J|A|C|S
COMMUNICATIONS

Published on Web 07/11/2006

Asymmetric Allylboration of Cyclic Imines and Applications to Alkaloid Synthesis

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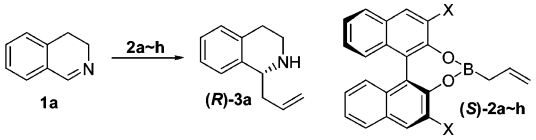
The enantioselective allylboration of carbonyl compounds has become a prominent tool for asymmetric synthesis, with many reported applications to the synthesis of natural products.[1,2] In contrast, the corresponding reaction with imines as a route to homoallylic amines is much less developed: There are only a few examples of asymmetric allylborations with acyclic imines as substrates[3] and no examples with cyclic imines. With acyclic imines (or other C=N functionalities), other elegant allylation strategies have been developed[4] to access homoallylic amines, compounds which are important synthetic intermediates.[5] However, the analogous enantioselective allylation of cyclic imines is very rare,[6,7] even though the chiral α-allyl cyclic amines produced are also valuable building blocks. Previously, such compounds have been prepared by less direct routes for syntheses of numerous natural products and bioactive molecules.[8] To the best of our knowledge, there has been only one report of successful enantioselective allylations of cyclic imines: 10 years ago, Nakamura and co-workers observed high selectivities with allylzinc reagents,[9] but there have been no published synthetic applications of this chemistry. Very recently, Itoh reported the first catalytic asymmetric allylation of a cyclic imine, but the selectivity was only modest (71% ee).[10] We now report the first enantioselective allylboration of cyclic imines along with some illustrative examples of applications to the synthesis of alkaloids.

It has been demonstrated that 3,3′-disubstituted binaphthol modified allylboronates can be used for enantioselective allylations of aldehydes and ketones (up to 98% yield and >99% *ee*).[11] Based on analysis of proposed transition state models, it was anticipated that acyclic (*E*) imines would be poor substrates, while cyclic (*Z*) imines would be good substrates for these reagents. When a prototypical cyclic imine, 3,4-dihydroisoquinoline (**1a)**, was treated with these allylboronates (**2a**−**h**, toluene, −78 °C to room temperature), reactions proceeded smoothly to give homoallylic amine **3a** in good yields (Table 1).

All of the 3,3′-disubstituted systems examined gave reasonable to excellent selectivities, while the unsubstituted parent binaphthol (**2a**) exhibited essentially no stereoselectivity. This lack of stereoselectivity and the sense of asymmetric induction observed may be explained using a six-membered chair transition-state model (Figure 1). The repulsion between one of the substituents on the BINOL and the methylene protons α to the imine nitrogen is the major destabilizing interaction in transition state B.

The desired amine was isolated by simple aqueous acid−base extraction, and the chiral ligands were recycled from the organic phases without detectable loss of enantiomeric purities. Thus, although stoichiometric amounts of reagents are employed, these reactions are quite practicable. Of the chiral boronates tested, **2h** gave the best enantioselectivity (Table 1, entry 8) and was chosen for further studies.

Table 1. Allylation of **1a** with Allylboronates **2a**−**h**



entry	X	yield[a] (%)	ee[b] (%)
1	H (**2a**)	<50	10
2	Me (**2b**)	94	75
3	I (**2c**)	87	77
4	CF_3 (**2d**)	83	84
5	Ph (**2e**)	90	87
6	4-MeO−C_6H_4− (**2f**)	94	88
7	3,5-$(CH_3)_2$−C_6H_3− (**2g**)	88	87
8	3,5-$(CF_3)_2$−C_6H_3− (**2h**)	92	95

[a] Isolated yields after acid−base extraction. [b] Determined by chiral HPLC analysis of the trifluoroacetamide. Absolute configuration based on rotation.[9]

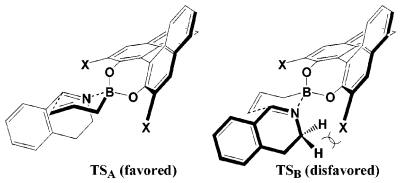


Figure 1. Proposed transition states.

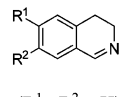
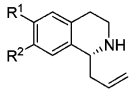
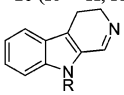
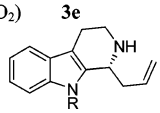
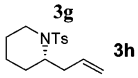
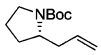
A variety of substituted dihydroisoquinolines (Table 2, entries 1−5) were subjected to allylboration using **2h**. Reactions of electron-rich substrates (Table 2, entries 2 and 3) were much slower than those of electron-poor substrates (Table 2, entries 4 and 5), so longer reaction times were required to get satisfactory yields. Nonetheless, good yields could be obtained in all cases, and selectivities observed were uniformly excellent (95 to 99% ee). 3,4-Dihydro-β-carboline (**1f)** could be allylated using **2h** without protecting the acidic indole functionality (Table 2, entry 6). *N*-Protected dihydro-β-carboline **1g** gave a similar result, indicating that the enantioselectivity of the reaction is not affected by the steric or electronic nature of the indole ring (Table 2, entry 7).

Aliphatic cyclic imines 1-pyrroline (**1i)** and Δ^1-piperideine (**1h**) were also subjected to the allylboration, giving the desired chiral cyclic pyrrolidine and piperidine with 92 and 91% ee, respectively (Table 2, entries 8 and 9). Slightly lower yields were obtained in both cases, likely due to the propensity of the starting imines to undergo rapid trimerization.[12] In these cases, products were isolated as Boc or tosyl derivatives to avoid possible problems with volatility or water solubility.

The allylation products can serve as building blocks for the synthesis of natural products. For instance, hydroboration of **3b** (9-BBN then H_2O_2/NaOH) followed by an intramolecular Mit-

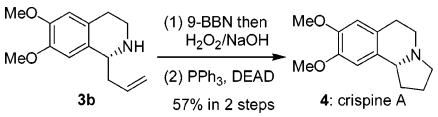
10.1021/ja0636791 CCC: $33.50

Table 2. Allylation of Cyclic Imines Using (*S*)-**2h**

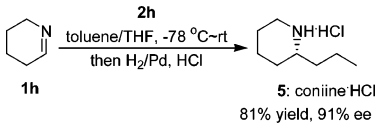
entry	imine	product	yield[a] (%)	ee (%)[c]
				
1	**1a** (R^1 = R^2 = H)	**3a**	92[b]	95
2	**1b** (R^1 = R^2 = OMe)	**3b**	78	98
3	**1c** (R^1, R^2 = OCH_2O)	**3c**	86	98
4	**1d** (R^1 = R^2 = Cl)	**3d**	88	95[d]
5	**1e** (R^1 = H, R^2 = NO_2)	**3e**	90	99
				
6	**1f** (R = H)	**3f**	80	94
7	**1g** (R = Ts)	**3g**	84	94
8	 **1h**	 **3h**	65[e]	91
9	 **1i**	 **3i**	71[e]	92

[a] Isolated yields after flash column chromatography on silica gel. [b] Isolated yields after acid−base extraction. [c] Determined by chiral HPLC analysis of trifluoroacetamides. [d] Determined by ^{19}F NMR of its *R*-MTPA amide. [e] The reaction was quenched using TsCl/pyridine/DMAP or $(Boc)_2O$/Et_3N/DMAP, and the ee of the product was determined by chiral HPLC analysis.

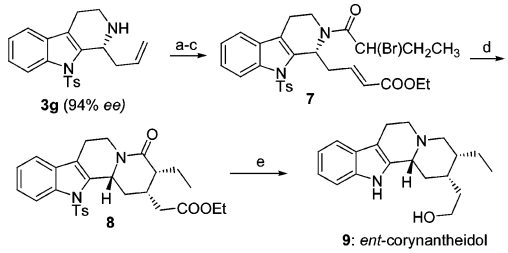
Scheme 1. Synthesis of (+)-Crispine A (**4**)



Scheme 2. Synthesis of *R*-(−)-Coniine·HCl (**5**)



Scheme 3. Synthesis of *ent*-Corynantheidol (**9**)[a]



[a] Reaction conditions: (a) (±)-$HO_2CCH(Br)CH_2CH_3$, DCC, CH_2Cl_2; (b) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O; (c) $Ph_3P{=}CHCOOEt$, CH_2Cl_2, 82% for 3 steps; (d) *n*-BuLi (1.2 equiv), THF, 63%; (e) LAH (15 equiv), THF, 79%.

sunobu reaction yielded (+)-crispine A (**4**), an antitumor alkaloid isolated from *C. crispus* (Scheme 1).[13]

Coniine (**5**), an alkaloid that has been the target of innumerable demonstrations of synthetic methodologies,[14] could be obtained in one pot from imine **1h** (Scheme 2).

This allylboration methodology was also applied to the total synthesis of the enantiomer of a more complex alkaloid corynantheidol, isolated from leaves of *Mitragyna parvifolia* (Roxb.) Korth (Scheme 3).[15] Thus, allylation product **3g** was treated with (±)-2-bromobutyric acid and DCC to give amide **6**, which was in turn converted to α,β-unsaturated ester **7**. *n*-BuLi induced intramolecular Michael addition led to the formation of all-*cis* trisubstituted δ-lactam **8**.[16] *ent*-Corynantheidol (**9**) was finally obtained after a global reduction using LAH. Of course, use of (*R*)-**2h**, readily prepared from (*R*)-1,1′-bi(2-naphthol), would have produced natural corynantheidol. These syntheses compare very favorably with previous syntheses in terms of both length and overall yields.[13b,14,17]

In summary, a general methodology for the enantioselective allylation of cyclic imines has been developed. The versatility of the allylation products has been demonstrated through efficient total syntheses of several naturally occurring alkaloids, and we expect that more applications of this methodology will be forthcoming.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support.

Supporting Information Available: Procedures for allylborations and spectroscopic data for compounds **3**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0636791