Enantioselective Synthesis

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Organocatalyzed Asymmetric Conjugate Addition of Heteroaryl and Aryl Trifluoroborates: a Synthetic Strategy for Discoipyrrole D**

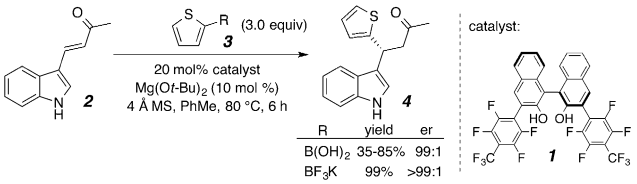
*Jiun-Le Shih, Thien S. Nguyen, and Jeremy A. May**

Abstract: *Bis-heteroaryl or bis-aryl stereocenters were formed by an organocatalytic enantioselective conjugate addition using the respective trifluoroborate salts as nucleophiles. Control studies suggested that fluoride dissociation is necessary in the anhydrous conditions. This strategy is applicable to the synthesis of discoipyrrole D, an inhibitor of BR5 fibroblast migration.*

Bis-heteroaryl and heteroaryl/aryl stereocenters are found in many bioactive compounds, including pharmaceutical agents and natural products.[1] Recent stereospecific[2] and enantioselective[3] C–C bond-forming methods have been reported for such stereocenters that usually rely on transition metal catalysis, limiting functional group tolerance. For example, compatibility with nitrogen-containing or electron-rich heterocycles is rare, although such compounds are important in pharmaceutical development.[4] Additionally, stereospecific approaches require prior synthesis of enantioenriched substrates. Currently, most enantioselective approaches are Friedel–Crafts 1,4-additions that limit the nucleophile's point of substitution. Our recent efforts in the synthesis of α-chiral heterocycles led us to believe that a 3,3′-$(C_7F_7)_2$-BINOL-catalyzed enantioselective addition would enable the use of heteroaryl and aryl nucleophiles to provide an orthogonal approach that was fully compatible with heterocycles.[5]

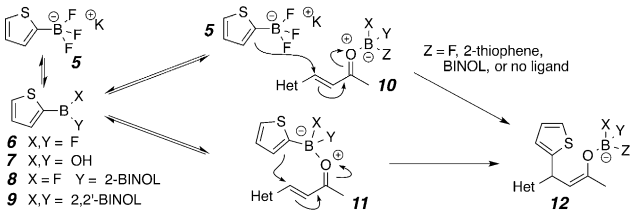
The conjugate addition of vinyl boronates was first reported by Suzuki et al.[6] Later, Chong et al. reported an enantioselective version with 3,3′-I_2-BINOL as a catalyst.[7] Subsequently, they reported the use of neat aryl boronate esters with enones at 120 °C. Harsh conditions were necessary due to the decreased activity of the aryl boronates.[8] These conditions were not shown to be compatible with heterocycles in the electrophile or the nucleophile. Furthermore, the use of boronic acids[9] or trifluoroborate salts would be preferred to boronate esters from a practical standpoint for ease of use and long-term stability.

Our studies led to 3,3′-$(C_7F_7)_2$-BINOL (**1**, Scheme 1) as a sufficiently reactive catalyst for the addition of conveniently handled boronic acids to β-heterocycle-appended enones.[5] In order to define reaction conditions that were strong enough to use aryl boronates as nucleophiles, yet mild enough to be compatible with heterocycles in either reacting partner, we used the model reaction in Scheme 1.



Scheme 1. Thiophenyl/indolyl stereocenter.

2-Thiophene boronic acid was the most reactive nucleophile in a preliminary screen, but the yield of product was 35–85 % depending on boronic acid purity. Careful observation showed that no boronic acid was present after 6 h. Instead, substantial amounts of thiophene were seen from protodeboronation. As the stereoselectivity was high, we postulated that improving the boronate stability would lead to a reliable reaction. In Suzuki couplings, boronate longevity increases with the trifluoroborate salt,[10,11] which hydrolyzes in situ to maintain a low concentration of boronic acid.[12] However, three potential problems for the reaction in Scheme 1 are: 1) the reaction must be anhydrous, preventing hydrolysis of **5** to the boronic acid **7** (Scheme 2), 2) the trifluoroborate salt would be poorly soluble in the nonpolar solvents, and 3) if fluoride dissociation from the trifluoroborate **5** to form difluoro boronate **6** (X,Y = F) were to occur, the latter may be Lewis acidic enough to proceed through a racemic reaction on its own via **11** (X,Y = F).



Scheme 2. Putative reaction mechanism.

With knowledge of these potential problems, we repeated the experiment in Scheme 1 with 2-thiophene potassium trifluoroborate (**3**, R = BF_3K), and butanone **4** was quickly formed in nearly quantitative yield and with exquisite stereoselectivity. While the use of heteroaryl trifluoroborates as nucleophiles without hydrolysis has been reported,[13] those

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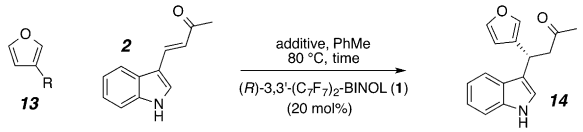
uses involved direct transfer to a highly reactive electrophile (e.g., addition of **5** to **10**, Scheme 2),[14] whereas BINOL catalysis generally proceeds through complex **11** (X,Y = BINOL).[15] An investigation was initiated to determine whether the operative mechanism proceeds through **10** or **11**.

The 3-furanyl trifluoroborate **13** was chosen to study the role of additives since it reacted more slowly than **3** (Table 1, entry 1). The trifluoroborate salt provided consistently good results, and a batch could be used reliably for months (entry 2). The omission of molecular sieves afforded no product (entry 3). These additives could potentially impact fluoride dissociation from the salt **5** to form adducts **8** or **9**, which have been invoked for boronate esters and acids in BINOL catalysis.[6,16,17] The aluminates in the zeolite-based sieves could absorb fluoride, though silicates did not (entry 4).[18] Silyl chlorides, known fluoride scavengers,[19] promoted the reaction, albeit to a lesser extent (entry 5). The addition of exogenous fluoride eliminated all reactivity, further supporting initial fluoride dissociation (entry 6). Thus, the mechanism appears to be fluoride loss to form **6** from **5**, formation of either **8** or **9** by the addition of BINOL, and then intramolecular reaction through **11**.[20]

A wide range of oxygen-, nitrogen-, and sulfur-containing heterocyclic trifluoroborates served as nucleophiles, as well as a styrenyl salt (Table 2, entry 1).[5] Dramatically different reactivity could be seen depending on the point of substitution of the nucleophile (entries 3 and 4). Importantly, the bond formation is controlled by the boron position and not Friedel–Crafts selectivity.[13,21] Benzo-fused heterocycles were slower to react (entries 6–11). Resonance-based electron donating groups gave a rapid reaction, even with halides present (entries 15–17). Rings with a ketone or aldehyde reacted slowly, but provided product in useful yields (entries 5 and 18). A sterically hindered nucleophile reacted admirably (entry 19). All the trifluoroborates gave excellent enantioselectivity. In contrast, boronic acids provided poor reactivity (entry 8) or selectivity (entries 12 and 20).

A range of heteroaryl enone substituents further demonstrated a broad substrate scope (Table 3). Both electron-rich and electron-deficient heterocycles provided product in high yield, though the latter required longer reaction times.[22] The only product not obtained with high stereoselectivity was thiazole **19b**, as the thiazole ring facilitates epimerization of the product (entry 2).[5b] α,β-Unsaturated carbonyls other

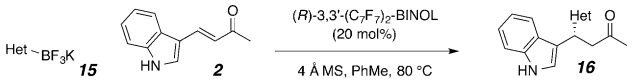
Table 1: Effect of additives in the reaction.

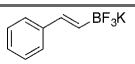
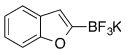
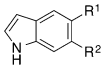
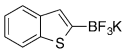
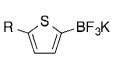


Entry	R	Additive	*t* [h]	Yield [%][a]	e.r.[b]
1	$B(OH)_2$	4 Å MS, $Mg(Ot\text{-}Bu)_2$ (0.1 equiv)	52	50	98:2
2	BF_3K	4 Å MS	50	80	98:2
3	BF_3K	none	48	0	–
4	BF_3K	dried SiO_2	65	0	–
5	BF_3K	TBS-Cl	9	53	91:9
6	BF_3K	4 Å MS, KHF_2	40	<5	–

[a] Determined by integration of ^{1}H NMR signals relative to methyl-4-nitrobenzoate as an internal standard. [b] Ratio determined by HPLC with chiral stationary phase.

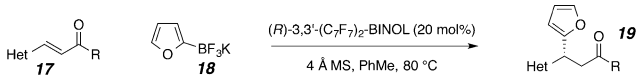
Table 2: Heteroaryl nucleophiles.

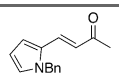
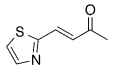
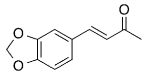
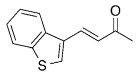
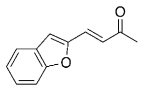
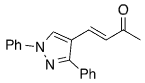
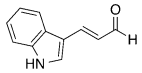
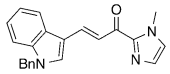


Entry	Nucleophile		Product	*t* [h]	Yield [%][a]	e.r.[b]
1			**16a**	5	97	>99:1
2[c]			**16a**	18	87	98:2
3		$R^1 = BF_3K$, $R^2 = H$, $R^3 = H$	**16b**[d]	9	96	99:1
4		$R^1 = H$, $R^2 = BF_3K$, $R^3 = H$	**16c**	50	86	95:5
5[e]		$R^1 = BF_3K$, $R^2 = H$, $R^3 = CHO$	**16d**	48	67	99:1
6			**16e**	84	94	96:4
7			**16f**	5	74	99:1
8[c]			**16f**	5	19	–
9		$R^1 = BF_3K$, $R^2 = H$	**16g**	51	78	99:1
10		$R^1 = H$, $R^2 = BF_3K$	**16h**	48	97	97:3
11			**16i**	48	87	96:4
12[c]			**16i**	22	63	60:40
13			**16j**[d]	53	99	>99:1
14		R = H	**16k**	7	98	99:1
15		R = Me	**16l**	5	97	>99:1
16		R = Cl	**16m**	6.5	93	99:1
17		R = Br	**16n**	5	97	97:3
18[e]		R = C(O)Me	**16o**	120	69	97:3
19			**16p**	48	89	>99:1
20[c]			**16p**	5	90	70:30

[a] Determined by integration of ^{1}H NMR signals relative to methyl-4-nitrobenzoate as an internal standard. [b] Ratio determined by HPLC with chiral stationary phase. [c] Reaction run with boronic acid. [d] Product characterized by X-ray diffraction to establish absolute stereochemistry. [e] Reaction run at 110 °C in PhCl.

Table 3: Heteroaryl electrophiles.



Entry	Electrophile	Product	*t* [h]	Yield [%][a]	e.r.[b]
1		**19a**	14	80	99:1
2		**19b**	30	94	89:11
3		**19c**	18	94	99:1
4		**19d**	23	85	99:1
5		**19e**	47	93	97:3
6		**19f**	47	93	>99:1
7		**19g**	7	84[c]	98:2
8		**19h**	48	94	99:1

[a] Determined by integration of ^{1}H NMR signals relative to methyl-4-nitrobenzoate as an internal standard. [b] Ratio determined by HPLC with chiral stationary phase. [c] Yield determined after reduction with $NaBH_4$.

than ketones were also examined. Aldehydes were functional, but provided slightly less product (entry 7). Esters and amides failed to provide product, but the excellent reactivity of the 2-acyl imidazole provides a synthetic equivalent for their access (entry 8).[3i,23]

Bis-aryl stereocenters were next examined. Some aryl trifluoroborates reacted well (Table 4, entry 6), but most were sluggish (entry 1). We hypothesized that fluoride dissociation was more difficult for the latter. Lithium salts could potentially drive the dissociation, as LiF formation would be energetically favored versus KF (−146 vs −134 kcal mol^{-1} $\Delta_f H°_{298}$, respectively).[24] LiCl was not effective (entry 2), but LiBr gave a significant increase in product formation (entry 3), allowing molecular sieves to be omitted.[17] The formation of KBr in the reaction would provide a stronger driving force than KCl (−10 kcal mol^{-1} vs −6 kcal mol^{-1}).[23] The use of LiBr proved general for electron-rich aryl trifluoroborate salts (entries 7–12). An alkyl group was a strong enough donor to effect the reaction (entry 13); however, unsubstituted phenyl borate reacted impractically slowly.[17] Halogenated aryls are viable if they also contain a donating group (entry 14). Notably, *ortho* substituted aromatics are excellent nucleophiles (entries 7–14), though they are often problematic in other methods for bisaryl centers.[2,3]

The effect of varying electronic substituents in the β-aryl ring of the electrophile is shown in Table 5. Substitution at the aryl 2-position slowed the reaction (entry 4), but still allowed for product formation in a high yield to provide a bis(*ortho*-aryl) stereocenter. Both electron-rich and deficient rings worked well.

To demonstrate the reaction's utility, a strategy to synthesize discoipyrrole D (**26**)[25] was formed. Several other natural products also contain the 2,3-dihydroxy-1-(3-indolyl)-propyl motif, including cytoblastin (**27**, Figure 1)[26] and the mucronatins (**28** and **29**).[27] Discoipyrrole D inhibits DDR2-dependent migration of BR5 fibroblasts (nonsmall cell lung cancer).[24] Intriguingly, it is formed naturally as a diastereo-

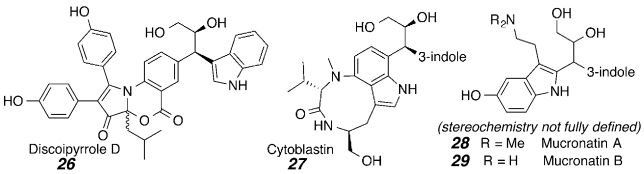
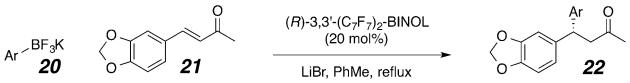
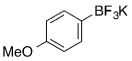
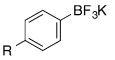
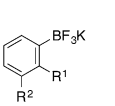
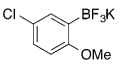


Figure 1. Indolyl propylene oxide natural products.

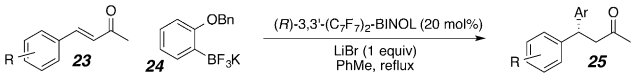
Table 4: Aromatic nucleophiles.



Entry	Nucleophile		Product	*t* [h]	Equiv LiBr	Yield [%][a]	e.r.[b]
1			**22a**	48	N/A[c]	15	–
2			**22a**	48	1.0[d]	53	–
3			**22a**	48	1.0	86	99:1
4			**22a**	48	1.0[e]	10	–
5		R = SMe	**22b**	46	1.0	75	99:1
6		R = NMe_2	**22c**	3	N/A[c]	94	98:2
7		R^1 = OMe, R^2 = H	**22d**	9	1.0	88	99:1
8		R^1 = SMe, R^2 = H	**22e**	15	1.0	97	98:2
9		R^1 = OMe, R^2 = OMe	**22f**	24	1.0	85	>99:1
10		R^1 = OPh, R^2 = H	**22g**	39	1.0	83	94:6
11		R^1 = OBn, R^2 = H	**22h**	17	1.0	92	99:1
12		R^1 = O*i*-Pr, R^2 = H	**22i**	4	2.0	89	98:2
13		R^1 = Me, R^2 = Me	**22j**	48	1.0	76	99:1
14			**22k**	20	2.0	98	95:5

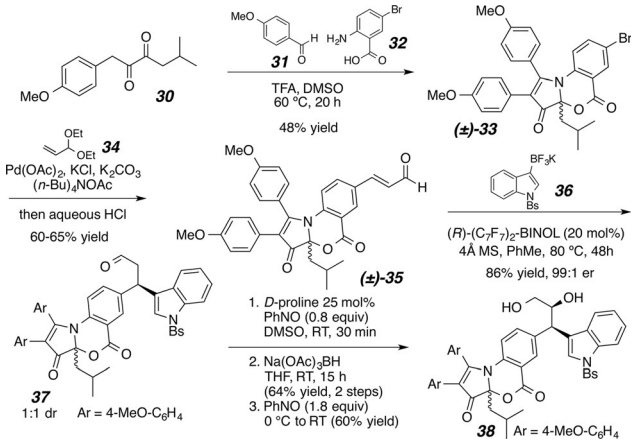
[a] Determined by integration of ^{1}H NMR signals relative to methyl-4-nitrobenzoate as an internal standard. [b] Ratio determined by HPLC with chiral stationary phase. [c] 4 Å MS used instead of LiBr. [d] LiCl used. [e] LiI used.

Table 5: Aryl-conjugated electrophiles.



Entry	R	Product	*t* [h]	Yield [%][a]	e.r.[b]
1	H	**25a**	23	88	>99:1
2	4-Br	**25b**	16	89	>99:1
3	3-Br	**25c**	15	83	95:5
4	2-Br	**25d**	46	86	>99:1
5	4-Cl	**25e**	20	81	97:3
6	4-F	**25f**	20	81	97:3
7	4-*t*Bu	**25g**	48	81	95:5
8	4-OMe	**25h**	15	83	>99:1
9	4-CF_3	**25i**	22	95	>99:1
10	4-Ph	**25j**	15	91	99:1
11	4-OH	**25k**	24	50	>99:1

[a] Determined by integration of ^{1}H NMR signals relative to methyl-4-nitrobenzoate as an internal standard. [b] Ratio determined by HPLC with chiral stationary phase.



Scheme 3. Strategy for discoipyrrole D synthesis.

meric mixture, with the stereocenters α and β to the indole invariant.

The three-component coupling of **30**, **31**, and **32** provided 22-Br-discoipyrrole A (**33**, Scheme 3).[24] At this point, the choice was made to incorporate **33** as the β-substituent of the enal **35** through a Heck reaction[28] since the carbonyl groups were likely to make it a poor nucleophile. Despite the discoipyrrole core being highly prone to decomposition,[17] the protected 3-indole trifluoroborate salt **36** reacted beautifully with high stereoselectivity. A proline-controlled oxidation,[29] followed by stepwise reduction[30] provided protected discoipyrrole D (**38**) in five transformations from the known compound **33**.

In conclusion, we report the organocatalyzed enantioselective formation of bis-heteroaryl and bis-aryl stereocenters. The use of nucleophilic trifluoroborate salts proved essential for reproducible reactivity. Preliminary studies indicate that fluoride dissociation is important for reactivity, which is highly unusual given the anhydrous conditions. The reaction performs well with *ortho*-substituted aryl nucleophiles and a broad scope of β-aryl enones and enals. This method formed the foundation of a short strategy to synthesize dihydroxyindolyl propane natural products.

Keywords: bis-aryl stereocenters · enantioselective catalysis · heterocycles · organocatalysis · trifluoroborate salts

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