Asymmetric Catalysis

DOI: 10.1002/ange.200902093

Chemoselective Asymmetric N-Allylic Alkylation of Indoles with Morita–Baylis–Hillman Carbonates**

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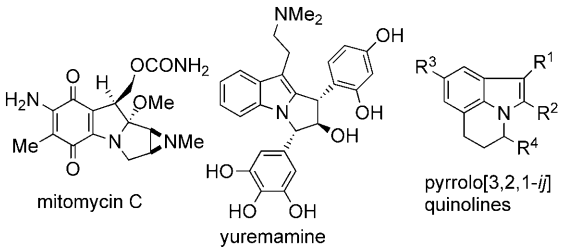
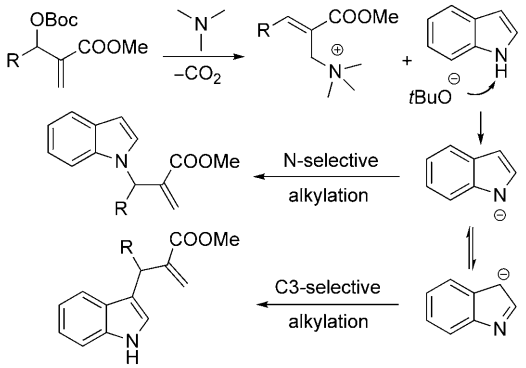
The indole framework represents a key structural motif in a large number of biologically active natural products and pharmaceutical compounds.[1] Consequently, modifications on the indole structure,[2] including the development of enantioselective variants,[3] have triggered increasing interests. Because of the inherent nucleophilic characteristics of indole compounds, their reactions preferentially take place at the C3-position of the ring system. As a result, the majority of enantioselective reactions of indoles focus on the C3-selective addition of electron-rich indoles to electrophilic imines, epoxides, carbonyl compounds, α,β-unsaturated carbonyl compounds, and nitroalkenes etc., thus leading to the formation of diversely structured enantioenriched C3-functionalized indole derivatives.[4] Recently, the enantioselective synthesis of C2-substituted indoles has also been realized through the asymmetric alkylation of 4,7-dihydroindoles and subsequent oxidation.[5]

In sharp contrast to the progress in enantioselective alkylation at the C3- or C2-positions, the asymmetric N-alkylation of indoles has been underdeveloped: probably because of the privileged C3-chemoselectivity of indole compounds. The limited examples include the palladium-catalyzed N-allylic alkylation of 3-substituted indoles developed by Trost et al.[6a] and the enantioselective intramolecular aza-Michael addition of tethered indole-2-carboxylates under chiral phase-transfer catalysis developed by Bandini et al.[6b] Indeed, N-alkylated indoles have been applied as useful intermediates for the synthesis of polyheterocycles[7] and occur widely among natural products and biologically active pharmaceuticals (Scheme 1).[8] For example, mitomycin C exhibits potent antitumour activity and is used clinically in the treatment of certain cancers.[8b] Yuremamine, which was recently isolated from the stem bark of *Mimosa hostilis*, shows hallucinogenic and psychoactive effects.[9] Pyrrolo[3,2,1-*ij*]-quinoline derivatives are active antihistamines and inhibitors of leukotriene, and they offer the possibility of a novel multimediator approach to the treatment of allergic diseases.[8c] Therefore, it would be extremely desirable to develop effective protocols to access optically pure N-alkylated indoles.



Scheme 1. Biologically active N-alkylated indole derivatives.

Recently, the allylic alkylation of Morita-Baylis–Hillman (MBH) adducts catalyzed by a metal-free organic Lewis base has emerged as an attractive strategy to prepare multifunctional compounds.[10] Our research group has also reported that modified cinchona alkaloids are outstanding catalysts for the asymmetric allylic alkylation of α,α-dicyanoolefins with MBH carbonates.[11] We anticipated that, as outlined in Scheme 2, the deprotonation of the acidic NH group of the indole ring by the *tert*-butoxy anion generated in situ would occur, and N- or C3-selective asymmetric allylic alkylation would followed to deliver valuable chiral indole derivatives.[12,13]



Scheme 2. Proposed N- or C3-selective allylic alkylation of indoles with MBH carbonates catalyzed by a tertiary amine. Boc = *tert*-butoxycarbonyl.

To our delight, we found that DABCO smoothly catalyzed the allylic alkylation of indole **1a** and MBH carbonate **2a** at 50 °C. The reaction showed excellent chemoselectivity, and the N-alkylation compound **3a** was isolated as the sole product (Table 1, entry 1).[14] Encouraged by this preliminary

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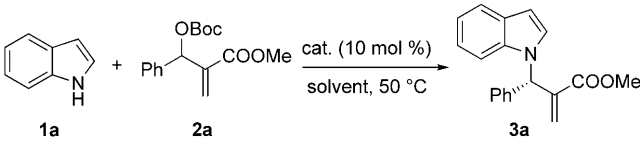
[**] We are grateful for the financial support from NSFC (20772084).
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200902093.

Table 1: Screening studies of organocatalytic N-allylic alkylation of indole **1a** with MBH carbonate **2a**.[a]



1a **2a** **3a**

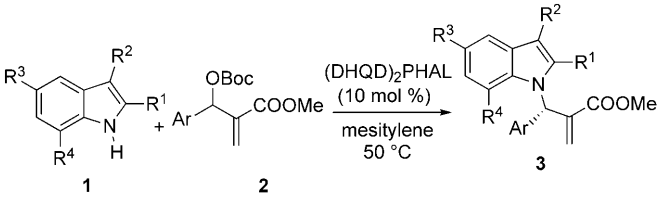
Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	DABCO	DCE	20	93	–
2	$(DHQD)_2AQN$	DCE	24	99	24
3	$(DHQD)_2PHAL$	DCE	42	96	67
4	$(DHQD)_2PYR$	DCE	42	96	48
5	$(DHQ)_2AQN$	DCE	42	62	−23
6	TMSQD	DCE	23	92	12
7	BzQD	DCE	59	43	0
8	$(DHQD)_2PHAL$	toluene	59	79	91
9	$(DHQD)_2PHAL$	*m*-xylene	59	80	91
10	$(DHQD)_2PHAL$	mesitylene	59	82	91
11	$(DHQD)_2PHAL$	$PhCF_3$	36	92	83
12	$(DHQ)_2PHAL$	mesitylene	60	76	−52

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **1a**, 0.2 mmol of **2a**, and 0.01 mmol of catalyst in 1 mL solvent. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. DABCO = 1,4-diazabicyclo[2.2.2]octane, $(DHQD)_2AQN$ = hydroquinidine (anthraquinone-1,4-diyl) diether, $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether, $(DHQD)_2PYR$ = hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQ)_2AQN$ = hydroquinine (anthraquinone-1,4-diyl) diether, TMSQD = 9-trimethylsilylquinidine, BzQD = 9-quinidinyl benzoate, $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether, DCE = 1,2-dichloroethane.

result, we examined the enantioselective variant in the presence of chiral tertiary amine catalysts. A modified cinchona alkaloid[15] $(DHQD)_2AQN$ (10 mol%) showed high catalytic activity, and **3a** was obtained in quantitative yield after 24 hours, albeit with poor enantioselectivity (24% *ee*; Table 1, entry 2). Then we tested other tertiary amines derived from cinchona alkaloids (Table 1, entries 3–7) and found that $(DHQD)_2PHAL$ served as the best catalyst, which gave the product with 67% *ee* (Table 1, entry 3). Subsequently, we screened more parameters to optimize the reaction. Pleasingly, the choice of solvent had a significant effect on enantiocontrol. An excellent *ee* value (91%) was attained in toluene even though the reaction rate was slightly slower (Table 1, entry 8). Similar results were observed in *m*-xylene and mesitylene (Table 1, entries 9 and 10). A higher reactivity was observed in $PhCF_3$, but the *ee* value was lower (Table 1, entry 11). In addition, $(DHQ)_2PHAL$ gave **3a** with the opposite configuration, although the enantioselectivity was modest under the optimal reaction conditions (Table 1, entry 12).

Next, the scope of the new N-allylic alkylation reaction was explored with a variety of indoles **1** and MBH carbonates **2**. The reaction was generally conducted with 10 mol% of $(DHQD)_2PHAL$ in mesitylene at 50°C. The results are summarized in Table 2. In general, for MBH carbonate **2a**, variation in the substitution pattern on the indole unit was well tolerated. 3-Methylindole (**1b**) gave 83% *ee* in 93% yield (Table 2, entry 2). Notably, both 3-indolylpropanoate (**1c**) and the protected tryptamine **1d** gave high enantioselectivities with good yields (Table 2, entries 3 and 4). The effects of having a substituent at the 5-position of the indole unit was also explored (Table 2, entries 5–7). Indole **1f** bearing a strong electron-withdrawing group (NO_2) gave decreased enantioselectivity, even though higher reactivity was observed (Table 2, entry 6).[13] 7-Bromoindole (**1h**) exhibited lower reactivity as a result of steric hindrance. Four equivalent of MBH carbonate **2a** was required to ensure a better conversion, and a moderate *ee* value was obtained (Table 2, entry 8). Importantly, indole-2-carboxylates **1i** and **1j** could be successfully alkylated. In these cases $(DHQD)_2AQN$ proved to be a superior catalyst in $PhCF_3$. High enantioselectivities were afforded when the diphenylmethyl esters were used (Table 2, entries 9 and 10).[16] Moreover, a number of MBH carbonates have also been explored in the alkylation reaction with indoles. High enantioselectivities (81–93% *ee*) and moderate to good yields (71–99%) were attained for MBH carbonates bearing electron-deficient or electron-rich aryl or heteroaryl groups (Table 2, entries 11–

Table 2: Asymmetric N-allylic alkylation of indoles **1** with MBH carbonates **2**.[a]



1 **2** **3**

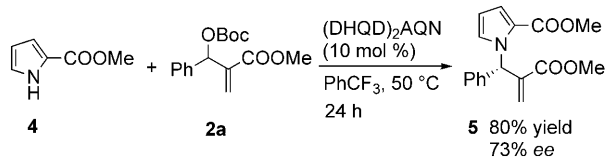
1a $R^1 = R^2 = R^3 = R^4 = H$
1b $R^1 = R^3 = R^4 = H$, $R^2 = Me$
1c $R^1 = R^3 = R^4 = H$, $R^2 = CH_2CH_2CO_2Me$
1d $R^1 = R^3 = R^4 = H$, $R^2 = CH_2CH_2NPhth$
1e $R^1 = R^2 = R^4 = H$, $R^3 = Br$
1f $R^1 = R^2 = R^4 = H$, $R^3 = NO_2$
1g $R^1 = R^2 = R^4 = H$, $R^3 = MeO$
1h $R^1 = R^2 = R^3 = H$, $R^4 = Br$
1i $R^1 = COOCHPh_2$, $R^2 = R^3 = R^4 = H$
1j $R^1 = COOCHPh_2$, $R^2 = R^4 = H$, $R^3 = Me$

Entry	**1**	Ar	*t* [h]	Product	Yield [%][b]	*ee* [%][c]
1	**1a**	Ph	59	**3a**	82	91
2	**1b**	Ph	94	**3b**	93	83
3	**1c**	Ph	116	**3c**	68	90
4	**1d**	Ph	54	**3d**	69	85
5	**1e**	Ph	54	**3e**	97	81
6[d]	**1f**	Ph	66	**3f**	91	62
7	**1g**	Ph	46	**3g**	99	87
8[e]	**1h**	Ph	90	**3h**	79	71
9[f]	**1i**	Ph	31	**3i**	91	90
10[f]	**1j**	Ph	24	**3j**	91	86
11	**1a**	*p*-MeOPh	38	**3k**	72	89
12	**1a**	*p*-ClPh	47	**3l**	89	80
13	**1a**	2-furyl	16	**3m**	77	90
14	**1a**	*m*-MePh	67	**3n**	71	87
15	**1d**	*p*-ClPh	96	**3o**	79	85[g]
16[f]	**1i**	*p*-MeOPh	40	**3p**	99	93

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **1**, 0.2 mmol of **2**, and 10 mol% of $(DHQD)_2PHAL$ in 1.0 mL mesitylene at 50°C. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] At 25°C. [e] 0.4 mmol of **2a** was used. [f] With 10 mol% of $(DHQD)_2AQN$ in $PhCF_3$. [g] The absolute configuration of **3o**[17] was determined by X-ray analysis (see the Supporting Information). The absolute configurations of the other products were assigned by analogy. Phth = phthaloyl.

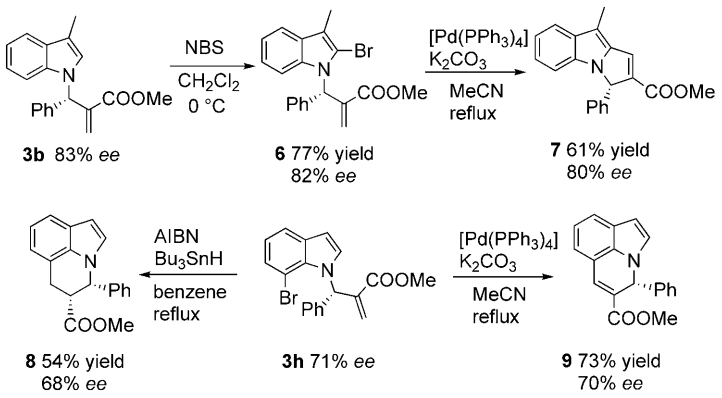
16). MBH carbonates with β-alkyl substitution were tested but showed much lower reactivity.

We have expanded the substrate scope by replacing the indole unit with methyl pyrrole-2-carboxylate **4**. The desired N-allylic alkylation product **5** was obtained in 80% yield with 73% *ee* (Scheme 3).[18]



Scheme 3. N-Allylic alkylation of pyrrole-2-carboxylate.

Apart from the traditional derivation of the C=C bond of the allylic products,[19] some fused-ring systems could be efficiently synthesized from the newly prepared N-allylic indole compounds. Although the direct oxidative Heck reaction of **3b** resulted in limited success,[2d] a regioselective bromination was easily realized by simply treating **3b** with NBS (Scheme 4). The subsequent palladium-catalyzed intra-



Scheme 4. Synthesis of the fused, cyclic indole systems. AIBN = 2,2′-azobisisobutyronitrile, NBS = *N*-bromosuccinimide.

molecular Heck reaction of **6** afforded the desired pyrrolo-[1,2-*a*]indole framework **7**, which possesses the core structure of the natural product Yuremamine (61% yield, 80% *ee*; see Scheme 1,).[20] On the other hand, an intramolecular radical cyclization or Heck reaction of **3h** could be smoothly conducted to deliver pyrrolo[3,2,1-*ij*]quinoline derivatives **8** and **9**, respectively. These derivatives might find valuable applications in medicinal chemistry.[8c]

In conclusion, we have developed the first asymmetric and chemoselective N-allylic alkylation of indoles with Morita-Baylis–Hillman carbonates. This method was achieved by employing metal-free catalysis of modified cinchona alkaloids. Either electron-rich or electron-deficient indoles could be employed and moderate to excellent enantioselectivity was achieved (62–93% *ee*). This reaction also provides a convenient method to prepare multiply functionalized pyrrolo[1,2-*a*]indole and pyrrolo[3,2,1-*ij*]quinoline derivatives, which may have potential use in the synthesis of biologically important materials. This work is currently underway in our laboratory.

Received: April 19, 2009
Revised: May 18, 2009
Published online: June 24, 2009

Keywords: chemoselectivity · indoles · Morita–Baylis–Hillman carbonates · N-allylic alkylation · organocatalysis

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