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Synthetic Methods

Enantioselective Copper-Catalyzed Borylative Cyclization for the Synthesis of Quinazolinones

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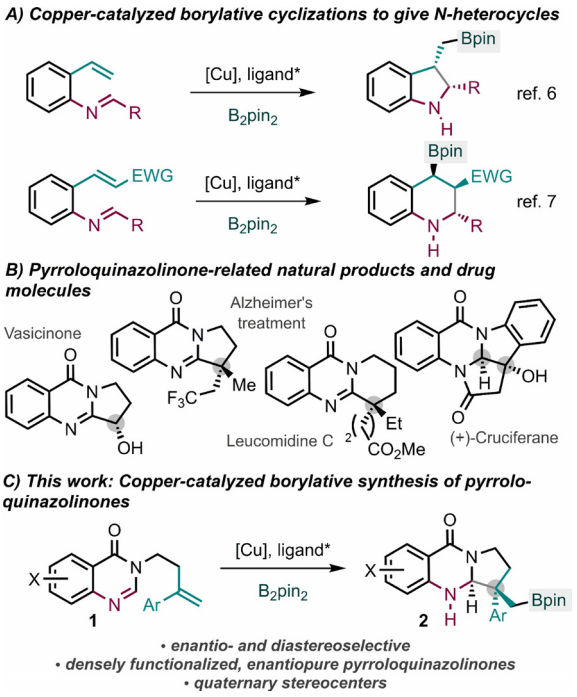
Abstract: *Quinazolinones are common substructures in molecules of medicinal importance. We report an enantioselective copper-catalyzed borylative cyclization for the assembly of privileged pyrroloquinazolinone motifs. The reaction proceeds with high enantio- and diastereocontrol, and can deliver products containing quaternary stereocenters. The utility of the products is demonstrated through further manipulations.*

Since the seminal reports of Hosomi[1] and Miyaura,[2] the copper-catalyzed borylative functionalization of olefins has emerged as a powerful method for stereocontrolled, complex molecule construction.[3] Subsequent studies by Ito and Sawamura,[4] and others,[5] have shown the utility of this process in cyclization reactions. In particular, several groups have used this strategy to construct valuable nitrogen-containing heterocycles, such as indolines[6] and tetrahydroquinolines[7] (Scheme 1 A). In particular, Lautens has recently described a copper-catalyzed stereoselective synthesis of tetrahydroquinolines through a conjugate borylation/Mannich cyclization cascade.[7a] This process illustrates the potential of copper-catalyzed borylative cyclizations by: 1) forming several stereocentres with high control; 2) incorporating a boron group that can undergo further derivatization; 3) preparing an important class of nitrogen-containing heterocycle, in this case tetrahydroquinolines

Quinazolinones display important bioactivity.[8] In particular, pyrroloquinazolinones are common tricyclic motifs found in drug molecules and natural products (Scheme 1 B). It is important to prepare these compounds enantioselectively as quinazolinone enantiomers can display different bioactivities.[9] Few current methods for the construction of quinazolinones are enantioselective,[8,10] and classical chiral resolution and chiral pool synthesis are typically used, for example, to access the enantiopure quinazolinones shown in Scheme 1 B.[11] More recently, dihydroquinazolinones have been prepared enantioselectively, typically from 2-aminobenzamide and aldehydes,[12] however, few enantioselective methods extend to the delivery of important pyrroloquinazolinone scaffolds.[12h] Thus, new enantioselective approaches to pyrroloquinazolinone building blocks are needed for the synthesis of known and as yet unknown bioactive targets.



Scheme 1. Copper-catalyzed borylative cyclizations for the enantioselective synthesis of N-heterocycles. A) Enantioselective approaches to indolines and tetrahydroquinolines. B) Biologically active pyrroloquinazolinones. C) Enantioselective, copper-catalyzed borylative synthesis of pyrroloquinazolinones.

We recognized that the enantioselective, copper-catalyzed borylative cyclizations of substrates **1**, involving intramolecular addition of an organocopper intermediate to a C=N electrophile,[3a] would constitute a valuable route to important enantiomerically enriched pyrroloquinazolinone derivatives **2** (Scheme 1 C). The resulting new process is highly enantio- and diastereoselective, uses an inexpensive and non-toxic catalyst, and exploits commercially available chiral ligands.

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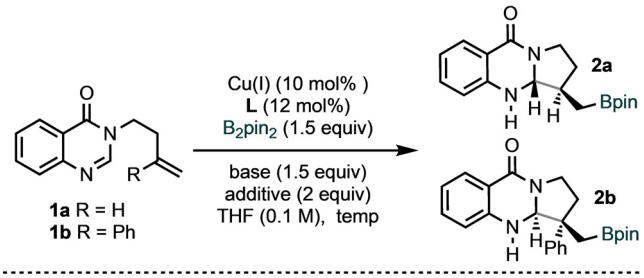
Furthermore, through subsequent derivatization, a variety of potentially bioactive quinazolinones can be accessed.

We initially examined the borylative cyclization of substrate **1a** using CuCl and ligand Ph-BPE (**L1**, Table 1). Although this ligand is commonly used in related copper-catalyzed functionalizations, its use here proved ineffective (Table 1, entry 1).[13] Fortunately, screening of other phosphine ligands (Table 1, entries 1–3) revealed both ligands **L2** ((*S*,*S*)-BDPP)[5f,g,i] and **L3** ((*R*)-QuinoxP®)[4a,b,5j] gave the product **2a** with encouraging enantiocontrol, albeit in moderate yield. Additional phosphine and NHC ligands that have been used in previous borylative functionalizations were unsuccessful here (See Supporting Information).[14] We then tested copper sources, bases and solvents (Table 1, entries 4–6) and found $Cu(MeCN)_4PF_6$ with KO*t*Bu in THF to be optimal (Table 1, entry 6).

Interestingly, the addition of alcohols greatly influenced the yield of the process (Table 1, entries 7 and 8), and **2a** was isolated in high yield, with excellent diastereo- and enantiocontrol (Table 1, entry 8). The exact role of the alcohol in this process remains unclear although it may facilitate catalyst turnover by protonation of a copper–amide intermediate to deliver product and regenerate a copper alkoxide.[15] Finally, we tested the phenyl-substituted substrate **1b** under our optimized conditions (Table 1, entries 9 and 10). Although ligand **L3** was unsuccessful (Table 1, entry 9), the product **2b** was isolated in excellent yield and with very high diastereo- and enantiocontrol when using ligand **L2** (Table 1, entry 10). Exposing substrate **1a** to the latter conditions gave **2a** in substantially reduced yield (Table 1, entry 11).

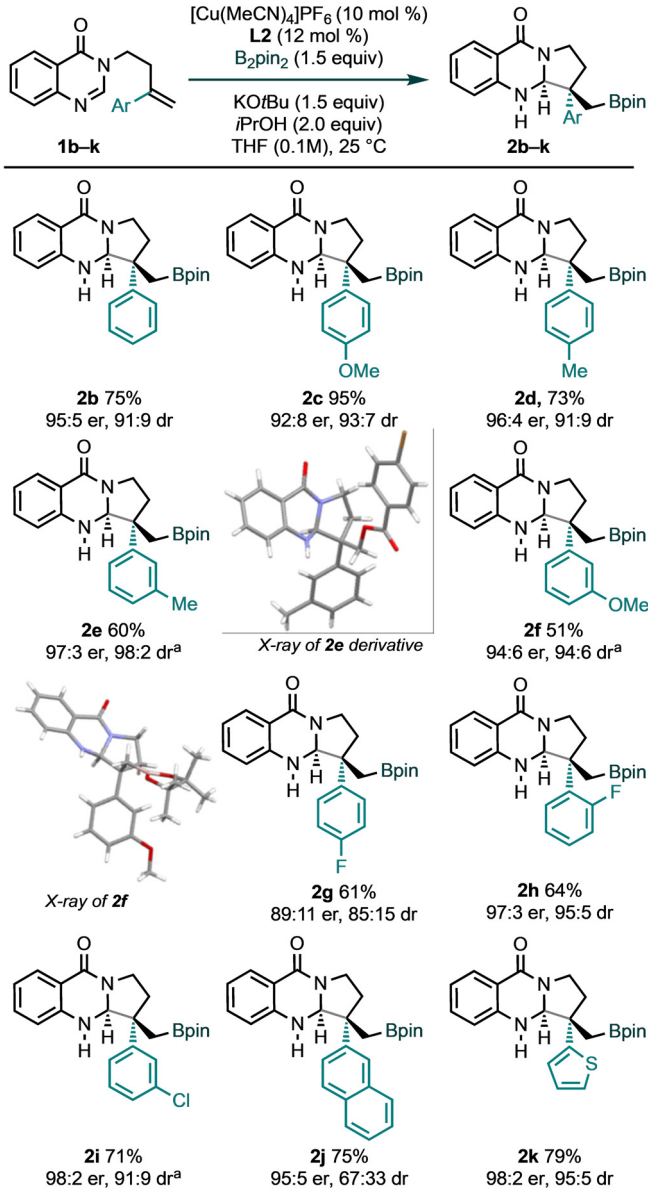
We next explored the performance of various aryl-substituted alkenes **1b**–**1k** in the process (Scheme 2). In almost all cases, borylative cyclization and construction of two adjacent stereocentres—including a quaternary stereocentre—proceeded efficiently to deliver pyrroloquinazolinones **2b**–**k** with very good to excellent enantio- and diastereocontrol. For example, aryl groups bearing electron-rich substitu-

Table 1: Reaction optimization.[a]



Entry	Cu[I]	Additive	Ligand	Yield	dr	er
1[b,c]	CuCl	–	**L1**	10	83:17	64:26
2[b,c]	CuCl	–	**L2**	51	>95:5	83:17
3[b,c]	CuCl	–	**L3**	15	>95:5	79:21
4[b,d]	CuCl	–	**L3**	10	>95:5	98:2
5[b,d,e]	CuCl	–	**L3**	11	>95:5	95:5
6[b,d]	$Cu(MeCN)_4PF_6$	–	**L3**	35	>95:5	94:6
7[b,d]	$Cu(MeCN)_4PF_6$	*t*BuOH	**L3**	85	>95:5	84:16
8[b,d]	$Cu(MeCN)_4PF_6$	*i*PrOH	**L3**	82	>95:5	93:7
9[d,f]	$Cu(MeCN)_4PF_6$	*i*PrOH	**L3**	87	80:20	58:42
10[d,f]	$Cu(MeCN)_4PF_6$	*i*PrOH	**L2**	75	91:9	95:5
11[b,d]	$Cu(MeCN)_4PF_6$	*i*PrOH	**L2**	10	87:13	95:5

[a] For further details of the reaction optimization, see the Supporting Information. Reaction conditions: **1** (0.2 mmol), B_2pin_2 (0.3 mmol), Cu^I (10 mol%), ligand (12 mol%) in THF (2.0 mL) at 25 °C or 35 °C for 2–6 h under nitrogen. The diastereoselectivity was determined by ^1H NMR analysis of the crude product mixtures. NMR yields are given. [b] With **1a** to give **2a.** [c] Using NaO*t*Bu (1.5 equiv). [d] Using KO*t*Bu (1.5 equiv). [e] Using dioxane (0.2 M). [f] With **1b** to give **2b**.

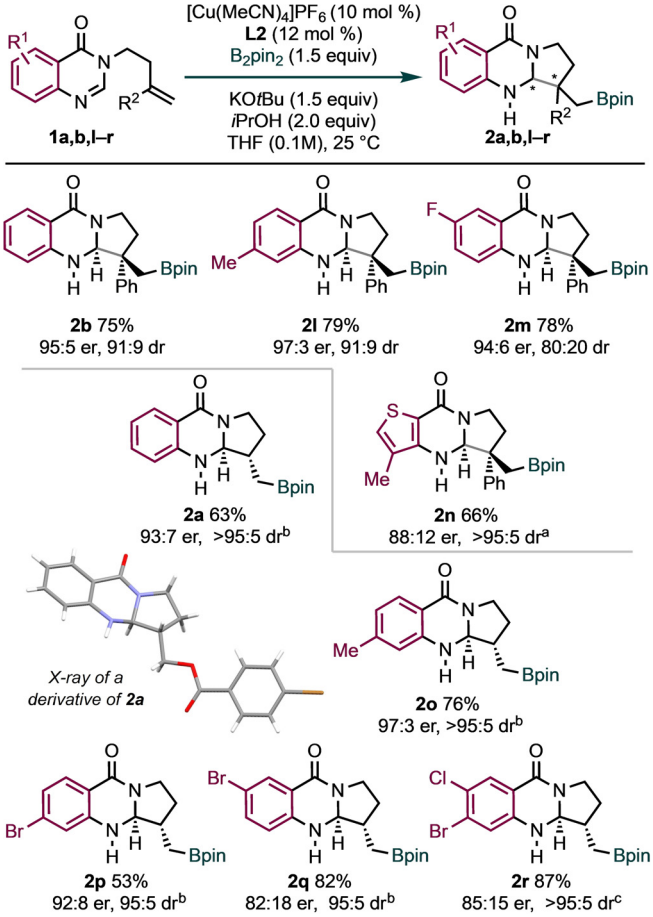


Scheme 2. Scope with respect to the alkene. Reaction conditions: **1** (0.2 mmol), B_2pin_2 (0.3 mmol), $[Cu(MeCN)_4]PF_6$ (0.02 mmol), **L2** (0.024 mmol), KO*t*Bu (0.3 mmol in 1 M sol. THF), *i*PrOH (0.4 mmol) in THF (1.7 mL) at 25 °C for 2–4 h under nitrogen. Yields of isolated product are given. The diastereoselectivity was determined by ^1H NMR analysis of the crude products and er values were measured by HPLC on chiral stationary phase. [a] Reaction run at 0 °C.

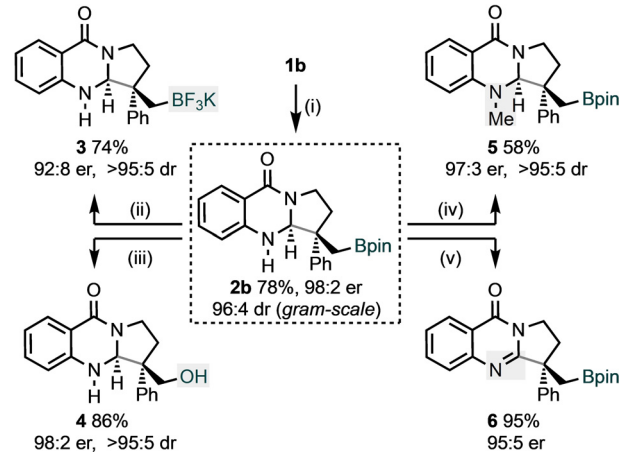
ents at both *meta*- and *para*-positions gave products with very high enantiocontrol (**2c–2f**). *Ortho*-, *meta*- and *para*-halogenated aryl groups were also well tolerated (**2g–2i**). Finally, substrates bearing 2-napthyl and 2-thienyl groups gave the desired products in high yield and with excellent enantiocontrol (**2j**, **2k**). Additional substrates bearing heteroaryl groups gave rise to unstable products (see Supporting Information). The relative and absolute stereochemistry of the products was determined by X-ray crystallographic analysis of a derivative of **2e** and **2f**.[16]

Various substitution on the aryl ring of the amidine component of **1** was also tolerated (Scheme 3). For example, the methyl- and fluorine-containing products **2l** and **2m** were obtained in high yield and with good to excellent enantiocontrol. A thiophene-fused substrate was also compatible with our standard conditions to give **2n** with moderate enantiocontrol. Building on our initial optimization (Table 1, entry 8), we investigated the scope of the process with additional monosubstituted alkene substrates **1o–r**. The product **2o** was obtained in high yield and with excellent diastereo- and enantiocontrol, thus suggesting that electron-rich substrates are particularly well-suited to the process. Halogenated substrates were also tested (**2p–2r**); borylative cyclization proceeded well, albeit with lower enantiocontrol for substrates **1q** and **1r**. The relative and absolute stereochemistry of the products **2a**, **2o–2r** was assigned after X-ray crystallographic analysis of a derivative of **2a**.[16] Substrates bearing substitution at the terminus of the alkene proved unreactive (see Supporting Information).

The functionality in the dihydroquinalozinone products **2** presents opportunities for further transformations (Scheme 4). The material (**2b**) for these transformations was obtained by performing the enantioselective, borylative cyclization on a gram-scale; essentially identical yield,



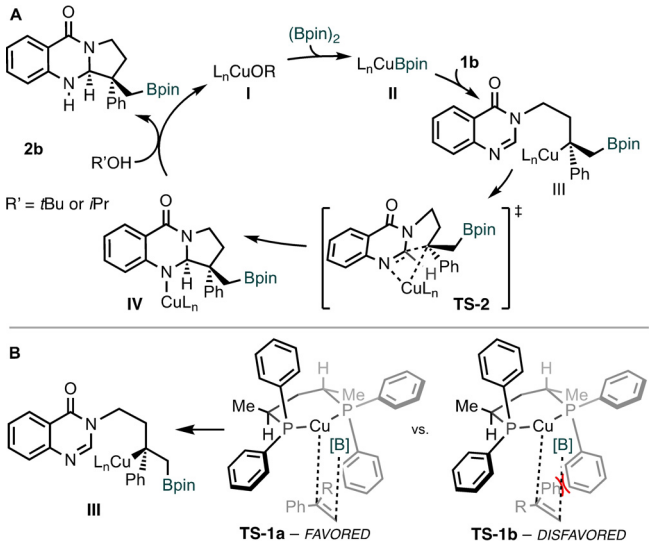
Scheme 3. Scope with respect to the amidine. Reaction conditions: **1** (0.2 mmol), B_2pin_2 (0.3 mmol), $[Cu(MeCN)_4]PF_6$ (0.02 mmol), **L2** (0.024 mmol), KO*t*Bu (0.3 mmol in 1 M sol. THF), *i*PrOH (0.4 mmol) in THF (1.7 mL) at 25 °C or 30 °C for 2–4 h under nitrogen. Yields of isolated product are given. The diastereoselectivity was determined by ^{1}H NMR analysis of the crude products. *ee* values were measured by HPLC on chiral stationary phase. [a] Reaction was run without *i*PrOH. [b] B_2pin_2 (0.4 mmol), KO*t*Bu (0.4 mmol in 1 M sol. THF) and (*R*)-QuinoxP® **L3** (0.024 mmol) were used. [c] (*R*,*R*)-(−)-2,3-bis(*tert*-Butylmethylphosphino)benzene (BenzP*; 0.024 mmol) was used as a ligand.



Scheme 4. Gram-scale reaction and derivatizations of **2b**. Conditions: (i) see Scheme 2; (ii) KHF_2 4 equiv, MeOH/H_2O, 0 °C to RT; (iii) H_2O_2 2 equiv, K_2CO_3 2 equiv, THF, −20 °C; (iv) NaH 1.5 equiv, MeI 1.5 equiv, THF, 0 °C to RT; (v) DDQ 1.5 equiv, CH_2Cl_2, 0 °C to RT.

enantio- and diastereocontrol were observed (c.f. Table 1, entry 10). We first converted product **2b** into the trifluoroborate salt **3**,[17] and the alcohol **4**; the latter by oxidation with H_2O_2. Methylation of the free amine group was also carried out to give product **5**. Finally, oxidation with DDQ provided pyrroloquinazolinone product **6**. It is noteworthy that judicious choice of oxidant (H_2O_2 or DDQ) leads selectively to either product **4** or **6**. Products related to **6** are common in medicine (Scheme 1B)[8] and our preparation of **6** represents a rare example of an enantioselective approach to this class of compound.

We propose a tentative mechanism and stereochemical model to rationalize the observed outcome of the cyclization of aryl-substituted alkene substrates **1b** (Scheme 5). Upon formation of copper–boryl species **II**, enantioselective borocupration occurs across the double bond of the alkene to give **III**. Our stereochemical model (Scheme 5B) suggests this addition occurs with the smaller methylene group (R) oriented towards the ligand P-aryl ring, rather than the larger phenyl group on the substrate (**TS-1a** vs. **TS-1b**). Based



Scheme 5. Proposed catalytic cycle and model for the origin of stereocontrol.

on previous reports, a favourable face-to-face interaction between the phenyl group on the alkene of the substrate and the P-aryl ring might further stabilize **TS-1a**, whereas unfavourable edge-to-face interactions might be present in **TS-1b**.[18] The diastereoselective, C–C bond-forming cyclization of **III** can then proceed via **TS-2** to give the intermediate **IV**. We suggest that copper coordinates to the nitrogen atom during this step, in agreement with previous reports.[19] Finally, in line with the positive influence of alcohols on reactivity, we suggest that R′OH (R′ = *i*Pr, *t*Bu) protonates intermediate **IV** to give the desired product **2b** and regenerate the active copper alkoxide catalyst **I**.

A highly enantio- and diastereoselective copper-catalyzed borylative cyclization constructs two adjacent stereocentres—including a quaternary stereocentre—and delivers a range of pyrroloquinazolinone derivatives that are currently difficult to access. The new process exploits an inexpensive and non-toxic copper catalyst and commercially available chiral phosphine ligands. Selective manipulation of the products allows access to enantiomerically enriched quinazolinones of medicinal relevance.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric · boron · copper · cyclization · nitrogen-containing heterocycles

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