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Catalytic Asymmetric Synthesis of α -Arylpyrrolidines and Benzo-fused Nitrogen Heterocycles

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Abstract

Herein we report a practical two-step synthetic route to α -arylpyrrolidines consisting of Suzuki-Miyaura cross-coupling and enantioselective copper-catalyzed intramolecular hydroamination reactions. The excellent stereoselectivity and broad scope for the transformation of substrates with pharmaceutically relevant heteroarenes render this method a practical and versatile approach for pyrrolidine synthesis. Additionally, this intramolecular hydroamination strategy facilitates the asymmetric synthesis of tetrahydroisoquinolines and medium ring dibenzo-fused nitrogen heterocycles.

Graphical Abstract

Here, it is shown that an enantioselective copper-catalyzed intramolecular hydroamination reaction can be used jointly with the Suzuki-Miyaura cross-coupling to yield a diverse array of α -arylpyrrolidine scaffolds that contain pharmaceutically relevant heteroarenes with excellent enantiomeric purity under very mild conditions. Further, this intramolecular hydroamination strategy is applicable to the asymmetric syntheses of six- to nine-membered benzo-fused nitrogen heterocycles.

Keywords

asymmetric synthesis; copper; hydroamination; pyrrolidines; benzo-fused nitrogen heterocycles

Saturated nitrogen heterocycles are among the most prevalent structural subunits in medicinal agents^[1] and bioactive alkaloids^[2]. In particular, enantioenriched α -aryl-substituted pyrrolidines are a common class of therapeutics^[3], as well as useful chiral controllers^[4] in asymmetric catalysis. For example, the recent emergence of enantiopure α -arylpyrrolidines in treatments for hepatitis C^[5] and mantle cell lymphoma^[6] highlights their value in this regard (Figure 1, A). The predominance of α -heteroaryl substituents in these

Dedicated to Professor Ronald Raines in celebration of his 60th birthday

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pyrrolidine substructures is due, in part, to the well-known therapeutic and physicochemical properties provided by these fragments.^[7] Therefore, the development of synthetic routes that are capable of incorporating diverse heteroaryl substituents into stereodefined α -arylpyrrolidines is of great interest.

The asymmetric synthesis of α -arylpyrrolidines has been the subject of considerable effort.^[9] Important strategies to accomplish this include directed C-H arylation,^[9a] hydrogenation of cyclic enamines,^[9c] [3+2] cycloaddition,^[9g] arylation/cyclization cascades^[9i] and reductive cyclization reactions^[9j]. Further, based on the carbamate-directed asymmetric lithiation method pioneered by Hoppe^[10] and Beak^[11], Campos and colleagues at Merck developed the first enantioselective α -arylation of *N*-Boc-pyrrolidines. Their impressive protocol featured a (–)-sparteine-mediated^[12] asymmetric α -lithiation and the subsequent transmetalation with ZnCl₂, followed by a Negishi coupling with an aryl bromide (Figure 1, B-a).^[13] In 2018, Zhang disclosed an elegant enantioselective cobalt-catalyzed radical cyclization of preformed *N*-tosylhydrazones to furnish α -arylpyrrolidines (Figure 1, B-b).^[14] To date, these two reports are the only catalytic examples that enable the installation of heteroaryl substituents with precise stereochemical control at the α -position of pyrrolidines. While the industrial manufacture of enantioenriched α -arylpyrrolidine compounds typically relies on chiral pool synthesis from proline via substrate-controlled asymmetric induction,^[5] more versatile and catalytic methods that are amenable to the preparation of molecules with drug-like structural features would be useful for early-stage drug research development.

In 2013, Hirano and Miura^[16] and our laboratory^[17] reported the enantioselective copper-catalyzed hydroamination of olefins, in which C-N bonds are formed by the reaction of chiral alkylcopper(I) species (generated *in situ* through the hydrocupration of olefins) with an electrophilic aminating reagent. Many variants of the intermolecular hydroamination reactions have since been reported,^[18] including a regioselective, intramolecular reaction used to synthesize chiral aziridines.^[19] We decided to see whether this chemistry could be utilized for the preparation of other enantiomerically enriched nitrogen heterocycles. Herein, we report a versatile two-step synthesis of enantioenriched α -arylpyrrolidines that is compatible with a broad range of heteroaryl substituents (Figure 1, C). Furthermore, we describe the asymmetric synthesis of enantiopure benzo-fused nitrogen heterocycles bearing six- to nine-membered rings.

Initially, hydroxylamine benzoate **1aa** was evaluated as a model substrate in the copper-catalyzed hydroamination reaction. Upon subjecting **1aa** to a THF solution of CuH catalyst (formed from Cu(OAc)₂, (*S*)-DTBM-SEGPHOS (**L1**), and diethoxy(methyl)silane (DEMS)) at ambient temperature, the desired pyrrolidine product **2a**^[20] was obtained in 78% yield with 97.5:2.5 *er* (Table 1, entry 1). A significant quantity of a byproduct, derived from the reductive cleavage of the N-O bond of the substrate, was observed. To minimize this undesired process, the reactivity of the N-O bond in the electrophilic amine source was varied through modification of the hydroxylamine ester.^[21] While the use of electron-rich *p*-(*N,N*-dimethylamino)benzoate **1ab** provided **2a** in higher yield (entry 2), employing pivalate **1ac** further improved both yield and enantioselectivity (entry 3). We next investigated the use of various chiral bisphosphine ligands and found that (*R,R*)-Ph-BPE (**L3**) offered the best reactivity and enantioselectivity (entry 5–7).^[22] The use of other ligands such as (*R,R*)-

*i*Pr-DUPHOS (**L2**) and (*S*)-DTBM-BIPHEP (**L6**) was less successful (entries 4 and 10). Switching from phenyl to isopropyl or ethyl substituents on the phospholane backbone led to a significant attenuation of reactivity (entries 8 and 9).

Having optimized the intramolecular C-N bond-forming step, we evaluated several routes for the preparation of the hydroxylamine pivalate substrates. It was important that the selected method can easily: (1) incorporate a range of heteroaryl substituents, and (2) start from a common building block that can be prepared on a large scale. The most efficient strategy was determined to entail a Suzuki-Miyaura cross-coupling of a vinylboronate ester precursor **3**. This was prepared by the Zr-catalyzed syn-hydroboration of the terminal alkyne,^[23] which left the N-O bond intact. Intermediate **3** was used in cross-coupling reactions with a wide range of aryl bromides (Table 2, left column, **1a-c**, **1b-o**).^[24] Although oxidative addition of N-O bonds has been noted in other palladium-catalyzed cross-coupling reactions,^[25] the corresponding hydroxylamine pivalates were successfully obtained. Among the heteroaryl bromides tested, a pyrazole (**1f**), pyrimidines (**1g**, **1h**), azaindoles (**1i**, **1j**), a furan (**1k**), and a pyridine (**1l**) gave higher yields than a thiazole (**1m**) or imidazoles (**1n**, **1o**).^[8b26]

Like the Pd-catalyzed cross coupling reaction, the subsequent enantioselective copper-catalyzed intramolecular hydroamination proved to be tolerant of a wide range of functional groups and α -heteroaryl substituents.^[27] Good yields (62–83%) and excellent enantioselectivities (97.5: 2.5–99.5: 0.5 *er*) were obtained for most α -arylpyrrolidine products (Table 2, right column, **2a-l**). Two exceptions were substrates bearing an N-Boc indole (**2e**) or an *N*-Ts azaindole (**2j**), for which moderate yields were observed, along with a slight increase in the quantity of substrate lost to reduction of the N-O bonds. The absolute stereochemistry of pyrrolidine product **2l** was determined as *R* by single crystal X-ray crystallography (see the SI for details). While the conversion of five-membered azoles such as a thiazole (**2m**) and imidazoles (**2n**, **2o**) was comparable to that of other examples, significant erosion of the enantioselectivity was observed.^[28] In these cases, we found that the use of **L3** and dimethoxy(methyl)silane (DMMS) not only improved the enantioselectivity, but also led to higher yields.^[29]

Our efforts next focused on exploring the asymmetric synthesis of nitrogen heterocycles with other ring sizes. In comparison with α -arylpyrrolidines, the synthesis of four- and six-membered nitrogen heterocycles proceeded slowly.^[30] For example, the synthesis of α -phenylpiperidine **5** resulted in a lower yield (Scheme 1, A) than the corresponding α -phenylpyrrolidine **2a** (45% vs 95 %).^[31] Varying a number of reaction parameters (ligand, solvent, temperature and concentration) did not further improve the results. Aiming to facilitate the cyclization process, we introduced a geometric constraint into the linear carbon chain of the starting material by introducing an aryl group between the olefin and the hydroxylamine-*O*-pivalate-containing side chain. This modification restored the high reactivity in the catalytic event, providing chiral tetrahydroquinoline **7** in excellent yield and enantioselectivity (86% yield, 99.5: 0.5 *er*; Scheme 1, B).

Successful construction of the enantioenriched tetrahydroquinoline led us to examine dibenzo-fused nitrogen reported as the average of two runs. *er* was determined by SFC. [c]

dioxane/H₂O = 3/1 (0.30 M), 80 °C. [d] Cu(OAc)₂ (8.0 mol%), (*R,R*)-Ph-BPE (8.8 mol%), DMMS (2.5 equiv). [e] (*R,R*)-Ph-BPE (4.4 mol%), DMMS (2.5 equiv). heterocycles with medium ring sizes,^[32] as many compounds with these structural elements are found in pharmaceuticals and bioactive alkaloids (Scheme 2, A).^[33] Our approach to access the core structural scaffolds requires either a four- or a five-step synthetic sequence, all of which culminated with the enantioselective Cu-catalyzed intramolecular hydroamination. For instance, oxazonine **10** was prepared in five steps in excellent yield and enantioselectivity, starting from salicylaldehyde (Scheme 2, B). Similar efficiency and selectivity were observed in the synthesis of azepine **11** and oxazocine **12** (Scheme 2, C).^[34]

In conclusion, we have developed a practical two-step synthetic route to enantiopure α -arylpyrrolidines comprising Suzuki-Miyaura cross-coupling and enantioselective copper-catalyzed intramolecular hydroamination reactions. This approach provides an efficient method to prepare pyrrolidines bearing pharmaceutically relevant α -heteroaryl substituents including pyrazoles, pyrimidines, azaindoles, pyridines, furans, thiazoles and fused imidazoles with high levels of enantiomeric purity under very mild conditions. Moreover, we applied this intramolecular hydroamination strategy to asymmetric syntheses of six- to nine- membered benzo-fused nitrogen heterocycles. While (*S*)-DTBM- SEGPHOS worked well for most α -arylpyrrolidines, (*R,R*)-Ph-BPE provided better results for substrates containing five-membered azoles as well as for the synthesis of medium ring benzo-fused nitrogen heterocycles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- [30]. Our attempts to synthesize an enantioenriched α -phenylazetidine resulted in a 30% isolated yield. ¹H NMR analysis indicated the formation of several byproducts; see the SI for details.
- [31]. (R,R)-Ph-BPE and DMMS replaced (S)-DTBM-SEGPHOS and DEMS. However, under our standard hydroamination conditions (footnote b, Table 2), formation of 2-phenylpiperidine 5 was not detected from 4 (footnote b, Scheme 1) while 2-phenylpyrrolidine 2a was isolated in 83% yield from 1ac.
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A. Enantiopure α -Arylpyrrolidine Scaffolds in Recent Pharmaceuticals

B. Synthesis of Enantiopure α -Heteroarylpyrrolidines

a. Asymmetric α -Arylation

b. Asymmetric Radical Cyclization

C. This Work: Suzuki-Miyaura Cross-Coupling and Intramolecular Hydroamination

Figure 1.

A) Recent examples of pharmaceuticals bearing enantiopure α -heteroarylpyrrolidines. B) Current synthetic approaches to enantiopure α -heteroarylpyrrolidines. C) Our protocol features Pd-catalyzed Suzuki-Miyaura coupling and enantioselective Cu-catalyzed intramolecular hydroamination. Boc = tert-butyloxycarbonyl; rt = room temperature; cat. = catalytic; FG = functional groups; TS = toluenesulfonyl; pin = pinacolato; piv = pivalate; Bn = benzyl.

Scheme 1.

Synthesis of Enantiopure α -Arylpiperidine and Tetrahydroquinoline^[a] [a] Isolated yields are reported as the average of two runs. Reaction conditions: 0.50 mmol **4** or **6** (1.0 equiv), Cu(OAc)₂ (4.0 mol%), (*R,R*)-Ph-BPE (4.4 mol%), DMMS (2.5 equiv), THF (1.0 mL), see the SI for details. [b] No product was observed using (*S*)-DTBM-SEGPHOS as the ligand.

Scheme 2.

Synthesis of Enantiopure Dibenzo-fused Nitrogen Heterocycles^[a] [a] Isolated yields are reported as the average of two runs. Reaction conditions: 0.50 mmol **4** or **6** (1.0 equiv), $\text{Cu}(\text{OAc})_2$ (4.0 mol%), (R,R) -Ph-BPE (4.4 mol%), DMMS (2.5 equiv), THF (1.0 mL), see the SI for details. [b] See SI for detailed synthetic sequences of azepine and oxazocine analogs. PG = protecting groups.

Table 1.

Optimization of Enantiopure α -Arylpyrrolidine Synthesis^[a]

Entry	Substrate	Chiral Ligand	Yield 2a [%] ^[b]	er ^[c]
1	1aa	L1	78	97.5: 2.5
2	1ab	L1	83	97.5: 2.5
3	1ac	L1	90	99.0: 1.0
4	1ac	L2	-	-
5	1ac	L3 ^[d]	91	97.5: 2.5
6	1ac	L3	95	99.5: 0.5
7	1ac	L3 ^[e]	66	99.0: 1.0
8	1ac	L4	28	95.0: 5.0
9	1ac	L5	35	94.0: 6.0
10	1ac	L6	73	97.5: 2.5

^[a] **1aa**, R¹ = phenyl; **1ab**, R¹ = 4-dimethylaminophenyl; **1ac**, R¹ = *tert*-butyl. Reaction conditions: 0.20 mmol **1** (1.0 equiv), Cu(OAc)₂ (4.0 mol %), chiral bisphosphine ligands (4.4 mol%), diethoxy(methyl)silane (2.5 equiv), THF (0.40 mL), see details in the Supplementary Information.

^[b] Yields were determined by ¹H NMR using 1,2-dibromoethane as an internal standard.

^[c] Enantiomeric ratio (*er*) was determined by supercritical fluid chromatography (SFC).

^[d] With 4.4 mol% PhsP.

^[e] With 2.2 mol% PhsP. THF = tetrahydrofuran; *er* = enantiomeric ratio.

Table 2.

Scope of Enantipure α -Arylpyrrolidines^[a]

^[a]Unless noted, standard reaction conditions of the Suzuki-Miyaura coupling: 1.50–2.50 mmol arylbromides (1.0 equiv), **3** (1.3 equiv), SPhos-G3 (5.0 mol%), K₂CO₃ (3.0 equiv), THF/H₂O = 3/1 (0.30 M), 60 °C, see the SI for details.

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^{b)} Unless noted, standard reaction conditions of the intramolecular hydroamination: 0.50 mmol **1a-o** (1.0 equiv), Cu(OAc)₂ (4.0 mol%), (*S*)-DTBM-SEGPHOS (4.4 mol%), DEMS (2.5 equiv), THF (1.0 mL), see the SI for details. Isolated yields are