Organocatalytic Asymmetric Conjugate Additions of Oxindoles and Benzofuranones to Cyclic Enones

Fabio Pesciaioli,[a] Xu Tian,[b] Giorgio Bencivenni,[a] Giuseppe Bartoli,[a] Paolo Melchiorre*[b,c]

[a] Dipartimento di Chimica Organica 'A. Mangini', Università di Bologna, Viale Risorgimento 4, 40136 Bologna, Italy

[b] ICIQ, Institute of Chemical Research of Catalonia, Av. Països Catalans 16, 43007 Tarragona, Spain

[c] ICREA, Institució Catalana de Recerca i Estudis Avançats, Pg. Lluís Companys 23, 08010 Barcelona, Spain
E-mail: pmelchiorre@iciq.es

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Abstract: The asymmetric catalytic synthesis of densely functionalized molecules that contain vicinal quaternary and tertiary stereocenters is a challenge for modern chemical methodology. Here we show that a chiral primary amine, derived from natural molecules, efficiently catalyzes the stereoselective conjugate addition of oxindoles to cyclic enones, leading directly to valuable chiral scaffolds. Proof-of-concept for extending the method to benzofuranone derivatives is also provided.

Key words: asymmetric catalysis, ketones, Michael addition, quaternary carbon, organocatalysis

Reproducing the structural and stereochemical complexity inherent to natural molecules has always been a formidable vehicle for reaction invention.[1] This has inspired the discovery of catalytic asymmetric methods[2] which have now become a fundamental part of the chemist's repertoire for a variety of synthetic applications, especially in relation to the study of biologically active compounds. Indeed, many drugs used today are natural products or natural product derivatives.[3] Despite the substantial advances made to date, the catalytic and enantioselective generation of carbon stereocenters with four other carbon substituents remains a daunting target for synthesis.[4]

Recently, significant effort has been directed toward the enantioselective synthesis of 3,3-disubstituted oxindoles and derivatives. This is because of the prevalence of this privileged heterocyclic motif in biologically active natural molecules[5] and pharmaceutically relevant compounds (Figure 1).[6] In recent years, many research groups have taken up the challenge of stereoselectively assembling structurally complex oxindoles endowed with a quaternary stereogenic center at C3. It has thus become a benchmark for testing the power and potential of a given catalytic strategy. Both metal-[7] and organic-based[8] catalytic reactions have provided efficient solutions to this issue.

Among the various strategies devised to date, the direct conjugate addition of 3-substituted oxindoles to activated alkenes is one of the most versatile. An additional merit of this approach is that vicinal quaternary and tertiary stereocenters can be created at once. However, inferring high control over stereochemistry is difficult, as the catalyst must provide high levels of stereoselectivity in a sterically demanding C–C-bond-forming process.[9] To date, the acceptors employed in this powerful strategy have been restricted to enals[10a] and nitroalkenes.[10b–d] The conjugate addition of prochiral oxindoles to α,β-unsaturated ketones remains an elusive transformation.[11]

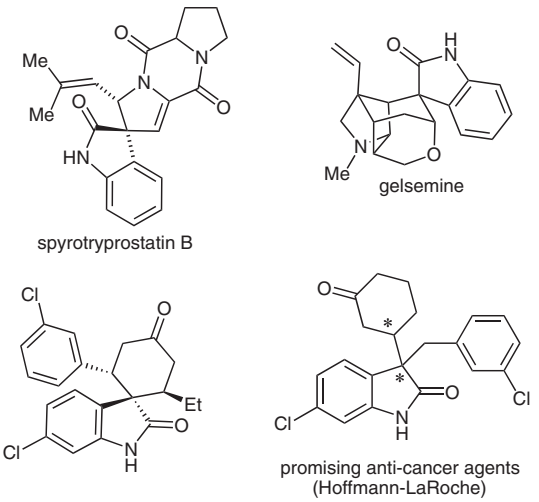

Figure 1 Representative naturally occurring and biologically active 3,3-disubstituted oxindoles bearing all-carbon quaternary stereocenters

Herein, we report the first highly stereoselective addition of *N*-Boc-protected oxindoles **1** to cyclic enones **2** under the catalysis of simple chiral primary amines, derived from natural cinchona alkaloids (Equation 1). The resulting polycyclic adducts **3**, having two contiguous stereocenters, one of which is quaternary by all-carbon substitution, are formed with high levels of diastereo- and enantioselectivity. Extension to 2(3*H*)-benzofuranone derivatives, an unprecedented nucleophilic component for conjugate additions, opens up new opportunities for the asymmetric synthesis of valuable heterocyclic compounds.

For exploratory studies, we selected the reaction between 3-benzyl oxindole (**1a**) and cyclohexen-2-one (**2a**), a combination of easily available starting materials that

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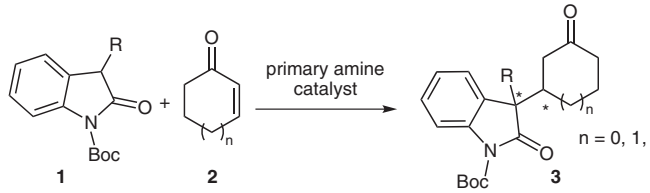


Equation 1 The direct conjugate addition developed in this study

would readily give access to valuable oxindole-based derivatives **3**.

Our laboratory and others, independently, have recently introduced 9-amino(9-deoxy)epi-cinchona alkaloids (Figure 2), chiral primary amines easily derived from natural sources, as general and effective catalysts for a wide variety of asymmetric β-functionalizations of ketones under iminium ion catalysis.[12,13] We have further demonstrated the ability of catalyst **A**, derived from hydroquinine, to combine orthogonal aminocatalytic modes (iminium and enamine activations) into one mechanism,[12d] thus promoting cascade reactions with α,β-unsaturated ketones[13e] and the challenging α,β-disubstituted enals.[13f] Thus, we hypothesized that catalyst **A** would efficiently promote the stereoselective addition of benzyl oxindole **1a** to enone **2a**. We report selected results of the optimization studies in Table 1.

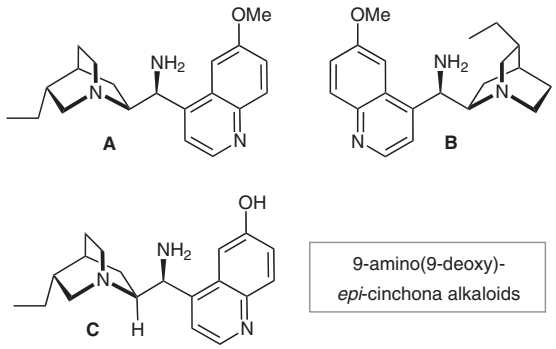
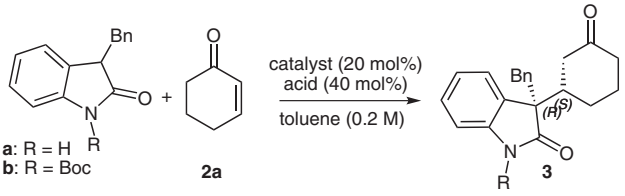


Figure 2 The primary amine catalysts used within this study

Indeed, 20 mol% of catalyst **A** in combination with an acidic co-catalyst (40 mol%) effectively promoted the reaction, furnishing the product with high enantioselectivity but moderate levels of relative stereocontrol (entry 1). All the attempts to improve the diastereoselectivity, either by lowering the reaction temperature or by using an external base to co-catalyze the process, did not reach useful synthetic standards (entries 2 and 3). Next, we focused on using *N*-Boc-protected oxindole **1b** as the nucleophilic component. As expected, the electronic influence of the Boc group greatly improved reactivity, lowering the pK_a of the oxindole.[14] More importantly, the reaction manifold was channelled toward a more diastereo- and enantioselective path (entry 4). This was probably due to steric effects.

When further optimizations were conducted in the presence of multifunctional catalyst **C**,[13c,d] which in principle may simultaneously activate both the electrophilic and nucleophilic components, no improvements were observed (entry 5). Finally, by varying the acidic additives, we found that 10 mol% of the primary amine **A** in combination with benzoic acid (20 mol%) provided the best results, efficiently catalyzing the process in toluene (0.2 M) at room temperature over 24 hours (5.2:1 dr, 96% ee, entry 9). These conditions were selected to examine the scope of the conjugate addition by evaluating a variety of oxindole and cyclic enone combinations (Table 2).

Table 1 Optimization Studies[a]



Entry	Amine	Acid[b]	R	Temp (°C)	Time (h)	Conv.[c] (%)	dr[c]	ee (%)[d]
1	A	*p*-NBA	H	r.t.	72	>95	2.4:1	80 (79)
2	A	*p*-NBA	H	0	72	32	3.5:1	91 (81)
3[e]	A	*p*-NBA	H	0	72	<5	–	–
4	A	*p*-NBA	Boc	r.t.	24	>95	5.5:1	92 (89)
5	C	benzoic	Boc	0	48	37	2.5:1	82 (91)
6	A	NBDP	Boc	r.t.	24	>95	4.2:1	93 (79)
7	A	benzoic	Boc	r.t.	24	>95	5.6:1	97 (84)
8	A	benzoic	Boc	0	48	92	6.6:1	96 (93)
9[f]	A	benzoic	Boc	r.t.	24	>95	5.2:1	96 (84)

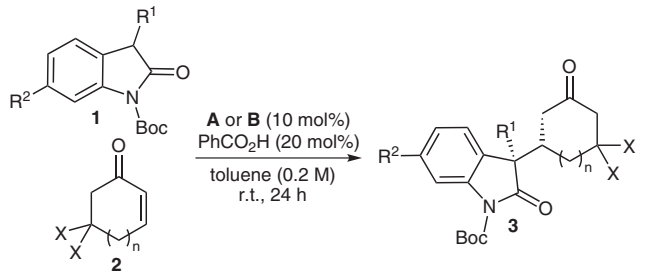
[a] The reactions were carried out on a 0.1 mmol scale with 1.2 equiv of **1** and $[\mathbf{2a}]_0$ = 0.2 M in toluene.
[b] Abbreviations: *p*-NBA, 4-nitrobenzoic acid; NBDP, *N*-Boc-D-phenylglycine.
[c] Determined by ^{1}H NMR analysis of the crude mixture.
[d] Determined by HPLC analysis on chiral stationary phases. Numbers in parenthesis refer to the ee of the minor diastereomer.
[e] Reaction carried out in the presence of 1.5 equiv of DABCO.
[f] 10 mol% of **A** and 20 mol% of benzoic acid was used.

In addition to cyclohexen-2-one **2a** (entries 1 and 2, Table 2), other cyclic enones proved to be suitable substrates. Using the cyclohexenone bearing two methyl groups at the 5-position led to the formation of product **3b** with decreased reactivity but a high degree of stereocontrol (entry 3). While 2-cycloheptenones afforded good results when reacted with oxindole **1b** (entry 5), 2-cyclopentenone followed a remarkably lower enantioselective path (entry 4). Oxindole with a methyl substituent at the 3-position gave similar results in the conjugate additions (entries 6–8). Using the more reactive 3-phenyl oxindole afforded almost perfect enantiocontrol, albeit at the expense of the relative stereochemistry (entry 9). Interestingly, the presented organocatalytic method allowed

the fast and highly stereoselective synthesis of **3h** (entry 10, see also Figure 1), a compound which has shown promising biological properties as an anticancer agent and which has recently been patented by Hoffmann-La Roche.[6d]

Finally, the pseudoenantiomeric catalyst **B**, derived from hydroquinidine, accounted for the possibility of accessing both antipodes of the products **3** (entries 2 and 7). Further investigation demonstrated the possibility of extending the reaction protocol to acyclic enones: reaction of 3-methyl-substituted oxindole with *trans*-4-phenyl-3-buten-2-one afforded the conjugate adduct in 95% ee but poor dr (1.4:1, see Supplementary Information for compound characterization and reaction conditions). As a limitation of the method, β-substituted cyclic enones, which would potentially give rise to challenging vicinal quaternary stereogenic centers, did not react under the described conditions.

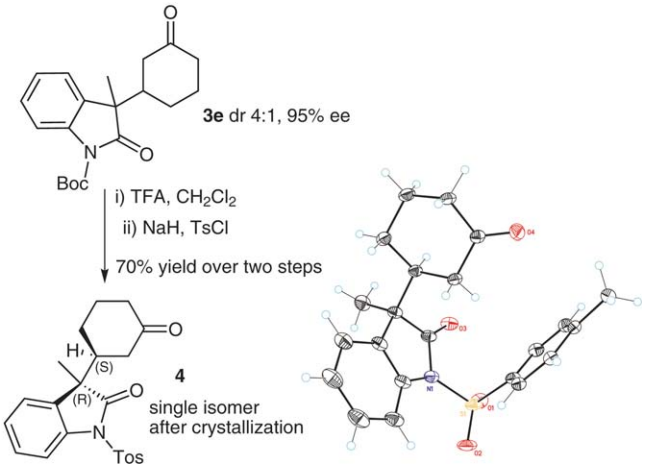
Table 2 Primary Amine Catalyzed Asymmetric Conjugate Addition of *N*-Boc Oxindoles to Cyclic Enones[a]



Entry	R^1, R^2	Catalyst	n, X	3	Yield (%)[b]	dr[c]	ee (%)[d]
1	Bn, H	A	1, H	**3a**	80	5.2:1	96
2	Bn, H	B	1, H	**3a**	94	5.2:1	98[e]
3	Bn, H	A	1, Me	**3b**	30	5.7:1	92
4[f,g]	Bn, H	A	0, H	**3c**	55	5.5:1	46
5[g]	Bn, H	A	2, H	**3d**	62	2.8:1	97
6	Me, H	A	1, H	**3e**	94	4:1	95
7	Me, H	B	1, H	**3e**	94	6:1	97[e]
8[g]	Me, H	A	2, H	**3f**	70	2.5:1	95
9[f]	Ph, H	A	1, H	**3g**	95	1.6:1	98
10	3-ClPhCH$_2$, Cl	A	1, H	**3h**	85	4:1	94

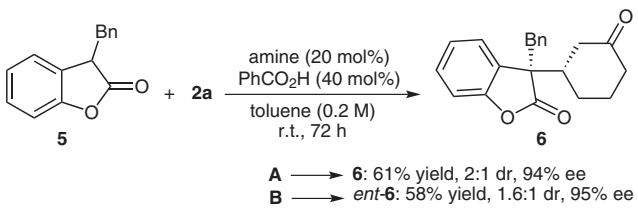
[a] The reactions were carried out at r.t. on a 0.2 mmol scale with 1.2 equiv of **1** and $[\mathbf{2}]_0$ = 0.2 M in toluene.
[b] Isolated yield (sum of diastereomers).
[c] Determined by ^{1}H NMR analysis of the crude mixture.
[d] Determined by HPLC analysis on chiral stationary phases.
[e] The opposite enantiomer of **3** has been obtained.
[f] Reaction at 0 °C.
[g] Reaction carried out in the presence of 20 mol% of the catalyst over 48 h.

To determine the stereochemical outcome of the reaction, diastereomeric **3e** was deprotected and further converted to the *N*-Tos derivative **4**. Crystals from **4** were suitable for X-ray analysis, which unambiguously established the relative as well as the absolute configuration for the major diastereomer (Scheme 1).[15]



Scheme 1 X-ray structure of the *N*-Tos derivative **4**[15]

Last, we wondered if the organocatalytic method could be extended to benzofuranone derivative **5**, a compound type that had not previously been explored in the context of asymmetric catalytic conjugate additions.[16] We tested the reaction of 3-benzyl benzofuranone **5** with cyclohexen-2-one **2a** under the catalysis of amines **A** and **B** (Scheme 2). Notably, both the antipodes of the corresponding product **6** bearing a quaternary stereocenter were prepared with good chemical yield and high enantioselectivity.



Scheme 2 Asymmetric synthesis of benzofuranone derivative bearing contiguous quaternary and tertiary stereocenters

In summary, we have presented a novel and easy way to access densely functionalized molecules that contain vicinal quaternary and tertiary stereocenters.[17] In view of the abundance of important indole- and benzofuranon-derived natural products bearing a quaternary stereocenter in the 3-position of the heterocycle, we believe this method could be useful in asymmetric synthesis. The research is based on the development of the first, highly stereoselective addition of oxindole to cyclic enones, using a readily available chiral primary amine catalyst. Moreover, we have extended asymmetric organocatalytic transformations to include an unprecedented compound class, benzofuranone derivatives. We expect these nucleophilic compounds will find application in other asymmetric

transformations aimed at preparing valuable nature-inspired compounds.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) **General Procedure**
All the reactions were carried out with no precautions to exclude moisture in undistilled toluene. In an ordinary vial equipped with a magnetic stir bar, amine **A** or **B** (0.02 mmol, 6.5 mg, 10 mol%) and benzoic acid (0.04 mmol, 4.9 mg, 20 mol%) were dissolved in toluene (1 mL). After stirring at r.t. for 10 min, the cyclic enones **2** (0.2 mmol) was added, followed by the addition of oxindole **1** or benzofuranone **5** (0.24 mmol, 1.2 equiv). The vial was sealed, and the mixture

stirred for 1 d at r.t. The crude mixture was diluted with CH_2Cl_2 and flushed through a short plug of silica, using CH_2Cl_2–EtOAc (1:1) as the eluent. Solvent was removed in vacuo, and the Michael adduct **3** or **6** was purified by flash column chromatography (silica gel, hexane–EtOAc). All new compounds gave satisfactory spectroscopic and analytical data. As a typical example, the data of the compound **3a** are given.

(*R*)-*tert*-Butyl 3-Benzyl-2-oxo-3-[(*S*)-3-oxocyclohexyl]-indoline-1-carboxylate (3a, Entry 1, Table 2)

Isolated as a mixture of diastereomers (5.2:1 dr) by column chromatography (hexane–acetone = 90:10) in 80% yield. The ee (96% ee) was determined by HPLC on a chiral stationary phase [Chiralpak AD-H; hexane–*i*-PrOH (98:2); 0.50 mL/min; λ = 214, 254 nm; t_R = 34.1 min(major), 41.7 min (minor, based on the racemic mixture)]; $[\alpha]_D^{rt}$ –17.37 (*c* 0.98, $CHCl_3$, dr = 5.2:1, 96% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47–1.64 (m, 2 H), 1.55 (s, 9 H), 1.70–1.81 (m, 1 H), 1.97–2.12 (m, 1 H), 2.15–2.32 (m, 1 H), 2.32–2.50 (m, 2 H), 2.55–2.61 (m, 2 H), [CH_2 A-B type spectrum (3.04, d, 1 H, J_{gem} = –12.8 Hz), (3.30, d, 1 H, J_{gem} = –12.8 Hz)], 6.72–6.77 (m, 2 H), 6.93–7.06 (m, 3 H), 7.13–7.31 (m, 3 H), 7.52–7.57 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1 (CH_2), 26.4 (CH_2), 28.3 (3× CH_3), 41.4 (CH_2), 42.2 (CH_2), 43.0 (CH_2), 46.2 (CH), 57.4 (C), 84.3 (C), 115.0 (CH), 123.6 (CH), 124.4 (CH), 126.9 (CH), 127.9 (CH), 128.6 (CH), 129.3 (C), 130.0 (CH), 135.1 (C), 140.3 (C), 148.8 (C), 177.2 (C), 210.6 (C). HRMS (EI): *m/z* calcd for $C_{26}H_{29}NO_4$: 419.2096; found: 419.2092.