Asymmetric Catalysis

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Catalytic Asymmetric Allylboration of Indoles and Dihydroisoquinolines with Allylboronic Acids: Stereodivergent Synthesis of up to Three Contiguous Stereocenters

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Abstract: *The catalytic asymmetric allylboration of cyclic imines with γ,γ-disubstituted allylboronic acids provides products with adjacent stereocenters in high yield and stereoselectivity. Various electrophiles, including 3,4-dihydroisoquinolines and indoles, were prenylated in a fully stereodivergent fashion by switching the E/Z geometry of the allylboronate and/or the enantiomer of the BINOL catalyst. 3-Methylindole provided products with three adjacent stereocenters with high stereoselectivity in one synthetic operation.*

The allylboration reaction has become an indispensable method for the stereoselective synthesis of homoallylic alcohols and amines.[1] Recently, our group described the first catalytic asymmetric synthesis of homoallylic alcohols from γ,γ-disubstituted allylboronic acids and ketones, furnishing products bearing adjacent quaternary stereocenters.[2] Extending this reaction to imines for the synthesis of chiral amines with adjacent stereocenters is important as these motifs are common in drug-like molecules and natural products.[3] In addition, a comparison of the asymmetric allylboration of ketones and imines using similar catalysts is highly interesting in terms of the stereoinduction.

Although great progress has been made towards the allylboration of imines,[4] asymmetric examples have remained sparse.[5] Hoveyda[5f] and co-workers recently reported on the catalytic asymmetric allylboration of phosphinoyl imines, which provides access to enantioenriched products containing adjacent stereocenters. While this work is impressive, the substrate scope is currently limited to monosubstitution at the γ-position of the allylboronate, and only the *anti* products could be formed. A complementary approach has been reported by the Aggarwal group[5g] for the enantiospecific allylboration of imines, ketimines, and indoles with enantioenriched γ,γ-disubstituted allylboronates. This method is impressive in its ability to provide amines with adjacent quaternary stereocenters in a stereodivergent manner, yet it proceeds through chirality transfer and requires enantioenriched precursors. Merging the merits of these two methods into a manifold wherein achiral γ,γ-disubstituted allylboronates undergo allylboration with imines in a catalytic asymmetric fashion would be highly desirable. In our quest to fill this niche, we thought that the allylboration of indole would be a fertile proving ground. Allylborations at the C2 position of indole have been reported by the groups of Aggarwal,[5g] Batey,[6] Bubnov,[7] and our group.[4c] A formidable challenge is to realize these reactions by asymmetric catalysis.

In our previous studies,[4c] we found that a highly diastereoselective allylboration of indole could be achieved under mild conditions using a γ,γ-disubstituted geranylboronic acid, thus forming an indoline bearing an exocyclic quaternary stereocenter. Chong[5b] and Wu have reported on the asymmetric allylboration of cyclic imines using BINOL modified allylboronates whereas the Schaus group[8] described the BINOL-catalyzed asymmetric crotylboration of highly reactive acyl imines. These studies, together with our previous experience,[2] suggested that BINOL-catalyzed allylborations are a promising synthetic method for the catalytic asymmetric allylation of indoles with allylboronic acids.

After extensive optimization, we found that (*S*)-3,3′-dibromo-BINOL (**3a**) catalyzed the efficient, highly diastereo- and enantioselective allylboration of indole (**2a**) with geranylboronic acid (**1a**) under mild conditions (Table 1, entry 1). Interestingly, commercially available **3a** has been shown to be one of the best catalysts for the asymmetric allylboration of ketones as well.[2] Performing the reaction in the absence of methanol substantially decreased the selectivity from 99% *ee* to 56% *ee* (compare entries 1 and 2). Hexafluoroisopropanol (HFIP) instead of MeOH also performed well as an additive but the *ee* and the yield were somewhat lower (entry 3). We also studied the effect of the BINOL substituents on the outcome of the reaction. When **3a** was replaced with non-substituted BINOL **3b**, **1a** did not react at all with **2a** (entry 4). This finding indicates the importance of non-hydrogen substituents at the 3- and 3′-positions for both stereoinduction and catalyst turnover. Indeed, iodo-substituted BINOL **3c** catalyzed the reaction with high enantioselectivity, albeit with low yield (entry 5). With bis(trifluoromethyl)phenyl-substituted BINOL **3d**, the yield (88%) and the *ee* value (94%) were close to the corresponding values observed for **3a** (compare entries 1 and 6). Partially saturated BINOL **3e** and phosphoric acid **3f**

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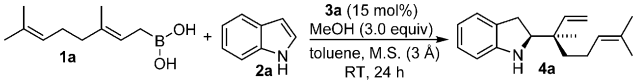
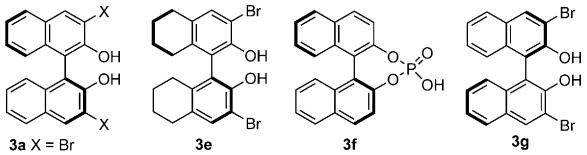
Table 1: Optimization of the reaction conditions for the catalytic asymmetric allylboration of indole with geranylboronic acid.[a]



Entry	Reaction conditions	*ee* [%][b]	Yield [%][c]
1	as is	99	94
2	no alcohol	56	67
3	HFIP instead of MeOH	96	86
4	**3b** instead of **3a**	no conversion	
5	**3c** instead of **3a**	98	12
6	**3d** instead of **3a**	94	88
7	**3e** instead of **3a**	no conversion	
8	**3f** instead of **3a**	no conversion	
9	with 1 equiv of DMSO	90	44

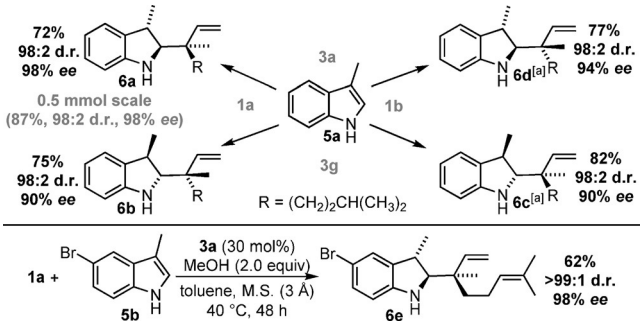
[a] **2a** (0.1 mmol), **1a** (0.15 mmol), MeOH (0.3 mmol), and **3a** (0.015 mmol, 15 mol%) were stirred in toluene (0.25 mL) at RT for 24 h. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Yield of isolated product.



(similar to the one successfully used for the catalytic asymmetric allylboration with allyl–Bpin derivatives)[9] could not be used as catalysts for this reaction (entries 7 and 8). The addition of one equivalent of DMSO was shown to inhibit the reaction (entry 9), presumably by reducing the reactivity of the boronate through Lewis acid–base interactions.

Subsequently, we studied the substrate scope of the reaction for three γ,γ-disubstituted terpene-derived boronic acids, **1a**–**1c** (Table 2), and various substituted indole derivatives (**2b**–**2d**). The allylation proceeded smoothly using both geranyl- and nerylboronic acids with brominated indole **2b**, providing the epimeric products **4b** and **4c** with high enantio- (90–98% *ee*) and diastereoselectivity (entries 1 and 2). A methoxy group at the same position was equally tolerated, providing the epimeric pair **4d** and **4e** with high selectivity (entries 3 and 4). Notably, a Bpin group on indole **2d** was unaffected, allowing for the isolation of compound **4f** (entry 5), which is primed for further elaboration of the C–B bond. Prenylboronic acid (**1c**) could also be used for allylboration and provided the corresponding product with high enantioselectivity (90% *ee*, entry 6).

The groups of Buchwald[10] and Carreira[11] have recently highlighted the importance of exploiting stereodiversity in molecules containing adjacent stereocenters, especially within the realm of medicinal chemistry. In line with this, the stereodivergent synthesis of all three stereoisomers (**4h**–**4j**) of **4a** was also conducted through the addition of either stereoisomeric boronic acids **1a** or **1b** to indole **2a** with **3a** or its enantiomer **3g** as the catalyst (entries 7–10).



Scheme 1. Synthesis of prenylated indolines with three adjacent stereocenters. Reaction conditions: **5a** (0.1 mmol), **1** (0.15 mmol), MeOH (0.2 mmol), and **3a** or **3g** (0.03 mmol, 30 mol%) were stirred in toluene (0.25 mL) in the presence of molecular sieves at 40°C for 48 h. [a] Stirred for 60 h.

Encouraged by the above results (entries 7–10), we wondered whether a similar level of stereocontrol could be harnessed in the reaction of C3-methylated indole, skatole (**5a**; Scheme 1). Upon allylation and saturation of the C2–C3 double bond, the resultant product would contain three contiguous stereocenters. Notably, examples of generating this level of stereochemical complexity in a single reaction step are generally reserved for cyclization reactions.[12] The desired reaction was feasible when the catalyst loading (30 mol%) was slightly increased and 2 equivalents of MeOH were used as the additive. Accordingly, the reaction between **1a** and **5a** to furnish **6a** proceeded in good yield (72%) and excellent enantioselectivity (98% *ee*). This reaction could also be scaled to 0.5 mmol with an increased yield (87%) at the same level of stereoselectivity. Again, the stereodivergent synthesis of half (**6a**–**6d**) of the possible stereoisomers was executed with similar levels of stereocontrol (90–98% *ee*). To determine the absolute configurations of these products, brominated skatole **5b** was prenylated under the same conditions as **5a**, providing indoline **6e**. Conversion of **6e** into the corresponding hydrochloride salt provided crystals suitable for X-ray analysis and insight into the stereoinduction of this system (Scheme 1).

Based on the above results we propose a model for the stereoselectivity observed in the allylboration of indoles,

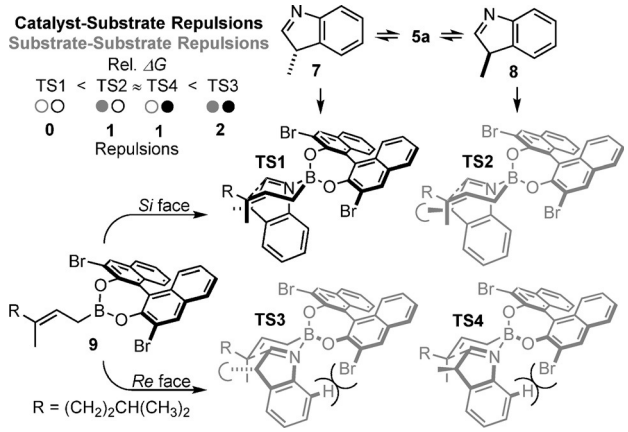
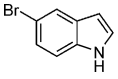
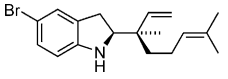
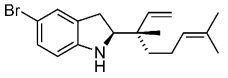
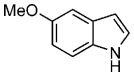
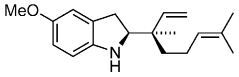
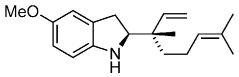
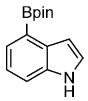
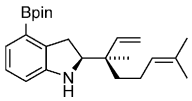
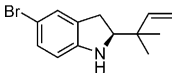
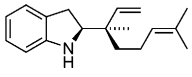
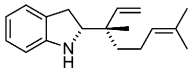
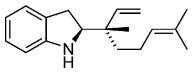
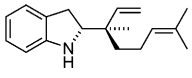
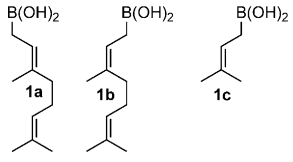


Figure 1. Stereoinduction model for the prenylation of skatole.

Table 2: Synthetic scope of the asymmetric prenylation of indoles.[a]

Entry	Boronic acid	Indole	Cat.	Product	Yield [%]	d.r.	*ee* [%]
1	**1a**	 **2b**	**3a**	 **4b**	93	99:1	90
2	**1b**	**2b**	**3a**	 **4c**	76	98:2	98
3	**1a**	 **2c**	**3a**	 **4d**	84	98:2	90
4	**1b**	**2c**	**3a**	 **4e**	60	97:3	90
5	**1a**	 **2d**	**3a**	 **4f**	79	97:3	98
6	**1c**	**2b**	**3a**	 **4g**	87	NA	90
7[b]	**1a**	**2a**	**3a**	 **4a**	94	97:3	99
8[b]	**1a**	**2a**	**3g**	 **4h**	86	97:3	94
9[c]	**1b**	**2a**	**3a**	 **4i**	74	98:2	92
10[c]	**1b**	**2a**	**3g**	 **4j**	86	97:3	90

[a] **2** (0.1 mmol) **1** (0.15 mmol), MeOH (0.3 mmol), and **3a** or **3g** (0.015 mmol, 15 mol%) were stirred in toluene (0.25 mL) in the presence of molecular sieves (M.S.) at 40°C. [b] At room temperature. [c] 36 h.



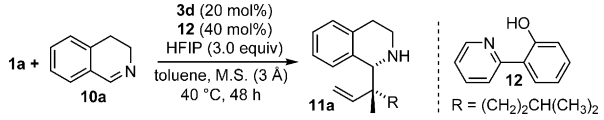
using skatole (**5a**) as an example (Figure 1). **5a** and its enantiomeric pair of reactive imine tautomers, **7** and **8**, are in equilibrium in the presence of the boronic acid.[4c,7] Depending upon which of these enantiomers merges with intermediate **9** and from which face it is attacked, four possible Zimmerman–Traxler (ZT) transition states (**TS1**–**TS4**) are possible.[13] Two of these transition states, namely **TS2** and **TS3**, can be immediately dismissed as unlikely owing to steric clashes between the C3 methyl group of **7** and **8** and the axial substituent at the γ-position of allylboronate intermediate **9**. Similarly, **TS3** and **TS4** can be discounted by evoking steric repulsion between the C7–H bond of the indole ring and the C–Br bond of BINOL. Thus **TS1** does not suffer from significant steric hindrance and is the most likely transition state. In this enantioselection process (Figure 1), the stereodifferentiation between the tautomeric forms **7** and **8** can be regarded as a boronic acid mediated dynamic kinetic resolution.

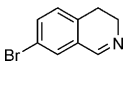
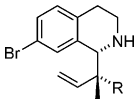
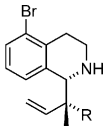
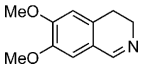
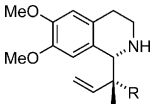
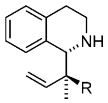
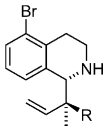
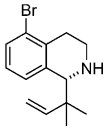
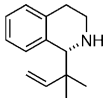
We envisioned that the catalytic cycle (given in the Supporting Information) of the allylboration of skatole (**5a**) would resemble that of our previously disclosed reaction with ketones.[2] The crucial additive, MeOH, has a dual role in the catalytic cycle: It is used for the esterification of the $RB(OH)_2$ group of the allylboronic acid, decreasing its reactivity and silencing the racemic background reaction[4c] while assisting in the liberation of the catalyst from the product. This explains why in the absence of MeOH (Table 1, entry 2), the reaction proceeds with poor enantioselectivity (56% *ee*) while providing the product in fairly good yield.

To further expand the synthetic scope of the highly selective allylboration, we also studied reactions of a related cyclic imine, dihydroisoquinoline (**10a**). Chong and Wu have shown[5b] that the parent (unsubstituted) allylboronate can be used for the asymmetric allylboration of **10a**. In their approach,[5b] stoichiometric amounts of BINOL derivatives were used to prepare BINOL-modified allylboronates, which were subsequently reacted with **10a**. We thought that our organocatalytic stereoinduction concept (Figure 1) could be applied for the allylboration of 3,4-dihydroisoquinolines with γ,γ-disubstituted allylboronic acids as well, providing facile access to enantioenriched α-prenylated tetrahydroisoquinolines, which are biologically relevant building blocks.[14] Using the same reaction conditions for the allylboration of dihydroisoquinoline (**10a**) that gave high yields and high selectivities for indole **2a** (94% yield, 99% *ee*) led to an inefficient process as **11a** was formed in 67% yield and 24% *ee* (Table 3, entry 1). However, slight changes in the reaction conditions substantially improved the yield and enantioselectivity. The use of BINOL derivative **3d** led to a high level of selectivity in the stoichiometric asymmetric allylation of **10a** reported by the Chong group.[5b]

We hypothesized that this catalyst would be more effective than **3a** for this class of electrophiles. Furthermore, we found that HFIP was superior to MeOH as an additive in this reaction. Interestingly, the addition of catalytic amounts

Table 3: Prenylation of 3,4-dihydroisoquinolines.[a]



Entry	Boronic acid	Dihydro-isoquinoline	Cat.	Product	Yield [%]	*ee* [%]
1[b]	**1a**	**10a**	**3a**	**11a**	67	24
2	**1a**	**10a**	**3d**	**11a**	74	90
3	**1a**	 **10b**	**3d**	 **11b**	72	91
4	**1a**	 **10c**	**3d**	 **11c**	66	87
5	**1a**	 **10d**	**3d**	 **11d**	42	93
6	**1b**	**10a**	**3d**	 **11e**	77	97
7	**1b**	**10c**	**3d**	 **11f**	72	96
8	**1c**	**10c**	**3d**	 **11g**	97	82
9	**1c**	**10a**	**3d**	 **11h**	81	89

[a] **10** (0.1 mmol), **1** (0.12 mmol), HFIP (0.3 mmol), **12** (0.04 mmol), and **3d** (0.02 mmol, 20 mol%) were stirred in toluene (0.25 mL) in the presence of molecular sieves at 40 °C for 48 h. In all reactions, a single diastereomer was formed. [b] Similar reaction conditions as for the allylboration of indole **2a**: **10** (0.1 mmol), **1** (0.15 mmol), MeOH (0.3 mmol), and **3a** (0.02 mmol, 20 mol%) were stirred in toluene (0.25 mL) at RT.

of pyridylphenol **12** was beneficial in obtaining high yields. Compound **12** has previously been used for the synthesis of stabilized acylboronates,[15] demonstrating its favorable bidentate interaction with boron centers. We assume that this favorable interaction with the boron center aids in catalyst turnover. All of these changes led to substantial improvements of the yield and selectivity of the allylboration of **10a**, affording **11a** in 74% yield and 90% *ee* (entry 2).

A variety of 3,4-dihydroisoquinolines **10b–10d** could be allylated under these optimized conditions in good to excellent enantioselectivities. Similar to the indole case, the yields and selectivities were high in the presence of an electron-withdrawing bromine (**10b–10c**) substituent (entries 3 and 4). We obtained crystals of the hydrochloride salt of **11b** that were suitable for X-ray structure determination. The absolute configurations of the prenylated isoquinoline derivatives **11a–11h** were assigned on the basis of these X-ray structural data. The high selectivity of the allylboration (93% *ee*) was maintained (entry 5) in the presence of methoxy groups (**10d**) while the yield was only modest (42%). When geranylboronic acid (**1a**) was replaced with nerylboronic acid (**1b**), the epimeric products **11e** and **11f** were obtained (entries 6 and 7) with very high diastereoselectivity and high enantioselectivity (96–97% *ee*). Similar to the indole case, prenylboronic acid **1c** reacted smoothly (entries 8 and 9) but with slightly lower enantioselectivity (82–89% *ee*) than the geranyl and neryl analogues (for a model of the stereoinduction, see the Supporting Information).

In summary, a highly regio-, diastereo-, and enantioselective allylboration of cyclic imines, including indoles and 3,4-dihydroisoquinolines, has been achieved using BINOL as the catalyst. The reaction employs differentially γ,γ-disubstituted allylboronic acids, resulting in homoallylic amines bearing adjacent tertiary and quaternary stereocenters. The reaction is stereodivergent and can provide the full tetrad of stereoisomers by changing the catalyst and/or the stereochemistry of the allylboronic acids. In the case of skatole (3-methylindole), products bearing three adjacent stereocenters were obtained in one step. These reactions provide biologically relevant architectures with both terpene and indoline/tetrahydroisoquinoline moieties and are well suited for exploitation in the realm of total synthesis and medicinal chemistry.

Experimental Section

In a glovebox, a 2 mL vial was charged with molecular sieves, **3a** (7.0 mg, 0.015 mmol), **2a** (12.0 mg, 0.100 mmol), and MeOH (0.3 mmol, 12 μL). Then **1a** (0.15 mmol, 0.25 mL of a 0.4 M solution in toluene) was added, and the reaction mixture was stirred at RT for 24 h. The product was purified by column chromatography on silica gel.

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Keywords: allylboration · asymmetric catalysis · indoles · organocatalysis · stereoselectivity

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