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Enantioselective addition of oxindoles to aliphatic α,β-unsaturated aldehydes

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ABSTRACT

A highly enantioselective organocatalytic oxindole addition to α,β-unsaturated aldehydes is reported. The reaction is catalyzed by simple and commercially available chiral secondary amines, affording the corresponding adducts with good yields and with moderate diastereoselectivities.

Nowadays, the efficient enantioselective construction of quaternary centers remains a challenging task in organic synthesis. These quaternary centers are found in numerous biologically active small molecules. In particular, oxindoles containing a chiral tetrasubstituted carbon at the benzylic (C3) position constitute a common structural motif in many biologically active compounds[1] and are broadly useful as synthetic intermediates for a diverse range of indole alkaloids.[2] For this reason, the development of new methods to synthesize chiral quaternary stereocenters at the C3 position of oxindoles has received much attention lately, and there are several examples in the literature concerning the C3-substitution of oxindoles by different methods: hydroxylation,[3] aldol reaction,[4] acyl migration,[5] and fluorination.[6]

Much effort has also been devoted to the asymmetric synthesis of 3-substituted oxindoles. For example, Buchwald reported very recently the enantioselective intermolecular coupling of oxindoles with aryl and allyl bromides catalyzed by Pd with excellent results.[7] In the field of asymmetric organocatalysis,[8] several groups have recently been interested in the synthesis of oxindoles. Thus, Chen and co-workers have described the organocatalytic asymmetric allylic alkylation of oxindoles with MBH carbonates catalyzed by chincona alkaloids with very good results,[9] and Barbas and co-workers have reported the nucleophilic addition of oxindoles to nitrostyrenes catalyzed by chiral thioureas, that affords the corresponding quaternary oxindoles in excellent yields and enantioselectivities.[10]

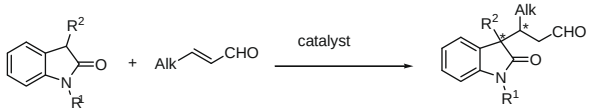
Based on these reports and on our previous work in organocatalysis,[11] we envisaged an easy entry to chiral quaternary oxindoles based in the nucleophilic addition of oxindoles to α,β-unsaturated aldehydes. It should be noticed that during the initial stages of this work, Melchiorre and co-workers uncovered the reaction of unsaturated aldehydes with oxindoles catalyzed by primary amines bearing a thiourea moiety.[12] While the reaction works well with cinnamaldehyde derivatives, with the use of aliphatic aldehydes however, the enantioselectivities are rather low (67% ee).

For this reason, we focused our attention on the reaction of oxindoles with aliphatic unsaturated aldehydes, in order to find suitable conditions that might provide the final products with high enantioselectivities (Scheme 1).

In an initial catalyst screening, we ran the addition reaction of 3-methyloxindole (**1a**) to 2-pentenal (**2a**) in toluene, and we used different commercially available chiral secondary amines as catalysts (Table 1). To our delight, we found that simple proline was able to catalyze the reaction, albeit with low enantioselectivities (Table 1, entry 1). Prolinol **II** gave even lower enantioselectivity (entry 2), and Jorgensen's catalyst **IV** did not afford full conversion after 5 days while giving the best enantioselectivities (entry 4). Gratifyingly, when the diphenyl prolinol derivative **III** was used, the reaction was efficiently catalyzed, achieving full conversion after 3d and affording the expected addition product **3a** with a diastereoselectivity of 2:1 and enantioselectivities of 82% and 95% for the major and the minor isomers, respectively (entry 3).

It is noteworthy that the reaction in other solvents such as CH_2Cl_2 or $CHCl_3$ gave slightly lower enantioselectivities; the addition of acid as additive (2-fluorobenzoic acid) also decreased the enantioselectivity of the reaction.

Once we found suitable conditions for the reaction of 3-methyl oxindole with 2-pentenal, we decided to determine the scope of the reaction with different aliphatic unsaturated aldehydes (Table 2). Gratifyingly, in all cases the methyloxindole addition took place with moderate yields, diastereoselectivities, and excellent enantioselectivities. For example, when 2-hexenal **2c** was used, the addition product **3c** was obtained with 69% yield, in a 2:1 diastereomeric ratio and with



Scheme 1. Proposed reaction.

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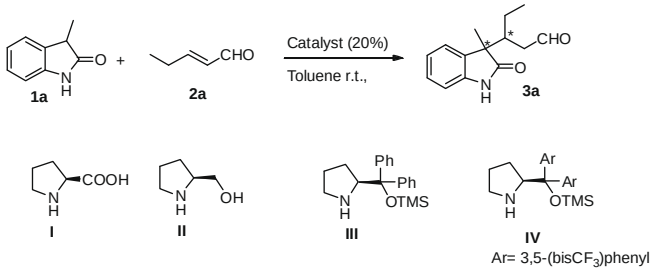
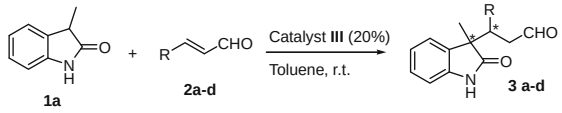
Table 1
Catalyst screening[a]



Entry	Catalyst	Time (d)	Conversion[b] (%)	dr[c]	ee[d] (%)
1	**I**	3	100	1:1.5	24, 55
2	**II**	3	100	1.2:1	9, 8
3	**III**	3	100	2:1	82, 95
4	**IV**	5	53	1:1.5	91, 94

[a] Experimental conditions: a mixture of **1a** (0.25 mmol), catalyst (20 mol %) and **2a** (0.30 mmol) in toluene (1 mL) was stirred at rt for the time shown in the Table.
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR.
[d] ee determined by chiral HPLC analysis.

Table 2
Reaction scope of methyl-oxindole[a]



Entry	Product	R	Time (d)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**3b**	Me	1	62	2:1	84, 85
2	**3a**	Et	2	68	2:1	82, 95
3	**3c**	*n*-Pr	2	69	2:1	87, 91
4	**3d**	*n*-Bu	2	73	2:1	83, 92

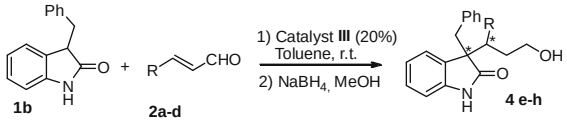
[a] Experimental conditions: a mixture of **1a** (0.25 mmol), catalyst (20 mol %), and **2a**–**d** (0.30 mmol) in toluene (1 mL) was stirred at rt for the time shown in the Table.
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR.
[d] ee determined by chiral HPLC analysis.

87% and 91% ee for the major and minor diastereomers, respectively (entry 3). The reaction worked also well with crotonaldehyde **2b** (entry 1), and with 2-heptenal **2d** (entry 4). In all the examples, we obtained good yields and good enantioselectivities, but a moderate diastereoselectivity (2:1 dr).

Next, we decided to investigate the scope of the reaction with different 3-substituted oxindoles. The reaction with 3-benzyloxindole **1b** (Table 3) worked satisfactorily, affording, after in situ reduction of the aldehydes **3e**–**h** with sodium borohydride in order to avoid isomerization reactions, the final compounds **4e**–**h** in good yields and enantioselectivities, again with a moderate diastereoselectivity (2:1 dr).

Finally, we decided to investigate the effect of the protection of the nitrogen of oxindole. For this reason, we synthesized *N*-Boc-methyloxindole **1c**. This compound was reacted with different aliphatic α,β-unsaturated aldehydes. The reaction afforded, after in situ reduction of the aldehydes **3i**–**l** with sodium borohydride, the alcohols **4i**–**l** in poor yields and more important, in essentially racemic form, as shown in Table 4, this is due to the fact that *N*-Boc-methyloxindole aldehyde derivatives (**3i**–**l**) at room temperature present a fast equilibration with the starting materials by a reversible Michael reaction.

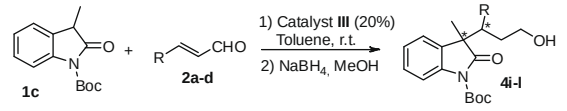
Table 3
Reaction scope of 3-benzyl-oxindole **1b**[a]



Entry	Product	R	Time (d)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**4e**	Me	1	72	2:1	65, 88
2	**4f**	Et	2	76	2:1	82, 87
3	**4g**	*n*-Pr	2	75	2:1	76, 82
4	**4h**	*n*-Bu	2	73	2:1	75, 81

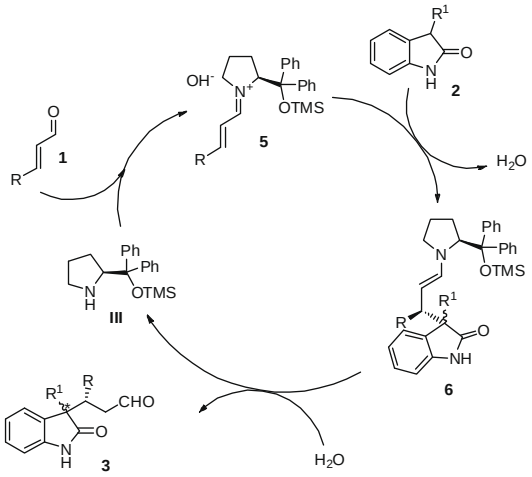
[a] Experimental conditions: a mixture of **1b** (0.25 mmol), catalyst (20 mol %), and **2a**–**d** (0.30 mmol) in toluene (1 mL) was stirred at rt for the time shown in the Table.
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR.
[d] ee determined by chiral HPLC analysis.

Table 4
Reaction scope of Boc-protected methyl-oxindole[a]



Entry	Product	R	Time (d)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**4i**	Me	2	35	2.5:1	Racemic
2	**4j**	Et	2	37	2.5:1	Racemic
3	**4k**	*n*-Pr	2	32	2:1	Racemic
4	**4l**	*n*-Bu	2	38	2.5:1	Racemic

[a] Experimental conditions: a mixture of **1c** (0.25 mmol), catalyst (20%), and **2a**–**d** (0.30 mmol) in toluene (1 mL) was stirred at rt for the time shown in the Table.
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR.
[d] ee determined by chiral HPLC analysis.



Scheme 2. Proposed mechanism and stereochemical outcome.

Tentatively, we assign the absolute configuration of the β carbon of the aldehyde in adducts **3** by assuming that the mechanism and transition states are similar to those described for other organocatalytic Michael additions catalyzed by diphenylprolinol derivatives reported in the literature.[13] Thus, efficient shielding of the *Si*-face of the chiral iminium intermediate **5** by the bulky aryl groups

of chiral pyrrolidine **III**, leads to stereoselective *Re*-facial nucleophilic conjugate addition by oxindole in its enol form, as shown in Scheme 2.

In summary, we have reported an enantioselective oxindole addition to α,β-unsaturated aldehydes. The reaction is efficiently catalyzed by commercially available chiral pyrrolidine derivatives and gives the corresponding adducts with moderate to good yields, moderate diastereoselectivities and good to excellent enantioselectivities.[14] Mechanistic studies, synthetic applications of this new methodology, and the discovery of new reactions based on this concept are ongoing in our laboratory.

Acknowledgments

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14. *Typical experimental procedure for the synthesis of compound* **4j**: To a stirred solution of catalyst **III** (16 mg, 0.05 mmol, 20 mol %) in toluene (1.0 mL), were added *E*-2-hexenal **2c** (30 mg, 0.30 mmol, 1.2 equiv), and 3-benzyloxindole **1b** (55 mg, 0.25 mmol, 1.0 equiv). The reaction was vigorously stirred at rt for 1 day. After reduction 'in situ' with $NaBH_4$, the crude product was purified by silica gel chromatography (hexane/EtOAc mixtures) to give the corresponding oxindole derivative **4j**. *Compound* **4j**: colorless oil. ^{1}H NMR (400 MHz. $CDCl_3$, TMS_{int}): δ (ppm) = 12.12 (d, J = 2.6 Hz, 2H), 9.56 (t, J = 1.6 Hz, 1H), 7.52–7.46 (m, 2H), 6.95–6.90 (m, 3H), 6.85–6.82 (m, 1H), 4.33 (d, J = 3.1 Hz, 1H), 2.50–2.41 (m, 1H), 2.29 (ddd, J^1 = 1.6 Hz, J^2 = 6.6 Hz, J^3 = 17.4 Hz, 1H), 2.03 (ddd, J^1 = 1.8 Hz, J^2 = 6.9 Hz, J^3 = 17.4 Hz, 1H), 1.38–1.20 (m, 4H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz. $CDCl_3$): δ (ppm) = 182.3, 136.5, 132.0, 130.6, 130.5, 128.6, 128.1, 127.0, 125.1, 125.0, 122.9, 122.7, 110.1, 63.1, 62.0, 43.0, 42.4, 35.0, 33.7, 22.5, 15.0. $[\alpha]_D^{25}$ −24.2 (c = 1.0, $CHCl_3$, mixture of diastereomers). HRMS(ESI): Calculated for $[C_{21}H_{26}NO_2]^+$: 324.1955; found: 324.1958. HPLC (Chiralpak® IC, 1 mL min^{-1}, hexanes:IPA 90:10, 254 nm): t_R = t_R = 8.00 min (major), 13.80 min (minor) [minor diastereomer], 11.0 (major), 16.15 (minor) [major diastereomer].