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Enantioselective Copper(II)-Catalyzed Conjugate Addition of Indoles to β-Substituted Unsaturated Acyl Phosphonates

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Abstract: The first copper-catalyzed enantioselective conjugate addition of indoles to β-substituted unsaturated acyl phosphonates was successfully realized by using a heteroarylidene-tethered bis(oxazoline) ligand. The reaction features high efficiency, cheap catalyst and broad generality. In the case of either β-alkyl- or β-aryl-substituted unsaturated acyl phosphonates, the 3-indolyl adducts were achieved in high yields with good to excellent enantioselectivities (up to 97% *ee*). The 3-indolyl adducts can serve as important intermediates in the synthesis of indole alkaloids.

Keywords: bis(oxazoline)s; conjugate addition; copper; enantioselectivity; indoles; unsaturated acyl phosphonates

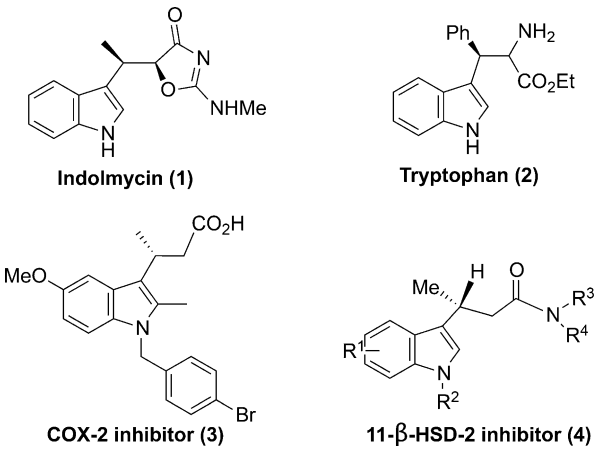


Figure 1. Selected examples of indole derivatives.

Indole derivatives represent one of the most privileged alkaloids and are ubiquitous in natural products and pharmaceutical compounds.[1] Among them, potential chiral 3-crotonyl or cinnamoyl group side chain-substituted indoles constitute an important structural motif in various biological molecules. For example, indolmycin (**1**) exhibits inhibition of prokaryotic tryotophanyl-tRNA synthetase (TrpRS),[2] and β-phenyltryptophan (**2**) has analgesic activities associated with anti-inflammatory properties.[3] Besides, synthetic compounds (**3**) and (**4**) are typical COX-2 inhibitor[4] and 11-β-HSD-2 inhibitors,[5] respectively (Figure 1).

Over the past two decades, extensive efforts have been devoted to the development of efficient methods for the preparation of chiral functionalized indole derivatives.[6] Among them, the asymmetric conjugate addition of indoles to unsaturated olefins (also called Friedel–Crafts reaction) represents a very powerful strategy.[7] By now, various electrophiles such as keto esters,[8] imines or enamines,[9] α′-hydroxy enones,[10] nitroolefins,[11] alkylidenemalonates,[12] unsaturated α-keto esters,[13] aldehyde or ketones,[14] have been successfully employed for the purpose. Besides, β-substituted unsaturated acyl phosphonate have also been introduced as a very useful synthon for enantioselective indole functionalization. For instance, in 2003, Evans et al. pioneered the first example of asymmetric conjugate addition of indoles to unsaturated acyl phosphonates using an Sc(III)-pybox complex, affording the *N*-protected indole products in high yields with excellent enantioselectivities.[15] Subsequently, Yamamoto et al. reported the same reaction catalyzed by an Al-bis(8-quinolinolato) complex. Excellent enantioselectivities (up to 98% *ee*) were achieved for the *N*-benzyl- and *N*-methylindole products, but only moderate enantioselectivity (58% *ee*) was obtained for the *N*-unprotected indoles.[16] In 2010, Jørgensen et al. employed a chiral thiourea to realize the organocatalytic addition reaction of unprotected indole to unsaturated acyl phosphonates, providing the indole adducts in 72–90% *ee*.[17] Akiyama et al.[18] and Kim et al.[19] reported, respectively, that chiral phosphoric acid and the complexes of Pd-BINAP could efficient-

ly catalyze this reaction, however, the substrate scope is mainly limited to either β-aryl- or β-alkyl-substituted acyl phosphonates. Despite these impressive advances, the generality of the reaction is restricted by substrate scope. To the best of our knowledge, no successful example of a catalytic asymmetric reaction of both β-alkyl- and β-aryl-substituted unsaturated acyl phosphonates with unprotected indoles has been reported. Therefore, the exploration of a facile, highly enantioselective method with broad generality is very valuable and still in great demand.

Our previous works have proved that heteroarylidene-tethered bisoxazolines (BOX **L1** and **L2**, Figure 2) are effective chiral ligands in some asymmetric reactions of indoles with electron-deficient olefins.[20] As a continuation of our ongoing research to explore new catalytic asymmetric methods using the simple and cheap catalytic system, we herein report the first copper-catalyzed conjugate addition of unprotected indoles to β-alkyl- and β-aryl-unsaturated acyl phosphonates, which afforded a broad range of optically active indole adducts in high yields with good to excellent enantioselectivities (up to 97% *ee*).

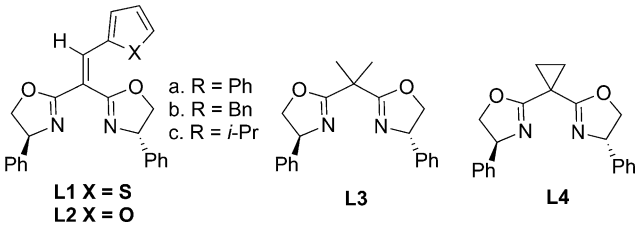
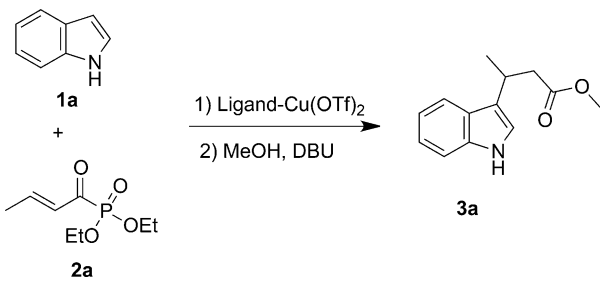


Figure 2. Screened bis(oxazoline) ligands.

Our initial investigation began with the conjugate addition of *N*-unprotected indole (**1a**) to β-methyl unsaturated acyl phosphonate (**2a**) as the model reaction (Scheme 1).[15] First, the reaction was carried out at 0 °C in the presence of 10 mol% **L1a**-Cu(OTf)$_2$ complex, followed by addition of MeOH and DBU. The results are listed in Table 1. Of all the six typical solvents screened, generally good yields of indole adduct **3a** were afforded, albeit with different enantioselectivities (entries 1–6). It turned out that $CHCl_3$ was the



Scheme 1. The model reaction for optimization.

Table 1. Optimization of the reaction conditions.[a]

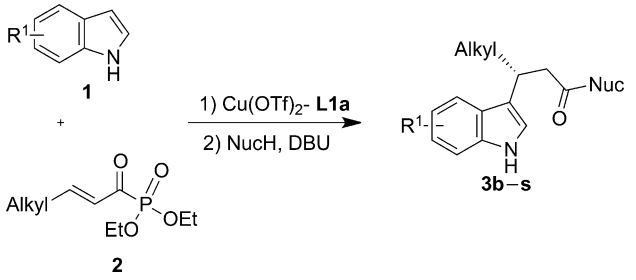
Entry	Ligand	Solvent	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**L1a**	DCM[d]	0	1	96	80
2	**L1a**	$CHCl_3$	0	1	94	84
3	**L1a**	DCE[e]	0	1	96	77
4	**L1a**	THF	0	4	89	78
5	**L1a**	Et_2O	0	4	88	80
6	**L1a**	toluene	0	4	92	78
7	**L1b**	$CHCl_3$	0	1	94	17
8	**L1c**	$CHCl_3$	0	1	94	-10
9	**L2a**	$CHCl_3$	0	1	95	81
10	**L2b**	$CHCl_3$	0	1	94	24
11	**L2c**	$CHCl_3$	0	1	95	-6
12	**L3**	$CHCl_3$	0	1	92	76
13	**L4**	$CHCl_3$	0	1	86	48
14	**L1a**	$CHCl_3$	−30	4	94	87
15	**L1a**	$CHCl_3$	−60	12	89	94
16[f]	**L1a**	$CHCl_3$	−60	24	76	94

[a] All reactions were carried out using 10% mol of ligand-Cu(OTf)$_2$ in solvent (2 mL) under nitrogen, then treated with MeOH (0.5 mL) and DBU (0.1 mL) for 1 h at room temperature.
[b] Isolated yield.
[c] Determined by HPLC.
[d] CH_2Cl_2.
[e] $ClCH_2CH_2Cl$.
[f] 5 mol% **L1a**-Cu(OTf)$_2$.

optimal solvent in terms of yield and *ee* value (entry 2, 94% yield and 84% *ee*). Subsequently, the effect of the ligand was also examined. The reaction proceeded smoothly within 1 h at 0 °C to give the desired adducts in quantitative conversions for all tested ligands (entries 7–11), whereas the enantioselectivities were very poor except for furyl-tethered BOX **L2a** bearing a phenyl group (entry 9, 81% *ee*). For comparison, Evans' ligand **L3** and cyclopropane-tethered BOX ligand **L4** were also tested, and furnished relatively lower *ee* values (entries 12 and 13). These preliminary results indicated **L1a** was the most effective ligand. The reaction temperature and the catalyst loading were next examined. When lowering the temperature to −30 and −60 °C, the enantioselectivities were improved obviously to 87% *ee* and 94% *ee*, respectively, albeit a longer reaction time was necessary (entries 14 and 15). When the reaction was carried out at a catalyst loading of 5 mol%, the enantioselectivity remained completely but the reactivity dropped slightly (entry 16). The absolute configuration of product **3a** was assigned to be *R* by comparison with the reported results in the literature.[17]

With the optimal conditions in hand [10 mol% **L1a**-Cu(OTf)$_2$, $CHCl_3$ as solvent, −60 °C], we next investigated the scope of indoles in this reaction. The results are summarized in Table 2. First, the nucleophilic reagents EtOH, BnOH or $BnNH_2$ were em-

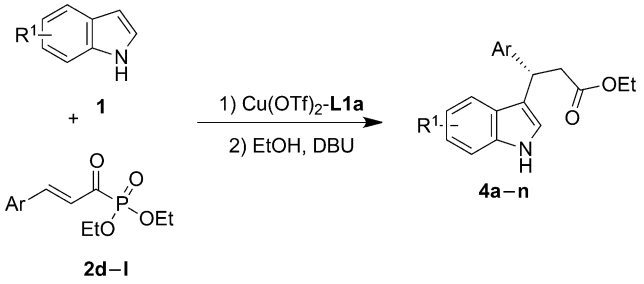
Table 2. The addition of various indoles to β-alkyl unsaturated acyl phosphonates.[a]



Entry	R^1	Alkyl	NucH	Yield [%][b]	*ee* [%][c]
1	H	Me (**2a**)	EtOH	90 (**3b**)	94
2	H	Me	BnOH	85 (**3c**)	94
3	H	Me	$BnNH_2$	94 (**3d**)	93
4	4-Me	Me	EtOH	86 (**3e**)	93
5	5-Me	Me	EtOH	88 (**3f**)	91
6	7-Me	Me	EtOH	87 (**3g**)	90
7	5-MeO	Me	EtOH	89 (**3h**)	93
8	5-F	Me	EtOH	78 (**3i**)	94
9	5-Cl	Me	EtOH	81 (**3j**)	94
10	5-Br	Me	EtOH	80 (**3k**)	95
11	5-CN	Me	EtOH	82 (**3l**)	95
12	5-CO_2Me	Me	EtOH	85 (**3m**)	94
13	5-NO_2	Me	EtOH	77 (**3n**)	94
14	6-F	Me	EtOH	73 (**3o**)	95
15	6-Cl	Me	EtOH	79 (**3p**)	95
16	6-Br	Me	EtOH	81 (**3q**)	96
17	H	*i*-Pr (**2b**)	EtOH	85 (**3r**)	93
18	H	Cy (**2c**)	EtOH	90 (**3s**)	95

[a] All reactions were conducted in $CHCl_3$ (2 mL) under nitrogen using 10 mol% of **L1a**-$Cu(OTf)_2$ at −60 °C for 12 h, then treatment by addition of EtOH, BnOH or $BnNH_2$ (0.5 mL) and DBU (0.1 mL) for 1 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.

Table 3. The addition of various indoles to β-aryl unsaturated acyl phosphonates.[a]



Entry	R^1	Ar	Time [h]	Yield [%][b]	*ee* [%][c]
1	H	Ph (**2d**)	8	95 (**4a**)	92
2	5-Me	Ph (**2d**)	8	92 (**4b**)	88
3	5-MeO	Ph (**2d**)	8	85 (**4c**)	95
4	7-Me	Ph (**2d**)	8	87 (**4d**)	90
5	5-Cl	Ph (**2d**)	24	93 (**4e**)	80
6	6-Br	Ph (**2d**)	24	90 (**4f**)	83
7	H	*p*-MeC_6H_4 (**2e**)	8	91 (**4g**)	87
8	H	*p*-$MeOC_6H_4$ (**2f**)	8	84 (**4h**)	80
9	H	*o*-MeC_6H_4 (**2g**)	8	85 (**4i**)	96
10	H	*p*-ClC_6H_4 (**2h**)	8	88 (**4j**)	94
11	H	*p*-BrC_6H_4 (**2i**)	8	92 (**4k**)	94
12	H	*p*-$CF_3C_6H_4$ (**2j**)	8	95 (**4l**)	97
13	H	2-naphthyl (**2k**)	8	98 (**4m**)	91
14	H	2-furyl (**2l**)	8	96 (**4n**)	78

[a] All reactions were conducted in $CHCl_3$ (2 mL) under nitrogen using 10 mol% of **L1a-**$Cu(OTf)_2$ at −60 °C for 8-24 h, then treatment by addition of EtOH (0.5 mL) and DBU (0.1 mL) for 1 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.

ployed instead of MeOH, both the high yields and *ee* values were almost maintained (entries 1–3). Second, for a series of indoles bearing electron-donating or electron-withdrawing substituents at different positions, they all worked well to furnish the corresponding products **3e**–**3q** in high yields and excellent enantioselectivities (entries 4–16, 73–89% yield and 90–96% *ee*), indicating that the substituents of indole had negligible influence on the reactivity and selectivity. To our delight, the reaction was also compatible with other β-alkyl group-substituted substrates and excellent enantioselectivities were observed in the reactions of β-isopropyl- or β-cyclohexyl-substituted acyl phosphonates **2b** and **2c** (entries 17 and 18, 93% and 95% *ee*, respectively).

The substrate scope was further extended to β-aryl-substituted unsaturated acyl phosphonates, as summarized in Table 3. Under the same conditions, it took only 8 h for the completion of the reaction between β-phenyl acyl phosphonate **2d** and indole at −60 °C, giving the desired product **4a** in 95% yield with 92% *ee*, which indicated the higher reactivity of **2d** comparing with that of **2a–c** (entry 1). In the case of indoles with an electron-donating group, the products **4b**–**4d** were all achieved in good results (entries 2–4, 88–95% *ee*); while in the case of indoles with an electron-withdrawing group, the reaction became sluggishly and a prolonged reaction time was needed for full conversion, the indole products were obtained in high yields with somewhat decreased *ee* values (entries 5, 6, 80–83% *ee*). The results showed the electron-withdrawing substituent on the indole ring had a negative effect on the reactivity and enantioselectivity of the reaction. Moreover, different substituted phenyl groups of the unsaturated acyl phosphonates were examined. All reactions could be completed within 8 h at −60 °C, exhibiting both high reactivities and good to excellent enantioselectivities (entries 7–12, 80–97% *ee*). In addition, 2-naphthyl-substituted acyl phosphonate **2k** was also a suitable substrate in this reaction, giving the indole adduct **4m**

in 98% yield with 91% *ee* (entry 13), whereas 2-furyl-substituted substrate **2l** furnished a relatively low enantioselectivity but excellent reactivity (entry 14, 96% yield and 78% *ee*). In most cases the catalyst **L1a**-Cu(OTf)$_2$ provided more higher *ee* values and yields than the previously reported methods in this reaction.[17,18] It was noteworthy that both β-alkyl- and β-aryl-substituted unsaturated acyl phosphonates gave good to excellent results, indicating a much broader substrate scope.

The absolute configuration of product **4k** was determined to be *S* on the basis of its single-crystal X-ray structure (Figure 3),[21] which could also be confirmed by comparison with previous reports.[17,18]

The stereochemistry outcome can be explained by Figure 3. In general, a four-coordinated Cu(II) complex prefers a square-planar geometry. When β-aryl unsaturated acyl phosphonate coordinates with the copper complex of thienyl-tethered bisoxazoline, a tetrahedral transition state is formed, subsequently indole attacks preferably from the *Si* face of unsaturated acyl phosphonate, leading to the formation of the predominant *S*-configured indole adduct. If using β-methyl unsaturated acyl phosphonate instead of the β-aryl substituted one, the same reaction mode would generate the major *R*-configured product. Given the higher enantioselectivity afforded by **L1a** in contrast to **L3** or **L4** (Table 1, entries 12 and 13), we believe that both the oxazoline ring and the heteroarylidene skeleton can provide a well-defined chiral environment in this catalytic transformation, which then has

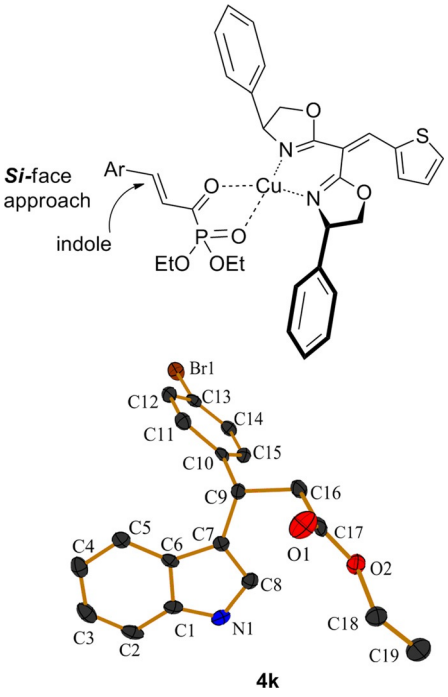
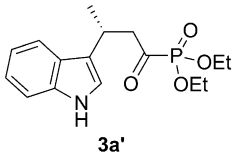


Figure 3. Plausible transition state model and X-ray structure of **4k**.

a cooperative effect on the enantioselectivity and reactivity of the reaction. The enantioselectivity of the direct addition product-indole acyl phosphonate should be identical with the resulting ester or amide, because this transformation is not related to the chiral center under mild reaction conditions. To confirm this deduction, we also separated the direct addition product **3a′** under the same catalytic reaction conditions. The enantioselectivity was determined to be 94% *ee*, which is the same as the level of **3a** (For details, see the Supporting information).



3a'

In summary, we have demonstrated the copper(II) complexes of heteroarylidene-tethered BOX ligand can efficiently catalyze the asymmetric conjugate addition of unprotected indoles to various β-substituted unsaturated acyl phosphonates. The reaction proceeded to completion within 24 h at −60 °C, affording the indole products in high yields and with good to excellent enantioselectivities. In comparison to the previously reported catalytic methods, the present method displays some significant advantages: (i) the simple and cheap catalyst (chiral copper complexes); (ii) broader substrate scope (almost the same high level of asymmetric induction for both β-alkyl- and β-aryl-substituted unsaturated acyl phosphonates); (iii) generally better enantioselectivities. The products of the reaction can be transformed into biologically active indole derivatives according to the previously reported methods.[22] Further studies to expand the scope of this methodology are underway in our laboratory.

Experimental Section

Typical Procedure for Asymmetric Conjugate Addition of Indoles to β-Substituted Unsaturated Acyl Phosphonates

To a Schlenk tube were successively added Cu(OTf)$_2$ (0.030 mmol), ligand **L1a** (0.033 mmol) and $CHCl_3$ (1.5 mL) under nitrogen. The solution was stirred for 2 h at room temperature, and then unsaturated acyl phosphonate **2a** (0.36 mmol) was added. The resulting mixture was cooled to −60 °C and stirred for 20 min, a solution of indole **1a** (0.30 mmol) in $CHCl_3$ (0.5 mL) was finally added by a syringe. After stirring for 12 h at −60 °C, MeOH (0.5 mL) and DBU (100 μL) were directly added to the reaction mixture and stirred for another 1 hour at room temperature. Saturated NH_4Cl solution (10 mL) was added and the mixture ex-

tracted with ethyl acetate (10 mL × 3). The organic layer was combined, and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and then concentrated to give the crude product, which was purified by flash column chromatography on silica gel (eluted with ethyl acetate/petroleum ether (1/10, v/v) to afford the desired indole product **3a**, (*R*)-methyl 3-(1*H*-indol-3-yl)butanoate, as a colorless oil; yield: 89%; $[\alpha]_D^{25}$: −3.5 (*c* 1.10, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (br s, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.31–7.12 (m, 2H), 6.95 (d, *J* = 2.1 Hz, 1H), 3.85–3.55 (m, 4H), 2.93 (dd, *J* = 15.0, 6.2 Hz, 1H), 2.68 (dd, *J* = 15.0, 8.6 Hz, 1H), 1.51 (d, *J* = 6.9 Hz, 3H); HPLC analysis (Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL min^{-1}, 254 nm): *t*(major) = 15.95 min, *t*(minor) = 28.63 min, 94% *ee*.

Acknowledgements

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