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Palladium-Catalyzed Enantioselective C-3 Allylation of 3-Substituted-1*H*-Indoles Using Trialkylboranes

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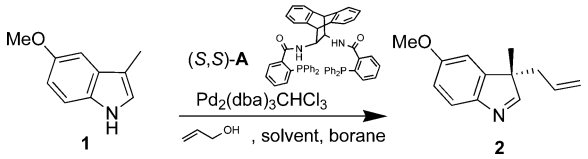
The asymmetric construction of a quaternary center at C-3 of the indole core represents a great synthetic challenge as well as a powerful entry into the structurally diverse family of indole alkaloids.[1] While many reports describe the asymmetric synthesis of 3,3-disubstituted oxindoles,[2] there is only one example of an enantioselective process that takes advantage of the nucleophilicity of the C-3 of indoles to build a quaternary center directly from 3-substituted indoles.[3,4] Recently, Tamaru and co-workers reported a C-3 selective palladium-catalyzed allylation of 1*H*-indoles promoted by triethylborane using allyl alcohols.[5] Of particular interest to us was the reaction of 3-methylindole which provided the corresponding 3-methyl-3-allyl-indolenine. Since this reaction seems to proceed via a π-allylpalladium intermediate, we envisioned that our chiral ligands[6] could be used to develop an enantioselective version. Here we report our progress in this area, which, to the best of our knowledge, is the first example of an enantioselective allylic alkylation using allyl alcohol as electrophile and reveals some insight into the mechanism of this interesting transformation.

Preliminary experiments indicated that the anthracene derived ligand **A** gave the best enantioselectivities and that 1 equiv of Et_3B and 3 equiv of allyl alcohol were necessary for the reaction to proceed in good yield. Solvent studies (Table 1) revealed that non-coordinating solvents provided higher selectivities with CH_2Cl_2 giving the best result. We then envisioned that, since the high selectivity for C-3 versus N-allylation might result from the borane being tightly bound to the indole nitrogen during the allylation step,[7] the nature of the borane should greatly influence the enantioselectivity. Indeed, we were pleased to observe an increase of the enantiomeric excess to 83% using the more bulky borane derived from the hydroboration of 1-hexene with 9-BBN (Table 1, entry 6). Further increasing the steric bulk of the borane using the dicyclohexylborane derivative was detrimental to the yield and enantiomeric excess, while using disiamylborane-C_6H_{13} completely inhibited the reaction. Finally, optimal conditions (entry 9) were achieved with 1.05 equiv of borane at 4 °C, providing the indolenine in 92% yield and 85% ee. The product is then liberated from the borane by basic hydrolysis or treatment with ethanolamine in THF.[8]

We then examined the effect of substitution of the indole on the outcome of the reaction (Table 2). Surprisingly, the electronic character of the indole seems to influence the selectivity, while the reactivity seems hardly affected (except for **3a** which failed to react). The electron-deficient indole **3b** reacts with moderate selectivity, and the enantiomeric excess increases in correlation with the electron-donating character of the C-5 substituent. Electron-donating substituents in the 4- and 6-position also give high selectivities, while the 7-substituted indole failed to react most likely because it prevents binding of the boron to the indole nitrogen. This electronic effect could be ascribed to the stronger boron−nitrogen interaction in electron-rich indoles.

With these results in hand, we examined the scope of this reaction using mainly readily available and synthetically relevant 5-methoxy-3-substituted indoles (Table 3). In all cases, high yields were achieved using the previously optimized conditions, with enantiomeric excess from 72 to 90%. Of particular interest are the substrates with a pendant nucleophile which cyclizes onto the imine under the reaction conditions (entries 3−11). In these cases, the corresponding indoline is obtained with a *cis*-5,5- or 5,6-fused ring system[9] found in numerous natural products.[1] These results also exemplify the very high chemoselectivity of this reaction since alcohol, phenol, carbamate,[10] and malonate functional groups are tolerated.[11]

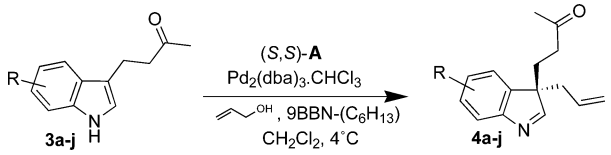
Table 1. Selected Optimization Studies for C-3 Allylation



entry	borane	*T* (°C)	solvent	yield[a] (%)	ee[b] (%)
1	Et_3B	25	DME	82	43
2	Et_3B	25	dioxane	85	33
3	Et_3B	25	THF	89	53
4	Et_3B	25	toluene	85	61
5	Et_3B	25	CH_2Cl_2	88	66
6	9-BBN-C_6H_{13}	25	CH_2Cl_2	88	83
7	$(Chx)_2B$-C_6H_{13}	25	CH_2Cl_2	70	70
8	Sia_2B-C_6H_{13}	25	CH_2Cl_2	nr	
9	9-BBN-C_6H_{13}	4	CH_2Cl_2	92	85

[a] All reactions were performed using 2.5 mol % of $Pd_2(dba)_3CHCl_3$, 7.5% of (*S*,*S*)-**A**, 1 (entries 1−6) or 1.05 equiv (entries 7−9) of borane and 3 equiv of allyl alcohol. [b] Enantiomeric excess was determined by chiral HPLC after reduction of the imine using $NaBH_3CN$.

Table 2. Effect of the Substitution of the Indole Benzene Ring

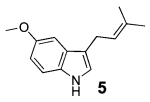
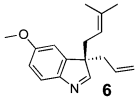
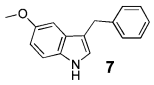
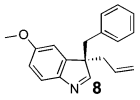
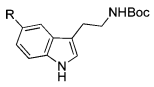
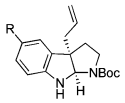
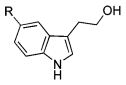
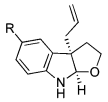
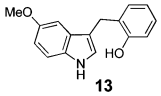
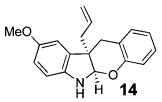
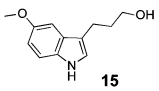
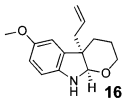
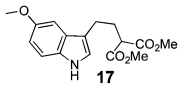
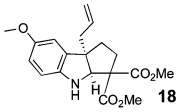
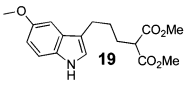
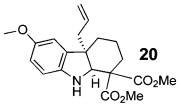
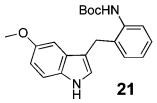
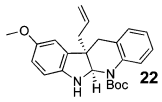


entry	R	product	yield[a] (%)	ee (%)
1	5-NO_2	**4a**	nr	
2	5-Br	**4b**	89	60
3	H	**4c**	92	74
4	5-MeO	**4d**	95	84
5	5-BnO	**4e**	87	83
6	5-HO	**4f**	88	86
7	5-Bn_2N	**4g**	94	90
8	4-MeO	**4h**	92	83
9	6-MeO	**4i**	89	78
10	7-MeO	**4j**	nr	

[a] All reactions were performed on a 0.2 mmol scale for 20 h at 4 °C using 2.5 mol % of $Pd_2(dba)_3CHCl_3$, 7.5% of (*S*,*S*)-**A**, 1.05 equiv of 9-BBN-(C_6H_{13}), and 3 equiv of allyl alcohol.

10.1021/ja0608139 CCC: $33.50

Table 3. Scope of the Reaction

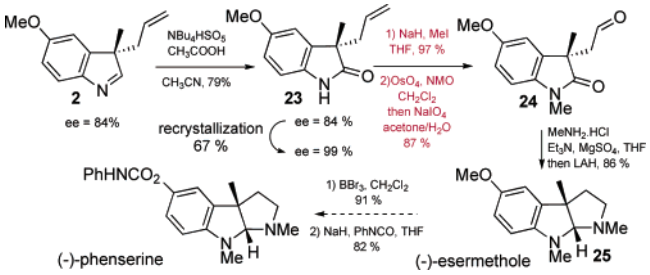
entry	substrate	product	yield[a] (%)	ee (%)
1	 **5**	 **6**	85	84
2	 **7**	 **8**	89	85
3	 **9a**	 R=H **10a**	87	72
4	**9b**	R=MeO **10b**	91	82
5	 **11a**	 R=H **12a**	90	81
6	**11b**	R=MeO **12b**	91	86
7	 **13**	 **14**	84	90
8	 **15**	 **16**	93	88
9	 **17**	 **18**	89[b]	84
10	 **19**	 **20**	85[b]	81
11	 **21**	 **22**	91	85

[a] All reactions were performed on a 0.2 mmol scale for 20 h using 2.5 mol % of $Pd_2(dba)_3CHCl_3$, 7.5% of (*S*,*S*)-**A**, 1.1 equiv of 9-BBN-(C_6H_{13}), and 3 equiv of allyl alcohol. [b] Cyclization to the indoline occurred after addition of ethanolamine to the indolenine in THF (5 min stirring for **18** and 24 h stirring for **20**).

We were also interested in the oxidation of indolenines which could allow an easy access to the oxindole family of natural products. After examining various oxidative conditions, we found that treatment of **2** with tetrabutylammonium oxone[12] and acetic acid gave oxindole **23** in good yield (Scheme 1). Recrystallization of **23** provided enantiopure material. Furthermore, after methylation and oxidative cleavage, aldehyde **24** was converted to (−)-esermethole by reductive amination−cyclization following Overman's procedure.[13] This intermediate has been previously used to synthesize (−)-phenserine,[2b] which is a drug candidate for treatment of Alzheimer's disease.

In summary, we have developed a new enantioselective C-3 allylation of 3-substituted indoles to give the corresponding 3,3-disubstituted indolenines and indolines. High enantioselectivities could be achieved using 9-BBN-C_6H_{13} as the promoter of the reaction, and electron-rich indoles give higher selectivities. The dependence of the selectivity on the nature of the borane suggests that, in addition to promoting the ionization of allyl alcohol,[14] the boron is directly involved in the enantiodiscriminating step. Studies to elucidate the mechanism of this reaction are underway and will be reported shortly.

Scheme 1 . Synthesis of (−)-Esermethole



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Supporting Information Available: Synthesis all new indole substrates, experimental details, and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The relative stereochemistry was confirmed by NOE on **12a** and **16**.
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