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Ligand Control of Diastereodivergency in Asymmetric Inverse Electron Demand Diels–Alder Reaction

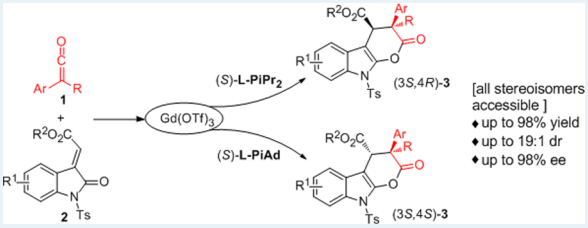
Xiaoyu Hao, Lili Lin, Fei Tan, Chengkai Yin, Xiaohua Liu, and Xiaoming Feng*

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu, People's Republic of China

Collaborative Innovation Center of Chemical Science and Engineering, Tianjin, People's Republic of China

Supporting Information

ABSTRACT: A diastereodivergent direct catalytic asymmetric inverse electron demand Diels–Alder reaction between ketenes and 3-alkylenyloxindoles was accomplished by using chiral *N,N′*-dioxide/gadolinium complexes. By adjusting only the substituents of the ligand and retaining other catalysis conditions, both *syn*- and *anti*-indole-fused dihydropyranones bearing two vicinal stereogenic centers were obtained in high yields with excellent ee values. Thus, by changing the configuration of the chiral ligands, all stereoisomers could be obtained from the same set of starting materials.



KEYWORDS: *asymmetric catalysis, N,N′-dioxide/gadolinium complexes, diastereodivergent, inverse electron demand Diels–Alder reaction, indole-fused dihydropyranones*

Despite great progress made on asymmetric synthesis, it remains a challenge for researchers to develop processes that can generate any stereoisomer of a molecule bearing multiple stereogenic centers.[1] The most difficult thing is to tune the diastereoselectivity efficiently.[2a] To date, different approaches have been developed, such as the use of distinct chiral catalysts,[2b−f] central metals,[2g,h] or ligands[2i,j] or the addition of different Lewis acids;[2k] however, it is rare for just changing the substituents of the ligand[2l,m] to inverse the diastereoselectivity, and it is still a promising field to study.

The [4 + 2] cycloadditions between an electron-poor diene and an electron-rich dienophile—namely, inverse electron demand Diels–Alder (IED DA) reactions—have attracted considerable attention.[3] The IED DA reaction of ketenes and 3-alkylenyloxindoles can construct indole-fused dihydropyranones with contiguous quaternary and tertiary stereocenters.[4] The products are attractive because they contain both an indole ring and dihydropyranone structures, which are privileged frameworks in both organic and medicinal fields.[5] Ye applied chiral N-heterocyclic carbenes to catalyzing the enantioselective IED DA reaction, and high yields as well as good ee values were obtained for anti products.[5i] However, syn products were not achieved, and also, the diastereoselectivity and enantioselectivity needed to be further improved. Herein, we report our efforts to develop *N,N′*-dioxide/$Gd(OTf)_3$ complexes for the highly diaseteroselective and enantioselective IED DA reaction of ketenes and 3-alkylenyloxindoles. What's more, by changing the R group of the ligands (Table 1), the diasteroselectivity can be switched; therefore, both *syn*- and *anti*-products can be achieved. Thus, changing the configuration of chiral ligands allows accessing to all possible stereoisomeric products of the IED DA reaction.

Initially, the reaction of ketene **1a** with 3-alkylenyloxindole **2a** was chosen as the model reaction to optimize the reaction conditions. When various metal salts were investigated by coordinating with (*S*)-L-$PiPr_2$ derived from (*S*)-pipecolic acid in CH_2Cl_2 at 30 °C (Table 1, entries 1−3), $Sc(OTf)_3$ complex gave only a trace amount of product **3a**. The complex of $La(OTf)_3$ gave 59% yield of the cycloaddition product, with no diastereo- or enantioselective induction. Inspiringly, the complex of (*S*)-L-$PiPr_2$ with $Gd(OTf)_3$ promoted the reaction smoothly (Table 1, entry 3), affording the lactone **3a** in 70% yield, 6.2:1 dr and 95% ee, and the syn product was the major one. To improve the reactivity, 4 Å MS was added to the catalytic system (Table 1, entry 4), and the yield was increased dramatically to 95% with dr and ee maintained. To our great surprise, when the amine moiety of the ligand was changed from 2,6-$iPr_2C_6H_3$ (ligand (*S*)-L-$PiPr_2$) to 1-adamantyl groups (ligand (*S*)-L-PiAd), the major product was reversed to *anti*-**3a** (1:7.3 dr) in 75% yield with 95% ee (Table 1, entry 5). Inspired by previous work,[6] the addition of $LiNTf_2$ to the (*S*)-L-PiAd/$Gd(OTf)_3$ system as counterion, the yield and dr were improved sharply to 94% and 1:15, and the ee was improved slightly to 96% (Table 1, entry 6). The results were further improved to 98% yield, 1:19 dr, and 97% ee when the reaction was performed at −10 °C (Table 1, entry 7). What's more, when the catalyst loading was lowered to 2 mol %, good results could still be obtained with the yield and dr decreased (88% yield, 1:15 dr and 97% ee, Table 1, entry 8). Thus, the optimal reaction conditions were established: (i) for syn isomers, 10

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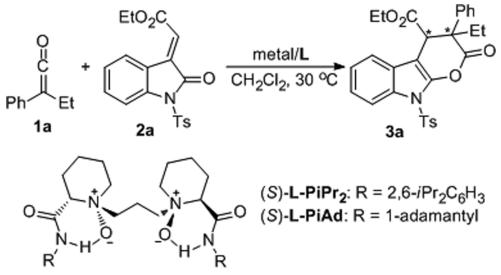
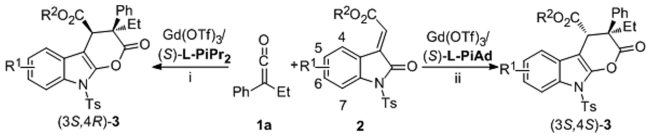
Table 1. Optimization of the Reaction Conditions[a]



entry	metal	L	yield (%)[b]	syn/anti[c]	ee (%)[d]
1	$Sc(OTf)_3$	(*S*)-L-PiPr$_2$	trace		
2	$La(OTf)_3$	(*S*)-L-PiPr$_2$	59	1:1	0/0
3	$Gd(OTf)_3$	(*S*)-L-PiPr$_2$	70	6.2:1	95
4[e]	$Gd(OTf)_3$	(*S*)-L-PiPr$_2$	95	6.4:1	95
5	$Gd(OTf)_3$	(*S*)-L-PiAd	72	1:7.3	95
6[f]	$Gd(OTf)_3$	(*S*)-L-PiAd	94	1:15	96
7[f,g]	$Gd(OTf)_3$	(*S*)-L-PiAd	98	1:19	97
8[f,g,h]	$Gd(OTf)_3$	(*S*)-L-PiAd	88	1:15	97

[a]Unless otherwise noted, the reactions were performed with metal/L (10 mol %, 1/1.2), **1a** (0.15 mmol), **2a** (0.10 mmol) in CH_2Cl_2 (0.2 mL) under nitrogen at 30 °C for 12 h. [b]Isolated yield. [c]Determined by ^{1}H NMR spectroscopy and chiral HPLC analysis. [d]Determined by chiral HPLC analysis. [e]4 Å MS (10.0 mg) was added. [f]$LiNTf_2$ was used. [g]The reaction was performed at −10 °C. [h]The catalyst loading was reduced to 2 mol %.

Table 2. Substrate Scope for 3-Alkylenyloxindoles 2[a]



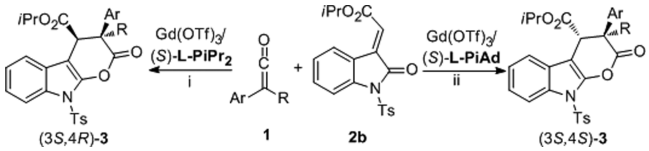
(3*S*,4*R*)-**3**	R^1, R^2	(3*S*,4*S*)-**3**
3a: 95% (6.4:1), 95% ee	H, Et	98% (19:1), 97% ee
3b: 80% (8:1), 96% ee	H, *i*Pr	97% (14:1), 97% ee
3c: 77% (10:1), 94% ee	H, *t*Bu	84% (4:1), 96% ee
3d: 96% (10:1), 86% ee	5-F, *i*Pr	97% (8.5:1), 96% ee
3e: 95% (11:1), 85% ee	5-Cl, *i*Pr	96% (6.4:1), 94% ee
3f: 90% (10:1), 94% ee	5-Br, *i*Pr	96% (7:1), 88% ee
3g: 86% (9:1), 95% ee	5-Me, *i*Pr	96% (16:1), 96% ee
3h: 80% (10:1), 96% ee	5-MeO, *i*Pr	92% (13:1), 98% ee
3i: 88% (14:1), 97% ee	6-Cl, *i*Pr	94% (17:1), 93% ee
3j: 70% (12:1), 96% ee	6-Br, *i*Pr	95% (19:1), 87% ee

[a]Unless otherwise noted, the reactions were run on 0.15 mmol of **1** and 0.1 mmol of **2** under the standard conditions i and ii. Yields of isolated products (diastereomeric mixture) after purification by flash chromatography. The dr (shown in parentheses) was determined by ^{1}H NMR analysis. The ee of the corresponding products was determined by chiral HPLC analysis.

mol % of $Gd(OTf)_3$/(*S*)-L-PiPr$_2$ (1:1.2) and 4 Å MS (10 mg) at 30 °C; (ii) for anti isomers, 5 mol % of Gd(OTf)3/(*S*)-L-PiAd (1:1.2) and $LiNTf_2$ (3 mg) at −10 °C.

With the optimized conditions in hand, we then set out to explore the scope of the reaction. First, various 3-alkylenyloxindoles **2** were investigated by reacting with ketene **1a** (Table 2). Different ester groups of **2** were tested. More sterically hindered isopropyl or tertbutyl substituted esters were suitable, transforming to corresponding *syn*- and *anti*-**3b**, **3c** in good to excellent yield and dr and ee values (77%−97%, 4:1−14:1, 94%−97% ee). The more steric hindrance of the R^2 group, the higher dr values for (3*S*,4*R*)-**3** were obtained; on the other hand, the lower the dr values for (3*S*,4*S*)-**3** were obtained. (Table 1, **3a**−**3c**) Electron-withdrawing or -donating substituents on the 5- or 6-position of the indole ring were also tested, and the desired both syn and anti products were obtained in good to excellent yields and dr and ee values (**3d**−**3j**, 70%−97%, 6.4:1−19:1, 85%−98% ee).

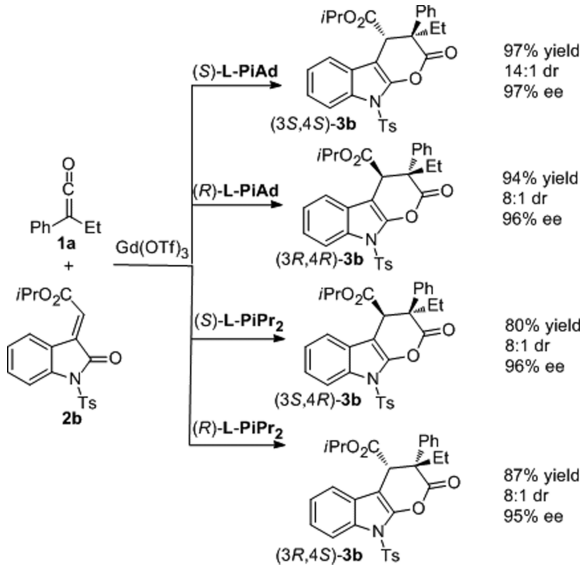
Table 3. Substrate Scope for Ketenes 1[a]



(3*S*,4*R*)-**3**	Ar, R	(3*S*,4*S*)-**3**
3k: 93% (7.3:1), 97% ee	Ph, *n*Pr	97% (18:1), 96% ee
3l: 83% (11:1), 98% ee	Ph, *n*Bu	96% (15:1), 98% ee
3m: 95% (14:1), 94% ee	3-FC_6H_4, Et	96% (12:1), 98% ee
3n: 95% (15:1), 97% ee	4-FC_6H_4, Et	96% (13:1), 98% ee
3o: 97% (13:1), 97% ee	4-ClC_6H_4, Et	98% (17:1), 98% ee
3p: 96% (14:1), 97% ee	4-$MeOC_6H_4$, Et	98% (5:1), 91% ee
3q: 88% (16:1), 98% ee	4-MeC_6H_4, Et	98% (12:1), 95% ee

[a]Unless otherwise noted, the reactions were run on 0.15 mmol of **1** and 0.1 mmol of **2** under the standard conditions i and ii. Yields of isolated products (diastereomeric mixture) after purification by flash chromatography. The dr (shown in parentheses) was determined by ^{1}H NMR analysis. The ee of the corresponding products was determined by chiral HPLC analysis.

Scheme 1. Synthesis of All Stereoisomers of 3b



Next, we turned our attention to the scope of the ketenes **1** (Table 3). Ketenes with *n*-propyl or *n*-butyl groups proceeded well under both catalyst systems, giving the *syn*- and *anti*-**3k**, **3l** in high yields (83%−97%) and with excellent ee values (>96%). Electron-withdrawing or -donating substituents on the aryl group of ketenes had little effect on the reactivities and stereoselectivities (**3m**−**3q**). The desired products were obtained in high yields and dr and ee values (88%−98% yield, 5:1−17:1, 85%−98% ee). The absolute configurations of the product **3a**, which was obtained from the $Gd(OTf)_3$/(*S*)-L-PiPr$_2$, system had been confirmed unambiguously to be (3*S*,4*R*), and that which was obtained from the $Gd(OTf)_3$/

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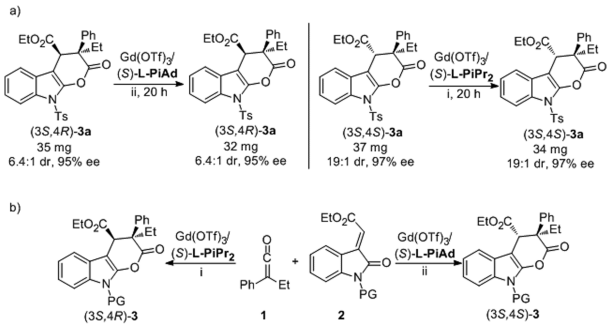
Scheme 2. Control Experiments[a]



entry	(3*S*,4*R*)-**3**	PG	(3*S*,4*S*)-**3**
1	nr	Bn	nr
2	97% (17:1) 97% ee	PhCO	96% (1:1) 90%ee/95% ee
3	96% (3:1) 74% ee	Ms	95% (6:1) 97% ee
4	96% (6.5:1) 95% ee	Ts	97% (19:1) 96% ee

[a]Unless otherwise noted, the reactions were run on 0.15 mmol of **1** and 0.1 mmol of **2** under the standard conditions i and ii. Yields of isolated products (diastereomeric mixture) after purification by flash chromatography. The dr (shown in parentheses) was determined by ^{1}H NMR analysis. The ee of the corresponding products was determined by chiral HPLC analysis.

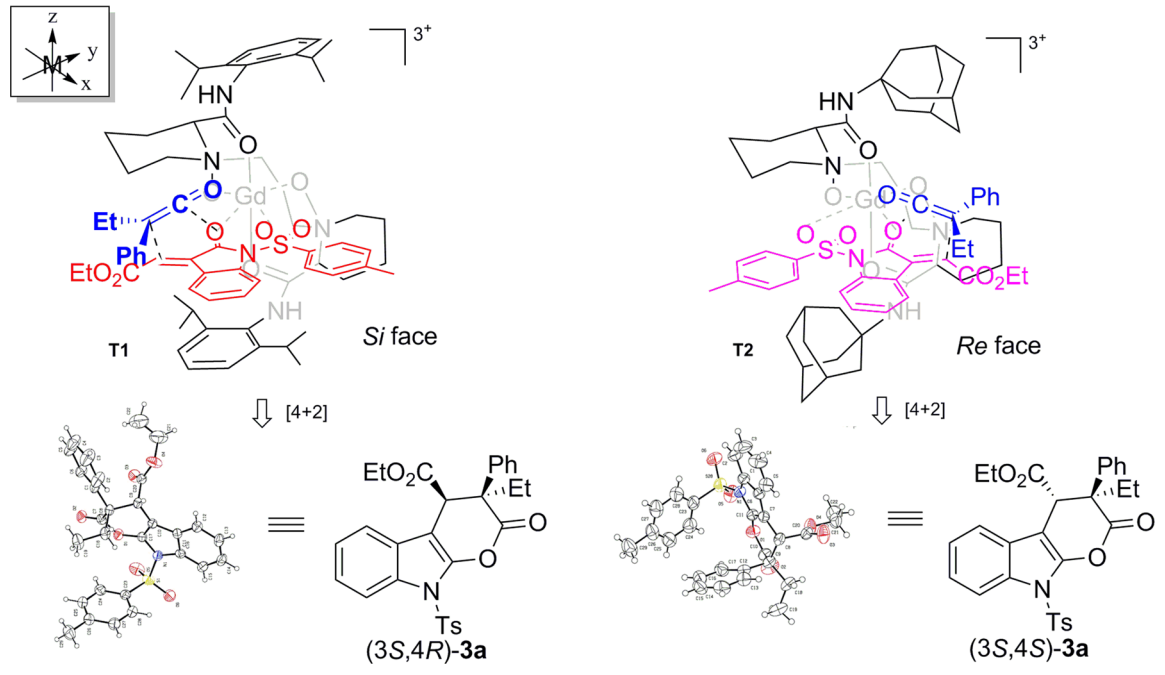
(*S*)-L-PiAd system had been confirmed unambiguously to be (3*S*,4*S*) by X-ray diffraction analysis.[7] The absolute configurations of the other products were determined by comparing the circular dichroism spectra with **3a**.

Then, we showed the possibility to establish all four stereoisomers of indole-fused dihydropyranones with our catalysts by using **3b** as an example (Scheme 1). From the same set of starting materials **1a** and **2b** as well as using $Gd(OTf)_3$ as the central metal, while the amine moiety of the ligand was 1-adamantyl amine, the products *anti*-**3b** appeared; On the other hand, when 2,6-*i*Pr$_2$C$_6$H$_3$ amine was used, the *syn*-**3b** were obtained. Thus, changing the configuration of chiral ligands from *R* to *S* all stereoisomers could be obtained.

To probe the mechanism of the diastereodivergent reactions in the presence of two different ligands, some control experiments were performed (Scheme 2). First of all, the reactions of products (3*S*,4*R*)-**3a** and (3*S*,4*S*)-**3a** were carried out under conditions ii and conditions i for 20 h, respectively (Scheme 2a). The dr values and ee values of (3*S*,4*R*)-**3a** and (3*S*,4*S*)-**3a** were unchanged. The phenomenon indicates to us that the diastereodivergency was generated from the different catalyst systems rather than the epimerization of the products. We assumed that the substrates **2** bound to the $Gd(OTf)_3$/(*S*)-L-PiPr$_2$ or $Gd(OTf)_3$/(*S*)-L-PiAd catalyst in a bidentate manner with a carbonyl group and sulfonyl group. In the meantime, the pyramidal sulfonyl protected amines provided an excellent sterical environment in the catalysis reactions, then the benzyl group, which has no coordinating site to the central metal, was used as a protecting group, and the reactions shut down (Scheme 2b, entry 1). Meanwhile, when benzoyl-protected 3-alkylenyloxindoles were used as the substrate, the reactions restarted (Scheme 2b, entry 2). Unfortunately, the $Gd(OTf)_3$/(*S*)-L-PiAd catalyst system failed to control the diastereoselectivity (1:1). On the other hand, when the protecting group was changed to a methanesulfonyl group, the dr value for the $Gd(OTf)_3$/(*S*)-L-PiAd catalyst system was improved, and that was decreased for $Gd(OTf)_3$/(*S*)-L-PiPr$_2$ catalyst system (Scheme 2b, entry 3 compared with entry 2). The phenomenon indicates that the pyramidal sulfonyl group helped to enhance the diaseteroselctivity of *anti*-**3** instead of the flat benzoyl group. The best results were obtained when the *p*-toluenesulfonyl group was used as a substrate (Scheme 2, entry 4). The result further demonstrates that the sterically hindered pyramidal sulfonyl group is crucial for the catalyst system.

On the basis of the absolute configuration of the product **3a**[7] as well as our previous study of the structure of *N*,*N*′-dioxide/

Scheme 3. Proposed Catalytic Model of the Catalytic Asymmetric Diastereodivergent Reactions



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metal complexes[8] and the control experiments, the catalytic models are proposed in Scheme 3. Because $Gd(OTf)_3$ is a strong Lewis acid, it coordinates with the four oxygens of *N*,*N*′-dioxide to form the octahedral **T1**, then 3-alkylenyloxindoles chelate to the catalyst with its two oxygen atoms in a bidentate manner, leading to a decrease in its LUMO energy. In the $Gd(OTf)_3$/(*S*)-L-$PiPr_2$ catalyst system, the oxygen at the C3-postion of the 3-alkylenyloxindole locates at the *y*-axis to avoid steric hindrance between the ester group on the substrate and the octahydrocyclo penta[*b*]pyrrole backbone on the right side of the ligand. Then ketene **1a**, being regarded as a dienephile, attacks the diene from the less hindered *Si* face because the *Re* face is hindered by 2,6-$iPr_2C_6H_3$, affording (3*S*,4*R*)-configured **3a** (Scheme 3, **T1**). This could explain the phenomenon with the more steric hindrance of R^2 of the esters, that the higher dr values of (3*S*,4*R*)-**3** were obtained (Table 2, **3a**−**3c**).

In the $Gd(OTf)_3$/(*S*)-L-PiAd catalyst system, the C3-postion of 3-alkylenyloxindole locates at the *x*-axis to avoid steric hindrance between the ester group on the substrate and the adamantyl group of the ligand. Then ketene **1a** attacks the functional groups of the substrate located at the *y*-axes from its *Re* face because the *Si* face is hindered by the adamantyl group of the ligand, producing the (3*S*,4*S*)-configured **3a** (Scheme 3, **T2**). This could also explain the phenomenon that with the more steric hindrance of the R^2 of the esters, the lower dr values of (3*S*,4*S*)-**3** were obtained (Table 2, **3a**−**3c**).

In summary, we have disclosed an example of stereodivergent IED DA reaction of ketenes and 3-alkylenyloxindoles. By changing the amide moieties of *N*,*N*′-dioxide ligands, both *syn*- and *anti*-indole-fused dihydropyranones bearing two vicinal stereogenic centers could be obtained with excellent yields (up to 99%) and dr (up to 19:1) and ee (98%) values. Thus, changing the configuration of chiral ligands enabled the preparation of all stereoisomers. The mechanism studied showed that the protecting group and the ligand structure played an important role in the diastereoselectivity switching. Studies to further explore diastereodivergent catalysis are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01719.

Experimental details, analytic data (NMR, HPLC, CD, and ESI−HRMS)(PDF)
Crystallographic data (CIF)
Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xmfeng@scu.edu.cn.

Notes

The authors declare no competing financial interest.

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