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Asymmetric Allylic Alkylation of Isatin-Derived Morita–Baylis–Hillman Carbonates with Nitroalkanes

Guo-Ying Chen, Fangrui Zhong, and Yixin Lu*

Department of Chemistry & Medicinal Chemistry Program, Life Sciences Institute, National University of Singapore, 3 Science Drive 3, Republic of Singapore, 117543

chmlyx@nus.edu.sg

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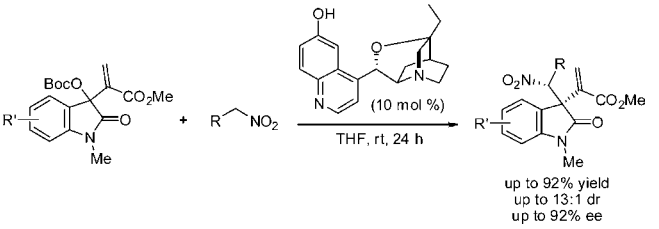
ABSTRACT



A stereoselective allylic alkylation of isatin-derived Morita–Baylis–Hillman (MBH) carbonates with nitroalkanes has been developed. In the presence of 10 mol % β-isocupreidine (β-ICD), 3,3′-disubstituted oxindoles were prepared with moderate diastereoselectivities and excellent enantioselectivities.

3,3′-Disubstituted-2-oxindoles bearing a quaternary stereogenic center[1] are widely present in natural products and bioactive molecules (Figure 1).[2] Because of their importance in biological sciences and synthetic organic chemistry, asymmetric preparation of such structural motifs has drawn much attention.[3] While most reported examples in the literature made use of 3-substituted oxindoles as a nucleophilic reaction partner,[4] approaches employing 3-substituted oxindoles as an electrophile for the construction of 3-quaternary chiral centers are much less common. Recently, Stoltz et al. disclosed a copper-catalyzed enantioselective synthesis of C3-quaternary oxindoles from C3-halooxindoles.[5] Subsequently, Chen and co-workers reported a Lewis base-catalyzed asymmetric allylic alkylation between the Morita–Baylis–Hillman (MBH) carbonates and α,α-dicyanooelfins.[6] Very recently, the same group extended α-angelica lactones as a potential nucleophile for an asymmetric assembly of 2-oxindoles containing a 3-quaternary stereogenic center.[7]

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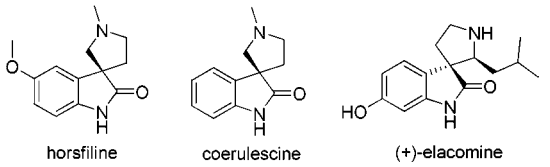


Figure 1. Examples of 3,3′-disubstituted oxindoles.

Asymmetric allylic substitution reaction of MBH adducts with various nucleophiles has been extensively investigated in the past years. While most reactions proceeded via widely accepted $S_N2'-S_N2'$ pathway,[8] alternative pathways leading to different regioisomers have also been reported.[9] Although nitroalkanes are valuable nucleophiles that are widely used in organic synthesis, surprisingly, their reactions with readily available MBH adducts were rarely explored.[10] We recently developed a regioselective and enantioselective allylic substitution of the MBH carbonates with nitroalkanes via an $S_N2'-S_N2$ reaction sequence.[9f] Given the biological importance of oxindole compounds, we were interested in an efficient preparation of 3,3′-disubstituted oxindoles via an allylic alkylation of isatin-derived MBH carbonates with nitroalkanes. Our working hypothesis is illustrated in Scheme 1. A chiral amine catalyst may initiate the reaction by an S_N2' reaction, and the in situ generated *tert*-butoxide can deprotonate nitroalkane substrates, which then add on at the 3-position of oxindoles, creating 3,3′-disubstituted oxindoles.[11]

For the initial screening, we examined the reaction between MBH carbonates **2** and nitromethane in the presence

Scheme 1. Preparation of 3,3′-Disubstituted Oxindoles via Allylic Alkylation of Isatin-Derived MBH Carbonates

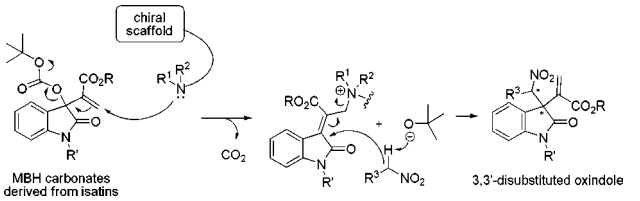
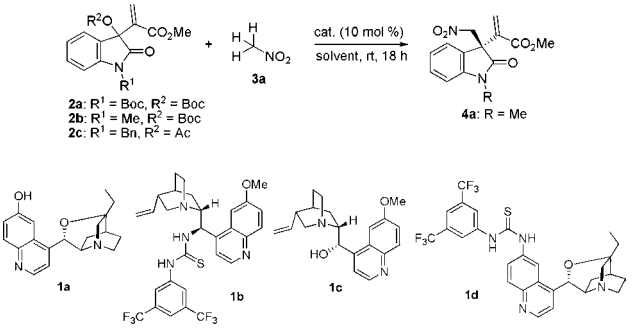


Table 1. Initial Reaction Screenings[a]



entry	**2**	solvent	cat	yield (%)[b]	ee (%)[c]
1	**2a**	THF	**1a**	NR	NR
2	**2b**	THF	**1a**	68	92
3	**2c**	THF	**1a**	NR	NR
4	**2b**	THF	**1b**	NR	NR
5	**2b**	THF	**1c**	NR	NR
6	**2b**	THF	**1d**	90	79
7	**2b**	Et_2O	**1a**	68	83
8	**2b**	CH_2Cl_2	**1a**	55	81
9	**2b**	$CHCl_3$	**1a**	50	65
10	**2b**	toluene	**1a**	68	84
11	**2b**	MeOH	**1a**	<10	64

[a] Reactions were performed with **2** (0.025 mmol), **3a** (0.25 mmol), and the catalyst (0.0025 mmol) in the solvent specified (0.1 mL). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. NR: No Reaction.

of a number of cinchona alkaloid-derived organic catalysts, and the results are summarized in Table 1. The MBH carbonate **2a** with an *N*-Boc group was found to be unsuitable for the reaction (entry 1). Reaction of *N*-methyl MBH carbonate **2b** and nitromethane catalyzed by β-ICD **1a** proceeded smoothly, and the desired substitution product was obtained in moderate yield and with excellent enantiomeric excess (entry 2). When *N*-benzyl MBH acetate **2c** was used, no reaction was observed, since acetate anion was unable to deprotonate nitroalkane **3a** (entry 3). A quick catalyst screening revealed that β-ICD (**1a**) was superior to other catalysts examined (entries 4−6). Solvent screening was then preformed, and THF was identified to be the best solvent for the reaction (entries 7−11).

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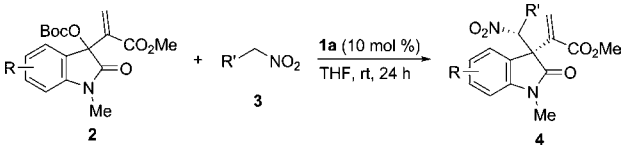
Table 2. Scope of the Reaction[a]



entry	R/R′/4	dr[b]	yield (%)[c]	ee (%)[d]
1	H/H/**4a**		68	92
2	5-Br/H/**4b**		43	92
3	5-Cl/H/**4c**		40	90
4	5-F/H/**4d**		42	90
5	5-MeO/H/**4e**		50	89
6	H/Me/**4f**	2:1	66	90/91
7[e]	H/Me/**4f**	2:1	66	91/88
8	5-Br/Me/**4g**	2:1	55	89/89
9[e]	5-Br/Me/**4g**	2:1	54	98/88
10	5-Cl/Me/**4h**	2:1	54	89/87
11	5-F/Me/**4i**	2:1	54	89/89
12	5-MeO/Me/**4j**	2:1	57	90/85
13[e]	5-MeO/Me/**4j**	2:1	66	91/90
14	7-Cl/Me/**4k**	2:1	62	84/81
15	7-F/Me/**4l**	2:1	50	87/86
16[e]	7-F/Me/**4l**	5:1	52	88/86
17	5,7-Me/Me/**4m**	2:1	55	90/89
18[f]	H/Et/**4n**	10:1	90	88
19[f]	5-MeO/Et/**4o**	13:1	92	89
20[f]	5-Br/Et/**4p**	5:2	70	87

[a] All reactions were performed with **2** (0.025 mmol), **3** (0.25 mmol), and **1a** (0.0025 mmol) in THF (0.1 mL). [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Isolated yield. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Reactions were performed with 0.2 mmol of MBH carbonates in THF (0.4 mL). [f] Reactions were performed without solvent and with 50 equiv of **3**; ee values of the major diastereomers.

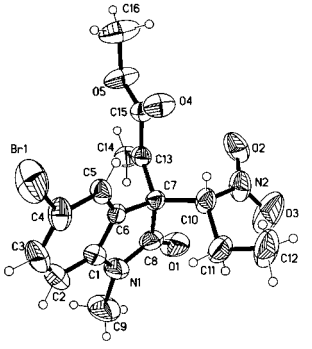
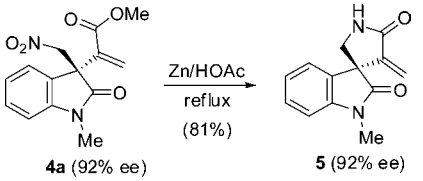


Figure 2. X-ray Structure of **4p**.

The substrate scope and reaction limitation were next studied (Table 2). The reaction between nitromethane and MBH carbonates derived from isatins with different substitutions led to the formation of desired allylation products in excellent enantioselectivities (entries 1−5). Employment of nitroalkanes other than nitromethane is interesting and may be very challenging, as such reaction would create vicinal quaternary and tertiary chiral centers. We were delighted to find that a more sterically hindered nitroethane was suitable for the reaction; the allylic substitution reactions proceeded effectively, giving rise to the products in moderate yields, with excellent ee values and low diastereoselectivities. The diastereomers, however, could be easily separated by column chromatography (entries 6−17). Furthermore, nitropropane turned out to be an excellent substrate, affording the alkylation products in good to excellent yields, high enantiomeric excesses, and up to 13:1 diastereomeric ratio (entries 18−20). The absolute configuration of the products was determined on the basis of X-ray crystallographic analysis of **4p** (Figure 2).

The allylation products are rich in functionality and thus can be readily manipulated for further structural elaborations. As an illustrative example, treatment of **4a** under reductive conditions afforded spirooxindole **5** containing a lactam[5,12] in good chemical yield, without any loss of enantiomeric excess (Scheme 2).

Scheme 2. Synthesis of a Spirooxindole



In conclusion, we have used nitroalkanes for the first time in the asymmetric allylic alkylation reaction with isatin-derived MBH carbonates, yielding allylation products with high enantiomeric excesses. The method described represents a facile approach to access biologically interesting 3,3′-disubstituted oxindole structural motifs. Biological evaluations of our synthetic molecules are underway.

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Supporting Information Available. Representative experimental procedures. HPLC chromatogram, analytical data, X-ray structure of **6p**, and NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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