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Chiral Brønsted Base-Promoted Nitroalkane Alkylation: Enantioselective Synthesis of *sec*-Alkyl-3-Substituted Indoles

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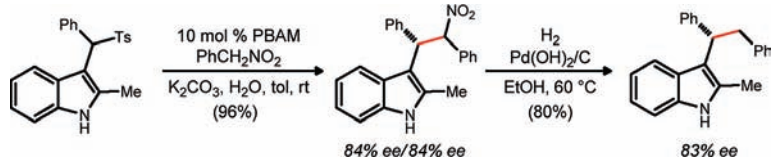
ABSTRACT



A Brønsted base-catalyzed reaction of nitroalkanes with alkyl electrophiles provides indole heterocycles substituted at C3 bearing a *sec*-alkyl group with good enantioselectivity (up to 90% ee). Denitration by hydrogenolysis provides a product with equally high ee. An indolenine intermediate is implicated in the addition step, and surprisingly, water cosolvent was found to have a *beneficial* effect in this step, leading to a one-pot protocol for elimination/enantioselective addition using PBAM, a bis(amidine) chiral nonracemic base.

Indole and pyrrole-derived small molecules bearing an *n*-alkyl substituent at C3 are very common, but the emergence of small molecules exhibiting a *sec*-alkyl substituent at C3 is more recent. Compelling biological activity can be associated with these congeners (Figure 1): the gonadotropin releasing hormone antagonist developed by Merck (**1**),[1] the antibiotic roseophilin (**2**),[2] and inhibitors of MDM2 in the spirotryprostatin class (**3**).[3]

Synthetic methods that provide for functionalization of the C3 indole carbon do not often translate to the production of chiral nonracemic products, though an exception to this is the Friedel-Craft alkylation[4] of indole where asymmetric versions have been reported.[5] While both metal-based chiral complexes and organocatalysts have been used to catalyze the addition of indoles to nitroalkenes,[6] there are currently no asymmetric additions to nonactivated α,β-substituted nitroalkenes, which would deliver highly substituted *sec*-alkyl substituents at the indole 3-position.[7,8]

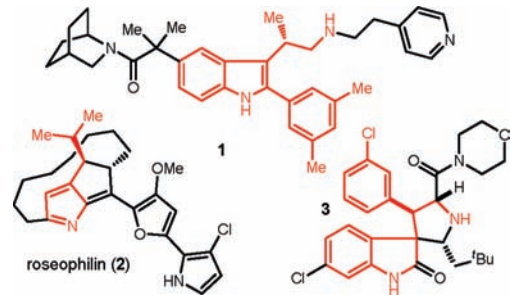


Figure 1. Examples of biologically active indole- and pyrrole-derived heterocycles bearing a chiral C3-*sec*-alkyl substituent.

In 2006, Petrini described an innovative solution to this structural motif using 3-(1-arylsulfonylalkyl) indole precursors to indolenine reactive intermediates.[9] They have

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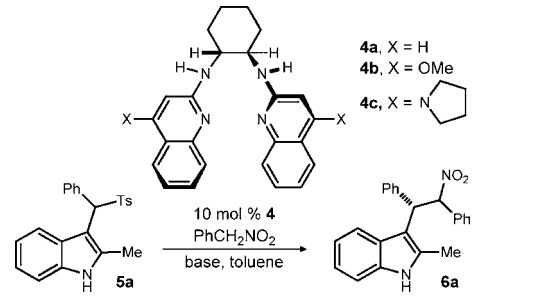
since reported a range of bases and nucleophiles to effect the elimination and subsequent addition.[10] A variety of indolenine precursors have also been reported to be generated using both acidic[11] and basic[12] reaction conditions. Though a broad scope of additions has already been demonstrated (Grignard, nitroalkane, malonate, malononitriles), there have been very few asymmetric variations reported.[13−16] More recently, a Brønsted-base catalyzed asymmetric addition of malononitrile using a cinchona based thiourea catalyst was reported with high selectivity.[17] This has prompted us to report our findings on the catalytic, enantioselective Michael addition of arylnitromethanes to indolenine intermediates. In the context of BAM (Bis(AMidine)) catalysis,[18] this is the first report of their use as chiral Brønsted bases.[19]

To gauge the reactivity of nitroalkanes with sulfone **5a** using a BAM catalyst, the Petrini protocol was utilized for direct comparison. In this experiment using dichloromethane, conversion to the desired nitroalkane alkylation product (**6a**) was observed, but with low enantioselectivity (20% ee, Table 1, entry 1). Use of toluene improved selectivity to 60% ee (Table 1, entry 2). Attempts to improve enantioselection by lowering the temperature provided lower conversion and enantioselection (Table 1, entries 3−4), likely due to the heterogeneity of the reaction mixture and the sluggish elimination step. There was no change in diastereoselection throughout the reaction optimization process.[20] Considering the possibility that the sto-

Table 1. Optimization of Enantioselective Additions to Sulfonylmethyl Indoles[a]



entry	catalyst	base	temp (°C)	M	ee (%)[b]
1[c]	**4c**	KF/Alumina	rt	0.2	20
2	**4c**	KF/Alumina	rt	0.2	60
3	**4c**	KF/Alumina	−20	0.2	57
4	**4c**	KF/Alumina	−78	0.2	49
5	**4c**	KF	rt	0.1	68
6	**4c**	Na_2CO_3	rt	0.1	61
7	**4c**	K_2CO_3	rt	0.2	70
8	**4a**	K_2CO_3	rt	0.2	56
9[d]	**4b**	K_2CO_3	rt	0.2	73
10	**4c**	K_2CO_3	rt	0.1	78
11[d]	**4c**	**K_2CO_3**	**rt**	**0.1**	**81**

[a] All reactions were performed using 2 equivalents of phenylnitromethane on a 0.1 mmol scale and resulted in less than 1.5:1 dr material and between 30−80% yield. Absolute stereochemistry assigned by correlation. See Supporting Information for details. [b] Enantiomeric ratios were measured using chiral stationary phase HPLC and are reported for the major diastereomer. [c] Dichloromethane was used instead of toluene. [d] One equivalent of phenylnitromethane was used.

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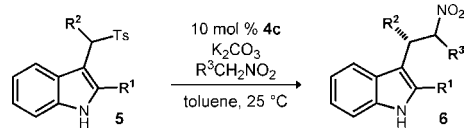
ichiometric base might intervene during the addition as an achiral base, we examined several alternatives (Table 1, entries 5−7). Potassium fluoride (without alumina) provided a slight improvement while sodium and potassium carbonate provided similar enantioselection.

We briefly investigated BAM catalyst alternatives.[18] The less Brønsted basic catalyst **4a** (Table 1, entry 8) gave lower enantioselection while increasing the catalyst Brønsted basicity (**4b**) increased enantioselection (Table 1, entry 9).[21] Our most Brønsted basic catalyst H,[4]PyrrolidineQuin-BAM (**4c**, PBAM) provided the highest enantioselection under the given conditions. Decreasing the concentration (Table 1, entry 10) and the equivalents of nucleophile (Table 1, entry 11) further improved enantioselection, thereby defining the optimal conditions.

The substrate scope was investigated next (Table 2). Aryl rings bearing electron donating as well as electron withdrawing groups were tolerated (Table 2, entries 2−4), yielding the product with good enantioselection. Sterically hindered (Table 2, entry 5) and heterocyclic (Table 2, entry 6) substituents were tolerated, but a lowering of ee was observed. We were encouraged to see that selectivity remained relatively constant for the aliphatic analog tested (Table 2, entry 7). Though ester substituents gave slightly lower ee (Table 2, entries 8−9) we were encouraged by an improvement in diastereoselection to 3:1. Variations at the 2-position of the indole were also tolerated (Table 2, entries 10−11), but the lower enantioselection suggests the need for a steric influence at the indole C2. These observations translated to a pyrrole electrophile, as **5l** (Table 2, entry 12) furnished **6l** with good enantioselection. Electronic modifications of the nitroalkane pronucleophile (Table 2, entries 13−14) demonstrated that electron rich arylnitroalkanes result in improved enantioselection, whereas electron deficient aryl nitroalkanes provide substitution products with lower enantioselection. The use of nitroethane was also less selective (Table 2, entry 15), but gave encouraging results.

Table 2. Chiral Base-Catalyzed Enantioselective Nitroalkane Alkylations[a]



entry	R^1	R^2	R^3		ee (%)[b]	yield (%)[c] (conv)
1	Me	Ph	Ph	**a**	81/81	78(85)
2	Me	^{p}BrC$_6$H$_4$	Ph	**b**	82/75	74(76)
3	Me	^{p}MeOC$_6$H$_4$	Ph	**c**	81/81	68(88)
4	Me	^{p}F$_3$CC$_6$H$_4$	Ph	**d**	84/74	71(78)
5[e]	Me	^{o}MePh	Ph	**e**	76/70	76(95)
6	Me	^{2}Furyl	Ph	**f**	53/44	69(99)
7	Me	^{n}Bu	Ph	**g**	76/74	51(56)
8[d]	Me	CO_2Me	Ph	**h**	66/47	47(52)
9[d,e]	Me	$CO_2{}^t$Bu	Ph	**i**	65/66	55(70)
10	H	Ph	Ph	**j**	40/0	65(68)
11[e]	Ph	Ph	Ph	**k**	74/72	49(52)
12[e]	2,5-Me-Pyrrole	Ph	Ph	**l**	72/69	69(79)
13	Me	Ph	^{p}MeOC$_6$H$_4$	**m**	89/85	52(77)
14	Me	Ph	^{p}O$_2$NC$_6$H$_4$	**n**	37/43	63(86)
15[e,f]	Me	Ph	Me	**o**	66/67	65(87)

[a] All reactions were performed on a 0.1 mmol scale using a standard 22 h reaction time and 7 equivalents of K_2CO_3. Diastereomeric ratios observed for crude reaction mixtures were measured by ^{1}H NMR spectroscopy and ranged from 1:1 to 1.5:1 dr. See Supporting Information for complete details. [b] Enantiomeric ratios were measured using chiral stationary phase HPLC. [c] Isolated yields with conversions in parentheses. [d] Three to one dr observed. [e] Seventy-two hour reaction time. [f] One and a half equivalents of nitroethane used.

Experiments directed at probing the influence of base solubility revealed a beneficial water effect. We hypothesized that water might solubilize the inorganic base in a biphasic mixture, and in so doing, further limit the possible contribution of direct K_2CO_3-mediated substitution that would lead to racemic product formation. Furthermore, toluene sulfinate would also be solubilized by water. In a control experiment where water is used as solvent (no toluene), the product forms in high yield but as the racemate (Table 3, entry 1). However, when water was used as a cosolvent (2:1, toluene:water), dramatic increases in yield and enantioselection (Table 3, entry 2) were observed.

In a second line of optimization, we hypothesized that the reactive indolenine intermediate might be formed fully *in situ* prior to the addition of pronucleophile (Table 3, Method B). This also provided the desired substitution products with similar enantioselection in most cases. Together, these methods suggest that similar indolenine intermediates are formed, leading to enantioselective product-forming pathways. Attenuations in enantioselection can be attributed, at least in part, to achiral base-promoted product formation. Table 3 compares these two methods across a range of substrates.

Both methods A and B gave high enantioselection for the various aryl analogs tested (Table 3, entries 4−9). Use of *para*-methoxy phenylnitromethane leads to an increase in ee for method A and B, but a significant difference in the major and minor diastereomers is observed in the latter (Table 3, entry 11). The furan analog saw a sharp increase in ee from the original method (53% ee/44% ee) to the new methods, as both gave 90% ee for the major diastereomer (Table 3, entries 12−13). The aliphatic analog (Table 3, entries 14−15) saw a small drop in ee from the original method, as well as in yield. The ester derivative (Table 3, entry 16) provided a small increase in ee while 3:1 dr was

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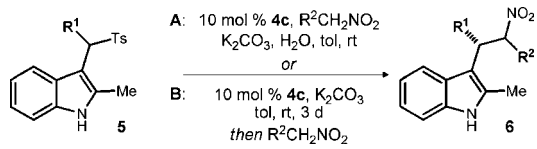
(19) For a recent review: Ting, A.; Goss, J.; McDougal, N.; Schaus, S. In *Asymmetric Organocatalysis*; Springer: Berlin/Heidelberg, 2009; Vol. 291, pp 145−200.

(20) Material enriched in one diastereomer by column chromatography (4:1) was resubmitted to the reaction conditions to give material with the same diastereoselection (4:1).

(21) Hess, A. S.; Yoder, R. A.; Johnston, J. N. *Synlett* **2006**; 0147−0149.

Table 3. Chiral Base-Catalyzed Enantioselective Nitroalkane Alkylations Improved by a Semiaqueous, One-Pot Protocol[a]



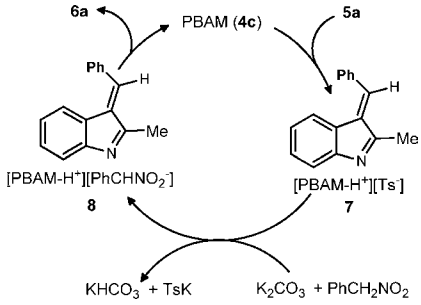
entry	R^1	R^2	method		ee (%)[b]	yield[c]
1[d]	Ph	Ph	water	**a**	0/0	83
2			A	**a**	86/86	96
3			B	**a**	88/89	85
4	$^{p}BrC_6H_4$	Ph	A	**b**	87/86	84
5			B	**b**	88/86	94
6	$^{p}MeOC_6H_4$	Ph	A	**c**	85/85	92
7			B	**c**	87/88	66
8	$^{p}F_3CC_6H_4$	Ph	A	**d**	84/76	83
9			B	**d**	88/78	83
10	Ph	$^{p}MeOC_6H_4$	A	**m**	87/87	72
11			B	**m**	90/75	82
12	^{2}Furyl	Ph	A	**f**	90/79	87
13			B	**f**	90/81	72
14	^{n}Bu	Ph	A	**g**	71/70	42
15			B	**g**	73/59	48
16[e]	CO_2Me	Ph	A	**h**	76/65	89
17[e]			B	**h**	50/38	71
18	Ph	Me	A	**o**	–	0
19			B	**o**	10/10	68

[a] All reactions were performed on a 0.1 mmol scale using a standard 22 h reaction time and 7 equivalents of K_2CO_3. Diastereomeric ratios observed for crude reaction mixtures were measured by ^{1}H NMR spectroscopy and ranged from 1:1 to 1.5:1 dr. See Supporting Information for complete details. [b] Enantiomeric ratios were measured using chiral stationary phase HPLC. [c] Isolated yields. [d] Reaction run in water for 5 days. [e] Three to one dr observed.

maintained. Unfortunately, the nitroethane addition product was produced with significantly lower ee for method B and did not produce any product for method A (Table 3, entries 18−19). The increased solubility of the nitroethane in water may have contributed to the low yield of the reaction.

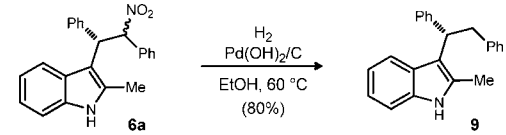
Using the data from all three methods and control experiments, a working mechanism is proposed in Scheme 1. We

Scheme 1. Proposed Cycle for Chiral Base Catalysis of Nitroalkane Alkylations by an *in situ*-formed Indolenine



hypothesize that both PBAM and potassium carbonate can effect the elimination of toluene sulfinate. However, when only potassium carbonate is used the reaction is much slower (50% conversion after 22 h), leading to the conclusion that the organocatalyst is a more effective promoter of indolenine formation. If potassium carbonate regenerates PBAM from its sulfinic acid salt, the catalyst can then deprotonate the nitroalkane to form the nucleophilic nitronate. Alternatively, the PBAM-HTs-indolenine complex (**7**) could react with the potassium nitronate, PBAM-nitronic acid salt, or the simple nitronic acid enantioselectively. Based on the observations outlined above, we favor the first of these possibilities wherein the PBAM-nitronate salt reacts with the indolenine selectively.

Scheme 2. Convergence of Diastereomeric Nitroalkanes to a *sec*-Alkyl 3-Substituted Indole with High Enantioselection



Nitroalkanes offer many opportunities for functionalization through reduction (tryptamine analogs), oxidation (Nef) and removal (denitration).[22] Using modified conditions for the cleavage of benzylic nitro bonds by Carreira[23] we were able to denitrate in high yield while enantioenrichment was conserved (Scheme 2). Denitration gives products (**9**) that would result from the enantioselective Friedel−Crafts reaction between indole and stilbene, a reaction not yet developed.

In conclusion, an enantioselective Brønsted base-catalyzed alkylation of nitroalkanes has been developed using indolenine electrophiles. The final protocol provides β-substituted tryptamine analogs and illustrates how these enantioselective reactions at room temperature can be improved by the addition of water.[24]

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Supporting Information Available: Complete experimental details and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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