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Rhodium-Catalyzed 1,4-Additions to Enantiopure Acceptors: Asymmetric Synthesis of Functionalized Pyrrolizidinones

Ludivine Zoute, Gabriele Kociok-Köhn, and Christopher G. Frost*

Department of Chemistry, University of Bath, Bath BA2 7AY, U.K.

c.g.frost@bath.ac.uk

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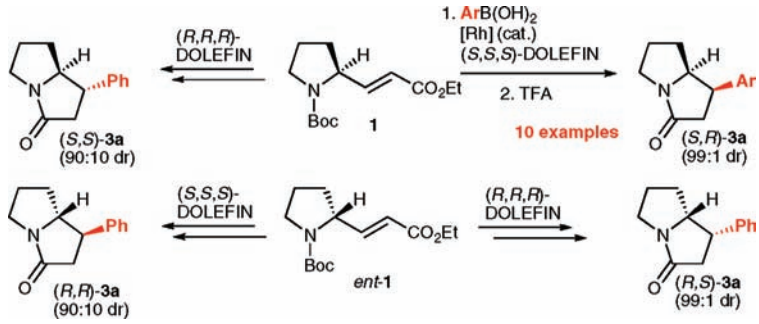
ABSTRACT



The rhodium-catalyzed 1,4-addition of arylboronic acids to an enantiopure heterocyclic acceptor proceeds under ligand control to effect an asymmetric synthesis of functionalized pyrrolizidinones. The protocol allows convenient access to all four stereoisomers of pyrrolizidinone 3a (Ar = Ph) by appropriate selection of substrate and catalyst.

The stereoselective construction of C−C bonds using the rhodium-catalyzed 1,4-addition of organometallics is widely regarded as important methodology for organic synthesis.[1] For the addition of aryl and alkenylboronic acids, the reaction is routinely carried out in aqueous solvents and can afford excellent enantioselectivities across a wide range of alkene acceptors. In the majority of reported additions to prochiral acceptors, a single stereocenter is established by an asymmetric carbometalation under control of an enantiopure rhodium complex. The sense of asymmetric induction can be reliably predicted by means of simple stereochemical models when using enantiopure BINAP (or related ligands).[2] Interestingly, despite the tremendous synthetic potential there are relatively few examples of rhodium-catalyzed 1,4-additions to enantiopure acceptors.[3] In this context we report a convenient stereoselective route to functionalized pyrrolizidinones utilizing the rhodium-catalyzed 1,4-addition

(1) For reviews, see: (a) Hayashi, T. *Synlett* **2001**, 879–887. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196. (d) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 4313–4327. (e) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13–21. (f) Yoshida, K.; Hayashi, T. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 3. First report: (g) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

(2) For a discussion of the mechanism, see: Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052–5058.

(3) (a) Ramnauth, J.; Poulin, O.; Bratovanov, S. S.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2571–2573. (b) Chen, Q.; Kuriyama, M.; Soeta, T.; Hao, X.; Yamada, K.; Tomioka, K. *Org. Lett.* **2005**, *7*, 4439–4441. (c) de la Herran, G.; Mba, M.; Murcia, M. C.; Plumet, J.; Csaky, A. G. *Org. Lett.* **2005**, *7*, 1669–1671. (d) Hargrave, J. D.; Bish, G.; Frost, C. G. *Chem. Commun.* **2006**, 4389–4391. (e) Segura, A.; Csaky, A. G. *Org. Lett.* **2007**, *9*, 3667–3670. (f) Chapman, C. J.; Matsuno, A.; Frost, C. G.; Willis, M. C. *Chem. Commun.* **2007**, 3903–3905. (g) Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Deng, J. Z.; Nguyen, D. N.; Potteiger, C. M.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *Org. Lett.* **2008**, *10*, 3235–3238. (h) Chapman, C. J.; Hargrave, J. D.; Bish, G.; Frost, C. G. *Tetrahedron* **2008**, *64*, 9528–9539.

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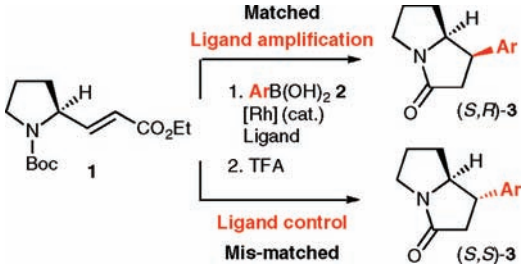
of arylboronic acids to an enantiopure acceptor **1** derived from (*S*)-prolinol (Scheme 1).

Scheme 1. Asymmetric Synthesis of Pyrrolizidinones



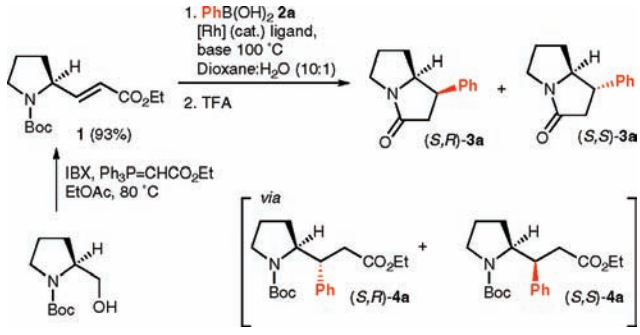
Moreover, we show that the reaction proceeds under ligand control and the diastereoselectivity of the process can be switched to afford (*S*,*R*)-**3** or (*S*,*S*)-**3** by changing the enantiomer of ligand employed in the rhodium-catalyzed 1,4-addition.

The enantiopure acceptor **1** was prepared in one step from *N*-Boc-L-prolinol using 2-iodoxybenzoic acid (IBX) as an in situ oxidant in the presence of a stabilized Wittig reagent.[4] An initial investigation of the rhodium-catalyzed 1,4-addition of phenylboronic acid to **1** employing a variety of reaction conditions followed by deprotection of the Boc group and lactamization revealed a high-yielding and stereoselective route to the desired pyrrolizidinones (Table 1). In the absence of added ligand, the optimal reaction conditions employed 1 equiv of Cs_2CO_3 and 4 equiv of boronic acid to afford a good yield of product **3a** with a preference for the (*S*,*R*)-diastereomer (entry 3). The inclusion of certain achiral bidentate phosphine ligands led to enhanced diastereoselectivity via an amplification of the inherent substrate control (entries 4 and 5).

The use of enantiopure ligands (Figure 1) in the catalytic addition to enantiopure **1** presents a situation where internal or external diastereocontrol may predominate (double stereodifferentiation).[5] The application of (*S*)-BINAP as (matched) ligand afforded results comparable to those using dppf, demonstrating a preference for the (*S*,*R*)-diastereomer (entry 6). Interestingly, with (mismatched) (*R*)-tol-BINAP the stereoselectivity switched to afford the (*S*,*S*)-diastereomer albeit with a lower diastereomeric ratio (entry 7). Superior catalyst control was observed with the commercially available chiral bicyclo[2.2.2]octadiene (DOLEFIN) ligands described by Carreira and co-workers.[6] Thus, the matched (*S*,*S*,*S*)-ligand gave the (*S*,*R*)-diastereomer in high yield and with excellent diastereoselectivity (entry 8). The mismatched (*R*,*R*,*R*)-ligand also provided product with useful selectivity for the (*S*,*S*)-diastereomer (entry 10).

The synthesis of the enantiomeric substrate *ent*-**1** (from (*R*)-prolinol) allowed the efficient preparation of all four

Table 1. Ligand Control in the Synthesis Of Pyrrolizidinones[a]



entry	ligand	base	% conversion[b] (% yield)[c]	dr ((*S*,*R*)-**3**:(*S*,*S*)-**3**)[d]
1[e]	none	KOH	36	80:20
2[e]	none	LiOH	66	85:15
3[e]	none	Cs_2CO_3	93 (77)	80:20
4	dppp	Cs_2CO_3	98	94:6
5	dppf	Cs_2CO_3	91	96:4
6[f]	(*S*)-BINAP	Cs_2CO_3	98	95:5
7	(*R*)-tol-BINAP	Cs_2CO_3	58	13:87
8	(*S*,*S*,*S*)-DOLEFIN	Cs_2CO_3	97 (89)	99:1
9[g]	(*S*,*S*,*S*)-DOLEFIN	Cs_2CO_3	98	97:3
10	(*R*,*R*,*R*)-DOLEFIN	Cs_2CO_3	99 (94)	10:90

[a] Reaction conditions for 1,4-addition: **1** (1.0 equiv), $PhB(OH)_2$ (4.0 equiv), $[Rh(C_2H_4)_2Cl]_2$ (3 mol %), ligand (7 mol %), base (1.0 equiv), dioxane/H_2O (10:1), 100 °C, 16 h. [b] Determined by ^1H NMR of the crude mixture of **4a**. [c] Isolated yield of **3a**. [d] Determined by ^1H NMR of the crude mixture after cyclization. [e] $[Rh(cod)Cl]_2$ used as catalyst. [f] $[Rh(C_2H_4)_2(acac)]$ used as catalyst. [g] Using 2 equiv of $PhB(OH)_2$.

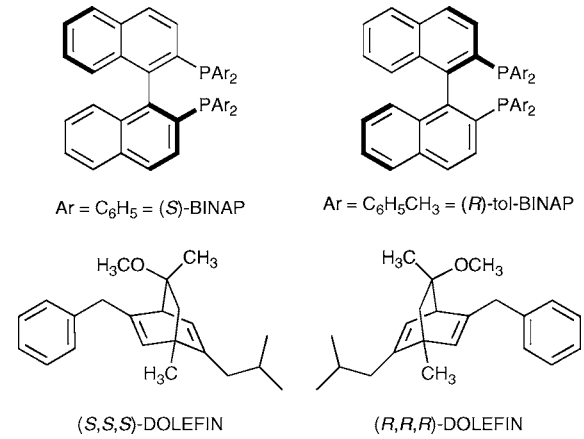
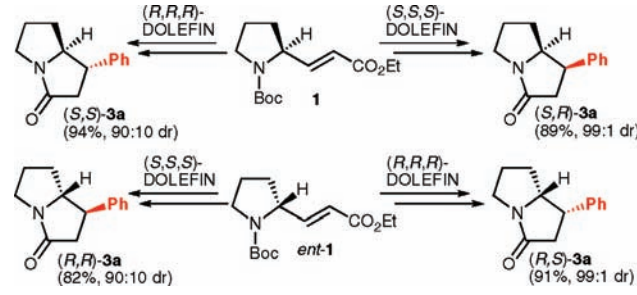


Figure 1. Enantiopure ligands used.

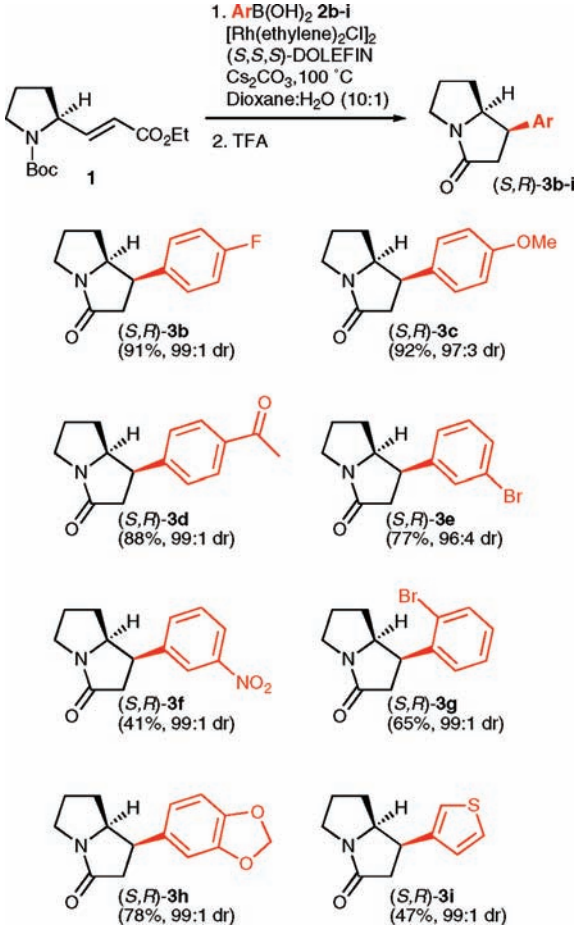
Scheme 2. Matching Substrate and Catalyst for High Selectivity



stereoisomers of pyrrolizidinone **3a** as illustrated in Scheme 2. The rational matching of substrate and catalyst enabled access to the two enantiomeric pyrrolizidinones (*S*,*R*)-**3a** and (*R*,*S*)-**3a** with very high stereoselectivity.

With the optimized set of reaction conditions, we next explored the scope of the process with respect to the boronic acid; in all cases the enantiopure acceptor **1** was employed as substrate. The diastereoselectivity was consistently high for a range of boronic acids (Scheme 3).

Scheme 3. Asymmetric Synthesis of Pyrrolizidinones; Scope of Boronic Acid



The stereochemistry of the major diastereomer was assigned by analysis of ^{1}H NMR and NOE spectra as (*S*,*R*) and confirmed for the crystalline product **3b** by X-ray crystallography (Figure 2).[7] It is useful to note that both electron-donating and electron-withdrawing substituents are tolerated alongside a range of substitution patterns. Lower yields were obtained in the case of 3-nitrophenylboronic acid and 3-thiopheneboronic acid with protodeboronated (hetero)arene observed as a side product from

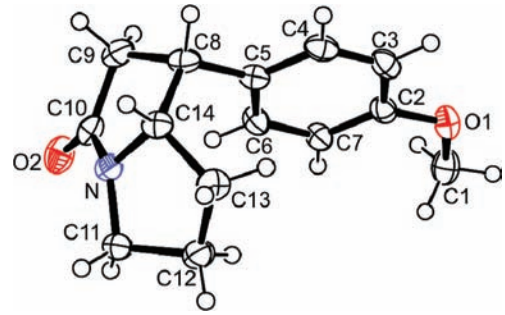
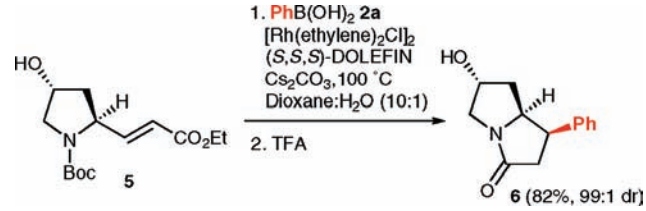


Figure 2. ORTEP drawing of pyrrolizidinone (*S*,*R*)-**3c**.

the conjugate addition. This reflects the lower reactivity of these particular boronic acids in rhodium-catalyzed addition reactions.[8]

To broaden the synthetic scope of the reaction, the asymmetric addition of phenylboronic acid to 4-hydroxyproline derivative **5** was carried out (Scheme 4).[9] Pleasingly,

Scheme 4. Addition to 4-Hydroxyproline Derivative



deprotection of the Boc group and lactamization furnished the hydroxy-functionalized pyrrolizidinone **6** in good yield and high diastereoselectivity.

In conclusion, we have developed a versatile ligand-controlled synthesis of functionalized pyrrolizidinones utilizing the rhodium-catalyzed 1,4-addition of arylboronic acids to enantiopure acceptors generated from commercially available amino acids. Although access to all possible stereoisomers is possible, rational matching of substrate and catalyst results in very high diasteroselectivity. This is observed in

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(7) The relative configuration within **3c** was determined using single crystal X-ray analysis, with the absolute configuration (*S*,*R*) assigned from the known configuration of the (*S*)-stereocenter of the pyrrolidine ring derived from (*S*)-prolinol.

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the case of (*S*,*S*,*S*)-DOLEFIN ligand with (*S*)-**1** and (*R*,*R*,*R*)-DOLEFIN ligand with (*R*)-**1**.

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Supporting Information Available: Experimental procedures, CIF file, and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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