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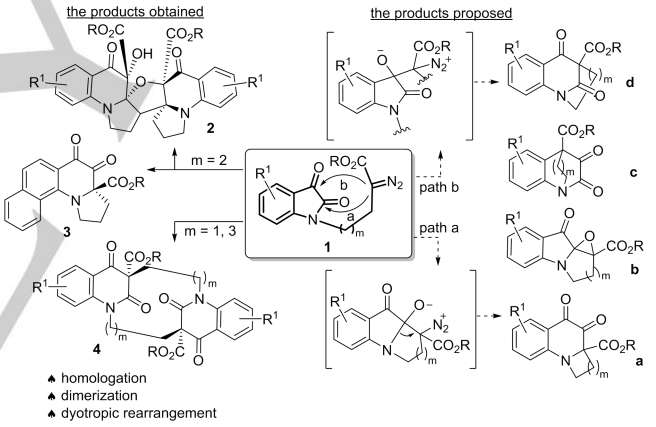
Chiral Lewis Acid Catalyzed Reactions of α-Diazoester Derivatives: Construction of Dimeric Polycyclic Compounds

Fei Tan, Xiaohua Liu,* Yan Wang, Shunxi Dong, Han Yu, and Xiaoming Feng*

Abstract: An unexpected cascade homologation/dyotropic rearrangement/interconversion/[3+2] cycloaddition reaction of α-diazoester-terminated *N*-propyl substituted isatin derivatives was achieved in the presence of a chiral *N,N′*-dioxide-Sc(III) complex catalyst. This catalytic manifold allows a rapid construction of several classes of dimeric polycyclic compounds with good yield and high level of diastereo- and enantioselectivity (up to 99% ee). Furthermore, in cases of the substrates with other alkyl linkage, the reactions proceeded to give macrocyclic dimers via intermolecular-homologation process.

Cascade or domino reactions provided concise and efficient methods for rapid construction of complex molecules from simple starting materials.[1] Remarkable progress has been made in the area of asymmetric organocatalytic cascade or domino reactions over the past two decades.[1b-f] In addition, metal-complex-involved processes also attracted considerable interest, thereof the enantioselective version, in sharp contrast, was rare.[2] Generally, the nature of the ligands bound to metal precursors displays an appreciable influence on both the rates (slowdown, maintenance, or acceleration) and the selectivities of the transformations.[3] In consequence, developing single metal complex catalyst promoted cascade reaction for one-pot synthesis of complicate compounds with high diastereo- and enantioselectivity is fascinating but challenging.

α-Diazo carbonyl compounds are a type of important synthons exhibiting rich and unexpected chemistry.[4] Enantioselective catalytic homologation of ketones and α-diazoesters has proven efficient to build quaternary carbon stereocenters, enabling the rapid generation of structural complexity.[4e,5] The Maruoka group reported the first case of enantioselective ring expansion of cyclohexanone with α-diazoester catalyzed by chiral $AlMe_3$/BINOL complex.[5a] Later on, our group utilized chiral *N,N′*-dioxide-metal Lewis acid catalysts to accomplish both intermolecular[5b,c] and intramolecular[5d] homologation reaction of α-diazoesters. We attempted to combine the intramolecular strategy and key skeleton of isatin to build polycyclic molecules containing quaternary carbon center from the simple substrates **1** (Scheme 1, center). In principle, initiated by the nucleophilic attack of diazo-carbon to either carbonyl group (path a and path b), various cyclic products (a–d) could be generated. In fact, unique cascade reactions occurred in the presence of a chiral scandium(III) complex of *N,N′*-dioxide,[6] affording optically active dimeric polycyclic product **2**, ring-expansion compound **3** (also as the proposed product **a**), or macrocyclic dimer **4** as the major one via several interesting steps (Scheme 1, left), depending on the length of the tether and the backbone of oxindole unit. Herein, we demonstrate a chiral Lewis acid promoted enantioselective cascade reactions of isatin derivatives **1** bearing an α-diazoester-terminated *N*-propyl substituent. The formation of dimeric tetrahydrofuran-bridged products **2** possibly involves intramolecular homologation of isatin, dyotropic rearrangement,[7] interconversion and formal intermolecular [3+2]-cycloaddition. One exception is the generation of ring-expansion product **3** from a naphthalene-ring-containing isatin derivative via intramolecular homologation. Moreover, the substrates with two- or four-carbon alkyl tether between isatin skeleton and α-diazoester unit undergo intermolecular homologation to deliver macrocyclic products **4**. As molecules consisting of two complex monomeric units with multiple chiral centers have been found in a number of natural products,[8] the discovery of novel dyotropic reaction and dimerization process is supposed to be useful for the rapid and efficient construction of complex target molecules.



Scheme 1. Possible reactions of isatin-derivatives **1** bearing an α-diazoester-terminated *N*-alkyl substituent.

The length of the tether between isatin skeleton and α-diazoester unit has a direct influence on the intramolecular reaction by the ring-size of the reaction intermediate with a range of conformations, so we initially synthesized the substrate **1a** bearing a three-carbon chain for the reaction (Table 1). A series of metal salts combined with chiral *N,N′*-dioxide L-$RaPr_2$ was tested (See SI Table S1 for details). Only $Sc(OTf)_3$ yielded the compound **2a** in 19% yield and 99% *ee* as the major product (Table 1, entry 1). The structure of **2a** was later determined to be a novel dimeric multiple-ring scaffold with five chiral centers by X-ray crystallographic analysis.[9] Other metal salts, such as $Y(OTf)_3$, $La(OTf)_3$, $Gd(OTf)_3$, and $Yb(OTf)_3$, led to the decomposition of **1a** (entry 2). Next, the influence of *N,N′*-dioxide ligands was studied. With respect to the amino acid backbone, the ligand L-$PrPr_2$ derived from *L*-proline afforded **2a** in 31% yield and 42:58 d.r., with 95% *ee* and 8% *ee* for each diastereomer (entry 3). *L*-Pipecolic acid derived *N,N′*-dioxide L-

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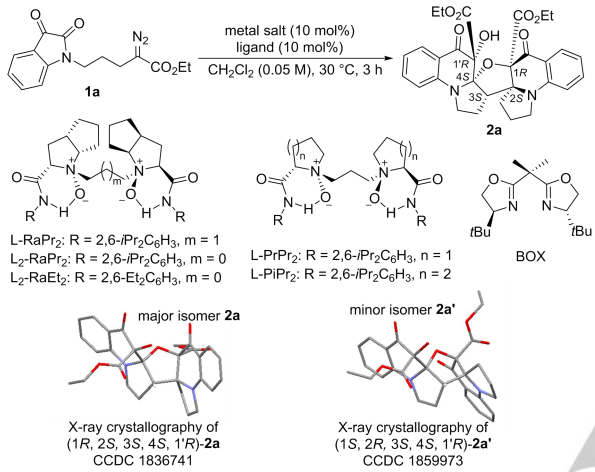
$PiPr_2$ produced **2a** in 37% yield with an inversion of diastereoselection and a decrease in enantioselectivity (entry 4). The product **2a** was identified as the isotactic dimer which contains two precursors with the same configuration, whereas the other diastereomer **2a'** was identified as a syndiotactic dimer which generated from a pair of enantiomers according to X-ray crystal analysis.[9] Ligand L_2-$RaPr_2$ bearing a two-carbon tether sharply improved the yield of **2a** with retained *ee* value, but the third diastereomer **2a''** emerged at the same time because of the existence of five contiguous stereocarbon centers in the products (entry 5 versus entry 1). The total yield reached to 84% and the optically pure isomer **2a** was isolated in 70% yield (entry 5). Moreover, it was found that the amide units of the ligand also made a difference, and the less bulky groups at the 2,6-position of the aniline (L_2-$RaEt_2$) resulted in both low yield and poor diastereomeric control in the reaction (entry 6 versus entry 5). Finally, investigation of the additives (See SI Table S7 for details) showed that the addition of benzoic acid or strong base hampered the generation of **2a** (entries 7–8). To our delight, the addition of 10 mol% of $NaBAr^F_4$ increased the total yield to 97%, and the major isomer **2a** was obtained in 80% yield with 99% *ee* (entry 9 versus entry 5). In contrast, using BOX ligand instead of L_2-$RaPr_2$ led to decomposition of the substrate without generation of the dimeric product **2a** (entry 10). In the absence of ligand, decomposition of **1a** was sluggish and no desired dimers were detected (entry 11). These results indicated that not only central metal but also chiral ligand were crucial for the reactivity. Currently, the origin of this remarkable ligand-accelerated catalysis[3a] is not fully understood. We hypothesized that the coordination of L_2-$RaPr_2$ to central metal Sc^{III} manifested in a stronger chiral Lewis acid, as well as a more favorable interaction and steric effect with **1a**.

After establishing the optimized conditions (Table 1, entry 9), we examined the generality of the reaction (Table 2). Three-carbon tethered isatin derivatives **1** with variation of the ester groups of diazoester unit or at the aryl substituent of the isatin backbone could undergo the enantioselective cascade reaction well to yield the desired dimer **2**. It was found that ester groups investigated (**1b**–**1g**) had a negligible effect on the enantioselectivity in all cases (≥99% *ee*), whereas the diastereoselection and isolated yield of the major isomers

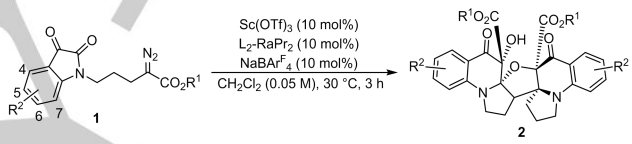
Table 1. Optimization of the reaction conditions.



Entry[a]	Metal salt	Ligand	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	$Sc(OTf)_3$	L-$RaPr_2$	19	>19:1[d]	>99/–
2	$Yb(OTf)_3$	L-$RaPr_2$	–	–	–
3	$Sc(OTf)_3$	L-$PrPr_2$	31	38:62	95/8
4	$Sc(OTf)_3$	L-$PiPr_2$	37	20:80	61/7
5	$Sc(OTf)_3$	L_2-$RaPr_2$	84 (70)	–[e]	>99/–
6	$Sc(OTf)_3$	L_2-$RaEt_2$	70	54:46	>99/31
7[f]	$Sc(OTf)_3$	L_2-$RaPr_2$	3	>19:1[d]	>99/–
8[g]	$Sc(OTf)_3$	L_2-$RaPr_2$	–	–	–
9[h]	$Sc(OTf)_3$	L_2-$RaPr_2$	97 (80)	–[e]	>99/–
10[h]	$Sc(OTf)_3$	BOX	–	–	–
11[h]	$Sc(OTf)_3$	–	–	–	–

[a] Metal salt (10 mol%) and ligand (10 mol%) was stirred in tetrahydrofuran (0.2 mL) at 30 °C for 0.5 h. After evaporation in vacuo, **1a** (0.1 mmol) in CH_2Cl_2 (0.05 M) were added at 30 °C, and the catalytic system continued stirring at 30 °C for 3 h. [b] Isolated yield, and data in the parentheses related to the isolated yield of major diastereomer **2a**. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis. [e] Mixture of three-pair diastereomers, not determined. [f] 20 mol% $PhCO_2H$ was added. [g] 20 mol% DMAP was added. [h] 10 mol% $NaBAr^F_4$ was added. DMAP = 4-dimethylaminopyridine, $NaBAr^F_4$ = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

Table 2. Scope of ester groups and substituents at the aryl ring of isatin.



Entry[a]	R^1	R^2	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Me	H	72 (**2b**)	86:14	>99
2	*n*Pr	H	99 (**2c**)	90:10	99
3	*i*Pr	H	99 (**2d**)	92:8	>99
4	Allyl	H	99 (**2e**)	90:10	>99
5	Benzyl	H	89 (82) (**2f**)	–[e]	>99
6	Cholesteryl	H	62 (**2g**)	92:8	–
7	*n*Pr	4-F	74 (**2h**)	89:11	>99
8	*n*Pr	5-F	87 (66) (**2i**)	–[e]	>99
9	*n*Pr	6-F	77 (71) (**2j**)	–[e]	>99
10	*n*Pr	7-F	76 (72) (**2k**)	–[e]	>99
11	*n*Pr	5-Cl	82 (63) (**2l**)	–[e]	>99
12	*n*Pr	5-Br	82 (74) (**2m**)	–[e]	>99
13	*n*Pr	5-I	83 (73) (**2n**)	–[e]	>99
14	*n*Pr	5-Me	74 (55) (**2o**)	–[e]	>99
15	*n*Pr	5-MeO	72 (51) (**2p**)	–[e]	>99

[a] The same conditions as described in footnote [a] and [h] of Table 1. [b-e] The same with those in footnote [b-e] of Table 1.

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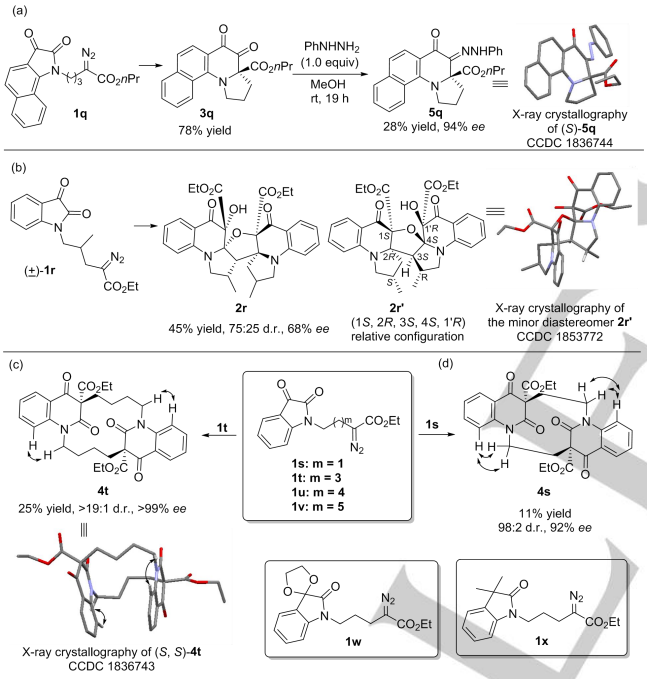
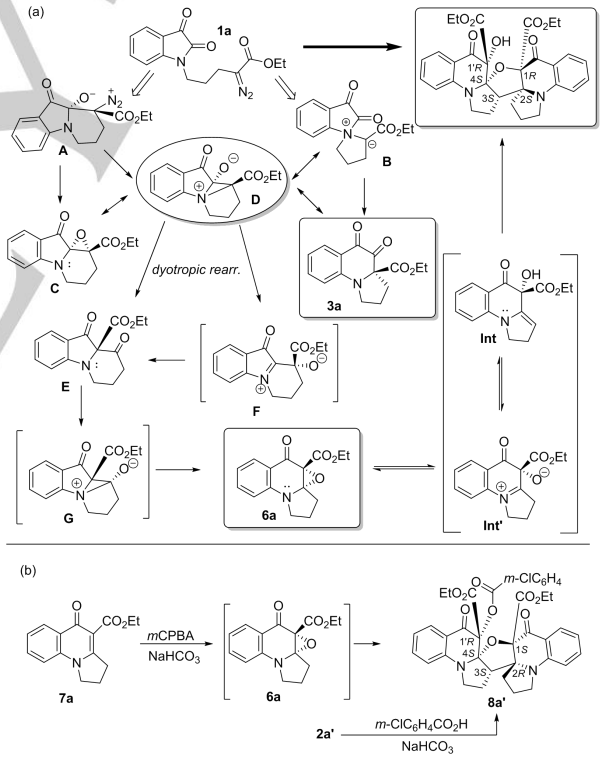
depends on substituents of ester. (entries 1-6). Substrate **1b** with methyl ester lowered the yield and diastereoselectivity, while bulkier esters (**1c**–**1f**) gave higher yield and diastereoselectivity (entries 1-3). Remarkably, substrate **1g** with multiple chiral center contained cholesteryl ester underwent the reaction smoothly to generate **2g** in 62% yield with 92:8 d.r. (entry 6). Next, the influence of position and electronic nature of substituents on the aromatic ring of isatin was evaluated (entries 7-15). All the substrates (**1h**–**1k**) with a fluoro-substituent at different position of isatin produced the products (**2h**–**2k**) with excellent enantioselectivity (>99% *ee*), and 5-fluoro-substituted isatin **1i** provided a higher yield (87%), while the others exhibited better diastereoselectivity (entries 7-10). The electronic property of the substituents at the C5 position of the isatins (**1l**–**1p**) displayed an obvious impact upon the yield and diastereoselection (entires 11-15). 5-Chloro-substituted **1l** yielded the dimers with lower diastereoselectivity in comparison with 5-bromo (**1m**) and 5-iodo (**1n**) substituted ones (entries 11-13). 5-Methyl and 5-methoxyl substituted substrates **1o** and **1p** gave lower yield and diastereoselectivity than 5-halo substituted ones (entries 14-15 vs entries 11-13).



Scheme 2. Scope of the tethers linking isatin and α-diazoester and others.

It is noteworthy that the substrate **1q** containing a naphthalene ring gave a ring-expansion product **3q** via the shift of nitrogen of isatin with 78% yield (Scheme 2a). None of the ester-shift and the corresponding dimers were detected probably owing to the steric hindrance. The determination of the structure and enantioselectivity was confirmed after the transformation into phenylhydrazine derivative **5q** (Scheme 2a)[9]. Nevertheless, the tethers that connect the isatin and the diazoester units exhibit a substantial effect on the reaction, which could be envisioned that the stereo-arrangement, steric hinderance, and conformation limitation of the ring with different size would affect the rearrangement (Scheme 2b–2d). Introducing a methyl group to the middle carbon of the three-carbon-unit tether (**1r**) did not affect the reaction process but lowered both the yield and the enantioselectivity of the dimeric products **2r** and **2r'** (Scheme 2b). The relative configuration of minor diastereomer **2r'** was determined from X-ray crystal structure,[9] which is a syndiotactic dimer generated from a pair of enantiomers of the intermediate. The substrate **1t** containing a four-carbon-unit chain produced a macrocyclic dimer **4t** in a yield of 25% with >99% *ee* (Scheme 2c), which was later defined to be a scaffold containing two quinoline-2,4(1*H*,3*H*)-dione units linked by two four-carbon chains via an X-ray crystallography analysis.[9] It was generated through intermolecular homologation between the 3-carbonly group of isatin skeleton and the diazoester unit from two reactants separately, however, the rearrangement sequence is different from an intermolecular ring-expansion example in our previous study.[5b] Shortening the length of tether to two-carbon unit (**1s**) led to the formation of a new dimer **4s** in 11% yield with 98:2 d.r. and 93% *ee* (Scheme 2d). The structure was similar to dimer **4t** according to 2D-NMR spectral analysis. However, when the length of carbon-tether further increased, the catalytic reaction of **1u** and **1v** became slow and messy. The aforementioned results imply that the length of of alkyl tethers in substrates had a considerable effect on the reaction pathway. Additionally, the carbonyl group of isatin was proved to be essential, since no reaction occurred when substrate **1w** or **1x** was utilized.



Scheme 3. Proposed cascade process embodied in the formation of dimer **2**.

Based on previous studies[5b-d,6] and control experiments, we propose a cascade process as shown in Scheme 3a (See SI for details). When the substrate **1a** is mixed with the L_2-$RaPr_2$/$Sc(OTf)_3$ catalyst,[9] the nucleophilic addition of diazo-carbon to the carbonyl group of the amide might proceed to yield the intermediate **A**. Subsequently, the migration of oxygen or nitrogen with the release of N_2 result in the generation of intermediate **C** and **D**, respectively. Alternatively, the exclusion

of N_2, and nucleophilic addition of *N*-atom of the isatin to the carbene intermediate might generate ylide intermediate **B**, followed by a [1,2]-rearrangement to provide intermediate **3a**. It is interesting that a stereospecific dyotropic reaction takes place from intermediate **C** or **D** through highly synchronous symmetry-allowed mechanism.[7a,b] This pathway allows the formation of ester or oxygen rearrangement intermediate **E** or **F**. Then, an intramolecular amine attacks the carbonyl group of six-membered ring in **E** yields the intermediate **G**. Finally, aza-ring breaks to afford the ring-expansion product **6a**, which can interconvert into the precursor **Int** and tautomer **Int'** to undergo formal [3+2] cycloaddition. Thus, the dimeric product **2a** and the related diastereomers are afforded.

We speculated that **6a** was the key intermediate which could undergo dimerization process to form the polycyclic dimer **2a**. In order to prove it, the substrate **7a** was synthesized and treated with *m*CPBA to give the dimerization product **8a'** probably via intermediate **6a** (Scheme 3b). Product **8a'** is in accord with the esterification of the diastereomer **2a'** with 3-chlorobenzoic acid. This result supports the cascade process we proposed above.

In summary, we have developed a mild catalytic system for the highly chemo- and enantioselective homologation/dyotropic transformation/[3+2]-cycloaddition of α-diazoester-terminated *N*-alkyl substituted isatin derivatives. Several classes of polycyclic compounds were readily obtained in good chemical yield with high level of stereoselectivity. It also showed that the length of tether in substrates affected the chemoselectivity. Meanwhile, chiral Lewis acid catalyst was found to be crucial to the reactivity and stereoselectivity in the cascade reactions. The utility of the methodology in the synthesis of relative biologically active molecules is in progress.

Acknowledgements

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Keywords: asymmetric catalysis • cascade reaction • chiral Lewis acid • α-diazoester • dyotropic transformation • polycyclic compound

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[9] CCDC 1836741 (**2a**), CCDC 1859973 (**2a'**), CCDC 1836744 (**5q**), CCDC 1853772 (**2r'**), CCDC 1836743 (**4t**), and CCDC 1836738 (**L_2-RaPr$_2$**/Sc(OTf)$_3$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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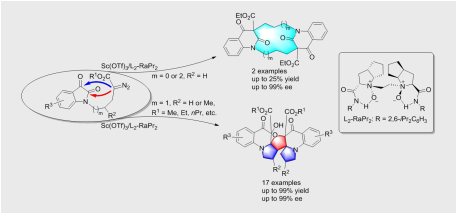

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A highly chemo- and enantioselective homologation/dyotropic transformation/ interconversion/[3+2]-cycloaddition cascade process of α -diazoester-terminated isatin derivatives with a three-carbon tether was achieved. Dimeric polycyclic compounds containing multiple quaternary carbon centers were synthesized in one-pot assisted by chiral *N*,*N*'-dioxide-Sc(III) complex catalyst. Other intermolecular homologation occurred to give macrocyclic dimers from the related substrates with two- or four-carbon tether.