)_3$	**L1**	42	91:9	13
7	$Y(OTf)_3$	**L1**	91	94:6	19
8	$Tb(OTf)_3$	**L1**	>99	94:6	20
9	$Yb(OTf)_3$	**L1**	93	93:7	22
10	$Lu(OTf)_3$	**L1**	81	94:6	23
11	$Er(OTf)_3$	**L1**	>99	95:5	23
12[g]	$Er(OTf)_3$	**L2**	87	92:8	38
13[g]	$Er(OTf)_3$	**L3**	>99	98:2	84
14[g]	$Er(OTf)_3$	**L4**	93	95:5	61
15[h]	$Er(OTf)_3$	**L5**	>99	>99:1	97
16[h]	$Er(OTf)_3$	**L6**	93	>99:1	55
17[g]	$Er(OTf)_3$	**L7**	93	>99:1	96

[a] Unless otherwise noted, all reactions were carried out with 10 mol% of **L**/metal (1:1), **1a** (0.1 mmol), and **2** (30 μL, 4.0 equiv) in CH_2Cl_2 (1.0 mL) under N_2 at 0°C for 48 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; the isomer of **3a** was confirmed by ^1H NMR spectroscopy. [d] Determined by chiral HPLC analysis; the absolute configuration of *endo*-**3a** (3*aS*,4*S*,7*aR*) was determined by comparison with literature data. [e] n.d.: not determined. [f] acac: acetylacetone. [g] Reaction time: 2 h. [h] Reaction time: 15 min.

With the optimized catalyst in hand, other reaction parameters were explored (Table 2). It was found that the solvent also affected the reaction greatly (Table 2, entries 1–7). The reaction in CH_2ClCH_2Cl provided an excellent yield (>99%) and diastereoselectivity (>99:1 d.r.), but the enantioselectivity of the adduct was slightly diminished (Table 2, entry 2 versus entry 1). The use of $CHCl_3$ led to a dramatic loss of enantioselectivity and reactivity (Table 2, entry 3). Et_2O, THF, and CH_3CN gave high yields and moderate enantioselectivities (Table 2, entries 4–6). Toluene is not suitable, because the reaction in this solvent provided **3a** with low enantioselectivity and yield (Table 2, entry 7). Thus, CH_2Cl_2 was proven to be the best solvent for the HDA reaction. Furthermore, reduction of the catalyst loading to 0.5 mol% led to no loss of yield, enantioselectivity, or diastereoselectivity (Table 2, entry 8). When the catalyst

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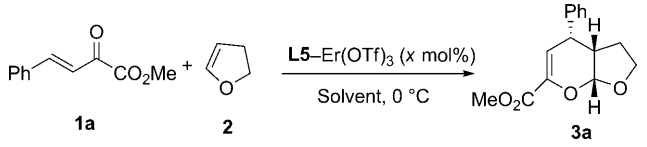
Table 2. Optimization of the reaction conditions.



1a 2 3a

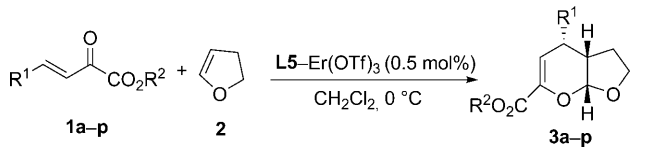
Entry[a]	Solvent	t	x [mol%]	Yield [%][b]	*endo*/*exo*[c]	*ee* [%][d]
1	CH_2Cl_2	15 min	10	>99	>99:1	97
2	CH_2ClCH_2Cl	15 min	10	>99	>99:1	95
3	$CHCl_3$	24 h	10	>99	98:2	13
4	Et_2O	24 h	10	>99	95:5	44
5	THF[e]	24 h	10	>99	89:11	63
6	CH_3CN	24 h	10	98	97:3	55
7	toluene	24 h	10	45	94:6	50
8	CH_2Cl_2	2 h	0.5	>99	>99:1	97
9	CH_2Cl_2	24 h	0.075	>99	>99:1	97
10[f]	CH_2Cl_2	2 h	0.05	>99	>99:1	92
11[g]	CH_2Cl_2	2 h	0.5	>99	>99:1	97

[a] Unless otherwise noted, all reactions were carried out with x mol% of **L5**/Er(OTf)$_3$ (1:1), **1a** (0.1 mmol), and **2** (30 μL, 4.0 equiv) in solvent (1.0 mL) under N_2 at 0°C. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; the isomer of **3a** was confirmed by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis. [e] THF: tetrahydrofuran. [f] The reaction was carried out with 0.05 mol% of **L5**/Er(OTf)$_3$ (1:1), **1a** (0.1 mmol), and **2** (30 μL, 4.0 equiv) in CH_2Cl_2 (1.0 mL) under N_2 at 25°C. [g] The reaction was carried out with 0.5 mol% of **L5**/Er(OTf)$_3$ (1:1), **1a** (0.1 mmol), and **2** (30 μL, 4.0 equiv) in CH_2Cl_2 (1.0 mL) under an air atmosphere at 0°C.

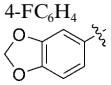
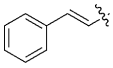
loading was further lowered to 0.075 mol%, the reaction was carried out smoothly with excellent results, but a longer reaction time was required (Table 2, entry 9).[19] The catalyst loading could even be decreased to 0.05 mol% at 25°C, in which case the enantioselectivity was reduced to 92% *ee* (Table 2, entry 10). It is also notable that the process is tolerant to air and moisture (Table 2, entry 11). Therefore, the optimal reaction conditions were **L5**/Er(OTf)$_3$ (0.5 mol%), **1a** (0.1 mmol), and **2** (0.4 mmol) in CH_2Cl_2 (1.0 mL) at 0°C.

Next, under the optimized conditions, the substrate scope of the HDA reaction was evaluated; the corresponding products were obtained in mostly high yields (50 to >99%) with excellent diastereoselectivities (>99:1 d.r.) and *ee* values (89–99%). When the effect of the ester group of the β,γ-unsaturated α-ketoesters was tested, an ethyl group showed lower reactivity than the methyl group (Table 3, entry 2 versus entry 1), although the diastereoselectivity and enantioselectivity were both excellent. The aromatic ketoesters underwent the HDA reactions to give the optically active adducts in excellent yields (81 to >99%), diastereoselectivities (>99:1 d.r.), and *ee* values (in the range of 92–99%), regardless of the electronic and steric properties of the substituents (Table 3, entries 3–12). However, the 3-$NO_2C_6H_4$-substituted β,γ-unsaturated α-ketoester needed more time and a higher temperature to complete the conversion (Table 3, entry 6). Furthermore, the substrate with a cinnamyl group also gave an excellent yield and *ee* value (Table 3, entry 13). Condensed-ring and heteroaromatic β,γ-unsaturated α-ketoesters were also found to be excellent substrates for the reaction and afforded the desired products

Table 3. Substrate scope of the asymmetric HDA reactions of β,γ-unsaturated α-ketoesters **1** and 2,3-dihydrofuran (**2**).



1a–p 2 3a–p

Entry[a]	R^1	R^2	Product	t [h]	Yield [%][b]	*ee* [%][c]
1	Ph	Me	**3a**	2	>99	97 (3*aS*,4*S*,7*aR*)
2	Ph	Et	**3b**	2	86	97 (3*aS*,4*S*,7*aR*)
3	4-MeC_6H_4	Me	**3c**	2	>99	97
4	4-$MeOC_6H_4$	Me	**3d**	2	>99	95
5	3-$MeOC_6H_4$	Me	**3e**	2	>99	97
6[d]	3-$NO_2C_6H_4$	Me	**3f**	36	81	92
7	4-ClC_6H_4	Me	**3g**	2	>99	97
8	2-ClC_6H_4	Me	**3h**	2	95	99
9	2,4-$Cl_2C_6H_3$	Me	**3i**	24	90	94
10	4-BrC_6H_4	Me	**3j**	2	>99	97
11	4-FC_6H_4	Me	**3k**	2	98	97
12		Me	**3l**	12	99	97
13		Me	**3m**	12	93	94
14	2-naphthyl	Me	**3n**	12	92	98
15	2-thienyl	Me	**3o**	12	93	95
16[e]	Me	Et	**3p**	12	50	89 (3*aS*,4*S*,7*aR*)

[a] Unless otherwise noted, all reactions were carried out with 0.5 mol% of **L5**/Er(OTf)$_3$ (1:1), **1** (0.1 mmol), and **2** (30 μL, 4.0 equiv) in CH_2Cl_2 (1.0 mL) under N_2 at 0°C and the diastereoselectivity of the product was >99:1. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; the absolute configurations of *endo*-**3a**, **3b**, and **3p** were determined by comparison with literature data. [d] The reaction was carried out at 35°C. [e] The reaction was carried out at −20°C.

with good outcomes (Table 3, entries 14 and 15). Moreover, good enantioselectivity was observed with an aliphatic β,γ-unsaturated α-ketoester (50% yield, >99:1 d.r., 89% *ee*; Table 3, entry 16).[20]

The synthesis of 3,4-dihydro-2*H*-pyrans with an extremely low catalyst loading is propitious for atom economy and industrial synthesis. Although the asymmetric HDA reactions of β,γ-unsaturated α-ketoesters with 2,3-dihydrofuran had been reported,[13,14,16] most of these transformations required 10 mol% or more of catalyst loading for sufficient formation of the product and maintenance of the enantioselectivity. In our studies, for most substrates, excellent enantioselectivities (95–99% *ee*) and diastereoselectivities (>99:1 d.r.) with good yields (78 to >99%) were obtained by using 0.075 mol% catalyst, albeit with somewhat longer reaction times (Table 4). This is the first example of the asymmetric inverse-electron-demand HDA reaction of α,β-unsaturated carbonyl compounds and electron-rich alkenes with such a low amount of catalyst (0.075 mol%).

Subsequently, we carried out a generality study of the catalytic cycloaddition with other electron-rich alkenes as part of an expansion of the reaction (Scheme 3).[21] Compared with the reaction with 2,3-dihydrofuran (**2**), the cycloaddition of 3,4-dihydro-2*H*-pyran required a higher temperature to achieve complete conversion (Scheme 3, equation 1).

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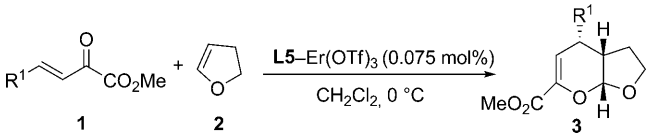
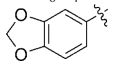
Table 4. Asymmetric HDA reactions of β,γ-unsaturated α-ketoesters **1** and 2,3-dihydrofuran (**2**) with 0.075 mol% catalyst loading.



1 2 3

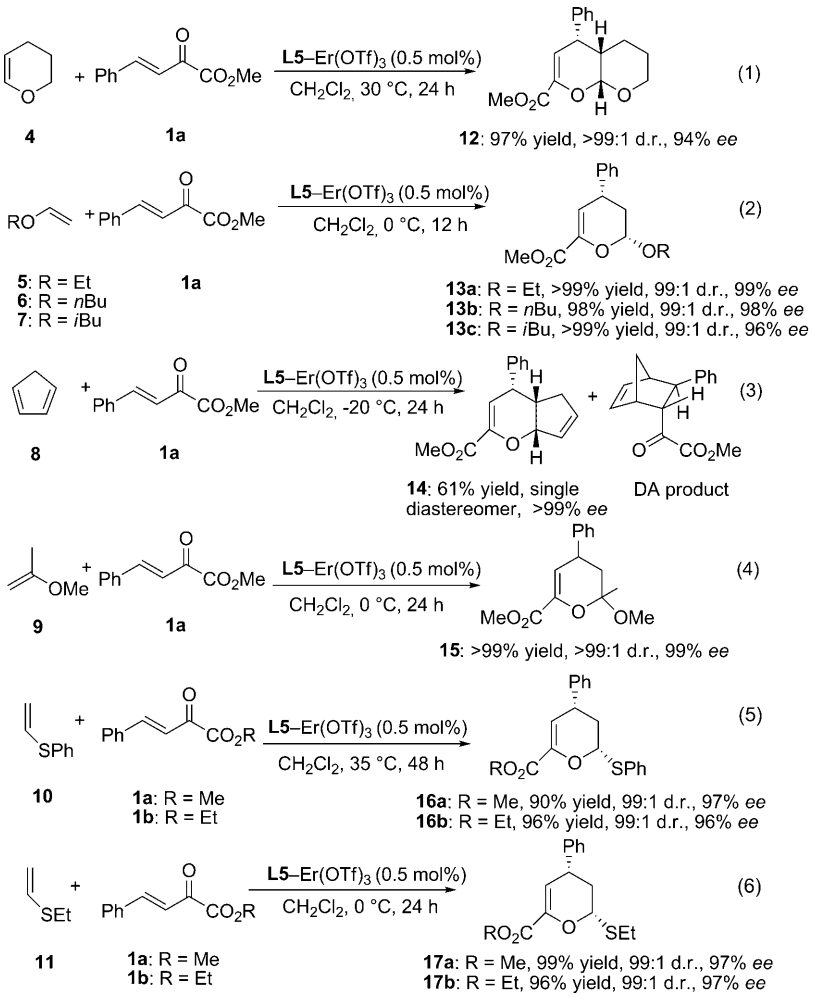
Entry[a]	R^1	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	Ph	**3a**	12	>99	97
2[d]	4-MeC_6H_4	**3c**	12	>99	97
3	4-$MeOC_6H_4$	**3d**	24	>99	95
4[d]	4-ClC_6H_4	**3g**	12	>99	97
5	2-ClC_6H_4	**3h**	12	84	99
6	4-BrC_6H_4	**3j**	12	98	97
7	4-FC_6H_4	**3k**	12	97	97
8		**3l**	24	93	96
9	2-naphthyl	**3n**	24	78	98
10	2-thienyl	**3o**	24	90	95

[a] Unless otherwise noted, all reactions were carried out with 0.075 mol% of **L5**/Er(OTf)$_3$ (1:1), **1** (0.1 mmol), and **2** (60 μL, 8.0 equiv) in CH_2Cl_2 (1.0 mL) under N_2 at 0°C, and the diastereoselectivity of the product was >99:1. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The quantity of **2** used was 30 μL (4.0 equiv).

Acyclic vinyl ethers were found to be very efficient dienophiles in this reaction (98 to >99% yields, 99:1 d.r., and 96–99% *ee*; Scheme 3, equation 2). In our previous studies, the **L5**/Cu(OTf)$_2$ complex could efficiently catalyze the reaction of β,γ-unsaturated α-ketoesters and cyclopentadiene.[22] It is interesting that **L5**/Er(OTf)$_3$ worked as well as **L5**/Cu(OTf)$_2$ with moderate chemoselectivity and excellent enantioselectivity (Scheme 3, equation 3). It is notable that the more sterically hindered alkene **9**, which afforded product **15** with a quaternary carbon center, gave excellent results (>99% yield, >99% d.r., >99% *ee*; Scheme 3, equation 4). Vinyl sulfides also functioned efficiently as dienophiles to give products **16a**,**b** and **17a**,**b** stereoselectively (Scheme 3, equations 5 and 6). However, the reactivity of phenyl(vinyl)sulfane was lower than that of other electron-rich alkenes (Scheme 3, equation 5).

The low catalyst loading and inexpensive starting materials and catalyst for this HDA reaction offered a practical way to scale up production. As shown in Scheme 4, with treatment of 5 mmol of the starting material under the optimized conditions, the reaction proceeded smoothly, and the desired addition product **3a** was obtained in >99% yield with >99:1 d.r. and 97% *ee*. Moreover, the reaction could be amplified to the gram scale with a good *ee* value and excellent yield in the presence of only 0.05 mol% of catalyst at 25°C.

The potential biological activities exhibited by the 3,4-dihydro-2*H*-pyrans and the derived ring-fused tetrahydropyrans[2] mean that the structural elaboration of this core is extremely important (Scheme 5). Reduction of **13a** smoothly generated the primary allylic alcohol **18** in excellent yield (>99%) without loss of the diastereo- and enantioselectivity (99:1 d.r., 99% *ee*); this product might exhibit biological activity.[23] To show an example of potential transformations on the ring-fused bicyclic HDA adducts, we subjected compound **12** to catalytic hydrogenation in the presence of Pd/C. Hydrogenation of the 3,4-dihydro-2*H*-pyran ring occured highly selectively to give the tetrahydropyran as a single isomer. The desired product **19** was obtained in 81% yield and without loss of enantioselectivity (94% *ee*). This compound could be con-



Scheme 3. Enantioselective inverse-electron-demand HDA reactions of alkenes **4**–**11** with **1**.

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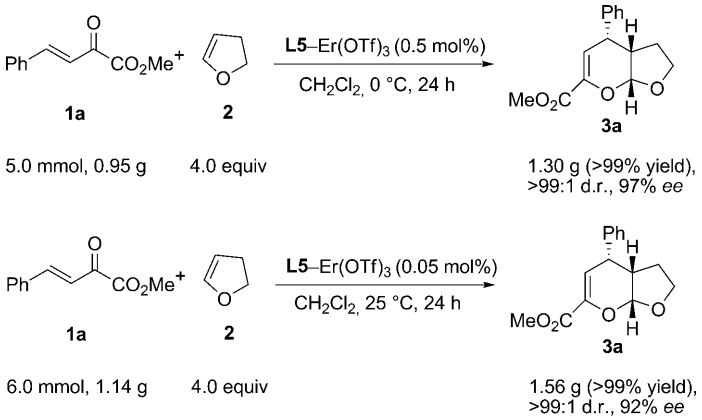
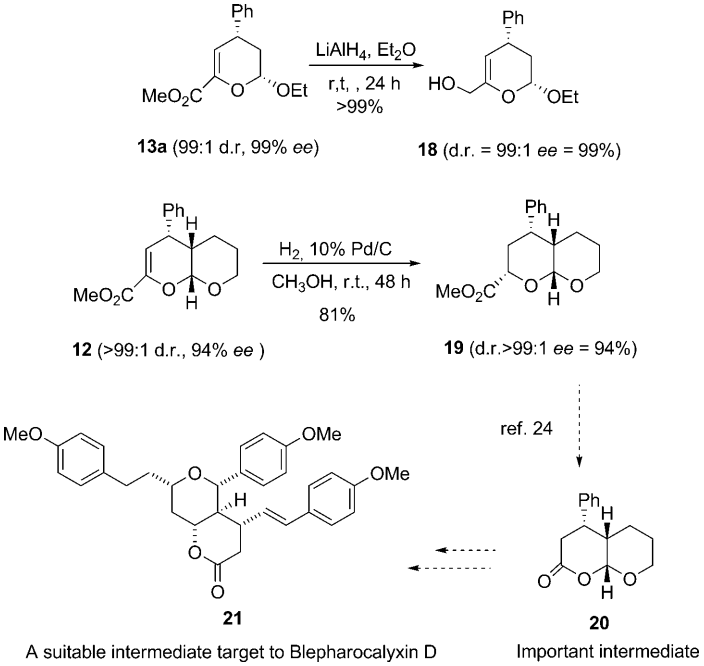


Scheme 4. The gram-scale asymmetric synthesis of **3a**.



Scheme 5. Reduction of compounds **12** and **13a**, and an example of the synthetic application of this methodology.

verted into bicyclic lactone **20** through a series of steps.[24] Moreover, ring-cleavage reactions of the hexahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran-2-one ring system[25] might lead to the formation of **21**, which was a suitable intermediate target for blepharocalyxin D.[5,24]

To gain insight into the origin of the stereoinduction, the nonlinear effect (NLE) for the present system was investigated by varying the *ee* value of the chiral *N*,*N*′-dioxide **L5**. As shown in Figure 1, a positive nonlinear effect was observed, which suggests that the complex $[(\mathbf{L5})_2Er(OTf)_3]$ might be involved at the step before the reactive intermediate. The racemate complex was thermodynamically more stable than the chiral one. As found in Girard and Kagan's excellent review of nonlinear effects, the homochiral complex seemed to be more active than the heterochiral one, which resulted in the positive NLE.[26]

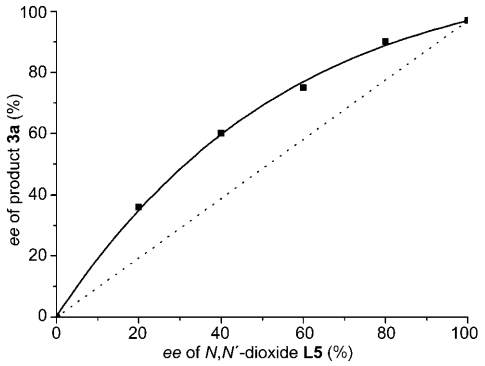


Figure 1. Investigation of the nonlinear effect.

Conclusion

The general and highly enantioselective inverse-electron-demand hetero-Diels–Alder reaction of β,γ-unsaturated α-ketoesters and electron-rich alkenes catalyzed by an *N*,*N*′-dioxide/erbium(III) complex with a remarkably low catalyst loading (0.5–0.05 mol%) was successfully established. Under mild conditions, a series of substituted 3,4-dihydro-2*H*-pyrans were obtained in excellent yields (up to >99%) with excellent enantioselectivities (up to >99% *ee*) and diastereoselectivities (up to >99:1 d.r.) by an operationally simple protocol. We have shown that the HDA adducts can be reduced to the corresponding dihydropyran and tetrahydropyran derivatives with potential biological activity without loss of optical purity. Meanwhile, a positive nonlinear correlation was observed. Further studies of the reaction mechanism of the catalytic system are under way.

Experimental Section

Preparation of the catalytic solution ($c = 0.002$ mol L^{-1}): A mixture of Er(OTf)$_3$ (6.1 mg, 0.01 mmol) and *N*,*N*′-dioxide **L5** (6.5 mg, 0.01 mmol) were added to a volumetric flask (5 mL). Anhydrous THF (5.0 mL) was then added.

Representative experimental procedure (Table 2, entry 8): A dry reaction tube was charged with catalyst solution (250 μL; 0.5 mol% loading). After the solvent was removed in vacuo, β,γ-unsaturated α-ketoester **1a** (0.1 mmol) was weighed into the flask under nitrogen and kept at ambient temperature for 0.5 h. CH_2Cl_2 (1.0 mL) was then added. The mixture was stirred at 25 °C for 30 min and then cooled to 0 °C. Subsequently, 2,3-dihydrofuran (**2**; 30 μL) was added at 0 °C, and the reaction mixture was stirred for an additional 2 h. The residue was purified by flash chromatography on silica gel to afford the desired product **3a**.

General experimental procedure for the scale-up reaction: A mixture of β,γ-unsaturated α-ketoester **1a** (5 mmol, 0.95 g), Er(OTf)$_3$ (15.4 mg, 0.025 mmol), and *N*,*N*′-dioxide **L5** (16.2 mg, 0.025 mmol) was added to a flask under nitrogen and kept at ambient temperature for 0.5 h. Anhydrous CH_2Cl_2 (50 mL) was then added, and the solution was stirred at 25 °C for 0.5 h. Subsequently, 2,3-dihydrofuran (**2**; 1.5 mL) was added at 0 °C, and the reaction mixture was stirred for an additional 24 h. The resi-

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due was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 1:4) to afford the desired product **3a**. The procedure of the scaled-up reaction in the presence of 0.05 mol% of catalyst at 25°C was similar to the procedure described above.

General experimental procedure for hydrogenation of compound 12: Pd/C (0.025 mol, 6.19 mg, 10% equiv) was added to a solution of the HDA product **12** (>99:1 d.r., 94% *ee*, 0.25 mmol, 68.6 mg) in MeOH (3.0 mL) at room temperature. Under an H_2 atmosphere, the mixture was allowed to stir for 48 h. Filtration followed by removal of the solvent under reduced pressure and silica gel flash column chromatography (ethyl acetate/petroleum ether, 1:8) afforded ring-fused tetrahydropyran **19** (81% yield, >99:1 d.r., 94% *ee*).

General experimental procedure for hydrogenation of compound 13a: $LiAlH_4$ (1.175 mol, 46.9 mg, 2.5 equiv) was added portionwise to a solution of the HDA product **13a** (0.47 mol, 124.1 mg) in anhydrous Et_2O (10 mL) in a 50 mL flask under nitrogen with ice cooling. The reaction mixture was then stirred at room temperature. After 24 h, the mixture was hydrolyzed with saturated aqueous Na_2SO_4 solution (80 μL) and stirred for a few minutes. The mixture was then filtered through celite and dried. Filtration followed by removal of solvent under reduced pressure and silica gel flash column chromatography (ethyl acetate/petroleum ether, 1:9) afforded primary allylic alcohol **18** (>99% yield, 99:1 d.r. and 99% *ee*).

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[20] The reaction gives 100% conversion, but the product is presumably unstable on the column during purification; see reference [9a].

[21] The absolute configurations of *endo*-**5a** (2*R*,4*R*), *endo*-**8a** (4*R*,4*aS*,7*aS*), *endo*-**10b** (2*S*,4*R*), and *endo*-**11b** (2*S*,4*R*) were determined by comparison with literature data, the *endo*:*exo* ratios were determined by HPLC analysis, and the isomers of **4a**–**11a**, **10b**, and **11b** were confirmed by ^{1}H NMR spectroscopy.

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