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Direct asymmetric vinylogous Michael addition of 3-alkylidene oxindoles to chalcones catalyzed by a chiral *N*,*N*′-dioxide ytterbium(III) complex†

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A chiral ytterbium(III)–*N*,*N*′-dioxide catalyst system has been developed for the catalytic direct asymmetric vinylogous Michael addition of 3-alkylidene oxindoles to chalcones, delivering the γ-substituted alkylideneoxindoles in high yields, enantioselectivities and good *Z*/*E* selectivities under mild reaction conditions.

The asymmetric vinylogous Michael addition, being one of the most powerful synthetic methods to construct versatile and useful building blocks with high levels of structural complexity, occupies a preeminent position in the field of organic chemistry.[1] Nevertheless, the formation of dienolates and the poor regioselectivity caused by the competition between the α and γ positions of the nucleophilic dienolate are challenging.[2] For these reasons, catalytic asymmetric vinylogous Michael reactions have attracted much attention in recent years. Most of the pioneering studies used silicon dienolates[3] as the nucleophiles, which participate in the vinylogous Mukaiyama–Michael reaction. This process could achieve considerable regioselectivity and reactivity. However, there are two disadvantages to this process: one is the complexity of the procedure caused by the need to prepare the silicon dienolates beforehand, and the other is the formation of silanes as side products. To meet the requirements of a convenient procedure and atom economy, the direct vinylogous Michael addition was developed. The formation of dienolates was promoted by Lewis acid or base *in situ*. Butyrolactones,[4] butyrolactams,[5] azalactone heterocycles,[6] α,α-dicyanolefins,[7] β-alkyl-substituted cyclohexenones,[8] linear α,β-unsaturated ketones,[9] olefinic lactones,[10] α-alkylidene pyrazolinones[11] and 3-alkylidene oxindoles[12] have been reported as nucleophiles in direct vinylogous Michael addition. Among them, 3-alkylidene oxindoles, which exhibit intriguing biological activities, are the core structures of a range of medicinally and biologically important compounds, as well as a number of natural products, and are appealing to chemists.[13] The Casiraghi group employed the bifunctional cinchona alkaloid/thiourea for the direct vinylogous Michael addition of 3-alkylidene oxindoles to nitro-olefins.[12a,b] Later, the Wang group reported the addition of 3-alkylidene oxindoles and trifluoromethylated nitro-olefins using the same catalysts.[12c] Recently, this group developed the vinylogous Michael addition of 3-alkylidene oxindoles to α-substituted β-nitroacrylate by a squaramide catalyst.[12d] To the best of our knowledge, electrophiles are limited to nitro-olefins, with no reports about the direct vinylogous Michael addition of 3-alkylidene oxindoles and the less reactive α,β-unsaturated ketones. We herein developed a catalytic direct asymmetric vinylogous Michael reaction of 3-alkylidene oxindoles with chalcones. By using a chiral ytterbium(III)–*N*,*N*′-dioxide catalyst system, high yields, good *Z*/*E* selectivities and excellent enantioselectivities were achieved for γ-substituted alkylideneoxindoles.

Initially, 3-alkylidene oxindole **1a** was reacted with chalcone **2a** in THF at 30 °C with 10 mol% of the Yb(OTf)$_3$–**L2** complex. Without any additive, no product was observed (Table 1, entry 1). It was envisioned that bases might promote dienolization of **1a**, hence enhancing its nucleophilicity and making the reaction with **2a** take place. Indeed, when 2 equivalents of K_2CO_3 were added to the system, the reaction did occur, affording the γ-addition product **3a** with a 43% yield, 40% ee and 85 : 15 *Z*/*E* ratio (Table 1, entry 2). To our delight, better results (61% yield, 85% ee and 78 : 22 *Z*/*E* ratio) were obtained with *N*,*N*-dimethylpyridin-4-amine (DMAP) as the base (Table 1, entry 3). Next, in addition to Yb(OTf)$_3$, other metals,[14] including Y(OTf)$_3$, Sc(OTf)$_3$ and La(OTf)$_3$ were also evaluated. (Table 1, entries 4–6), but Yb(OTf)$_3$ still worked the best. Evaluation of the structures of the *N*,*N*′-dioxide ligands revealed that these structures exerted an obvious influence on both the reactivity and enantioselectivity of the reaction. Chiral *N*,*N*′-dioxide ligands **L1** and **L3** derived from L-proline and L-ramipril gave lower reactivities and enantioselectivities than did ligand **L2** derived from L-pipecolic acid (Table 1, entries 7 and 8 *vs.* 3). Solvent screening indicated that CH_2Cl_2 was a better solvent, generating the product with a 68% yield, 87% ee and 79 : 21 *Z*/*E* ratio (Table 1, entry 9). Increasing the

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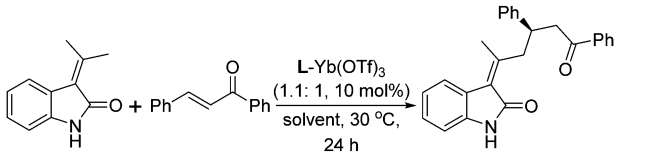
Table 1 Optimization of direct vinylogous Michael addition of 3-alkylidene oxindole (**1a**) to chalcone (**2a**)[a]



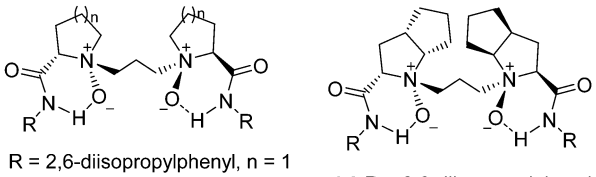
1a 2a 3a

Entry	Ligand/metal	Base	Yield[b] (%)	ee[c] (%)	*Z*/*E*[d]
1	**L2**/Yb(OTf)$_3$	—	0	—	—
2	**L2**/Yb(OTf)$_3$	K_2CO_3	43	40	85/15
3	**L2**/Yb(OTf)$_3$	DMAP	61	85	78/22
4	**L2**/Y(OTf)$_3$	DMAP	48	80	78/22
5	**L2**/Sc(OTf)$_3$	DMAP	16	22	76/24
6	**L2**/La(OTf)$_3$	DMAP	61	18	58/42
7	**L1**/Yb(OTf)$_3$	DMAP	53	59	71/29
8	**L3**/Yb(OTf)$_3$	DMAP	27	48	80/20
9[e]	**L2**/Yb(OTf)$_3$	DMAP	68	87	79/21
10[e,f]	**L2**/Yb(OTf)$_3$	DMAP	77	92	81/19
11[e,f,g]	**L2**/Yb(OTf)$_3$	DMAP	91	94	81/19
12[e,f,g,h]	**L2**/Yb(OTf)$_3$	DMAP	88	96	83/17

[a] Unless otherwise noted, reactions were performed with ligand (11 mol%), metal (10 mol%), **1a** (0.12 mmol), **2a** (0.10 mmol) and base (2 eq.) in THF (0.5 mL) at 30 °C for 48 h. [b] Isolated yield of *Z*/*E*-**3a**. [c] The ee value, which was determined by chiral HPLC analysis, refers to the *Z* isomer. [d] The *Z*/*E* ratio was determined by ^{1}H NMR analysis. [e] The reactions were carried out in CH_2Cl_2 (0.5 mL). [f] 6 eq. DMAP was added. [g] 20 mg of 4 Å MS was added and the reactions were carried out at 30 °C for 24 h. [h] The reaction was carried out at 0 °C for 48 h.

amount of DMAP to 6 equivalents improved the yield, ee and *Z*/*E* ratio to 77%, 92% and 81 : 19, respectively (Table 1, entry 10). We were delighted that the addition of 4 Å molecular sieves (MS) could notably increase the reaction rate, allowing the reaction to be terminated within 1 day to give **3a** with a 91% yield, 94% ee and 81 : 19 *Z*/*E* ratio (Table 1, entry 11). By lowering the reaction temperature from 30 °C to 0 °C, the ee value and *Z*/*E* ratio of the product further increased to 96% and 83 : 17, respectively, but the reactivity slightly decreased (Table 1, entries 12 *vs.* 11) (Fig. 1).

With the optimal conditions established, the scope of the chalcones **2** was investigated. As shown in Table 2, the electron-withdrawing as well as electron-donating substituents on the aromatic ring R^1 of the substrate **2** (Table 2, entries 1–11) were well tolerated. Especially note that the multi-substituted substrate **2q** afforded the product **3q** with an 81% yield, 84% ee and 84 : 16 *Z*/*E* ratio (Table 2, entry 17). Furthermore, heteroaromatic-substituted **2r** and the fused-ring substrate **2s** were also suitable substrates for the reaction, and high yields, ee and *Z*/*E* ratios were obtained (Table 2, entries 18 and 19). Next, the aromatic ring R^2 of the substrate **2** was also tested (Table 2, entries 12–16).

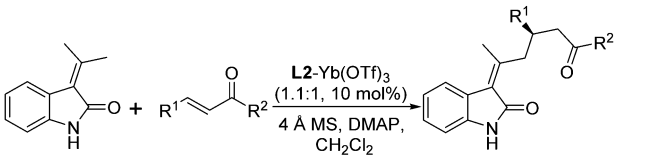


L1 R = 2,6-diisopropylphenyl, n = 1
L2 R = 2,6-diisopropylphenyl, n = 2

L3 R = 2,6-diisopropylphenyl

Fig. 1 Screened ligands in this study.

Table 2 Substrate scopes of substituted chalcones **2** and 3-alkylidene oxindole **1a**[a]



1a 2 *Z*-3

Entry	R^1, R^2	Yield[b] (%)	ee[c] (%)	*Z*/*E*[d]
1	Ph, Ph	88 (**3a**)	96(*R*)	83/17
2	4-FC$_6$H$_4$, Ph	83 (**3b**)	96(*R*)	85/15
3	4-ClC$_6$H$_4$, Ph	81 (**3c**)	94(*R*)	90/10
4	4-BrC$_6$H$_4$, Ph	82 (**3d**)	90(*R*)	91/9
5[e]	4-F$_3$CC$_6$H$_4$, Ph	88 (**3e**)	90(*R*)	85/15
6	4-MeC$_6$H$_4$, Ph	91 (**3f**)	94(*R*)	84/16
7[e]	4-MeOC$_6$H$_4$, Ph	86 (**3g**)	95	83/17
8	3-ClC$_6$H$_4$, Ph	96 (**3h**)	95(*R*)	87/13
9[e]	3-O$_2$NC$_6$H$_4$, Ph	81 (**3i**)	92	82/18
10	3-MeC$_6$H$_4$, Ph	91 (**3j**)	96(*R*)	83/17
11	3-PhOC$_6$H$_4$, Ph	88 (**3k**)	97(*R*)	80/20
12	Ph, 4-FC$_6$H$_4$	96 (**3l**)	96(*R*)	82/18
13[e]	Ph, 4-ClC$_6$H$_4$	83 (**3m**)	93(*R*)	82/18
14[e]	Ph, 4-BrC$_6$H$_4$	73 (**3n**)	93(*R*)	78/22
15[e]	Ph, 4-MeC$_6$H$_4$	67 (**3o**)	97(*R*)	82/18
16[e]	Ph, 4-MeOC$_6$H$_4$	66 (**3p**)	96	81/19
17[e]	3,4-Cl$_2$C$_6$H$_3$, Ph	81 (**3q**)	84(*R*)	84/16
18	3-Thienyl, Ph	77 (**3r**)	92	85/15
19[e]	3-Napthyl, Ph	88 (**3s**)	91(*R*)	86/14

[a] Unless otherwise noted, reactions were performed with **L2** (11 mol%), Yb(OTf)$_3$ (10 mol%), **1a** (0.12 mmol), **2** (0.10 mmol), DMAP (6 eq.) and MS (4 Å, 20 mg) in CH_2Cl_2 (0.5 mL) at 0 °C for 48 h. [b] Isolated yield of *Z*/*E*-**3**. [c] The ee value, which was determined by chiral HPLC analysis, refers to the *Z* isomer. [d] The *Z*/*E* ratio was determined by ^{1}H NMR analysis. [e] The reaction was carried out at 30 °C for 48 h.

Whether electron-withdrawing or electron-donating groups were substituted, the desired products were furnished with excellent enantioselectivities and good *Z*/*E* selectivities. Because of the lower reactivity at 0 °C, the reactions with substrates **2m–2p** were carried out at 30 °C, which also gave products with acceptable yields (Fig. 2).

Encouraged by these results, further examination of the substrates was focused on substituted 3-alkylidene oxindoles **1**.[15] Varying the substituents on the benzene ring of oxindole, such as in **3t** and **3u**, had no obvious influence on the enantioselectivity, *Z*/*E* selectivity and yield. Benzylidene oxindole **1v** was also successfully employed in the reaction and delivered adduct **3v** with an 84% yield, 94% ee and 85 : 15 *Z*/*E* ratio. In addition, the 3-alkylidene oxindole **1w**, having a prostereogenic site at the γ-position, also participated in this reaction, albeit producing a slightly lower yield and ee value.

In order to confirm the absolute configurations of the products, **3a** was oxidized to the known **4a** by treatment with ozone (Scheme 1). The absolute configuration of the product **4a** was confirmed to be *R* by comparison with the reported value of its optical rotation.[16] Thus, the configuration of the product **3a** was indicated to be *R*. Then, the absolute configurations of **3b–3f**, **3h**, **3j–3o**, **3q**, **3s**, and **3t** were determined to be *R* by comparing the Cotton effects in their CD spectra to that of **3a** (see the ESI† for details).

For the purpose of examining the synthetic potential of the catalyst system, a gram-scaled reaction was performed (Scheme 2).

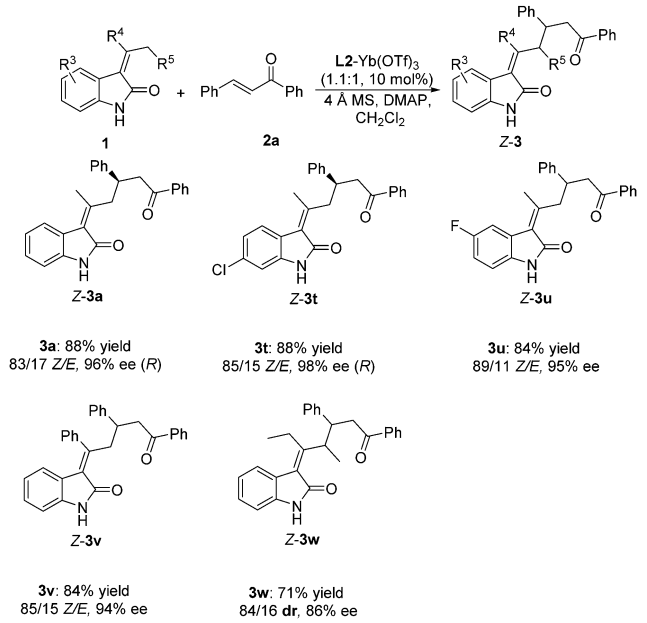
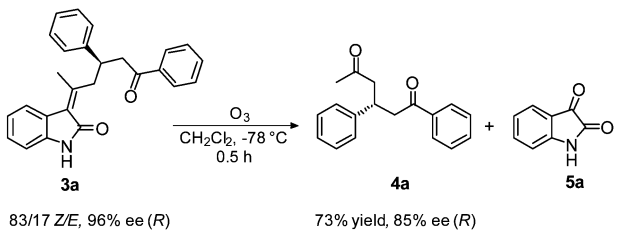
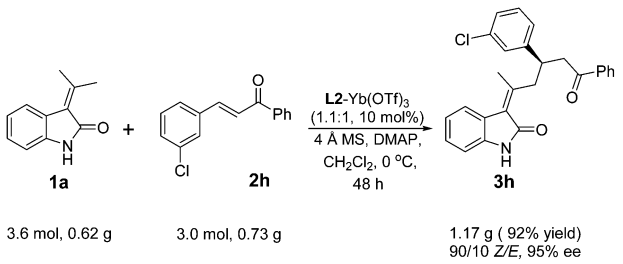


Fig. 2 Generality of direct vinylogous Michael addition of substituted 3-alkylidene oxindoles **1** to chalcone **2a**.



Scheme 1 Ozone oxidation of **3a**.



Scheme 2 Gram-scaled version of the reaction.

As shown in Scheme 2, under the optimized reaction conditions (Table 1, entry 12), 3 mmol of chalcone **2h** reacted with 1.2 equivalents of **1a**, giving 1.17 g (92% yield) of the desired product **3h** with a 90/10 *Z*/*E* and 95% ee.

In summary, we have developed a direct and highly enantioselective vinylogous Michael addition of 3-alkylidene oxindoles to chalcones. In the presence of a chiral ytterbium(III)–*N*,*N*′-dioxide complex, a wide range of substituted chalcones as well as 3-arylidene- and 3-alkylidene-substituted oxindoles were tolerated under mild reaction conditions, giving the corresponding γ-addition products in high yields, enantioselectivities and *Z*/*E* selectivities. Meanwhile, the synthetic potential of this methodology was also demonstrated by the excellent results obtained on a gram scale.

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