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Organocatalytic and Electrophilic Approach to Oxindoles with C3-Quaternary Stereocenters

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ABSTRACT

A Lewis base-catalyzed asymmetric allylic alkylation of Morita−Baylis−Hillman carbonates derived from isatins has been investigated, which provides an electrophilic pathway to access oxindoles bearing C3-quaternary stereocenters. Excellent diastereoselectivity and high enantioselectivity have been obtained in the vinylogous functionalization of α,α-dicyanoolefin nucleophiles, giving multifunctional products with vicinal quaternary and tertiary chiral carbon centers.

The development of synthetic protocols that can access quaternary chiral carbon centers remains as one of the most challenging subjects in asymmetric catalysis.[1] The construction of oxindole architectures with a 3,3-disubstituted pattern is of particular importance and attracts continuing interest because such motifs exist in a great amount of natural products and pharmaceutically relevant compounds.[2] Undoubtedly, the application of nucleophilic 3-substituted oxindoles provides the most straightforward and convenient pathway to synthesize the target oxindoles, and a variety of asymmetric reactions have been well presented in the past years.[3] On the other hand, recently Stoltz and co-workers reported an elegant and unusual copper-catalyzed enantioselective synthesis of C3-quaternary oxindoles, in which a highly electrophilic *o*-azaxylylene was involved from C3-halooxindoles in the presence of excess base.[4] Nevertheless, the discovery of an alternative catalytic asymmetric process that employs the oxindole moiety as the electrophilic partner is still in demand.

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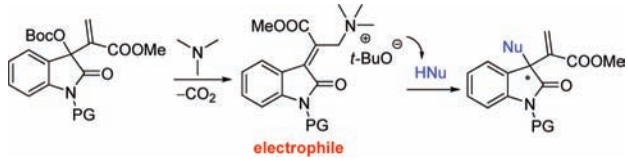
Recently, we[5] and others[6] have developed a number of highly stereoselective allylic alkylation reactions of Morita−Baylis−Hillman (MBH) carbonates or acetates derived from aldehydes by the catalysis of metal-free Lewis basic tertiary amines or phosphines. However, to the best of our knowledge, the utilization of MBH products of ketone substrates, from which a quaternary carbon stereocenter would be generated, has not been reported yet. We wonder whether the MBH carbonates of isatins could be successfully applied in the Lewis base-catalyzed allylic alkylation reaction, and thus an electrophilic approach to afford 3,3-disubstituted oxindoles would be realized.[7] Moreover, the substitution diversity and molecular complexity could be well generated since an array of nucleophiles might be selected (Scheme 1).

Scheme 1. Electrophilic Approach to 3,3-Disubstituted Oxindoles



Inspired by these considerations, we initially investigated the possible C−C bond formation reaction of MBH carbonate **2a**, which was readily prepared from isatin,[8] and a vinylogous nucleophile **3a**,[9] by the catalysis of 1,4-diaza-bicyclo[2.2.2]octane **1a** (DABCO, 10 mol %, Figure 1) at

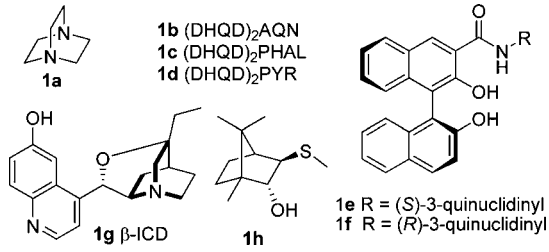
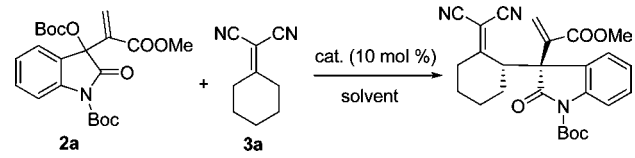


Figure 1. Structures of tested organocatalysts.

ambient temperature. It was pleasing that the reaction proceeded very efficiently in 1,2-dichloroethane (DCE), and the γ-regioselective allylic alkylation product **4a** was isolated in quantitative yield in less than 10 min (Table 1, entry 1),

Table 1. Screening Studies of Asymmetric Allylic Alkylation of MBH Carbonates from Isatin[a]



entry	cat.	temp (°C)	solvent	t (h)	yield[b] (%)	ee[c] (%)
1	**1a**	rt	DCE	0.1	99	/
2	**1b**	50	DCE	24	/	/
3	**1c**	50	DCE	24	/	/
4	**1d**	50	DCE	24	/	/
5	**1e**	50	DCE	24	/	/
6	**1f**	50	DCE	24	/	/
7	**1g**	50	DCE	17	74	50
8	**1h**	50	DCE	24	54	<5[d]
9	**1g**	50	CCl_4	10	99	75
10	**1g**	50	THF	10	46	69
11	**1g**	50	toluene	14	74	79
12	**1g**	50	m-xylene	11	76	80
13	**1g**	50	mesitylene	11	75	80
14	**1g**	50	$PhCF_3$	35	86	75
15	**1g**	rt	m-xylene	36	78	82
16	**1g**	−10	m-xylene	36	88	83
17	**1g**	−20	m-xylene	96	25	/

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2a**, 0.12 mmol of **3a**, and 10 mol % of **1** in 0.5 mL of solvent. [b] Isolated yield. [c] Based on chiral HPLC analysis; in general, dr >99:1. [d] dr = 1.6:1.

also with excellent diastereoselectivity (dr >99:1). Subsequently, we intended to develop an enantioselective variant. Unfortunately, a number of modified cinchona alkaloids **1b**−**1f**, which have afforded good results in the asymmetric allylic alkylation of MBH carbonates from aldehydes,[5] exhibited no catalytic activity in the model reaction even at higher temperature, probably because they could not initiate the catalytic cycle for the steric reasons (entries 2−6). To our gratification, another known chiral tertiary amine derived from quinidine, β-ICD **1g**,[6b,e] demonstrated high catalytic efficacy and delivered moderate enantiocontrol (entry 7). A sulfide compound **1h** could promote the allylic alkylation reaction, but poor diastereo- and enantioselectivity were observed (entry 8).[10] Then, more reaction conditions were screened with **1g** to improve the enantioselectivity. It was found that solvent had dramatic effects on the outcomes (entries 9−14), and higher ee values could be obtained in arene materials (entries 11−13). The reaction could be

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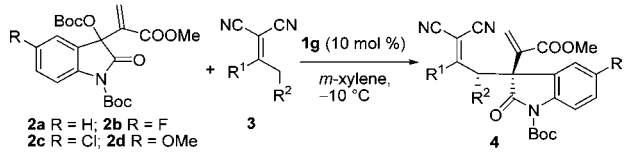
smoothly conducted at room temperature in *m*-xylene (entry 15), and more satisfactory results were attained at −10 °C (entry 16). Nevertheless, further decreasing the reaction temperature resulted in very sluggish conversion (entry 17). Some additives were further explored, but the superior results have not been obtained.[11]

Consequently, the substrate scope and limitations were explored under the optimal conditions. The results were summarized in Table 2. At first, a spectrum of α,α-dicyanoolefins derived from ketones (Figure 2) was investigated.[12] In general, excellent diastereoselectivity was attained in the tested reactions. The vinylogous nucleophiles **3a**−**3g** derived from cyclic aliphatic or aromatic ketones could be well tolerated, affording products with high yields and good enantioselectivity (Table 1, entries 1−7), except for substrate **3b** from cyclopentone, which delivered moderate yield due to the double allylic alkylation (entry 2). On the other hand, good results were normally obtained from α,α-dicyanoolefins **3h**−**3m** derived from acyclic ketones (entries 8−13). It should be pointed out that incomplete conversion was observed for substrate **3l** from *tert*-butyl methyl ketone due to steric hindrance (entry 12). In addition, poor regioselectivity was given when **3m** from unsymmetrical ethyl methyl ketone was applied, while both adducts could be easily separated (entry 13). We also investigated the substitution effect on the aryl ring of the oxindole moiety. Satisfying data were provided for substrates **2b** and **2c** bearing electron-withdrawing groups (entries 14 and 15). Nevertheless, slightly lower reactivity was observed for **2d** with the electron-donating group, while the similar ee value was gained (entry 16). It was noteworthy that almost all products were solid, thus the enantiomerically pure material could be easily obtained by recrystallization (see entry 8, data in parentheses).

Table 2. Substrate Scope and Limitations[a]



entry	2	3	*t* (h)	yield[b] (%)	ee[c] (%)
1	**2a**	**3a**	36	**4a**, 88	83
2[d]	**2a**	**3b**	46	**4b**, 50	80
3	**2a**	**3c**	47	**4c**, 89	78
4	**2a**	**3d**	60	**4d**, 84	80
5	**2a**	**3e**	60	**4e**, 96	79
6	**2a**	**3f**	24	**4f**, 81	87
7	**2a**	**3g**	35	**4g**, 98	82[e]
8	**2a**	**3h**	60	**4h**, 82 (69)[f]	80 (98)[f]
9[g]	**2a**	**3i**	69	**4i**, 64	85[h]
10	**2a**	**3j**	45	**4j**, 88	88
11[i]	**2a**	**3k**	60	**4k**,70	85
12[i]	**2a**	**3l**	96	**4l**, 38	77
13[d]	**2a**	**3m**	43	**4m**, 50 (**4m′**, 38)[j]	81 (75)[j]
14	**2b**	**3a**	40	**4n**,83	85
15	**2c**	**3a**	65	**4o**, 82	85
16	**2d**	**3a**	50	**4p**, 60	82

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2**, 0.12 mmol of **3**, and 10 mol % of **1g** in *m*-xylene (0.5 mL) at −10 °C. [b] Isolated yield. [c] Based on chiral HPLC analysis; in general, dr >99:1 (if involved). [d] 0.2 mmol of **3b** was used. [e] The absolute configuration of **4g** was determined by X-ray analysis (see Figure 3). The other products were assigned by analogy. [f] Data in parentheses referred to recrystallization. [g] At rt. [h] dr = 83:17. [i] At 0 °C. [j] Data in parentheses referred to the regioselective product.

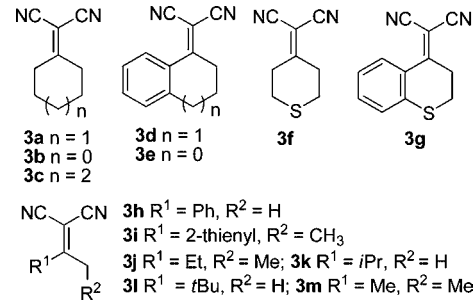


Figure 2. Structures of vinylogous nucleophiles.

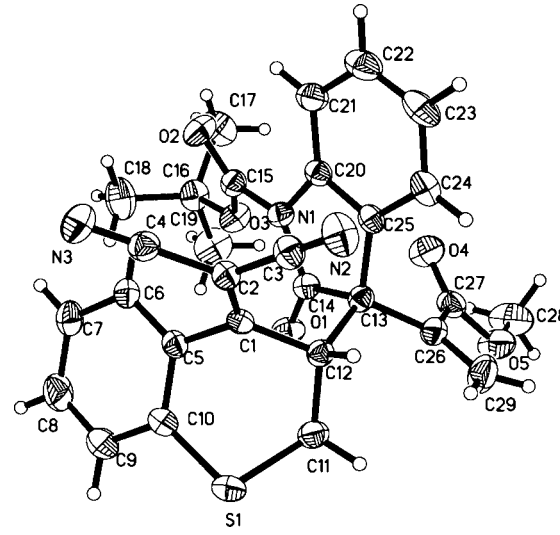


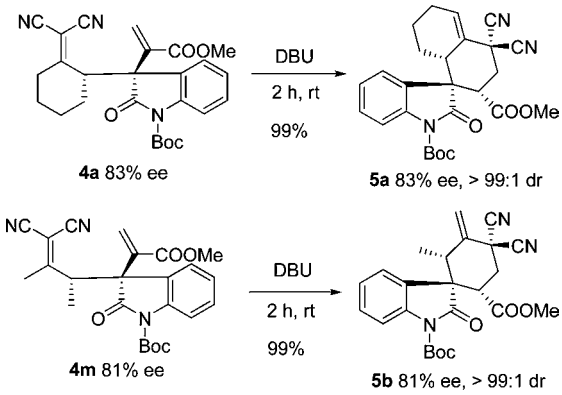
Figure 3. X-ray structure of enantiopure **4g**.

The multifunctional allylic−allylic products could be efficiently converted to spirocyclic oxindoles with high molecular complexity.[13] As illustrated in Scheme 2, in the presence of DBU, an intramolecular Michael addition of **4a** efficiently proceeded to give tetracyclic oxindole **5a** without loss of enantiopurity. Importantly, the annulation reaction exhibited remarkable diastereoselectivity, and the isomerization of the double bond also showed exclusive

(11) (*S*)-BINOL (50%, 85% ee), (*R*)-BINOL (55%, 84% ee), 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea(61%, 85% ee), $LiClO_4$ (<20% yield).

(12) α,α-Dicyanoolefins derived from aldehydes failed to give the desired products.

Scheme 2. Synthesis of Spirocyclic Oxindoles



regioselectivity.[5a] The same diastereocontrol was also observed for product **4m** derived from acyclic substrate, and an interesting spirocyclic compound **5b** bearing an *exo*-methylene group was cleanly and quantitatively isolated.

In conclusion, we have developed the first Lewis base-catalyzed allylic alkylation reaction of Morita−Baylis−Hillman carbonates from isatins and nucleophilic α,α-dicyanoolefins, which provides an electrophilic process to oxindoles with C3-quaternary stereocenters. β-ICD demonstrated to be a good chiral inducer for the asymmetric transformations, and excellent diastereoselectivity (up to >99:1 dr) and good enantioselectivity (up to 88% ee) have been obtained for an array of products with high molecular complexity. We believe that the synthetic strategy presented herein might be expanded to construct valuable oxindoles with more structural diversity.[14] The results will be reported in due course.

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Supporting Information Available: Experimental procedures, structural proofs, NMR spectra, and HPLC chromatograms of the products and cif file of enantiopure **4g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Currently, moderate enantioselectivity has been obtained when other nucleophiles, such as malononitrile, were applied by the catalysis of β-ICD (71% yield, 59% ee); see the Supporting Information.