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A room temperature copper catalyzed *N*-selective arylation of β -amino alcohols with iodoanilines and aryl iodides

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Abstract

An efficient method is described for the synthesis of *N*-(2-aminophenyl)-2-hydroxyethylamines via a copper catalyzed *N*-selective arylation of β -amino alcohols with iodoanilines. The corresponding coupling products are useful intermediates for the synthesis of a variety of *N*-2-hydroxyethyl-substituted benzimidazoles, benzimidazolones, and iminobenzimidazoles. We found that 2-iodoaniline only arylates certain amino alcohols but not amines lacking a hydroxyl group. We also demonstrate the arylation of sterically demanding β -amino alcohols, such as ephedrine and prolinol with aryl iodides at room temperature.

Keywords

Cross-coupling; Copper catalysis; Arylation; Amino Alcohol; Iodoaniline; Benzimidazole

1. Introduction

2-(1,2-Dihydro-2-iminobenzo[*d*]imidazol-3-yl)ethanol (**1**), 1-(2-hydroxyethyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (**2**), and 2-(1*H*-benzo[*d*]imidazol-1-yl)ethanol (**3**) are important scaffolds for medicinal chemistry and/or asymmetric catalysis (Fig. 1; **4–12**).^{1–10} Our interest in these *N*-2-hydroxyalkyl decorated heterocycles stems from a recent High Throughput screening campaign aimed at identifying orexin receptor agonists of potential use for the treatment of narcolepsy, during which we identified compounds related to structures included in Fig. 1.⁶ Known synthetic protocols toward these important heterocycles primarily exploit S_NAr-type reactivity to produce intermediate **15** from 2-fluoro nitrobenzene (**13**) and amino alcohol **14**,^{2,8} followed by a subsequent reduction (nitro to amino) and cyclization of intermediate amino alcohol **15** with the relevant electrophilic partner to produce benzimidazoles **3** (from reaction with aldehydes, carboxylic acids or carboxylic acid equivalents),^{3,4,11} benzimidazolones **16** (from reaction with carbonyl diimidazole),⁸ or iminobenzimidazoles **17** (from capping with cyanogen bromide).^{2,6} Alternatively, the latter can also be obtained from direct alkylation of iminobenzimidazole **18** with primary epoxides or bromomethylketones followed by ketone reduction.^{6,12} Given the difficulty in controlling chemoselectivity for *N*1 versus *N*3 alkylation, the latter approach is limited to symmetrical benzimidazoles. Moreover, reaction with internal epoxides or more hindered stereogenic 2-bromoalkylketones is problematic, thereby precluding introduction of an α -stereogenic aminoethanol fragment (*R*).

In the context of our above mentioned medicinal chemistry program regarding orexin receptor agonists, we sought to explore methodology for the direct synthesis of *N*-2-aminoaryl substituted amino alcohols, such as **21** via a *N*-selective copper catalyzed arylation of unprotected amino alcohols **20** with iodoanilines **19** (Eq. 1). Such an approach would alleviate problems associated with the direct alkylation of iminobenzimidazole **18**, and allows the introduction of α -stereogenic amino alcohols, of which many are commercially available. Compared to the S_NAr route depicted in Fig. 2, this route would be one-step shorter, and potentially occur under milder conditions (lower temperatures, no reducing agents). Furthermore, the number of commercially available 2-iodo/bromo-anilines exceeds that of the corresponding 2-fluoronitroarenes (Aldrich), thus enabling the expansion of chemical diversity in the corresponding 2-amino-aniline products.

(1)

Over the past two decades or so, palladium and copper catalyzed carbon–nitrogen bond formation for the synthesis of *N*-arylamines has gained a lot of attention.^{13,14} Of these, the copper catalyzed variant remains attractive for industrial applications due to lower catalyst costs and enhanced stability toward air and moisture, resulting in a significant increase in research on ligand-assisted carbon–nitrogen bond formation under milder reaction conditions.¹⁴ Despite these advances, there remain relatively few reports on the *N*-selective arylation of α -amino alcohols,¹⁵ and most include only glycinol.^{16–18} The Buchwald group has been particularly active in this area, and disclosed a ligand-free copper catalyzed arylation of α -amino alcohols.¹⁵ Although this report describes the first and only examples of α -amino alcohols more complex than glycinol, there remain some limitations including the use of higher temperatures and/or strong base. Furthermore, β -branching or a secondary amine is only tolerated separately, not together. Important for our intended purpose (Eq. 1), this report remains to the best of our knowledge the only one describing a singular example documenting a cross-coupling of 2-iodoaniline with a α -amino alcohol (2-amino-1-phenylethanol).¹⁵ In what follows, we describe a room temperature copper catalyzed *N*-selective arylation of a variety of α - and other amino alcohols with iodoaniline. We also demonstrate the effectiveness of our conditions for the *N*-selective arylation of α -amino alcohols containing a secondary amine, including those with β -branching, with a variety of aryl iodides.

2. Results and discussion

Our investigations began with exploring conditions for the arylation of 2-amino-1-phenylethanol with 2-iodoaniline (Table 1), a combination reported singularly by Job and Buchwald.¹⁵ Using 2.5% of CuI and 2 equiv of NaOH in isopropanol at 90 °C, they obtained *N*-(2-aminophenyl)-2-amino-1-phenylethanol **15a** in 63% yield.¹⁵ We decided to frame our exploratory ligand screening to reaction conditions at room temperature, with mild base (Cs₂CO₃) and 10% CuI as the catalyst. As shown in Table 1 (entry 1), under these milder conditions, omission of an external ligand resulted in low conversion (~11% isolated yield after 14 h), indicating the ineffectiveness of the amino alcohol starting material for ligand acceleration. Proline (**L1**), a ligand described by Ma and co-workers for copper

catalyzed *N*-arylation of amines including glycinol (>80 °C),^{16d} yielded 45% of product **21a** (entry 2). Picolinic acid (**L2**) did not fare better than ligandless conditions, providing low yields of the *N*-arylated product (~15%, entry 3). Interestingly, this ligand was reported to yield selective *O*-arylation of 3-aminophenol.^{17b} Next, we examined isobutyrylcyclohexanone (**L3**), a catalyst described by Buchwald for the *N*-selective copper catalyzed arylation of amino alcohols under mild conditions (5% CuI, Cs₂CO₃, room temperature).^{16c} Although the *N*- versus *O*-selectivity and yield was modest for the only α -amino alcohol (glycinol) included in that report, this ligand provided the first breakthrough for our screen, yielding product **21a** in 60% isolated yield (entry 4). Gratifyingly, evaluation of other α -diketone ligands led us to identifying tetra-methylheptane-3,5-dione (**L4**) as an efficient ligand for this transformation (88% yield, entry 5). This catalyst was originally described by Merck for the Ullman-type coupling of phenols,¹⁹ and later utilized by Buchwald for the room temperature copper catalyzed arylation of amines.^{17a} In the latter report, this more sterically hindered α -diketone **L4** was less effective than butyrylcyclohexanone (**L3**).^{17a} In an attempt to increase steric bulk, we prepared mixed adamantyl/*tert*-butyl α -diketone **L5**, which however did not further improve the yield (84%, entry 6). Finally, we found pyrrole-2-carboxylic acid **L7** and indole-2-carboxylic acid **L6** to be equally effective as α -diketones **L4** and **L5** (81–87%, entries 7–8).^{20,21}

We selected α -diketone **L4** and indolecarboxylic acid **L6** for further evaluation as they are both commercially available at more viable prices than pyrrolecarboxylic acid **L7**. As shown in Table 2, lowering the catalyst and ligand loading by half (5% CuI, 10% ligand) provided results similar to our initial conditions (entry 3), whereas further reduction in catalyst and ligand loading were less satisfactory (entry 1), as was reduction of only ligand loading (entry 2). Further experiments were thus continued with the use of 5 mol % CuI and 10 mol % ligand. A solvent screen indicated that DMSO was superior to all other solvents examined (entries 4–9), with dimethylacetamide (DMA) as a viable runner-up (entry 6). Comparing entry 3 to the last two entries demonstrate that the milder carbonate base Cs₂CO₃ was more effective than sodium or potassium carbonate.

Using our optimized reaction conditions, we explored the scope of the arylation of various α -amino alcohols with 2-iodoaniline, 2-amino-3-iodopyridine, and Boc-protected 2-iodoaniline. As shown in Table 3, we found that 2-amino-3-iodopyridine was an excellent donor for the arylation of 2-hydroxyphenethylamine **20a**, yielding *N*-arylated product **21b** in 78–80% yield (entry 1). Secondary amines flanked by a stereogenic hydroxy-substituent (**20b**) performed equally well, providing product **21c** with iodoaniline in 77% and Boc-protected product **21d** after coupling with *N*-Boc-2-iodoaniline (~90%, entries 2–3). Next, a series of α -amino alcohols derived from α -amino acids were examined. All substrates (**20c–f**) were arylated in good to moderate yield with iodoaniline (entries 4–7). There is a clear trend toward lower reactivity with increased steric hindrance; with the sterically demanding *t*-butylglycinol **20f** affording the lowest yield (~50%, entry 7).²² However, using Boc-protected iodoaniline drastically improved the yield of the corresponding arylation product **21i** to 81% (entry 8).

Next, amino alcohols other than α -amino alcohols and non-hydroxylated amines were investigated. As shown in Table 4, longer chain amino alcohols 4-aminobutanol (**20g**) and 6-aminohexanol (**20h**) also reacted smoothly with 2-iodoaniline at room temperature, although the yields appear to diminish with increasing chain length (entries 1–2). Interestingly, 4-hydroxypiperidine (**20i**) was readily arylated (55–60%, entry 3), whereas 3-hydroxymethylpiperidine was unresponsive to the copper catalyzed arylation with iodoaniline (recovered starting material, entry 4). Primary or secondary amines that do not contain a free hydroxy-group were completely inert to the reaction conditions, as shown by the attempted arylation of benzylamine and morpholine (entries 5 and 6). From the latter two

examples, it appears that a hydroxy-functionality is crucial for the successful arylation with iodoaniline. The poor conversion under ligandless conditions (Table 1, entry 1), in combination with the successful arylation of 6-aminohexanol and 4-hydroxypiperidine (Table 4, entries 2 and 3) appear to preclude a simple model where the amino alcohol acts as a bidentate ligand for copper. Perhaps hydrogen bonding involving the alcohol is important. At this point, we do not have sufficient data to provide a reasonable hypothesis.

The requirement for an alcohol group is specific for the arylation with 2-iodoaniline. Indeed, the room temperature copper catalyzed arylation of a wide range of amines with aryl halides other than iodoaniline has been documented in the literature.^{13,14,16,17} A notably mild procedure was reported by Buchwald with isobutyrylcyclohexanone (**L3**).^{17a} Using their conditions (5 mol % CuI, 20 mol % **L3**, 2 equiv Cs₂CO₃, room temperature), arylation of benzylamine with 3,4-dimethyl-1-phenyliodide provided 96% of product. We were therefore not surprised that our conditions (5 mol % CuI, 10 mol % **L4**, 2 equiv Cs₂CO₃, DMSO, room temperature) provided similar results (91% isolated yield). As noted in the Introduction, although a room temperature copper catalyzed *N*-selective arylation of amino alcohols other than α -amino alcohols and glycinol (mainly longer chain α -amino alcohols) has been achieved previously, to the best of our knowledge, there are no examples with sterically demanding α -amino alcohols under similarly mild conditions. In Table 5, we tabulate data indicating that our conditions are particularly efficient for α -amino alcohols containing a secondary amine, including those with β -branching. Thus, ephedrine was efficiently arylated with a range of methyl, dimethyl, or methoxy-substituted phenyliodides in yields >70–75% at room temperature (entries 1–5). The final entry shows the arylation of the secondary amino alcohol prolinol with phenyliodide in 77–82% isolated yield.

3. Conclusion

In this manuscript, we disclosed an efficient copper catalyzed *N*-selective arylation of α -amino alcohols with 2,2,6,6-tetramethylheptane-3,5-dione or indole-2-carboxylic acid as efficient supporting ligands for this process. Although indole-2-carboxylic acid is very rarely included as a ligand for copper catalyzed *N*- or *O*-arylation processes, we found it performing as an excellent supporting and accelerating ligand for this copper catalyzed *N*-arylation of amino alcohols. To the best of our knowledge, this represents the first example of such a cross-coupling at room temperature with α -amino alcohols more complex than glycinol, including examples with secondary amines flanked with a stereocenter, such as ephedrine. We also found that the oxidative coupling partner 2-iodoaniline uniquely engages with amino alcohols, but not amines that do not possess a hydroxy-substituent. 4-Piperidinol, α - and some longer chain α -amino alcohols were readily arylated with 2-iodoaniline, whereas 3-hydroxymethylpiperidine was resistant. Finally, this straightforward synthesis of *N*-(2-aminoaryl)-substituted α -amino alcohols streamlines access to *N*-2-hydroxyethyl substituted benzimidazoles, benzimidazolones, and iminobenzimidazoles as important scaffolds for medicinal chemistry efforts.

4. Experimental section

Unless otherwise noted, commercially available materials were used without further purification. All solvents were of HPLC or ACS grade. Anhydrous solvents were purchased from commercial sources. Reactions were performed under an atmosphere of argon with magnetic stirring unless noted otherwise. Flash chromatography (FC) was performed using *E Merck* silica gel 60 (240–400 mesh). Thin layer chromatography was performed using pre-coated plates purchased from *E. Merck* (silica gel 60 PF254, 0.25 mm) that were visualized using a KMnO₄ or Ce(IV) stain. Nuclear magnetic resonance (NMR) spectra were recorded on a *Varian Inova*-400, *Varian Inova*-500 spectrometer at operating

frequencies of 400/500 MHz (^1H NMR) or 125/100 MHz (^{13}C NMR). Chemical shifts () are given in parts per million relative to residual solvent and coupling constants (J) in Hertz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet. Electrospray ionization mass spectra (ESI-MS) were obtained with an *Agilent Technologies* 6130 Quadrupole LC/MS.

4.1. General experimental procedure

Into a flame dried Schlenk tube containing a magnetic stir bar was added aryl iodide (1.0 mmol), amino alcohol (1.1 mmol), Cs_2CO_3 (652 mg, 2.0 mmol; or 977 mg, 3.0 mmol for entries 1–5 in Table 5, which employ ephedrine hydrochloride salt) and CuI (9.5 mg, 0.05 mmol). Under an atmosphere of argon, DMSO (2 mL) and 2,2,6,6-tetramethylheptane-3,5-dione (21.0 μL , 0.1 mmol) or indole-2-carboxylic acid (0.1 mmol) were added and the reaction mixture was stirred at room temperature for 14 h. After addition of ethyl acetate (15 mL) and brine (5 mL), the organic layer was separated and the aqueous layer extracted with ethyl acetate (3×20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 before passing it through a short pad of silica gel. The filtrate was concentrated and purified via flash column chromatography to afford the corresponding arylated product.

4.2. 2-(2-Aminophenylamino)-1-phenylethanol (**21a**)¹⁵

Using the general procedure, title compound **21a** was obtained as a dark red semi-solid with yields ranging from 86 to 89% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 85–87% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ^1H NMR (500 MHz, CDCl_3): 3.24 (dd, $J=12.5$, 9.1 Hz, 1H), 3.37 (dd, $J=12.5$, 3.3 Hz, 1H), 3.54 (br s, 4H), 4.90 (dd, $J=9.1$, 3.3 Hz, 1H), 6.72 (m, 3H), 6.85 (m, 1H), 7.36 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3): 52.2, 72.5, 112.8, 117.1, 119.6, 121.0, 126.2, 128.2, 128.8, 134.8, 137.2, 142.4; ESI-MS ($\text{M}+\text{H}$)⁺ calcd for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}$: 229.1, found: 229.0; HRMS m/z (ESI) calcd for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}$ [($\text{M}+\text{H}$)⁺]: 229.1335, found: 229.1324.

4.3. 2-(2-Aminopyridin-3-ylamino)-1-phenylethanol (**21b**)

Using the general procedure, title compound **21b** was obtained as a dark red semi-solid with yields ranging from 78 to 82% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 76–79% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ^1H NMR (500 MHz, CDCl_3): 2.15 (br s, 4H), 3.22 (m, 2H), 4.91 (m, 1H), 6.66 (m, 1H), 6.76 (d, $J=7.7$ Hz, 1H), 7.19 (m, 1H), 7.34 (m, 4H), 7.51 (d, $J=4.9$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): 51.7, 72.6, 115.9, 118.3, 126.1, 128.4, 129.0, 131.8, 137.1, 142.2, 149.5; ESI-MS ($\text{M}+\text{H}$)⁺ calcd for $\text{C}_{13}\text{H}_{16}\text{N}_3\text{O}$: 230.1, found: 230.1; HRMS m/z (ESI) calcd for $\text{C}_{13}\text{H}_{16}\text{N}_3\text{O}$ [($\text{M}+\text{H}$)⁺]: 230.1288, found: 230.1279.

4.4. (1*R*,2*S*)-2-(2-Aminophenylamino)-1-phenylpropan-1-ol (**21c**)

Using the general procedure, title compound **21c** was obtained as a dark red semi-solid with yields ranging from 76 to 78% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 75–79% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ^1H NMR (500 MHz, CDCl_3): 1.06 (d, $J=6.5$ Hz, 3H), 3.31 (br s, 4H), 3.75 (d, $J=6.3$ Hz, 1H), 4.97 (d, $J=3.0$ Hz, 1H), 6.74 (m, 2H), 6.85 (m, 2H), 7.34 (m, 1H), 7.40 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3): 14.3, 54.6, 74.1, 114.2, 117.5, 119.7, 121.1, 126.2, 127.6, 128.5, 135.2, 136.3, 141.8; ESI-MS ($\text{M}+\text{H}$)⁺ calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}$: 243.1, found: 243.1.

4.5. *tert*-Butyl 2-((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-ylamino)phenylcarbamate (**21d**)

Using the general procedure, title compound **21d** was obtained as a brown solid with yields ranging from 87 to 93% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 87–90% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 1.01 (d, *J*=6.4 Hz, 3H), 1.53 (s, 9H), 3.49 (br s, 1H), 3.78 (d, *J*=6.5 Hz, 1H), 4.02 (br s, 1H), 5.03 (s, 1H), 6.26 (br s, 1H), 6.75 (t, *J*=7.6 Hz, 1H), 6.92 (d, *J*=8.0 Hz, 1H), 7.17 (t, *J*=7.8 Hz, 2H), 7.26 (m, 1H), 7.37 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): 13.5, 28.6, 54.7, 72.5, 81.4, 114.5, 118.4, 124.4, 126.0, 126.8, 127.2, 127.8, 128.4, 141.8, 142.1, 154.9; ESI-MS (*M*+H)⁺ calcd for C₂₀H₂₇N₂O₃: 343.1, found: 343.0; HRMS *m/z* (ESI) calcd for C₂₀H₂₆N₂O₃K [(*M*+K)⁺]: 381.1575, found: 381.1561.

4.6. (*R*)-2-(2-Aminophenylamino)pentan-1-ol (**21e**)

Using the general procedure, title compound **21e** was obtained as a dark red semi-solid with yields ranging from 78 to 80% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 77–79% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 0.96 (t, *J*=7.3 Hz, 3H), 1.43 (dt, *J*=11.0, 5.8 Hz, 2H), 1.56 (m, 2H), 3.20 (br s, 4H), 3.51 (m, 2H), 3.78 (dd, *J*=10.9, 3.6 Hz, 1H), 6.73 (m, 3H), 6.84 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): 14.5, 19.7, 34.4, 54.9, 64.2, 113.6, 117.6, 119.2, 121.2, 134.7, 137.2; ESI-MS (*M*+H)⁺ calcd for C₁₁H₁₉N₂O: 195.1, found: 195.1; HRMS *m/z* (ESI) calcd for C₁₁H₁₉N₂O [(*M*+H)⁺]: 195.1492, found: 195.1489.

4.7. (*R*)-2-(2-Aminophenylamino)-4-methylpentan-1-ol (**21f**)

Using the general procedure, title compound **21f** was obtained as a dark red semi-solid with yields ranging from 70 to 73% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 68–72% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 0.91 (d, *J*=6.5 Hz, 3H), 0.96 (d, *J*=6.6 Hz, 3H), 1.40 (m, 1H), 1.50 (m, 1H), 1.74 (m, 1H), 3.04 (br s, 4H), 3.48 (dd, *J*=10.8, 5.2 Hz, 1H), 3.55 (m, 1H), 3.77 (dd, *J*=10.8, 3.4 Hz, 1H), 6.68 (m, 3H), 6.82 (t, *J*=7.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): 23.1, 25.2, 41.7, 53.1, 64.5, 113.4, 117.7, 119.2, 121.3, 134.6, 137.2; ESI-MS (*M*+H)⁺ calcd for C₁₂H₂₁N₂O: 209.1, found: 209.1; HRMS *m/z* (ESI) calcd for C₁₂H₂₁N₂O [(*M*+H)⁺]: 209.1648, found: 209.1638.

4.8. 2-(2-Aminophenylamino)-3-methylbutan-1-ol (**21g**)

Using the general procedure, title compound **21g** was obtained as a dark red semi-solid with yields ranging from 67 to 69% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 67–69% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 0.96 (d, *J*=7.1 Hz, 3H), 1.03 (d, *J*=7.2 Hz, 3H), 1.97 (m, 1H), 3.06 (br s, 1H), 3.29 (m, 1H), 3.41 (br s, 3H), 3.51 (m, 1H), 3.76 (d, *J*=8.6 Hz, 1H), 6.71 (m, 3H), 6.85 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): 19.1, 19.7, 29.8, 60.6, 62.0, 113.3, 117.9, 118.7, 121.4, 134.2, 137.9; ESI-MS (*M*+H)⁺ calcd for C₁₁H₁₉N₂O: 195.1, found: 195.1; HRMS *m/z* (ESI) calcd for C₁₁H₁₉N₂O [(*M*+H)⁺]: 195.1492, found: 195.1482.

4.9. (*S*)-2-(2-Aminophenylamino)-3,3-dimethylbutan-1-ol (**21h**)

Using the general procedure, title compound **21h** was obtained as a dark red semi-solid with yields ranging from 48 to 52% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 38–42% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 1.00 (s, 9H), 3.36 (dd, *J*=8.1, 4.0 Hz, 1H), 3.40 (br s, 4H), 3.54 (dd, *J*=11.0, 8.0 Hz, 1H), 3.87 (dd, *J*=11.0, 3.9 Hz, 1H), 6.67 (d, *J*=7.7 Hz, 1H), 6.80 (m, 3H); ¹³C NMR (125 MHz, CDCl₃): 27.1, 34.8, 62.2, 63.7, 112.9,

118.2, 118.4, 121.6, 133.0, 139.4; ESI-MS (M+H)⁺ calcd for C₁₂H₂₁N₂O: 209.1, found: 209.1; HRMS *m/z* (ESI) calcd for C₁₂H₂₁N₂O [(M+H)⁺]: 209.1648, found: 209.1638.

4.10. (S)-*tert*-Butyl (2-((1-hydroxy-3,3-dimethylbutan-2-yl) amino)phenyl)carbamate (**21i**)

Using the general procedure, title compound **21i** was obtained in 81% yield (single experiment) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**). ¹H NMR (500 MHz, CDCl₃): 0.97 (s, 9H), 1.49 (s, 9H), 3.31 (m, 2H), 3.47 (m, 1H), 3.85 (m, 2H), 6.17 (br s, 1H), 6.61 (td, *J*=7.5, 1.3 Hz, 1H), 6.79 (dd, *J*=8.3, 1.2 Hz, 1H), 7.00 (dd, *J*=7.8, 1.5 Hz, 1H), 7.09 (td, *J*=7.5, 1.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): 27.1, 28.2, 34.3, 62.6, 64.2, 81.0, 113.1, 116.7, 122.1, 127.2, 128.2, 145.2, 154.7; ESI-MS (M+H)⁺ calcd for C₁₇H₂₉N₂O₃: 309.2, found: 309.2; HRMS *m/z* (ESI) calcd for C₁₇H₂₉N₂O₃ [(M+H)⁺]: 309.2173, found: 309.2161.

4.11. 4-(2-Aminophenylamino)butan-1-ol (**21j**)

Using the general procedure, title compound **21j** was obtained as a dark red semi-solid with yields ranging from 62 to 64% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 59–61% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 1.73 (m, 4H), 3.14 (t, *J*=6.6 Hz, 2H), 3.30 (br s, 4H), 3.68 (t, *J*=6.1 Hz, 2H), 6.69 (m, 3H), 6.84 (t, *J*=7.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): 26.5, 30.8, 44.4, 62.8, 112.2, 116.8, 119.0, 121.0, 134.4, 138.0; ESI-MS (M+H)⁺ calcd for C₁₀H₁₇N₂O: 181.1, found: 181.1; HRMS *m/z* (ESI) calcd for C₁₀H₁₇N₂O [(M+H)⁺]: 181.1335, found: 181.1328.

4.12. 6-(2-Aminophenylamino)hexan-1-ol (**21k**)

Using the general procedure, title compound **21k** was obtained as a semi-solid with yields ranging from 63 to 67% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 55–58% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 1.45 (m, 4H), 1.58 (m, 2H), 1.67 (m, 2H), 2.93 (br s, 4H), 3.12 (t, *J*=7.1 Hz, 2H), 3.65 (t, *J*=6.5 Hz, 2H), 6.70 (m, 3H), 6.84 (t, *J*=7.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): 25.9, 27.3, 29.9, 32.9, 44.4, 63.0, 111.9, 116.8, 118.6, 121.0, 134.2, 138.4; ESI-MS (M+H)⁺ calcd for C₁₂H₂₁N₂O: 209.1, found: 209.1.

4.13. 1-(2-Aminophenyl)piperidin-4-ol (**21l**)

Using the general procedure, title compound **21l** was obtained as a brown solid with yields ranging from 58 to 62% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 53–57% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 1.76 (m, 3H), 2.05 (m, 2H), 2.74 (m, 2H), 3.14 (dt, *J*=10.2, 4.4 Hz, 2H), 3.86 (br s, 1H), 4.00 (br s, 2H), 6.76 (m, 2H), 6.96 (t, *J*=7.6 Hz, 1H), 7.03 (d, *J*=7.8 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): 35.7, 49.5, 68.2, 115.4, 118.8, 120.1, 124.8, 139.9, 141.7; ESI-MS (M+H)⁺ calcd for C₁₁H₁₇N₂O: 193.1, found: 193.0; HRMS *m/z* (ESI) calcd for C₁₁H₁₇N₂O [(M+H)⁺]: 193.1335, found: 193.1329.

4.14. (1*S*,2*R*)-2-(*N*-Methyl-*N*-phenylamino)-1-phenylpropan-1-ol (**24a**)²³

Using the general procedure, title compound **24a** was obtained as a colorless oil with yields ranging from 77 to 81% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 67–70% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 0.79 (d, *J*=6.4 Hz, 3H), 2.73 (s, 3H), 3.65 (s, 1H), 3.73 (m, 1H), 4.48 (m, 1H), 6.81 (t, *J*=6.8 Hz, 1H), 6.96 (dd, *J*=8.6, 4.5 Hz, 2H), 7.26 (m, 5H), 7.39 (t, *J*=6.2 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): 11.6, 31.1, 64.6, 75.6, 116.8, 119.8, 127.6,

128.3, 128.7, 129.4, 141.5, 151.6; ESI-MS (M+H)⁺ calcd for C₁₆H₂₀NO: 242.2, found: 242.1.

4.15. (1*S*,2*R*)-2-(*N*-Methyl-*N*-*p*-tolylamino)-1-phenylpropan-1-ol (24b)

Using the general procedure, title compound **24b** was obtained as a colorless oil with yields ranging from 73 to 76% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 68–72% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 1.20 (d, *J*=6.8 Hz, 3H), 2.28 (s, 3H), 2.29 (br s, 1H), 2.76 (s, 3H), 4.02 (dd, *J*=6.9, 5.4 Hz, 1H), 4.87 (d, *J*=5.1 Hz, 1H), 6.73 (m, 2H), 7.05 (d, *J*=8.3 Hz, 2H), 7.32 (m, 5H); ¹³C NMR (125 MHz, CDCl₃): 12.0, 20.3, 33.1, 60.5, 75.9, 114.4, 126.1, 126.7, 127.4, 128.2, 129.6, 142.7, 148.2; ESI-MS (M+H)⁺ calcd for C₁₇H₂₂NO: 256.1, found: 256.0; HRMS *m/z* (ESI) calcd for C₁₇H₂₂NO [(M+H)⁺]: 256.1696, found: 256.1681.

4.16. (1*S*,2*R*)-2-(*N*-(4-Methoxyphenyl)-*N*-methylamino)-1-phenylpropan-1-ol (24c)

Using the general procedure, title compound **24c** was obtained as a colorless oil with yields ranging from 72 to 76% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 69–71% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 0.79 (dd, *J*=6.8, 1.6 Hz, 3H), 1.53 (br s, 1H), 2.74 (s, 3H), 3.52 (dd, *J*=9.4, 6.2 Hz, 1H), 3.77 (s, 3H), 4.47 (d, *J*=9.3 Hz, 1H), 6.85 (dd, *J*=8.8, 1.7 Hz, 2H), 7.01 (m, 2H), 7.30 (m, 4H), 7.43 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): 10.3, 55.6, 66.3, 75.1, 77.2, 114.4, 119.5, 127.3, 127.9, 128.3, 129.0, 129.7, 141.3; ESI-MS (M+H)⁺ calcd for C₁₇H₂₂NO₂: 272.1, found: 272.0; HRMS *m/z* (ESI) calcd for C₁₇H₂₂NO₂ [(M+H)⁺]: 272.1645, found: 272.1645.

4.17. (1*S*,2*R*)-2-(*N*-Methyl-*N*-*m*-tolylamino)-1-phenylpropan-1-ol (24d)

Using the general procedure, title compound **24d** was obtained as a colorless oil with yields ranging from 76 to 80% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 69–73% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 1.22 (d, *J*=6.7 Hz, 3H), 2.10 (br s, 1H), 2.30 (s, 3H), 2.77 (s, 3H), 4.08 (dd, *J*=7.0, 5.4 Hz, 1H), 4.88 (d, *J*=5.2 Hz, 1H), 6.57 (q, *J*=7.7 Hz, 3H), 7.10 (t, *J*=7.8 Hz, 1H), 7.31 (m, 1H), 7.33 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): 12.1, 21.9, 32.7, 59.7, 76.1, 110.7, 114.3, 118.0, 126.0, 127.5, 128.3, 128.9, 138.7, 142.6, 150.2; ESI-MS (M+H)⁺ calcd for C₁₇H₂₂NO: 256.1 found: 256.0; HRMS *m/z* (ESI) calcd for C₁₇H₂₂NO [(M+H)⁺]: 256.1696, found: 256.1682.

4.18. (1*S*,2*R*)-2-(*N*-Methyl-*N*-(3,5-dimethylphenyl)amino)-1-phenylpropan-1-ol (24e)

Using the general procedure, title compound **24e** was obtained as a colorless oil with yields ranging from 77 to 79% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 72–74% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 1.26 (d, *J*=6.8 Hz, 3H), 2.34 (s, 6H), 2.40 (br s, 1H), 2.81 (s, 3H), 4.12 (qd, *J*=6.7, 4.9 Hz, 1H), 4.89 (d, *J*=5.1 Hz, 1H), 6.47 (s, 3H), 7.26 (m, 1H), 7.40 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): 12.4, 22.1, 33.1, 56.0, 76.4, 112.0, 119.4, 126.3, 127.7, 128.6, 138.9, 142.9, 150.7; ESI-MS (M+H)⁺ calcd for C₁₈H₂₄NO: 270.2, found: 270.1.

4.19. ((*S*)-1-Phenylpyrrolidin-2-yl)methanol (24f)

Using the general procedure, title compound **24f** was obtained as a colorless oil with yields ranging from 81 to 83% (three repetitions, same scale) with 2,2,6,6-tetramethylheptane-3,5-dione (**L4**) or 75–79% (three repetitions, same scale) with indole-2-carboxylic acid (**L6**). ¹H NMR (500 MHz, CDCl₃): 1.65 (t, *J*=4.9 Hz, 1H), 2.05 (m, 4H), 3.18 (td, *J*=9.4, 6.1 Hz, 1H), 3.54 (t, *J*=8.2 Hz, 1H), 3.70 (d, *J*=5.1 Hz, 2H), 3.90 (m, 1H), 6.74 (d, *J*=8.1 Hz, 3H),

7.26 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): 24.1, 29.1, 49.8, 60.4, 64.1, 112.6, 116.7, 129.5, 148.3; ESI-MS ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_{11}\text{H}_{16}\text{NO}$: 178.1 found: 178.0; HRMS m/z (ESI) calcd for $\text{C}_{11}\text{H}_{16}\text{NO}$ [$\text{M}+\text{H}$] $^+$: 178.1226, found: 178.1228.

4.20. (S)-3,3-Dimethyl-2-(2-phenyl-1H-benzo[d]imidazol-1-yl)butan-1-ol

Into a flame dried round bottom flask containing a magnetic stir bar was added (S)-2-(2-aminophenylamino)-3,3-dimethylbutan-1-ol (**21h**) (4.0 mg, 0.019 mmol), ammonium bromide (9.4 mg, 0.096 mmol), and benzaldehyde (2.3 μL , 0.023 mmol). MeOH (0.5 mL) was added into the reaction mixture and the slurry was stirred at room temperature for 18 h. The solvent was removed at this point and ethyl acetate (4 mL) and brine (1 mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 $\times$ 4 mL). Combined organic layer was dried over anhydrous Na_2SO_4 before passing it through a pad of silica gel. The filtrate was concentrated and purified via flash column chromatography (40% Hex in EA) to afford the product as an off white solid (3.9 mg, 70%). ^1H NMR (500 MHz, CD_3OD): 0.92 (s, 9H), 4.28 (m, 1H), 4.79 (m, 2H), 7.46 (m, 1H), 7.65 (m, 2H), 7.80 (m, 5H), 8.19 (d, $J=8.1$ Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): 25.8, 34.0, 55.7, 69.4, 113.1, 114.8, 124.0, 124.6, 127.2, 127.7, 128.9, 129.1, 130.2, 131.2; ESI-MS ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}$: 295.2, found: 295.2; HRMS m/z (ESI) calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}$ [$\text{M}+\text{H}$] $^+$: 295.1805, found: 295.1790.

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Fig. 1. *N*-2-Hydroxyalkyl-substituted iminobenzimidazole, benzimidazole, and benzimidazolone scaffolds and representative examples.

Fig. 2. Synthetic routes *N*-2-hydroxyalkyl-substituted benzimidazole, iminobenzimidazole, and benzimidazolone heterocycles.

Table 1

Ligand screening for the Cu-catalyzed arylation of amino alcohol **20a** with iodoaniline (**19**) at room temperature

Entry	Ligand	Yield %	Entry	Ligand	Yield % ^{a,b}
1	None	11	5	L4	88
2	L1	45	6	L5	84
3	L2	15	7	L6	81
4	L3	60	8	L7	87

^a Isolated yields reported as the average of three experiments.

^b NMR spectroscopic data for **21a** are in agreement with those reported in Ref. 15.

Table 2
Optimization of reaction conditions for the reaction depicted in Table 1 with ligands **L4** and **L6**

Entry	Mol % CuI	Mol % ligand	Base	Solvent	Yield % ^a (L4/L6)
1	2.5	5	Cs ₂ CO ₃	DMSO	51/47
2	5	5	Cs ₂ CO ₃	DMSO	60/58
3	5	10	Cs ₂ CO ₃	DMSO	87/86
4	10	10	Cs ₂ CO ₃	DMSO	81/75
5	5	10	Cs ₂ CO ₃	DMF	67/66
6	5	10	Cs ₂ CO ₃	DMA	75/73
7	5	10	Cs ₂ CO ₃	Dioxane	70/69
8	5	10	Cs ₂ CO ₃	Toluene	46/40
9	5	10	Cs ₂ CO ₃	DCM	56/50
10	5	10	Na ₂ CO ₃	DMSO	51/50
11	5	10	K ₂ CO ₃	DMSO	60/59

^a Isolated yields reported as the average of three experiments.

Table 3

Arylation of α -amino alcohols with 2-iodoaniline, *N*-Boc-2-iodoaniline and 2-amino-3-iodopyridine

Entry	Amino alcohol	Product	Yield % (L4/L6) ^a
1	20a	21b	80/78
2	20b	21c: R = H	77/77
3		21d: R = Boc	90/89
4	20c	21e	78/79
5	20d	21f	72/70
6	20e	21g	68/68
7	20f	21h: R = H	50/40
8		21i: R = Boc	NT ^b /81 ^c

^a Isolated yields reported as the average of three experiments.^b NT=Not Tested.

^cYield based on single experiment.

Table 4

Arylation of amines with 2-iodoaniline

Entry	Amine	Product	Yield % (L4/L6) ^a
1	20g	21j	63/60
2	20h	21k	65/57
3	20i	20l	60/55
4	20j	21m	NR ^b
5	22	23	NR ^b
6	20k	23	NR ^b

^a Isolated yields reported as the average of three experiments.^b NR=No Reaction. Starting materials were recovered.

Table 5

Arylation of secondary amines with aryl iodides

Entry	Product	Yield % (L4/L6) ^a
1	<p>24a</p>	79/69
2	<p>24b</p>	75/70
3	<p>24c</p>	74/70
4	<p>24d</p>	78/71
5	<p>24e</p>	78/73
6	<p>24f</p>	82/77

^a Isolated yields reported as the average of three experiments.