Asymmetric Catalysis

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Asymmetric Intramolecular Oxa-Michael Addition of Activated α,β-Unsaturated Ketones Catalyzed by a Chiral *N*,*N*′-Dioxide Nickel(II) Complex: Highly Enantioselective Synthesis of Flavanones**

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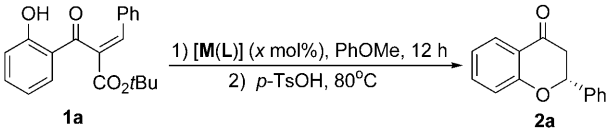
The conjugate addition of oxygen nucleophiles to electron-deficient olefins has been a significant challenge in organic synthesis, owing to the low reactivity coupled with the reversibility of the reaction.[1–3] In particular, enantioselective intramolecular oxa-Michael (IOM) addition, which provides a promising approach for synthesis of pharmaceutically and biologically active chiral chromanone skeletons, has been rarely explored.[4] Thus far, most reports have focused on catalysis though hydrogen bonding by employing organocatalysts of quinine or cinchona chiral scaffolds.[5] In 1999, Ishikawa and co-workers reported the first effective (−)-quinine-catalyzed asymmetric IOM addition to synthesize anti-HIV-1 active calophyllum coumarin.[5b] Recently, a remarkable strategy, employing *tert*-butyl ester activated α,β-unsaturated ketones as substrates, for the catalytic synthesis of chiral flavanones was developed by Scheidt and co-workers.[5d] Despite these impressive contributions, more efficient and practical catalytic systems for asymmetric intramolecular oxa-Michael addition are still in high demand.

Dicarbonyl compounds are promising candidates as substrates as they can chelate a series of Lewis acids, such as Fe^{II}, Co^{II}, and Ni^{II} complexes,[6] and engage in two-point binding to the central metal, which allows a chelate-ordered transition state. Also, as nickel is a nonprecious metal, nickel complex catalysts have been widely applied to catalytic organic synthesis.[7] Moreover, chiral nickel complexes are becoming practical and potential catalysts in enantioselective transformations.[8–11] *N*,*N*′-Dioxide ligands are excellent chiral scaffolds as they can coordinate many different metals and have been successfully applied in many asymmetric reactions.[12,13] Herein, we present a new, readily prepared,[14] chiral *N*,*N*′-dioxide nickel(II) complex catalyst that facilitates this intramolecular oxa-Michael addition with broad substrates in 90–99% yields with up to 99% *ee*.

Some representative screening results for the catalytic enantioselective IOM addition of the activated α,β-unsaturated ketone **1a** in the presence of an array of *N*,*N*′-dioxide complexes as catalysts (10 mol%) are presented in Table 1. Initially, *N*,*N*′-dioxide **L1** (see Figure 1) was complexed to several metal salts. Although [$Fe(acac)_2$] as the central metal showed ineffective asymmetric induction (Table 1, entry 1), complexes of other Group VIII metals Co^{II} and Ni^{II} showed good inducing potential with enantioselectivities of 63% and 83% *ee*, respectively (Table 1, entries 2 and 3), which confirmed our initial expectation. Then, the influence of the counterions of the [Ni^{II}(**L1**)] complex was investigated. Although $NiBr_2$, $Ni(ClO_4)_2\cdot 6H_2O$, and $Ni(OTf)_2$ showed excellent ability in other chiral Ni^{II}-catalyzed reactions, they gave only extremely poor results (Table 1, entries 4–6). Fortunately, when $Ni(Tfacac)_2\cdot 2H_2O$ was used, the desired

Table 1: Asymmetric IOM addition of α,β-unsaturated ketone **1a**.[a]



1a **2a**

Entry	M	Ligand	*x* [mol%]	Yield [%][b]	*ee* [%][c]
1	$Fe(acac)_2$	**L1**	10	88	0
2	$Co(acac)_2$	**L1**	10	97	63(*R*)
3	$Ni(acac)_2$	**L1**	10	96	83(*R*)
4	$NiBr_2$	**L1**	10	10	3(*R*)
5	$Ni(ClO_4)_2\cdot 6H_2O$	**L1**	10	5	5(*R*)
6	$Ni(OTf)_2$	**L1**	10	99	3(*R*)
7[d]	$Ni(Tfacac)_2\cdot 2H_2O$	**L1**	10	99	97(*R*)
8	$Ni(Tfacac)_2\cdot 2H_2O$	**L2**	10	84	0
9	$Ni(Tfacac)_2\cdot 2H_2O$	**L3**	10	trace	n.d.
10	$Ni(Tfacac)_2\cdot 2H_2O$	**L4**	10	98	96(*R*)
11	$Ni(Tfacac)_2\cdot 2H_2O$	**L5**	10	95	93(*R*)
12	$Ni(Tfacac)_2\cdot 2H_2O$	**L6**	10	91	13(*R*)
13	$Ni(Tfacac)_2\cdot 2H_2O$	**L7**	10	50	20(*R*)
14	$Ni(Tfacac)_2\cdot 2H_2O$	**L8**	10	90	18(*R*)
15	$Ni(Tfacac)_2\cdot 2H_2O$	**L9**	10	n.r.	n.d.
16	$Ni(Tfacac)_2\cdot 2H_2O$	**L1**	5	99	98(*R*)
17[e]	$Ni(Tfacac)_2\cdot 2H_2O$	**L1**	2	91	92(*R*)

[a] Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol), [**M**(**L**)] complex (1:1, *x* mol%), and PhOMe (0.5 mL) at 30°C for 12 h, then *p*-TsOH (0.2 mmol) was added at 80°C for 2 h. [b] Yield of isolated product; n.r. = no reaction. [c] Determined by chiral HPLC analysis. The absolute configuration was determined by comparison to literature data.[5d] n.d. = not determined. [d] Tfacac = 1,1,1-Trifluoroacetylacetonate. [e] 20 h was needed.

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product was obtained in 99% yield and with 97% *ee* (Table 1, entry 7). The disparate results were probably caused by the different electronic and steric properties of the counterions.[15]

Next, the structures of ligands were examined (**L1**–**L9**, Figure 1). The results showed that a linker chain of three carbon atoms in the ligand was essential for the asymmetric

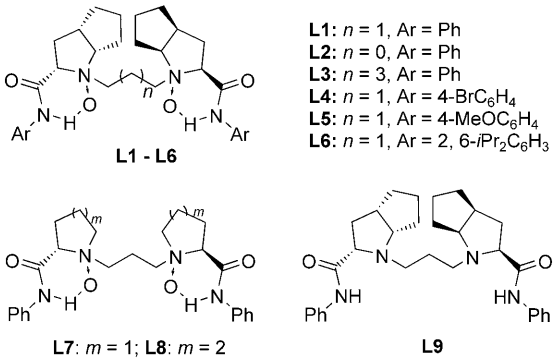
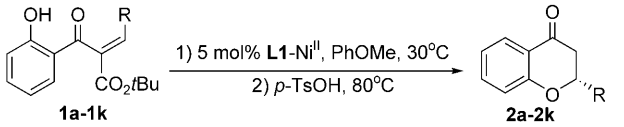


Figure 1. Ligands employed for the IOM addition.

addition. Ligand **L2** with a two-carbon atom linkage gave racemic product (Table 1, entry 8), whereas **L3** with a five-carbon atom linkage showed poor reactivity (Table 1, entry 9). Further studies on the amide moiety demonstrated that ligands **L4** and **L5** provided high yields (98% and 95%) and excellent *ee* values (96% *ee* and 93% *ee*) regardless of the electronic property of the substituents (Table 1, entries 10 and 11). Ligand **L6** with bulky isopropyl groups led to a dramatic decrease in enantioselectivity (Table 1, entry 12). L-Ramiprol acid derivative **L1** was superior to L-proline derived **L7** and L-pipecolic acid derived **L8** as the chiral backbone of the *N*,*N*′-dioxide in both reactivity and enantioselectivity (Table 1, entry 7 vs. entries 13 and 14). Moreover, when amide ligand **L9** was employed, the reaction did not take place, which revealed that the *N*-oxide group is essential for the reaction (Table 1, entry 15). Further optimization of the reaction conditions identified that adduct **2a** was produced in PhOMe with 5 mol% of [Ni(**L1**)(Tfacac)$_2$]·2H$_2$O (ratio 1:1) in 99% yield and 98% *ee* (Table 1, entry 16). The catalyst loading could be further reduced to 2 mol%, leading to 91% yield with 92% *ee* after 20 h (Table 1, entry 17). Furthermore, this process was tolerant to air and moisture.

Under the optimal reaction conditions (Table 1, entry 16), a series of representative olefin substrates (**1a**–**1k**) were investigated, and the corresponding products (**2a**–**2k**) were obtained in high yields and with up to 99% *ee* (Table 2). In the case of electron-poor substituents (**2b**–**2e**), the catalyst system [Ni(**L1**)(Tfacac)$_2$]·2H$_2$O led to excellent yields and enantioselectivities (Table 2, entries 2–5, 90–98% yields, 92–99% *ee*). Condensed ring substrates **1f** and **1g** also gave the desired products **2f** and **2g** in high yields and with 96% *ee* and 92% *ee*, respectively (Table 2, entries 6 and 7). The electron-rich substituents on **1h**–**1j** underwent the IOM addition and decarboxylation processes to yield the enantiomeric adducts (**2h**–**2j**) in excellent yields and with *ee* values in the range 84–93% *ee* (Table 2, entries 8–10). The aliphatic substrate **1k** was

Table 2: Olefin substrates for the catalytic asymmetric IOM addition.[a]



1a-1k **2a-2k**

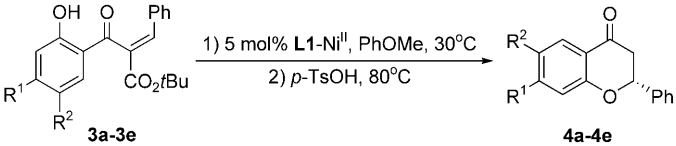
Entry	R	Product	Yield [%][b]	*ee* [%][c]
1	Ph	**2a**	99	98 (*R*)[e]
2	2-ClC_6H_4	**2b**	90	93 (*R*)[e]
3	4-BrC_6H_4	**2c**	95	97 (*R*)[e]
4	4-CNC_6H_4	**2d**	90	99
5	4-PhC_6H_4	**2e**	98	92
6	1-naphthyl	**2f**	98	96
7	2-naphthyl	**2g**	96	92 (*R*)[e]
8	3-MeC_6H_4	**2h**	98	93
9[d]	4-MeC_6H_4	**2i**	97	84 (*R*)[e]
10	2-MeC_6H_4	**2j**	99	86
11	Et	**2k**	90	85

[a] Unless otherwise noted, reactions were carried out with **1** (0.1 mmol), [Ni(**L1**)(Tfacac)$_2$]·2H$_2$O (5 mol%), and PhOMe (0.5 mL) at 30°C for 12 h, then *p*-TsOH (0.2 mmol) was added at 80°C for 2 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; see the Supporting Information for details. [d] 15 mol% catalyst was used. [e] The absolute configuration was determined by comparison to literature data.[5d]

also found to be suitable, affording chromanone **2k** in 90% yield and with 85% *ee* (Table 2, entry 11).

To extend the substrate scope, our further examination focused on the IOM addition of several representative phenol substrates (**3a**–**3e**). The results in Table 3 show that different phenol moieties were tolerated in the reaction and good to excellent results (up to 96% *ee*) were achieved (Table 3, entries 1–4). The methyl-substituted substrates **3a** and **3b** provided the corresponding products **4a** and **4b** in high yields and with 96% *ee* and 95% *ee*, respectively (Table 3, entries 1 and 2). The reaction of 4-methoxyphenyl-substituted **3c** gave the product **4c** in 95% yield and with 80% *ee* (Table 3, entry 3). Moreover, naphthyl-substituted **3d** was also found to be an excellent substrate for the reaction and afforded the

Table 3: Phenol substrates for the catalytic asymmetric IOM addition.[a]



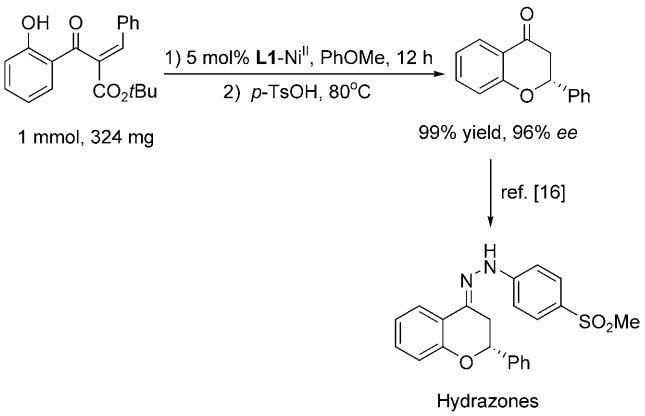
3a-3e **4a-4e**

Entry	R^1	R^2	Product	Yield [%][b]	*ee* [%][c]
1	H	Me	**4a**	97	96
2[d]	Me	H	**4b**	90	95 (*R*)[e]
3	H	MeO	**4c**	95	80
4	-(CH)$_4$-		**4d**	90	90 (*R*)[e]
5	H	Cl	**4e**	96	40

[a] Unless otherwise noted, reactions were carried out with **3** (0.1 mmol), [Ni(**L1**)(Tfacac)$_2$]·2H$_2$O (5 mol%), and PhOMe (0.5 mL) at 30°C for 12 h, then *p*-TsOH (0.2 mmol) was added at 80°C for 2 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis; see the Supporting Information for details. [d] 10 mol% catalyst was used. [e] The absolute configuration was determined by comparison to literature data.[5d]

desired product **4d** in 90% yield and with 90% *ee* (Table 3, entry 4). However, electron-poor substituents on the phenol moiety dramatically decreased the enantioselectivity (Table 3, entry 5).

In addition, when the reaction with **1a** was scaled up tenfold with 5 mol% nickel complex at ambient temperature in open vessel, good results (99% yield and 96% *ee*) were still obtained (Scheme 1). Significantly, flavanones can be easily transformed into versatile building blocks for pharmaceutical components, such as hydrazones.[16]



Scheme 1. Asymmetric IOM addition of **1a** on a tenfold scale (left) and example for its application (right).

In summary, we have developed a highly efficient catalytic enantioselective intramolecular oxa-Michael addition using a new chiral *N*,*N*′-dioxide nickel(II) complex. This process provided a promising approach for the synthesis of chiral flavanones with broad substrate scope and which was tolerant to air and moisture. In the presence of 5 mol% [Ni^{II}(**L1**)] complex, good to excellent enantioselectivities (up to 99% *ee*) and high yields were achieved for most of the substrates under mild conditions. Further investigations of the mechanism of this catalytic system are still in progress.

Experimental Section

General experimental procedure: A mixture of **L1** (2.7 mg, 0.005 mmol) and $Ni(Tfacac)_2{\cdot}2H_2O$ (2.0 mg, 0.005 mmol) in PhOMe (0.5 mL) was stirred at ambient temperature in an open vessel. Substrate **1** or **3** (0.1 mmol) was added, and the reaction mixture was stirred at 30 °C for 12 h. After completion of cyclization, *p*TsOH (34 mg, 0.2 mmol) was added, and the solution was heated to 80 °C for 2 h (monitored by TLC). The solution was then cooled, and the reaction mixture was purified by flash chromatography on silica gel to obtain the final product **2** or **4.**

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