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 1A). 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.[9] In particular, pyrroloquinazolinones are common tricyclic motifs found in drug molecules and natural products (Scheme 1B). 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 1B.[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 pyrroloquinazolinones are needed for the synthesis of known and as yet unknown bioactive targets.

We recognized that the enantioselective, copper-catalyzed borylative cyclizations of substrates 1, involving intramolecular addition of an organocopper intermediate to a C=N electrophile,[6c] would constitute a valuable route to important enantiothermically enriched pyrroloquinazolinone derivatives 2 (Scheme 1C). The resulting new process is highly enantio- and diastereoselective, uses an inexpensive and non-toxic catalyst, and exploits commercially available chiral ligands.
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). Fortunately, screening of other phosphine ligands (Table 1, entries 1–3) revealed both ligands L2 ((S,S)-BDPP) and L3 ((R)-QuinoxP/C23) 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). We then tested copper sources, bases and solvents (Table 1, entries 4–6) and found Cu(MeCN)4PF6 with KOtBu 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. 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 diastereoccontrol. For example, aryl groups bearing electron-rich substitu-

Table 1: Reaction optimization.

| Entry | CuI    | Additive | L2   | L3   | Yield | dr  | er   |
|-------|--------|----------|------|------|-------|-----|-----|
| 1[bc] | CuCl   | –        | L1   | 10   | 83:17 | 64:26 |
| 2[bc] | CuCl   | –        | L2   | 51   | >95:5 | 83:17 |
| 3[bc] | CuCl   | –        | L3   | 15   | >95:5 | 79:21 |
| 4[bc] | CuCl   | –        | L3   | 10   | >95:5 | 98:2 |
| 5[bc] | CuCl   | –        | L3   | 11   | >95:5 | 95:5 |
| 6[bc] | Cu(MeCN)4PF6 | – | L3   | 35   | >95:5 | 94:6 |
| 7[cd] | Cu(MeCN)4PF6 | iBuOH  | L3   | 85   | >95:5 | 84:16 |
| 8[cd] | Cu(MeCN)4PF6 | iPrOH  | L3   | 82   | >95:5 | 93:7 |
| 9[cd] | Cu(MeCN)4PF6 | iPrOH  | L3   | 87   | 80:20 | 58:42 |
| 10[cd] | Cu(MeCN)4PF6 | iPrOH  | L2   | 75   | 91:9  | 95:5 |
| 11[bc] | Cu(MeCN)4PF6 | iPrOH  | L2   | 10   | 87:13 | 95:5 |

[a] For further details of the reaction optimization, see the Supporting Information. Reaction conditions: 1 (0.2 mmol), B2pin2 (0.3 mmol), CuI (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 NaOttBu (1.5 equiv). [d] Using KOrBu (1.5 equiv). [e] Using dioxane (0.2 m). [f] With 1b to give 2b.
ents at both meta- and para-positions gave products with very high enantiocontrol (2e–2f). Ortho-, meta- and para-halo-
genated aryl groups were also well tolerated (2g–2i). Finally, substrates bearing 2-naphthyl and 2-thienyl groups gave the desired products in high yield and with excellent enantio-
control (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 enantio-
control. 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 stereo-
chemistry 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 dihydroquinazolinone 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, enantio- and diastereocontrol were observed (c.f. Table 1, entry 10). We first converted product 2b into the trifluo-
bororate salt 3,[17] and the alcohol 4; the latter by oxidation with H2O2. 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 (H2O2 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 ary1-substituted alkene substrates 1b (Scheme 5). Upon formation of copper–boryl species II, enantioselective bor-
ocupration occurs across the double bond of the alkene to give III. Our stereochemical model (Scheme 5 B) suggests this addition occurs with the smaller methylene group (R) oriented towards the ligand P-arly ring, rather than the larger phenyl group on the substrate (TS-Ia vs. TS-Ib). Based

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**Scheme 3.** Scope with respect to the amidine. Reaction conditions: 1 (0.2 mmol), Bpin2 (0.3 mmol), [Cu(MeCN)4]PF6 (0.02 mmol), L2 (0.024 mmol), KOtBu (0.3 mmol in 1 mL sol THF), H2O2 (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 1H NMR analysis of the crude products. ee values were measured by HPLC on chiral stationary phase. [a] Reaction was run without PrOH. [b] Bpin2 (0.4 mmol), KOtBu (0.4 mmol in 1 mL sol THF) and (R)-QuinoxP*L3 (0.024 mmol) were used. [c] (R,R)-(−)-2,3-bis(tert-Butyl-
methylphosphino)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) KHF2 4 equiv, MeOH/H2O, 0 °C to RT; (iii) H2O2 2 equiv, K2CO3 2 equiv, THF, −20 °C; (iv) NaH 1.5 equiv, Mel 1.5 equiv, THF, 0 °C to RT; (v) DDQ 1.5 equiv, CH2Cl2, 0 °C to RT.
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}. 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. Finally, in line with the positive influence of alcohols on reactivity, we suggest that R'OH (R' = iPr, 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 stereocenters—including a quaternary stereocenter—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 enantioomerically enriched quinazolinones of medicinal relevance.

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Conflict of interest

The authors declare no conflict of interest.

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