Asymmetric Catalysis

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A Catalytic Asymmetric Ring-Expansion Reaction of Isatins and α-Alkyl-α-Diazoesters: Highly Efficient Synthesis of Functionalized 2-Quinolone Derivatives**

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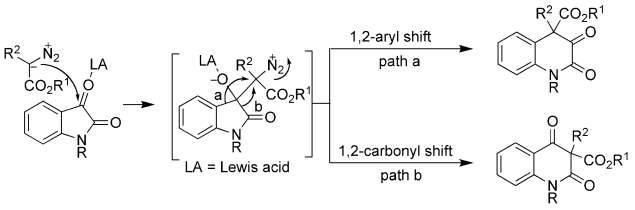
The ring-expansion reaction of cyclic ketones and diazo compounds is a classical way to expand the ring size of cyclic carbonyl compounds by one-carbon unit.[1] The ring expansion of isatin and other ketones with diazomethane was reported early in the last century.[2] Since then, a number of advances have been made, such as the development of variants that use α-diazoesters, which are more stable and less reactive than α-diazoalkanes.[3] However, the development of catalytic asymmetric variants seems particularly difficult. Innovative approaches have recently been reported by Kingsbury and co-workers[4] and by Maruoka and co-workers.[5] However, the catalytic reactions developed by these research groups involved the ring expansion of symmetric aliphatic cyclic ketones through 1,2-alkyl migration. Extremely low reaction temperatures and high catalyst loadings were required, especially when α-alkyl-α-diazoesters were used to incorporate all-carbon quaternary centers. To the best of our knowledge, asymmetric ring expansion of prochiral cyclic carbonyl compounds, which usually suffer from complicated regiochemical problems,[1a,2c] has not been documented to date. Although isatin was chosen as the substrate in the first example of a ring-expansion reaction with diazomethane, a reaction that was reported in the year 1919,[2a] an asymmetric ring expansion of isatins has not been reported. In this reaction multiple products are possible because of competitive 1,2-aryl migration and 1,2-carbonyl migration reaction pathways (Scheme 1).[2c,6] Thus, the development of a suitable catalyst for the ring expansion of unsymmetric substrates with high regio- and enantiocontrol is particularly desirable, albeit challenging. In a continuation of our research with diazo compounds,[7] we report herein a highly enantioselective ring-expansion reaction of isatins and α-alkyl-α-diazoesters involving 1,2-aryl migration.[8]



Scheme 1. Regiochemistry in the ring expansion of unsymmetrical substrates.

Quinolone scaffolds,[9] particularly functionalized 2-quinolones that contain a chiral quaternary center at C4, are common in natural products and medicinal molecules, such as the Melodinus alkaloids (scandine,[10] meloscine,[11] and meloscandonine),[12] melicodenine G,[13] and yaequinolone A1.[14] Efficient asymmetric approaches to incorporate this important molecular scaffold are limited,[15] as are the formations of chiral quaternary centers.[16] The asymmetric ring-expansion reaction of isatins and α-substituted α-diazoesters would be a straightforward method for preparing this quinolone compounds. In the presence of a $Sc(OTf)_3$ catalyst containing a *N*,*N*′-dioxide-based ligand,[17] we found that the asymmetric ring-expansion reaction of isatins and α-alkyl-α-diazoesters performed well with a catalyst loading as low as 0.05 mol%, thus providing highly functionalized C4-quaternary 2-quinolone derivatives with *ee* values as high as 99%. Moreover, the catalytic reaction shows high functional-group tolerance, which facilitates the further transformation of products into other useful synthetic intermediates.

We screened an array of chiral ligands and metal ions (see the Supporting Information) for their reactivity and ability to induce asymmetry in the ring-expansion reaction of *N*-benzyl isatin **2a** and α-benzyl-α-diazoacetate **1a**. This survey led to the following optimized reaction conditions: 0.2 mol% of a scandium(III) complex with the *N*,*N*′-dioxide ligand **L**, which was prepared from L-ramipril, CH_2Cl_2 as the solvent, and 30°C as the reaction temperature. The desired quinoline-2,3(1*H*,4*H*)-dione derivative **3a** was obtained in 91% yield with an *ee* value of 99% (Scheme 2); a byproduct derived from the 1,2-carbonyl migration pathway was obtained in 8% yield. This result shows that in this reaction the aryl group has a higher migratory aptitude than the carbonyl group.[2c]

We then explored the scope of this reaction with a range of α-alkyl-α-diazoesters (Scheme 2). Varying the ester group of the α-diazoester (**1a**–**1d**) had no adverse effect on yield and selectivity. The rate and enantioselectivity of the ring-

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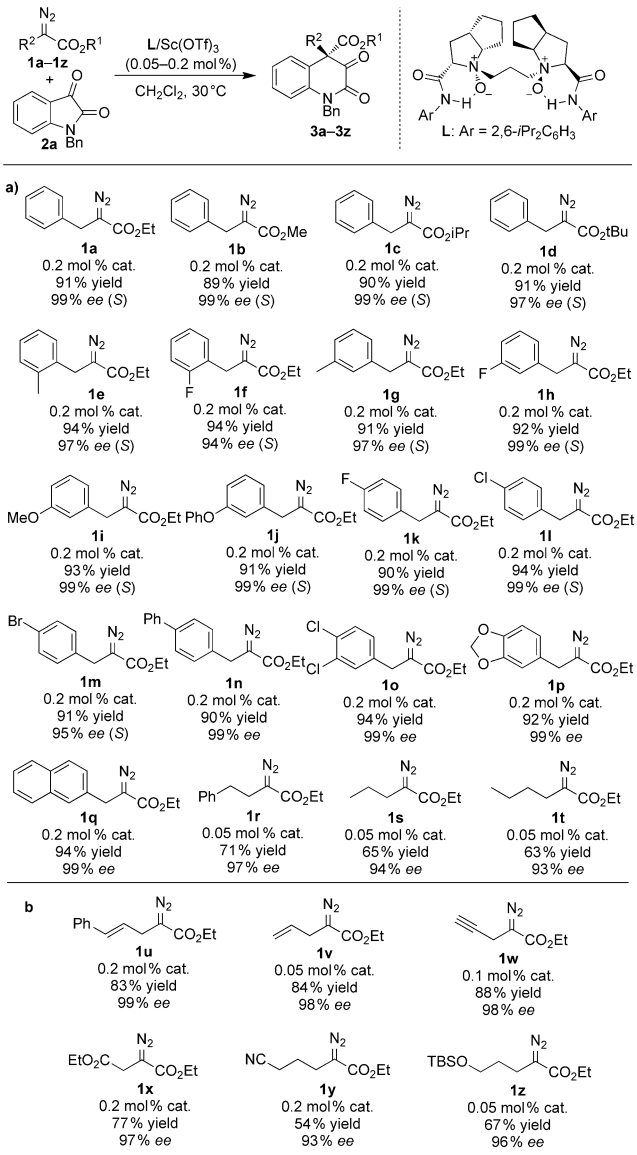
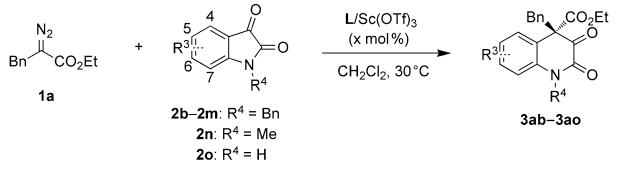


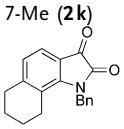
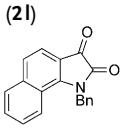
Scheme 2. Scope of α-alkyl-α-diazoesters in the catalytic asymmetric ring expansion. The reactions were performed with **L**/Sc(OTf)$_3$ (0.05–0.2 mol%, 1:1.2), **2a** (0.20 mmol), **1** (0.30 mmol), CH_2Cl_2 (0.2 mL) in 30°C for 5–50 h (for details, see the Supporting Information). Yields of isolated products are reported. The *ee* values were determined by HPLC using a chiral stationary phase. The absolute configuration of **3a** was determined to be *S* by X-ray crystallographic analysis, and those of **3b**–**3m** were assigned by comparing their circular-dichroism spectra with that of **3a**. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

expansion reactions of a series of substituted α-benzyl diazoacetates (**1e**–**1p**) were uniformly high. The electronic properties, bulkiness, or positions of the substituents on the benzyl group of diazoacetates had very little effect on the reaction outcome. 2-Naphthylmethyl-substituted α-diazoester **1q** was also well tolerated in this reaction. The reactions of diazoesters containing an ethylphenyl substituent or an alkyl substituent at the α position (**1r**–**1t**) were relatively fast. For these reactions, the catalyst loading was reduced to 0.05 mol%; the levels of enantioselectivity remained high, although the yields of the products **3r**–**3t** were lower owing to deleterious side reactions. Further exploration of the scope of the reaction with respect to the diazoester focused on the those containing substituents bearing functional groups (**1u**–**1w**). Cinnamyl, allyl, and alkynyl moieties proved to be well tolerated by the reaction, thus giving α-allylic and α-alkynylic ketone derivatives, respectively. Other α-alkyl diazoesters, which contained a terminal substituent, such as an ester, a nitrile, and a silyl ether group (**1x**–**1z**) were also transformed in this reaction with low catalyst loading. Generally, the levels of enantioselectivity in the reactions of all substrates were very high, ranging from 93% to 99% *ee*.

We then investigated the scope of the reaction with respect to the isatin substrate (Table 1). The position and electronic nature of substituents of the isatin had significant effects on both enantioselectivity and reactivity (Table 1, entries 1–10). Isatins **2b**–**2e**, which have substituents at the C5 position, gave lower levels of enantioselectivity and were less reactive than isatins with substituents at the C6 and C7 positions. For 5-halo-substituted isatins, both the reactivity and the enantioselectivity decreased in the order 5-F > 5-Cl > 5-Br > 5-I (Table 1, entries 1–4). The presence of a halo-substituent either at the C6 or the C7 positions of isatins did

Table 1: Scope of isatins in the catalytic asymmetric ring expansion.[a]

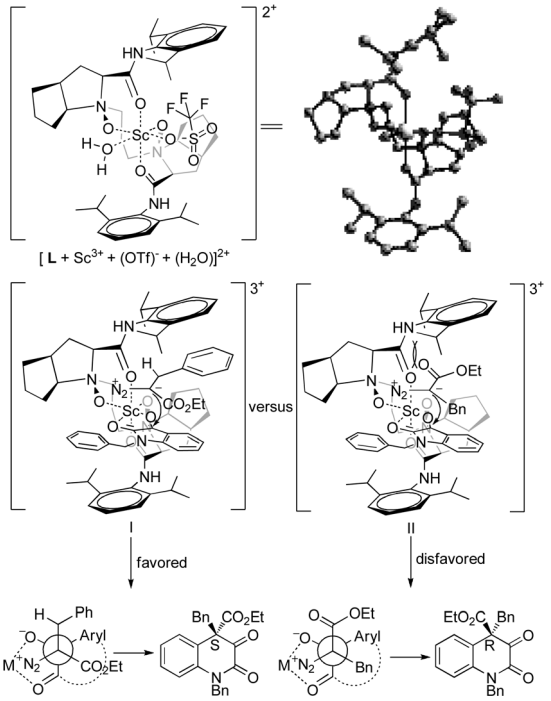


Entry	R^3 (**2**)	x [mol%]	*t* [h]	Yield [%][b] (**3**)	*ee* [%][c]
1	5-F (**2b**)	0.2	16	88 (**3ab**)	93 (*S*)
2	5-Cl (**2c**)	0.5	21	84 (**3ac**)	90 (*S*)
3	5-Br (**2d**)	0.5	32	84 (**3ad**)	87 (*S*)
4	5-I (**2e**)	0.5	48	76 (**3ae**)	80 (*S*)
5	6-F (**2f**)	0.2	15	90 (**3af**)	99
6	6-Br (**2g**)	0.2	30	89 (**3ag**)	98
7	7-F (**2h**)	0.2	8	80 (**3ah**)	98
8	7-Cl (**2i**)	0.2	20	82 (**3ai**)	97
9	7-Br (**2j**)	0.2	20	80 (**3aj**)	98
10	7-Me (**2k**)	0.2	32	82 (**3ak**)	96
11	 (**2l**)	0.5	40	80 (**3al**)	95
12	 (**2m**)	0.5	40	82 (**3am**)	97
13	H (**2n**)	0.2	10	91 (**3an**)	96 (*S*)
14[d]	H (**2o**)	0.5	52	78 (**3ao**)	96 (*S*)

[a] Unless specified otherwise, all reactions were performed with **1a** (0.30 mmol), **2** (0.20 mmol), **L**/Sc(OTf)$_3$ (0.2–0.5 mol%, 1:1.2), CH_2Cl_2 (0.2 mL) at 30°C. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. The absolute configurations of the products **3ab**–**3ae**, **3an**, and **3ao** were determined by comparing their circular-dichroism spectra with that of **3a**. [d] 0.15 mL of CH_2Cl_2 was used. Bn = benzyl.

not have an adverse effect on enantioselectivity (97–99% *ee*). Isatin **2k**, which has a methyl group at the C7 position, gave the corresponding product **3ak** in 82% yield and 96% *ee*. Isatins containing either a fused saturated or a fused unsaturated ring were good substrates, albeit the catalyst loading and the reaction time had to be increased a little (Table 1, entries 11 and 12). *N*-Methyl-protected isatin **2n** also gave the corresponding product in high yield and with a high *ee* value (Table 1, entry 13). Moreover, *N*-unprotected isatin **2o** was found to be a suitable substrate and gave the corresponding product **3ao** in 78% yield and 96% *ee*, albeit after a prolonged reaction time (Table 1, entry 14).

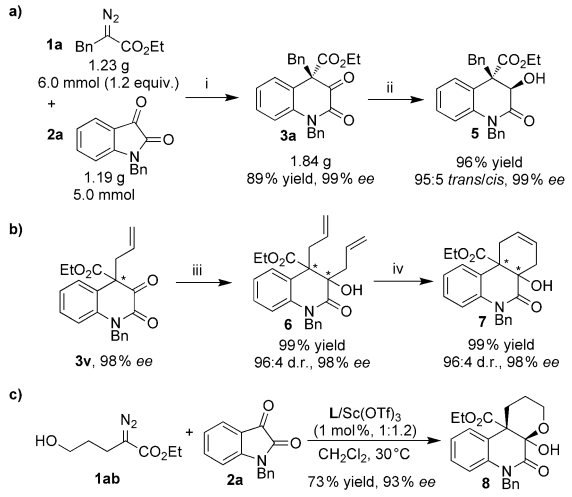
To gain information about how the catalyst induces asymmetry, the catalyst was analyzed by X-ray diffraction and high resolution mass spectrometry (HRMS). In the X-ray structure of the chiral metal—ligand complex **L**/Sc(OTf)$_3$ (Scheme 3), the two oxygen atoms of the amide moieties



Scheme 3. Proposed mechanism of the catalytic asymmetric ring expansion.

and the two oxygen atoms of the *N*-oxide moieties of the ligand **L**, together with the OTf^- ion and a molecule of H_2O form bonds with the scandium(III) center. HRMS analysis of a mixture of isatin **2a** and the catalyst, which was prepared in situ from Sc(OTf)$_3$, **L**, and **2a** (1:1:1) in CH_2Cl_2, confirmed that isatin interacts with the catalyst. A peak at *m*/*z* 490.7509 was detected and corresponds to the complex $[Sc^{3+}+\mathbf{2a}+(\mathbf{L}-H^+)]^{2+}$ (calc. *m*/*z* 490.7599). This result suggests that isatin **2a** could be activated upon coordination of the 1,2-dicarbonyl group with the Sc^{III} center in a bidentate fashion. To achieve high enantioselectivity, simultaneously discrimination of the prochiral faces of both the isatin and the approaching α-alkyl-α-diazoesters is crucial. In light of the structures of the catalyst and the product **3a**,[18] intermediates **I** and **II** are possible. The α-diazoester should preferentially approaches isatin **2a** from the *Si* face, because the *Re* face is shielded by one of the bulky 2,6-diisopropylaniline groups of the ligand. The prochiral faces of the α-alkyl α-diazoester **1a** are probably discriminated by the repulsive interaction between the ester group of the diazoester and the amide moiety of the ligand (Scheme 3, **I** versus **II**). We believe that as the electron-rich diazo-bearing carbon atom of **1a**, attacks, through its *Re* face, the isatin **2a**, the resulting complex would also exhibit the antiperiplanar relationship between the diazo moiety and the aryl ring that is necessary for the 1,2 aryl shift/dinitrogen extrusion process.[2c,6] If the reaction proceeds in this way, the product will be obtained with the observed *S* configuration. The results of the reactions using the various isatin and diazoester substrates support this proposed model (see the Supporting Information). When 4-bromoisatin **2p** was used, lower reactivity and reduced enantioselectivity were obtained. This result might be due to the fact that the C4 position of isatin is closer to the octahydrocyclopentapyrrole unit of the ligand than the other positions. The resulting repulsion would put the 4-substituted isatin at a disadvantage regarding activation. Similarly, the α-isopropyl substituent of diazoester **1aa** would incur steric hindrance in the arrangement depicted in Scheme 3, a fact that may explain its conversion into product in low yield and relatively low *ee* value (see the Supporting Information).

Next, the synthetic value of the reaction was investigated. The reaction of isatin **2a** was carried out on a gram scale (1.19 g, 5.0 mmol) to show the scalability of this method and gave the product **3a** in 89% yield and 99% *ee* (Scheme 4a). The product **3a** could be efficiently converted, through reduction using $NaBH_4$, into useful 3-hydroxyl 2-quinolone **5**.[14] The absolute stereochemistry of the secondary hydroxy group of **5** was determined to be *R* by using the modified Mosher-ester analysis. $TiCl_4$-catalyzed allylation of **3v** gave highly functionalized compound **6**, which contains two con-



Scheme 4. Applications of the catalytic asymmetric ring expansion. Reaction conditions: (i) **L**/Sc(OTf)$_3$ (0.2 mol%, 1:1.2), CH_2Cl_2, 30°C, 12 h; (ii) $NaBH_4$, CH_3OH, −20°C, 15 min; (iii) $H_2C{=}CHCH_2Si(CH_3)_3$, $TiCl_4$, CH_2Cl_2, −20°C, 15 min; (iv) Grubbs II (10 mol%), CH_2Cl_2, 24 h.

tiguous chiral quaternary stereocenters (Scheme 4b). Olefin metathesis of **6** using Grubbs' second generation catalyst afforded tricyclic compound **7** in 99% yield and 98% *ee*. Interestingly, when hydroxy-group-containing diazoester **1ab** was used, a cascade reaction occurred, thus affording product **8** with 73% yield and 93% *ee* (Scheme 4c).

In summary, we have described the first catalytic asymmetric ring-expansion reaction of isatins and α-alkyl-α-diazoesters, a reaction that gives the 1,2-aryl migration product preferentially. In the presence of 0.05–0.5 mol% of a $Sc(OTf)_3$ catalyst bearing an *N*,*N*′-dioxide ligand, a series of substrates underwent the reaction smoothly, providing highly functionalized C4-quaternary 2-quinolones in high yields (up to 94%) and with high levels of enantioselectivity (up to 99% *ee*). A range of functional groups was also tolerated under the mild reaction conditions. Based on an X-ray crystal structure of the catalyst, a reasonable model that explains the asymmetric induction was proposed. Further transformations of the highly functionalized products into useful molecules are underway.

Experimental Section

10–100 μL of **L**/$Sc(OTf)_3$ catalyst solution (0.01M in THF) was added to a dry reaction tube. After removing THF from the tube under vacuum and then filling the tube with N_2, isatin **2** (0.20 mmol) and CH_2Cl_2 (0.2 mL) were added at 30°C. After stirring the mixture for 0.5 h, α-diazoester **1** (0.30 mmol) was added, and the resulting mixture was stirred at 30°C for the indicated time. The crude mixture was purified by flash chromatography on silica gel (dichloromethane to 50:1 dichloromethane/acetone) to afford the desired product **3**.

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[18] CCDC 882157 (**3a**) and CCDC 882608 (the catalyst) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

