Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201300695

Asymmetric Michael Addition of Oxindoles to Allenoate Catalyzed by *N*-Acyl Aminophosphine: Construction of Functionalized Oxindoles with Quaternary Stereogenic Center

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Received: August 1, 2013; Published online: January 8, 2014

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300695.

Abstract: A novel reaction between ethyl allenoate and oxindoles that enables the asymmetric synthesis of 3,3-bisubstituted oxindoles with our previously established bifunctional *N*-acyl aminophosphine catalysts is reported. These products bearing a chiral quaternary carbon center at the C-3 position of the oxindoles may have potential significance in the synthesis of related structures. The best performance of these processes provides adducts with 92% yield and 94% *ee*.

Keywords: allenoates; asymmetric catalysis; chiral phosphines; Michael addition; oxindoles

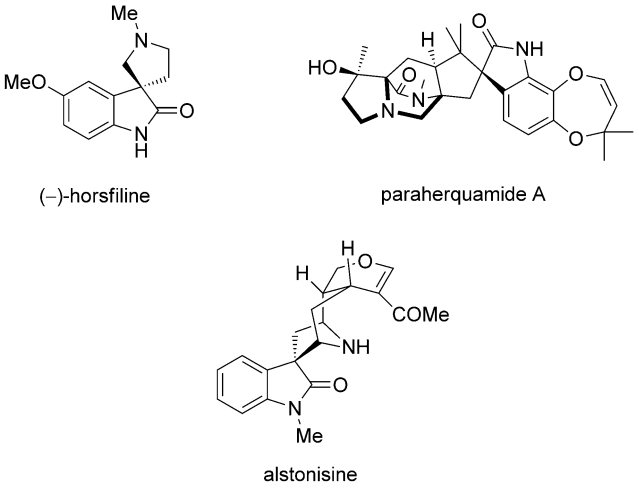
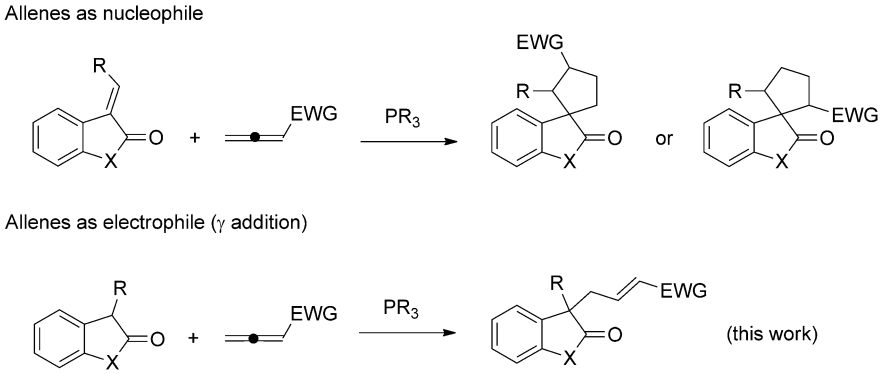


Figure 1. Oxindole structures in natural products.

Oxindoles are important structural skeletons prevalently occurring in many natural products and bioactive molecules.[1] Especially those featuring a stereogenic quaternary carbon center at the C-3 position (Figure 1) have stimulated considerable research enthusiasm due to the great substitution effect on the biological activities of these compounds. Therefore, the development of synthetic routes to construct a C-3 quaternary stereogenic center with control of the absolute configuration is of paramount importance. Recently, many powerful methods have been established using 3-substituted oxindoles, oxindoles, isatins or methyleneindolinones as the starting materials to construct chiral 3,3-disubstituted oxindole derivatives,[2] including a few examples of reactions with allenes in the presence of chiral phosphines as nucleophilic organocatalysts.[3]

The phosphine-catalyzed reactions with allenes have exhibited divergent reactivities derived from the versatility of the zwitterionic intermediate, which could act as a nucleophile or an electrophile, even combined with amphiphiles. When the activated π system acts as nucleophilic species, the reactions with various types of electrophiles like electron-deficient olefins,[4] imines,[5] or aldehydes[6] have been well documented in the literature. As shown in Scheme 1, this strategy has also been applied in the synthesis of spirocyclic oxindoles. On the other hand, upon protonation by a pronucleophile, the zwitterionic intermediate could switch to an γ-addition acceptor, which was first realized using allenoates by Lu in 1995[7] and further developed by Zhang and Fu in asymmetric ways with a variety of nucleophiles (Scheme 1).[8] As

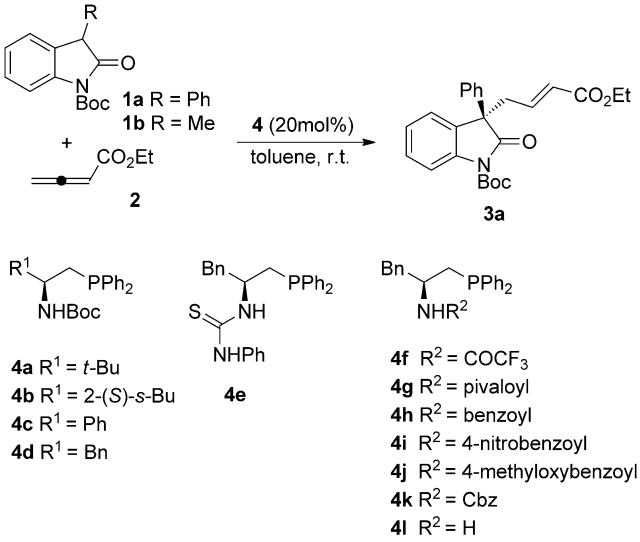


Scheme 1. Cycloadditions and γ-additions of allenoates.

far as we know, no reaction has been discovered with oxindoles through this pathway. Recently, our group has focused on the development of novel and easily accessible bifunctional *N*-acyl aminophosphine catalysts from amino acids, which has unambiguously proved valuable in all sorts of asymmetric cycloaddition reactions with allenoates.[9] As a follow-up of our program to extend the application scope of these versatile catalysts, herein, we present a highly enantioselective γ-addition of 3-substituted oxindoles to ethyl allenoate catalyzed by bifunctional *N*-acyl aminophosphines to construct a quaternary stereogenic center *via* C–C bond formation reactions.

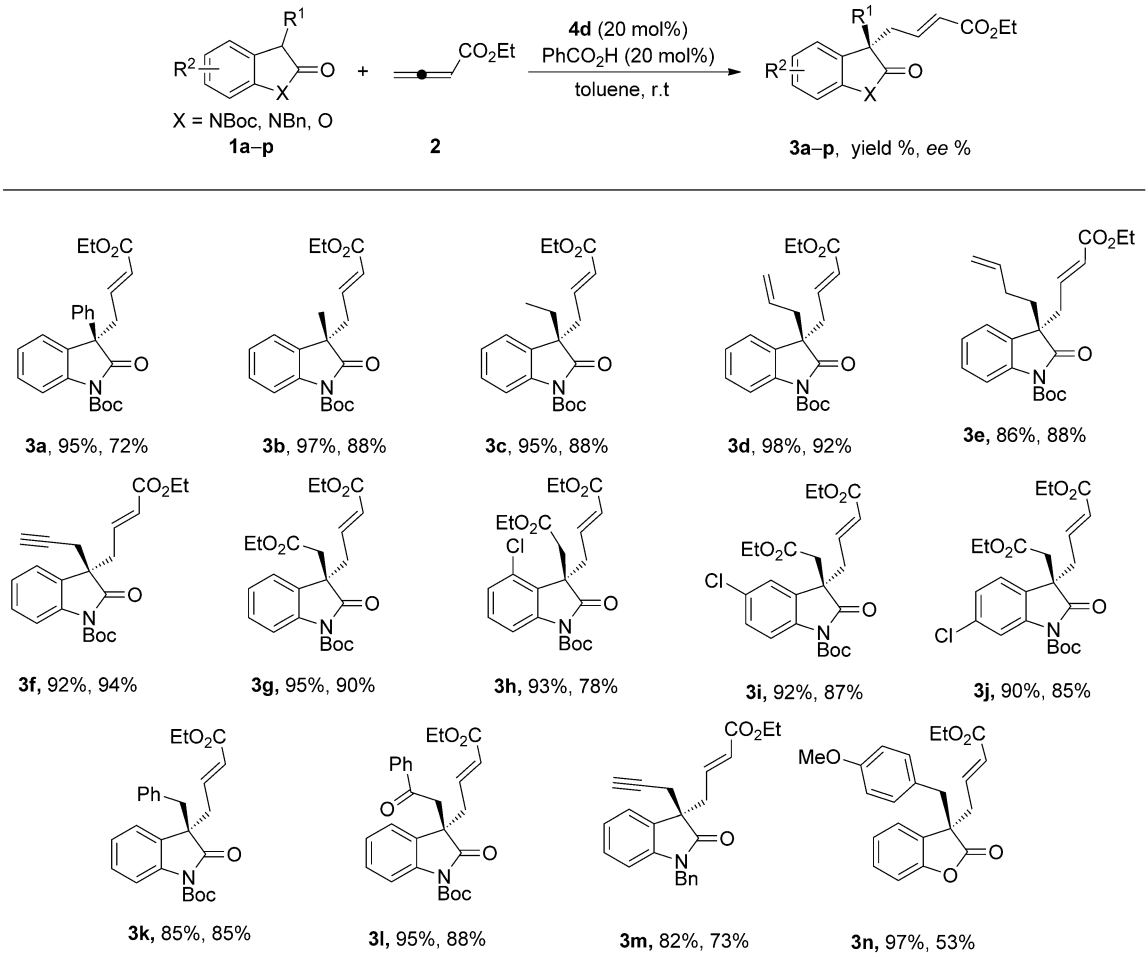
Initially, 3-phenyloxindole **1a** was chosen as pronucleophile in the γ-addition with ethyl buta-2,3-dienoate **2** for evaluation by the catalysts **4a–4l** (Table 1). Four catalysts with different chiral backbones were examined first. It was shown that the chiral backbones of these catalysts have a great effect on the enantioselectivity. The catalyst **4d**, which could be synthesized from phenylalanine in four steps, providing the adduct **3a** in 88% yield and 69% *ee* (Table 1, entry 4). An enhanced hydrogen bonding interaction in the catalyst reduced the enantioselecivity (Table 1, entry 5). Subsequently, an examination of catalysts **4f–4l** with different groups on the nitrogen was carried out (Table 1, entries 6–12). Previous studies[9a,c] have suggested that the hydrogen-bonding effects tuned by these protecting groups played an important role in the transition state with aminophosphine catalysts.[10] Introduction of a trifluoromethyl group into the catalyst **4f**, which means a strong acidity on the NH functionality, turned out to be detrimental to the enantioselectivity, although an excellent yield was obtained (Table 1, entry 6). On the other hand, the catalyst **4l** with a free amine provided a racemic product (Table 1, entry 12). The reactions with other acetyl or benzoyl amides also showed disadvantages in the results (Table 1). Further examinations on catalyst loading and temperature did not give any more satisfactory results (Table 1, entries 13 and 14). We conceived that replacement of the phenyl substituent by

Table 1. Screening of catalysts for the γ addition.[a]



Entry	R	Catalyst	Time [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	**4a**	8	81	7
2	**1a**	**4b**	8	79	49
3	**1a**	**4c**	8	90	40
4	**1a**	**4d**	8	88	69
5	**1a**	**4e**	8	83	19
6	**1a**	**4f**	8	97	9
7	**1a**	**4g**	8	83	7
8	**1a**	**4h**	8	92	57
9	**1a**	**4i**	8	90	57
10	**1a**	**4j**	8	83	45
11	**1a**	**4k**	8	71	60
12	**1a**	**4l**	8	88	0
13	**1a**	**4d**[d]	24	88	60
14	**1a**	**4d**[e]	72	78	65
15	**1b**	**4d**	8	82	80
16	**1b**	**4d**[f]	15	97	88

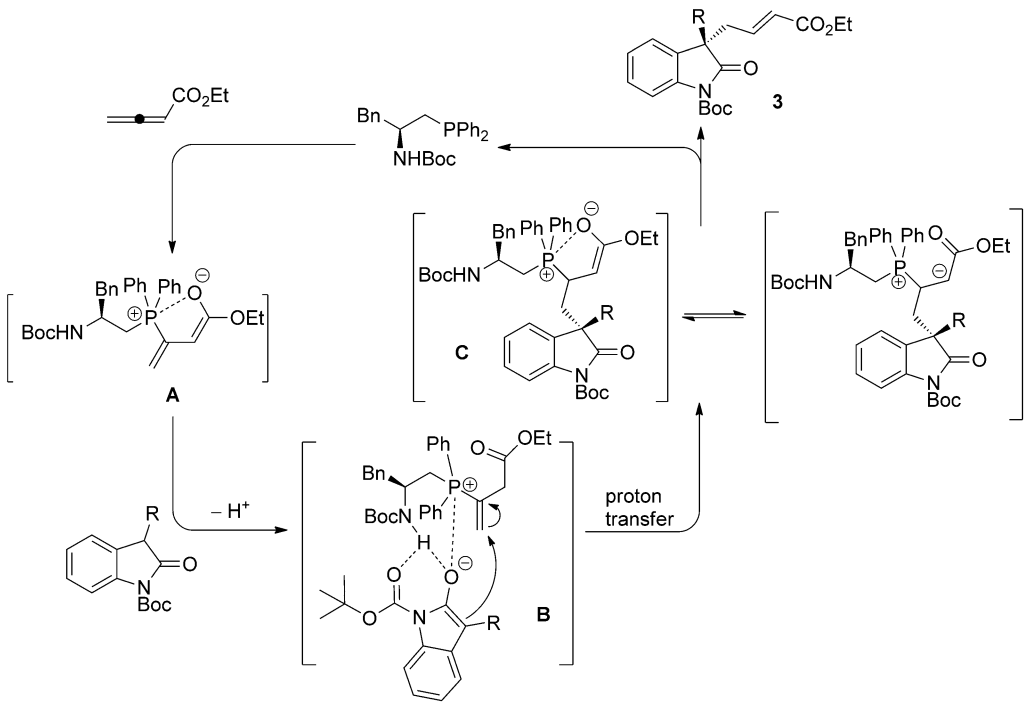
[a] Reactions were carried out with **1** (0.1 mmol, 1.0 equiv.) and **2** (0.2 mmol, 2.0 equiv.) in the presence of catalyst **4** (20 mol%) in toluene (1.0 mL) at room temperature.
[b] Yield of isolated products.
[c] Determined by chiral HPLC analysis.
[d] 10 mol% of **4d** was used.
[e] The reaction was performed at 0 °C.
[f] 20 mol% of benzoic acid was added.



Scheme 2. Enantioselective γ-addition of **2** with oxindole **1**.

a methyl group on the C-3 position of oxindole may reduce the reactivity of the substrate, thus a better stereochemical control may be achieved. To our delight, the desired addition product was isolated with a significant improvement in enantioselectivity (from 69% *ee* to 80% *ee*, Table 1, entry 15). Thus, with 3-methyloxindole **1b** as the new model substrate, the effects of solvents and additives were investigated (see the Supporting Information for details). The solvent screening showed that toluene remained the reaction medium of first choice. In view of the previous reports that acidic additives may enhance the reaction efficiencies,[7,8b,11] we examined several additives in this reaction. Although the reaction required a prolonged time when benzoic acid was utilized as additive, the Michael adduct was attained with up to 97% yield and 88% *ee*.

Having identified the optimal reaction conditions, we then explored the generality of the reaction regarding 3-substituted oxindoles (Scheme 2). As illustrated in Scheme 2, this catalyst system worked well with a range of oxindoles bearing phenyl, alkyl, and ester groups. Generally, the enantioselective umpolung additions proceeded smoothly with good yields in most cases. The 3-methyloxindole **1b** and allenoate **2** underwent γ addition with higher yield and enantioselectivity in the presence of 20 mol% benzoic acid. Allyl-substituted product **3d** was obtained in 98% yield and 92% *ee*. The isatin derivative with an elongated aliphatic chain led to a slight drop in yield and *ee* (product **3e**). Among all tested substrates, the 1-propynyl-substituted ones **3f** provided the best result with 92% yield and 94% *ee*. Subsequently, differently substituted oxindoles in the benzene ring were also surveyed. Most of them gave the corresponding products with good yields and acceptable enantiopurities. The 4-Cl substituted substrate gave its product in a satisfactory yield albeit with an obvious drop in the enantioselectivity. The investigation on the nitrogen protecting group proved that the oxindole with a Boc group was superior to that with a benzyl group in terms of both yield and *ee*. The similar benzofuran substrates evaluated gave inferior results, which indicated that the stereochemical control takes advantage of the carbonyl group of the Boc. The absolute configuration of this γ addition products was determined



Scheme 3. A possible reaction mechanism.

by X-ray crystal structure analysis of **3l** (see the Supporting Information for details)[12].

A possible mechanism accounting for this γ addition was proposed in Scheme 3. The zwitterionic intermediate **A** acted as a Brønsted base to deprotonate the active C-3–H of substrate **1** to generate anion **B**, which attacked the γ position of the phosphonium dienolate intermediate to provide ylide **C**. After the proton transfer and elimination of phosphine catalyst, the oxindole product **3** was obtained. The chirality transfer processes occurred in the C–C bond-forming step in which H-bonding and P–O interaction might play an important role to ensure a special spatial arrangement. Based on the previous mechanistic proposal in related reactions[4e,5d,7,10b,13] and our experimental results, a plausible transition state was proposed. The hydrogen-bonding interaction and P–O attraction might facilitate formation of an ion pair structure between the vinylphosphonium salt and the anionic nucleophile; the benzyl of the dienolate might block the *Si* face of the enolate and make the *Re*-face attack more favourable.

In conclusion, we have developed a novel reaction between allenoates and oxindoles that enables the asymmetric synthesis of 3,3-bisubstituted oxindoles with our previously established bifunctional *N*-acyl aminophosphine catalysts. These processes which featured the construction of a chiral quaternary carbon center at the C-3 position of oxindoles, may have potential significance in the synthesis of related structures of natural occurring products and pharmacologically active molecules. Further studies regarding the development of related reactions and applications are underway and will be reported in due course.

Experimental Section

General Procedure

To a stirred solution of oxindole **1** (0.1 mmol, 1.0 equiv.), catalyst **4** (0.02 mmol, 0.2 equiv.) and benzyl acid (0.02 mmol, 0.2 equiv.) in toluene (1.0 mL) was added ethyl 2,3-butadienoate (0.2 mmol, 2.0 equiv.) *via* syringe in one portion. The reaction solution was stirred at room temperature and monitored by TLC. After the reaction was complete, the mixture was directly purified by column chromatography on silica gel (petroleum ether/EtOAc as the eluent) to furnish the corresponding product **3**.

Acknowledgements

Financial support from National Basic Research Program of China (973 Program, 2010CB833300), the National Natural Science Foundation of China (Nos. 21032006, 203900502, 20532040, 21290180), and the Science and Technology Commission of Shanghai Municipality (11XD1406400) is acknowledged.

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[12] CCDC 941547 contains the supplementary crystallographic data for **3l**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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