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Access to Spirocyclic Oxindoles via N-Heterocyclic Carbene-Catalyzed Reactions of Enals and Oxindole-Derived α,β-Unsaturated Imines

Kun Jiang, Bhoopendra Tiwari, and Yonggui Robin Chi*

Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

robinchi@ntu.edu.sg

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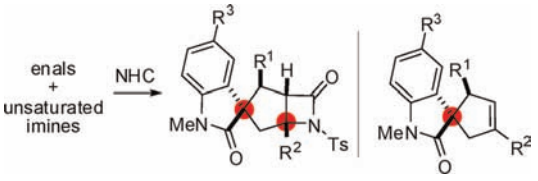
ABSTRACT



A diastereoselective access to β-lactam fused spirocyclic oxindoles and related compounds bearing all carbon spiro centers is described. This N-heterocyclic carbene-catalyzed process employed challenging β,β-disubstituted α,β-unsaturated imines to react with enals.

Spirocyclic oxindole is a class of unique scaffolds widely present in naturally occurring alkaloid-type products[1] and synthetic molecules[2] of interesting bioactivities (Figure 1). The synthesis of spirocyclic oxindoles has received considerable attention employing various methods such as Heck reactions,[3] cyclopropane expansions,[4] Diels–Alder reactions,[5] and [3 + 2] cycloadditions.[6] Recently with small organic molecule catalysts, a set of spirocyclic oxindole core structures has been constructed by the groups of

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Barbas,[7] Melchiorre,[8] Chen,[9] Gong,[10] Williams,[11] Scheidt,[12g] Lu,[12h] Wang,[12d,i] and others[12] using secondary amine, cinchona alkaloid, phosphine, or phosphoric acid catalysts. With N-heterocyclic carbene (NHC) catalysis,[13] the reactions of aldehydes, enals, or ketenes with isatins as activated ketone electrophiles can afford hetero-spirocyclic oxindoles (oxindole β- or γ-lactones), as disclosed by the groups of Nair[14] and Ye.[15] Built on the development of NHC-catalyzed enal activations by Bode, Glorius, Scheidt, Nair, Rovis, You, and others,[16] we are interested in the catalytically generated enal-derived homoenolate intermediates

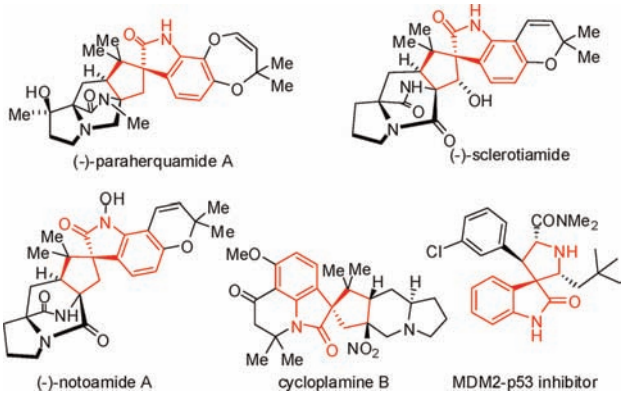
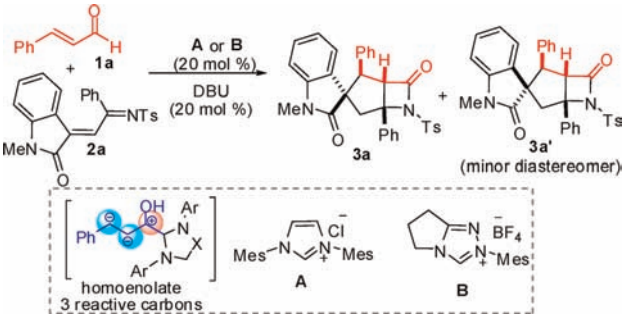


Figure 1. Examples of natural products and synthetic inhibitors containing spiro oxindole scaffolds.

containing three reactive carbons to build relatively sophisticated molecules.[17] Here we report an NHC-catalyzed synthesis of spiroindoles containing two quaternary carbons with one all carbon spiro center (Table 1). The catalytic reaction involves a cascade process of the three consecutive reactive carbons of enals and oxindole-derived β,β-disubstituted α,β-unsaturated imines. The postulated reaction pathway is similar to that reported by Bode et al. in related reactions between enals and β-monosubstituted unsaturated imines.[16i]

Table 1. Optimization of a Model Reaction[a,b]



entry	solvent	t (h)	yield[c] (%)	dr[d]
1[e]	THF	24	0[h]	
2	THF	1	93	82:18
3	CH_2Cl_2	2	78	86:14
4	CH_3CN	24	0[h]	
5[f]	THF/CH_3CN (1:1)	24	97	92:8
6[g]	THF/CH_3CN (3:1)	4	97	95:5

[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), **B** (0.02 mmol), solvent (1.0 mL) at rt. [b] For the results of the reactions on 0.5 and 1.0 mmol scales of **2a**, see ref 19. [c] Isolated yield of combined diastereomers (**3a** and **3a′**) based on **2a**. [d] dr (**3a**:**3a′**) determined via ^{1}H NMR of unpurified reaction mixture; relative stereochemistry of both diastereomers was determined via X-ray structures of **3a** and **3a′**.[18] [e] Used NHC precatalyst **A**. [f] THF/CH_3CN (1.0 mL + 1.0 mL). [g] THF/CH_3CN (1.5 mL + 0.5 mL). [h] No detectable formation of product via TLC and ^{1}H NMR analysis of crude reaction mixture.

Our initial studies using cinnamaldehyde (**1a**) and oxindole-derived β,β-disubstituted unsaturated imine **2a** as model substrates are briefed in Table 1. The imidazolium-based precatalyst **A**, previously used in enal activations,[13,14,16a−16c,16j,16k,16m,16p] was not effective in this reaction (Table 1, entry 1). When the triazolium-based catalyst **B** was used, the desired spiroindole product **3a** could be obtained in excellent isolated yield with 82:18 dr (Table 1, entry 2). Given the fact that simple β,β-disubstituted α,β-unsaturated imines or ketones were unreactive

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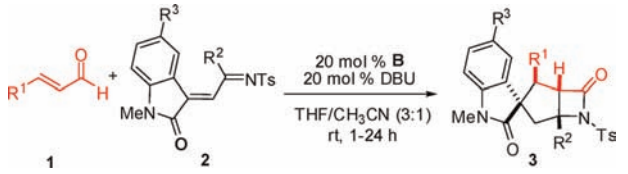
Table 2. Synthesis of Spirocyclic Oxindole **3**[a]



3	1, R^1	2, R^2, R^3	time (h)	yield (%)[b]	dr[c]
3b	4-BrC_6H_4	**2a**	3	93	9/1
3c	3-FC_6H_4	**2a**	3	89	9/1
3d	3-OMe, 4-$AcOC_6H_3$	**2a**	4	85	9/1
3e	4-MeC_6H_4	**2a**	4	93	8/1
3f[d]	4-$OMeC_6H_4$	**2a**	4	69	7/1
3g	2-naphthyl	**2a**	3	94	9/1
3h	2-furyl	**2a**	6	76	6/1
3i	Me	**2a**	2	90	2/1
3j	*n*-Pr	**2a**	1	93	2/1
3k	**1a**	4-BrC_6H_4, H	3	96	12/1
3l	**1a**	4-ClC_6H_4, H	4	94	9/1
3m	**1a**	4-FC_6H_4, H	3	90	12/1
3n	**1a**	4-PhC_6H_4, H	3	86	8/1
3o	**1a**	4-MeC_6H_4, H	2	77	6/1
3p[e]	**1a**	Ph, Br	24	72	9/1
3q[e]	**1a**	Ph, Cl	24	70	4/1
3r	**1a**	Ph, Me	2	91	9/1

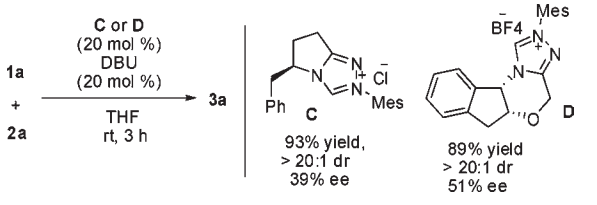
[a] Unless otherwise noted, reactions were performed with **1** (0.12 mmol), **2** (0.1 mmol), **B** (0.02 mmol), DBU (0.02 mmol), and THF/CH_3CN (1.5 mL + 0.5 mL). [b] Isolated yield (with a trace of minor diastereomers in some cases). [c] Determined via ^1H NMR of unpurified reaction mixture. [d] **B** (0.03 mmol), DBU (0.03 mmol). [e] **B** (0.04 mmol), DBU (0.04 mmol).

toward enals in NHC catalysis (see the Supporting Information), we were very delighted to see this challenging homoenolate addition to the sterically hindered β-carbon of **2a** to generate an all carbon quaternary center. Further condition optimizations indicated both the bases and solvents could significantly affect the reaction yields and diastereoselectivities (see the Supporting Information). Finally, by using a mixture of THF and CH_3CN as the solvents and DBU as the base, the reaction could afford **3a** with 97% yield and 95:5 dr (Table 1, entry 6).[18,19]

We next evaluated the scope of the reactions with respect to both the enal and the unsaturated imine substrates for the formation of the spiro bicyclic lactam products **3** (Table 2). Enals with β-(hetero)aryl substituents all gave the products in excellent yields and dr (Table 2, **3b**–**h**). One notable deviation was that when β-aryl enal with a strong electron-donating substituent (MeO) on the phenyl group was used, a drop in yield was observed (Table 2, **3f**). β-Alkyl enals reacted as well, albeit with relatively lower diastereoselectivity (**3i** and **3j**). The imines (**2**) bearing both electron-withdrawing and -donating functionalities (R^2) were found to be excellent substrates and gave the desired products in high yields and diastereoselectivities (**3k**–**o**). Reactions were slower with imines having R^3 as electron-withdrawing substituents (**3p** and **3q**) and required a higher catalyst loading compared to that using an imine with an electron-donating methyl substituent (Table 2, **3r**).

Our attempt to realize asymmetric reactions led to moderate enantioselectivites (Scheme 1). The sterically hindered β,β-disubstituted α,β-unsaturated imines (as well as the analogous enones) pose relatively low reactivities and have remained as challenging substrates in NHC catalysis. The currently explored chiral NHC catalysts (designed mainly for substrates such as β-monosubstituted enones and unsaturated imines)[13,16d–16g,16i,16l,16o] showed moderate enantioselectivities in our reactions after extensive optimizations. The product **3a** was obtained in 89% yield and 51% ee using the aminoindanol-derived catalyst **D** (Scheme 1).

Scheme 1. Enantioselective Synthesis of **3a**



The β-lactam adduct **3a**, stable at room temperature and with typical handlings (such as SiO_2 chromatography),

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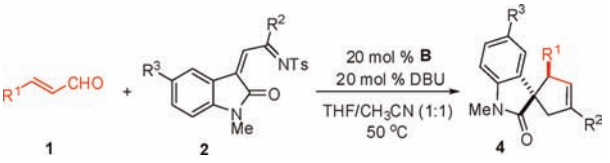
(18) The relative configurations of **3a**, **3a′**, **6**, and **8** were determined via X-ray analysis (see the Supporting Information). CCDC 865692 (**3a**), CCDC 865695 (**3a′**), CCDC 865694 (**6**), and CCDC 865693 (**8**) contain the supplementary crystallographic data.

(19) The reactions of **2a** on 0.5 mmol (208 mg) and 1.0 mmol (416 mg) scale under the conditions as in Table 1 (entry 6) gave the desired product **3a** in 84% and 81% yields, respectively, and 9:1 dr in both cases.

(20) For elegent enantioselecitive approaches to this type of oxindole spirocyclopentenes, see: (a) Voituriez, A.; Pinto, N.; Neel, M.; Retailleau, P.; Marinetti, A. *Chem.—Eur. J.* **2010**, *16*, 12541–12544. (b) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672–4675. (c) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837–7841.

was found to undergo a facile conversion to cyclopentene[20] **4a** (Table 3) at elevated temperatures. We later found that isolation of the lactam **3a** was not necessary; the NHC catalytic reactions carried out at 50 °C efficiently afforded **4a** (Table 3). This cyclopentene-forming reaction likely proceeded through a process similar to the decarboxylations observed in the related β-lactones derived from β-monosubstituted enones and enals.[16d,f,h,l] Both electron-rich and -deficient (hetero)aryl and alkyl enals reacted smoothly with various unsaturated imines to produce spirocyclopentene–oxindoles in good yields and diastereoselectivities (Table 3).

Table 3. Synthesis of Spirocyclopentene Oxindole **4**[a]



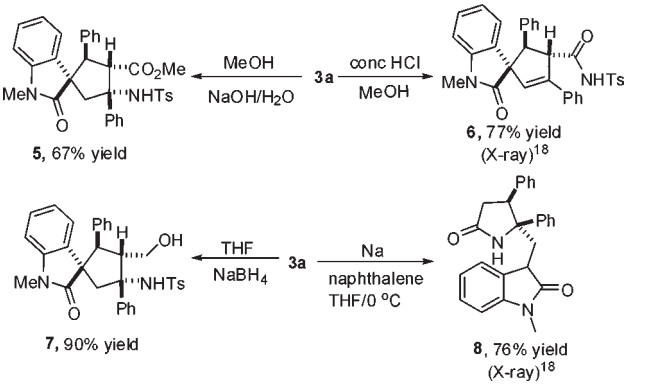
4	1, R^1	2, R^2, R^3	time (h)	yield[b] (%)	dr[c]
4a	**1a**	**2a**	9	93	9/1
4b	4-BrC_6H_4	**2a**	9	92	13/1
4c	4-MeC_6H_4	**2a**	9	91	12/1
4d	2-furyl	**2a**	9	52	6/1
4e	Me	**2a**	9	62	6/1
4f	**1a**	4-BrC_6H_4,H	7	66	17/1
4g	**1a**	4-MeC_6H_4,H	9	61	9/1
4h[d]	**1a**	Ph, Cl	24	63	13/1
4i	**1a**	Ph, Me	2	91	9/1

[a] Reaction conditions: **1** (0.12 mmol), **2** (0.10 mmol), **B** (0.02 mmol), DBU (0.02 mmol), THF/CH_3CN (1.0 mL + 1.0 mL). [b] Isolated yield (with trace of minor diastereomers in some cases). [c] Determined via ^1H NMR of unpurified reaction mixture. [d] **B** (0.04 mmol), DBU (0.04 mmol).

A few potentially useful synthetic transformations of the β-lactam products (**3**) were also examined (Scheme 2). For example, hydrolysis of the lactams (e.g., **3a**) under basic conditions could give protected cyclic β-amino acids (e.g., **5**) that are privileged building blocks for non-natural peptidic mimics (foldamers) of interesting properties.[21] Under acidic conditions, a retro-alkene amination adduct **6**, a substituted spiro cyclopentene, was obtained in good yield. On reduction with $NaBH_4$, **3a** produced cyclic γ-amino alcohol **7**. Under the conditions of Na/naphthalene,

(21) For a review, see: Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232.

Scheme 2. Synthetic Transformations of **3a**



an unexpected rearrangement of **3a** was observed to give pyrrolidinone **8** as a single diastereomer containing one quaternary carbon center. Such pyrrolidine derivatives are expected to have some applicatons in catalysis or as synthetic building blocks. The exact pathway of this transformation remains unclear at this point.

In summary, we have developed a diastereoselective method for a facile access to spirocyclic oxindoles containing two quaternary carbons including an all carbon spiro center. The reactions proceeded through enal-derived NHC-bounded homoenolate intermediates bearing three consecutive reactive carbons. Oxindole-derived α,β-unsaturated imines with β,β-disubstituents were used as the substrates. Ongoing work in our laboratory includes the evaluation of other challenging (e.g., sterically demanding) substrates under NHC catalysis, and the development of new catalytic strategies to control the enantioselectivities for this class of substrates that lead to products with chiral quaternary (spiro)carbon centers.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.