

Asymmetric Catalysis

Highly Enantioselective [3+3] Cycloaddition of Aromatic Azomethine Imines with Cyclopropanes Directed by π - π Stacking Interactions**

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The development of efficient and highly stereoselective catalysts is of central importance in asymmetric catalysis. Typically, new catalysts can be generated from new chiral scaffolds or through the modification of existing catalysts. The latter becomes especially attractive and of practical use if a simple manipulation of these readily available catalysts results in significantly improved efficiency and selectivity. Bisoxazoline (BOX) is an established privileged ligand in modern asymmetric catalysis, and the corresponding metal complexes have been applied to a wide variety of asymmetric transformations.^[1] To improve the efficiency and selectivity of the BOX ligands in specific reactions, we recently introduced a sidearm strategy which allows the modification of the ligands in a three-dimensional manner and has been successfully applied to several types of reactions.^[2,3] Metal catalysts based on these sidearm-modified BOX ligands usually exhibited higher efficiency and improved diastereo- and enantioselectivity, together with much higher stability and tolerance to impurities than the parent BOX ligands.^[2a] The role of the “sidearm” group was found to depend on the functionality of the sidearm.^[2,3] For example, sidearms containing a ligating donor function (D) would bind to the metal and modulate both the electronic properties and the micro-environment of the catalytic center (Figure 1a), and make it possible to tune the reaction efficiency and selectivity.^[3p] The sidearm group is also found to mainly exert a steric effect by virtue of its steric demand (Figure 1b).^[3f] Recently, we observed a new role of the sidearm group in a nickel-catalyzed [3+3] cycloaddition reaction of isoquinoline azomethine imines with cyclopropanes, in which a prominent π - π stack-directing effect of the sidearm proved to be crucial to the stereochemical control (Figure 1c).

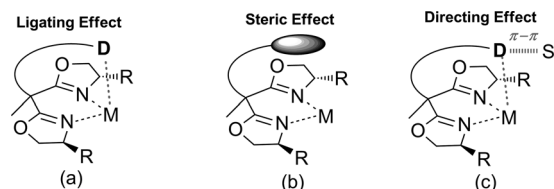


Figure 1. Roles of sidearms in metal/BOX complexes.

Tetrahydroisoquinoline, dihydroisoquinoline, and related polycyclic skeletons are widely present as core structures in a large number of natural products, bioactive molecules, and pharmaceuticals,^[4] and extensive efforts have been directed to the asymmetric construction of these structures in the last decades.^[4d,5–8] Recently, Charette and co-workers^[9] reported a non-asymmetric example of the [3+3] cycloaddition reaction of isoquinoline azomethine imines with donor-acceptor (D-A)-substituted cyclopropanes. Though the product was obtained in only 21 % yield, this reaction represents a facile and direct approach for the construction of 6,6,6-tricyclic dihydroisoquinoline derivatives. Inspired by this pioneering work, we wish to report here our efforts toward the realization of the first highly enantioselective version of this reaction and our understanding of the role of the sidearm group.

Initially, the reaction of isoquinoline azomethine imine **1a**^[7] with cyclopropane **2a** was examined under several sets of conditions previously reported for the asymmetric cycloaddition of cyclopropanes.^[10,11] Using DBFOX/Ni^{II}^[10a] the desired product **3aa** was obtained in 83 % yield and 30 % *ee*. While under the conditions for the asymmetric cycloaddition with aldehydes,^[10c] the reaction did not proceed even when the reaction time was extended to 2 days. We then moved on to evaluate a variety of BOX ligands;^[12a] selected results are tabulated in Table 1. In-BOX **L1a** provided a smooth reaction, and full conversion was achieved in 19 h, but the product was nearly racemic (2 % *ee*; Table 1, entry 1). **L1b** with a cyclopropylidene spacer gave 35 % *ee* (Table 1, entry 2). Introduction of a benzyl sidearm group provided no enhancement of the enantioselectivity (**L1c**; Table 1, entry 3). However, to our delight, the pseudo-*C*₃-symmetric trisoxazoline (TOX) ligand **L1d** containing an indane-derived oxazoline sidearm group delivered significantly improved enantioselectivity, notably with an inverted sense of asymmetric induction (Table 1, entry 4). The corresponding isopropyl-substituted ligand **L2d**^[10b] was equally efficient but less enantioselective (Table 1, entry 5).

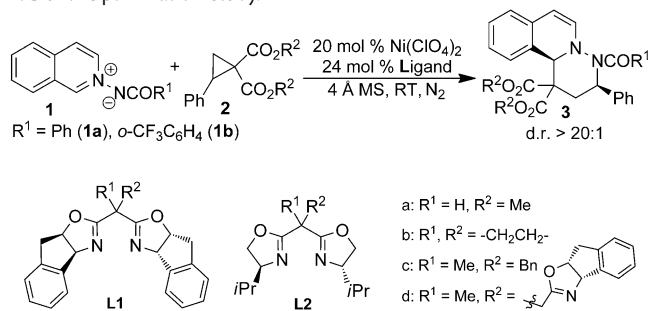
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[**] We are grateful for the financial support from the National Natural Sciences Foundation of China (nos. 20932008, 21072207, and 21121062), the Major State Basic Research Development Program (grant no. 2009CB825300), and the Chinese Academy of Sciences.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201207576>.

Table 1: Optimization study.^[a]


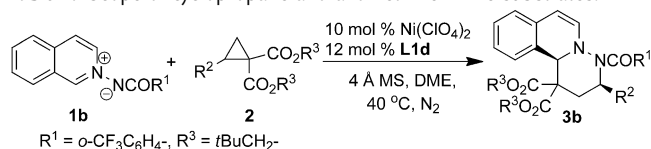
Entry	1	R ²	L	t [h]	Conv. [%] ^[b]	ee [%] ^[c]
1 ^[d]	1a	Me (2a)	L1a	19	96	(-)-2
2 ^[d]	1a	Me (2a)	L1b	11	> 99	(-)-35
3 ^[d]	1a	Me (2a)	L1c	65	97	(-)-31
4	1a	Me (2a)	L1d	20	> 99	56
5	1a	Me (2a)	L2d	19	> 99	34
6	1a	Et (2b)	L1d	54	70	65
7	1a	<i>i</i> Bu (2c)	L1d	120	26	72
8	1a	<i>t</i> BuCH ₂ (2d)	L1d	120	15	79
9 ^[e]	1b	<i>t</i> BuCH ₂ (2d)	L1d	42	99 ^[f]	95
10 ^[d,e]	1b	<i>t</i> BuCH ₂ (2d)	L1d	35	98 ^[f]	94

[a] Reaction conditions are described in the Supporting Information.

[b] Determined by ¹H NMR analysis. [c] Determined by HPLC on a chiral stationary phase. [d] With 10 mol % catalyst, 40 °C. [e] [1b]₀ = 0.05 M and 4 Å MS (200 mg). [f] Yield of isolated product based on 1b.

It was envisioned that the steric interaction of the two ester groups of the cyclopropane with the catalyst could interfere with the stereochemical control. Thus, the ester group was varied systematically in reactions with ligand **L1d**. As outlined in Table 1, when the R group of the ester was enlarged from methyl to neopentyl, the enantioselectivity of the reaction gradually improved from 56% to 79% *ee* in the order methyl < ethyl < isobutyl < neopentyl, but this was accompanied by severely decreased reactivity (Table 1, entries 4 and 6–8). To our delight, when an *ortho*-CF₃ group was introduced on the benzoyl ring of the azomethine imine, the reactivity issue was resolved, the reaction time was shortened from 120 h to 42 h, and the selectivity was also further improved; the cycloaddition product was obtained in 99% yield and 95% *ee* (Table 1, entry 9). Moreover, at a slightly elevated temperature (40 °C), the catalyst loading could be reduced to 10 mol % with the preservation of both stereoselectivity and yield (Table 1, entry 10).

Under optimized reaction conditions, a variety of cyclopropane diesters were then examined. As shown in Table 2, the steric and electronic properties of *para* and *meta* substituents on the phenyl group of D-A-substituted cyclopropane diesters had a slight influence on the yields (91–99%) and stereoselectivities (94–98% *ee* and d.r. > 20:1). D-A-substituted cyclopropane substrates with an electron-rich donor moiety exhibited apparently higher reactivities (Table 2, entries 2–4 vs. 5 and 6). D-A-substituted cyclopropanes having disubstituted aryl groups also reacted well (Table 2, entries 8 and 9). Notably, the reaction could be extended to substrates with heterocyclic, styryl, and vinyl donor groups with high diastereo- and enantioselectivities (Table 2, entries 10–13). It is worth mentioning that the

Table 2: Scope of cyclopropane and azomethine imine substrates.^[a]


Entry	1	R ²	t [h]	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	1b	Ph (2d)	35	98	> 20:1	94
2	1b	<i>p</i> -ClC ₆ H ₄ (2e)	34	99	> 20:1	97
3	1b	<i>p</i> -BrC ₆ H ₄ (2f)	31	98	> 20:1	98 ^[e]
4	1b	<i>p</i> -NO ₂ C ₆ H ₄ (2g)	92	95	> 20:1	97
5	1b	<i>p</i> -MeC ₆ H ₄ (2h)	24	98	> 20:1	96
6 ^[f]	1b	<i>p</i> -MeOC ₆ H ₄ (2i)	7	91	> 20:1	96
7	1b	<i>m</i> -MeC ₆ H ₄ (2j)	31	97	> 20:1	96
8	1b	3,4-Cl ₂ C ₆ H ₃ (2k)	74	95	> 20:1	95
9 ^[f]	1b	3,4-(MeO) ₂ C ₆ H ₃ (2l)	1.5	92	13:1	95
10 ^[f]	1b	2-furyl (2m)	2.0	97	> 20:1	92
11 ^[f]	1b	2-thienyl (2n)	1.5	99	> 20:1	94
12 ^[f]	1b	PhCH=CH (2o)	1.5	93	15:1	87
13 ^[f]	1b	CH ₂ =CH (2p)	50	92	> 20:1	89
14 ^[g]	1b	H (2q)	47	92	–	0
15 ^[f,h]	1b	<i>p</i> -MeOC ₆ H ₄ (2i)	25	87	> 20:1	95
16 ^[f]	1c	<i>p</i> -MeOC ₆ H ₄ (2i)	9	94	> 20:1	95
17 ^[f]	1d	<i>p</i> -MeOC ₆ H ₄ (2i)	9	85	11:1	86
18 ^[f]	1e	<i>p</i> -MeOC ₆ H ₄ (2i)	9	81	3:1	88

[a] Reaction conditions are described in the Supporting Information.

[b] Yield of isolated product based on 1. [c] *cis/trans*, determined by ¹H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase. [e] The absolute configuration was determined by X-ray analysis.^[12c] [f] Room temperature. [g] Catalyst loading = 20 mol %. [h] Catalyst loading = 5 mol % and [1b]₀ = 0.10 M in DME (20 mL).

simple cyclopropane diester **2q** also reacted smoothly with isoquinoline azomethine imine **1b**, but the product was racemic (Table 2, entry 14). This result indicates that the enantioselectivity was established in the first step—the nucleophilic attack and the simultaneous opening of the cyclopropane ring. In addition, the reaction can be scaled up to the gram scale with high enantioselectivity and only 5 mol % catalyst was required (Table 2, entry 15). The scope of the aromatic azomethine imines was also investigated (Table 2, entries 16–18). The position of a methyl substituent on the isoquinoline ring slightly influences the stereoselectivity, but high d.r. and excellent *ee* values could be maintained (85–94% yield, d.r. > 11:1, and 86–95% *ee*; Table 2, entries 16 and 17).

To understand the synergistic effects between the sidearm, diester groups, and the benzoyl group of the azomethine imine, density functional theory (DFT)^[13] studies were performed using the M06^[14] method, which was successfully employed for the nickel(II)-catalyzed reactions.^[15] The trioxazolone ligand **L1d** and substrates **1b** and **2d**, which lead to the best enantioselectivity, were employed in the calculation. After an extensive computational study, the optimized model of TOX/Ni^{II} coordination was obtained, which is a six-coordinate Ni^{II} complex^[16] with one molecule of isoquinoline

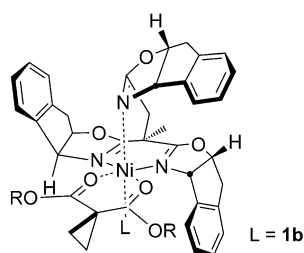
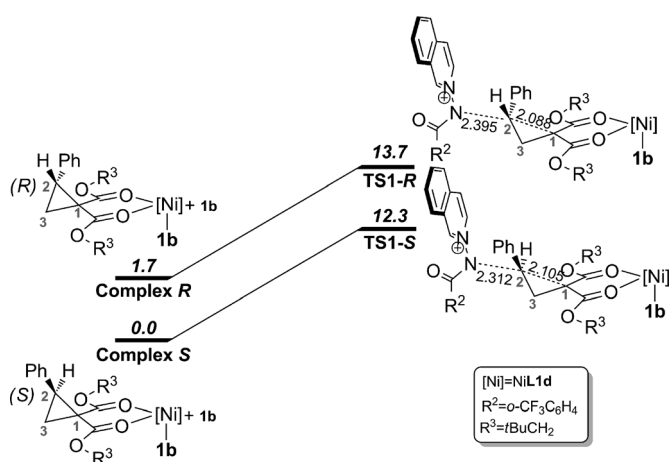


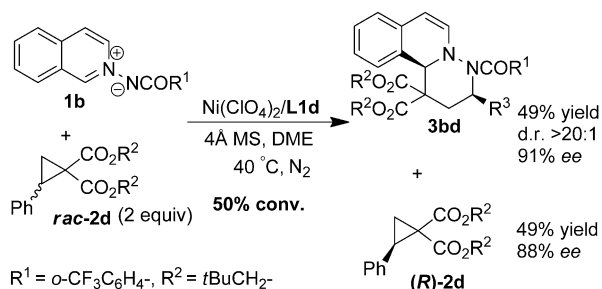
Figure 2. The coordination model of TOX/Ni^{II} complex.

azomethine imine **1b** coordinating to the nickel center (L = **1b**, Figure 2).^[12b] This model is consistent with the X-ray crystal structure analysis in our previous study^[3p] and was used here for explaining the stereochemistry. The calculated results show that the chiral Ni^{II} complex recognized the (*S*)-cyclopropane selectively. **Complex S** is favored by 1.7 kcal mol⁻¹ over **Complex R**. And transition state **TS1-S** is also more stable than **TS1-R** (Scheme 1). This effective discrim-



Scheme 1. The calculated pathway of the first step of the reaction. Bond lengths are in Å and the relative free energies in solvent ΔG_{sol} are in kcal mol⁻¹; calculated at UM06/6-31G*/LanL2DZ level.

ination between the two enantiomers of the D–A-substituted cyclopropanes suggests kinetic resolution of the cyclopropanes during the reaction. In fact, as shown in Scheme 2, when 2.0 equivalents of racemic **2d** were used under the standard reaction conditions, at 50% conversion both the



Scheme 2. Kinetic resolution experiments of cyclopropane **2d**.

cycloaddition product and the unreacted (*R*)-cyclopropane were isolated in nearly quantitative yields with high enantioselectivities. The relative rate constant was determined with an *S*-value of 45. This experiment strongly supports the calculated results.^[12b]

This calculation can also well explain the origin of the enantioselectivity. As shown in Figure 3b, the coordination of

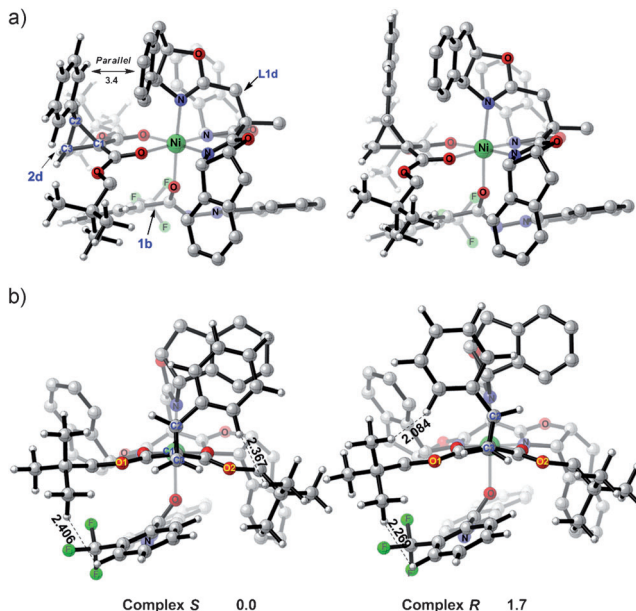
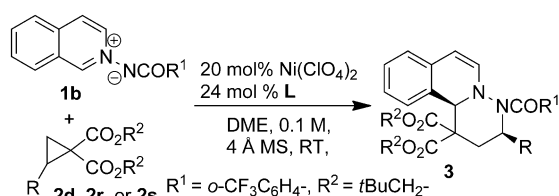


Figure 3. a) Side view and b) back view of the optimized structures of **Complex S** and **Complex R**. The relative free energies in solvent ΔG_{sol} are in kcal mol⁻¹; calculated at UM06/6-31G*/LanL2DZ level.

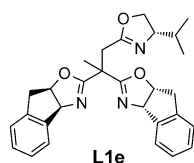
1b to the bottom of the **L1d**/Ni complex creates a confined chiral cavity which accommodates cyclopropane **2d** with its phenyl group pointing up to avoid the steric interaction with ligated **1b**. In **Complex S**, the phenyl group points towards the right side, and the right neopentyl ester group twists down to avoid interaction with the phenyl group (2.367 Å). In **Complex R**, however, the phenyl group is pointing to the left side, the coordination of **1b** hinders the left neopentyl ester group rotating down to release the strain, and the presence of the *ortho*-CF₃ group^[17] of azomethine imine **1b** further aggravates the steric repulsion between the ester group and the phenyl group (2.084 Å). As a consequence, the dihedral angle C2-C3-Ni-O1 in **Complex R** is -103.3° and the deviation is up to 13.3° from perpendicular, indicating a large repulsion between the phenyl group and the ester group. In contrast, the plane of the cyclopropane in **Complex S** is nearly perpendicular to the main coordination plane and the dihedral angle C2-C3-Ni-O2 is 88.3°, only 1.7° from perpendicular. These results are in agreement with the observed effects of the esters on the enantioselectivity (Table 1, entries 4, 6–8). Apart from these steric considerations, a remarkable π - π directing effect^[18] was revealed by calculation, which makes **Complex S** more favored over **Complex R**. As shown in Figure 3a, the indane group of the sidearm of **L1d** and the phenyl group of the cyclopropane in

Complex S are on the same side and parallel to each other. The distance between these two rings is about 3.4 Å. This beneficial π - π directing effect of the indane sidearm is distinct from other sidearm oxazolines lacking such an aromatic moiety. In fact, the beneficial effect of the indane-derived oxazoline sidearm was consistently observed in the ligand screening.^[12a] In the transition states of the azomethine imine attack and the simultaneous ring-opening step (Scheme 1), since the N1-C2 distances are rather long (2.312 Å in **TS1-S**, 2.395 Å in **TS1-R**), the factors that makes **Complex S** more stable than **Complex R** are also in effect in **TS1-S** and **TS1-R**.^[12a] Thus, in both coordination-activation (**Complex S**) and nucleophilic attack (**TS1-S**) processes, the (*S*)-cyclopropane substrate reacts preferably; this accounts for the high enantioselectivity and is consistent with the experimental results.^[12a]

To further verify the possible π - π stacking interaction between the sidearm in **L1d** and the phenyl group of the cyclopropanes, we conducted three control experiments. As shown in Scheme 3, when the indane-oxazoline sidearm was



- a) L = **L1e**, R = Ph (**2d**), 73% yield (74% conv., 120 h), 42% ee, d.r. = 14:1
 b) L = **L1d**, R = *o*-MeOC₆H₄ (**2r**), 95% yield, 72% ee, d.r. > 50:1
 c) L = **L1d**, R = Me (**2s**), 35% yield (40 °C, 10 d), 25% ee, d.r. > 25:1



Scheme 3. Control experiments.

replaced with an isopropoxyloxazoline group (**L1e**) which lacks such an aromatic moiety, dramatically decreased enantioselectivity was observed (42% ee vs. 94% ee). On the other hand, a drop in enantioselectivity was also observed in the reaction of cyclopropane **2r** which contains an *ortho* methoxy substituent on the phenyl group which can weaken the π - π interaction with the sidearm of **L1d**. As expected, the aliphatic-substituted cyclopropane **2s** reacted with significantly lower enantioselectivity. These results strongly support the directing effects of the π - π stacking interaction on the observed high reactivity and enantioselectivity in the current reaction system.

In summary, we have developed a highly enantioselective asymmetric [3+3] cycloaddition of D-A-substituted cyclopropane diesters with aromatic azomethine imines catalyzed by In-TOX **L1d**/Ni^{II}; this reaction provides a variety of 6,6,6-tricyclic dihydroisoquinoline derivatives in up to 99% yields with excellent diastereo- and enantioselectivities (up to 98% ee and > 20:1 d.r.). Experimental results and density

functional theory (DFT) study indicate that the π - π interaction between the indane group of the ligated sidearm and the phenyl group of the cyclopropane plays a key role in the control of enantioselectivity, which would provide an inspiration for the design of novel bifunctional catalysts. Further investigation on the working model and extensions of the current approach are ongoing in our laboratory.

Received: September 19, 2012

Published online: December 20, 2012

Keywords: [3+3] cycloaddition · dihydroisoquinolines · nickel · π interactions

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