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Copper-Catalyzed Arylation of β-Amino Alcohols

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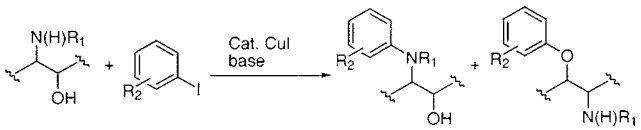
ABSTRACT



Methods for synthesizing *N*-aryl β-amino alcohols and *O*-aryl β-amino alcohols are described. The presence of a neighboring hydroxyl or amino group, respectively, is thought to activate β-amino alcohols toward these transformations. These protocols significantly increase access to a variety of arylated β-amino alcohols.

β-Amino alcohols are of interest in medicinal chemistry[1] and in catalytic organometallic chemistry,[2] where their use as ligands for enantioselective addition of organozinc reagents to carbonyls is well-known. The ubiquity of the β-amino alcohol motif has inspired several synthetic pathways to the *N*-aryl derivatives of β-amino alcohols;[3] perhaps the most practical route is the reaction of epoxides with anilines. The low reactivity of anilines with respect to aminolysis has prompted the development of metal amides and Lewis acid activators to overcome this limitation.[4] The use of tin(II) triflate and copper(II) triflate to catalyze the reaction of epoxides with even weak nucleophiles such as *p*-nitroaniline exemplifies this approach.[5] Another noteworthy route is the Ir-catalyzed asymmetric reduction of *N*-aryl imines, which has found use in the synthesis of the pesticide metalochlor.[6]

The Rh-catalyzed aminolysis of vinyl epoxides devised by Lautens provides an effective route to many *N*-aryl β-amino alcohols; a minor limitation is the need to employ an excess of amine.[7] Lautens has also developed a highly enantioselective version for *meso*-oxabicyclic alkenes.[8] Conditions for selective arylation of β-amino alcohols by S_NAr[9] have been discovered, but this approach has a limited substrate scope.

Ma has reported a mild and convenient method for the N-arylation of the structurally analogous α-amino acids.[10] The high reactivity of α-amino acids, as compared to that of simple amines, is attributed to the ability of these compounds to form a chelate with Cu(I). One might anticipate β-amino alcohols to react similarly to α-amino acids, but Ma found valinol to be no more reactive than benzylamine in his system. In contrast to this finding, Hida observed that β-amino alcohols are more reactive than simple amines in the Ullmann condensation with bromoanthroquinones;[11] however, the 100:1 molar ratio of amino alcohol to aryl bromide used by Hida generally makes the reaction impractical.

(1) In addition to epinephrine and β-blockers: Rogers, G. A.; Parsons, S. M.; Anderson, D. C.; Nilsson, L. M.; Bahr, B. A.; Kornreich, W. D.; Kaufman, R.; Jacobs, R. S.; Kirtman, B. *J. Med. Chem.* **1989**, *32*, 1217.

(2) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284.

(3) (a) Sasaki, T.; Mori, K.; Ohno, M. *Synth. Commun.* **1985**, 280. (b) Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synth. Commun.* **1981**, 376. (c) Barluenga, J.; Fañanas, F. J.; Yus, M. *J. Org. Chem.* **1979**, *44*, 4798. (d) Sanna, P.; Savelli, F. *J. Heterocycl. Chem.* **1984**, *21*, 297. (d) Rampalli, S.; Chaudhari, S. S.; Akamanchi, K. G. *Synthesis* **2000**, *1*, 78.

(4) (a) Harrak, Y.; Pujol, M. D. *Tetrahedron Lett.* **2002**, *43*, 819. (b) Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 4661. (c) Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195.

(5) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287.

(6) Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558.

(7) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319.

(8) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170.

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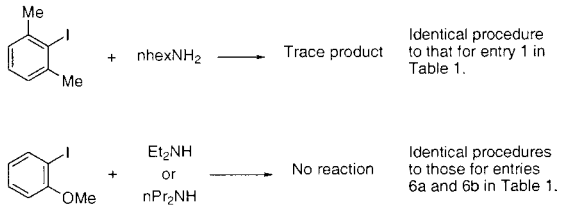
Recently, there has been renewed interest in Cu-catalyzed coupling reactions.[12] As a continuation of our long-standing interest in Pd-catalyzed C−N and C−O bond formation,[13] our group has contributed to the expansion of the analogous Cu-catalyzed chemistry.[14] In keeping with these efforts, we sought to develop a practical arylation reaction that would exploit the increased reactivity of β-amino alcohols.

A major challenge in the arylation of β-amino alcohols lies in controlling the site of reaction. During a preliminary survey of bases and solvents, the use of sodium *tert*-butoxide in DMSO was found to give moderately selective N-arylation (N/O ~5). Greater N/O selectivity on a humid day led to the deliberate addition of water and subsequent improvement of selectivity, culminating in a DMSO/H_2O (2:1) solvent system, with sodium hydroxide as base, yielding N/O >50. Eventually, 2-propanol was found to be essentially equivalent to the DMSO/H_2O system for N-arylation.

To assess the effect of the proximal hydroxyl group for the N-arylation of β-amino alcohols, the reactions shown in Scheme 1 were performed. While 2,6-dimethyl iodobenzene

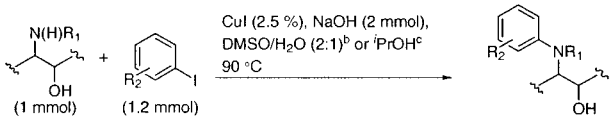
Scheme 1. Control Experiments for the Putative Chelation Effect

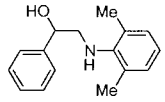
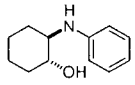
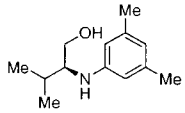
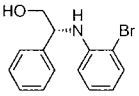
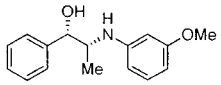
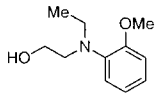
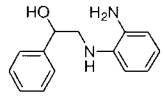


was used successfully in entry 1 of Table 1, the analogous reaction with *n*-hexylamine yielded only a trace amount of the desired product. Furthermore, the reactions of simple secondary amines yielded no product in contrast to entries 6a and 6b in Table 1.

Since the costs of β-amino alcohols and aryl iodides are frequently comparable, the use of either as the limiting reagent was explored. With sodium hydroxide as base, the yield is somewhat better using a moderate excess of aryl iodide rather than amino alcohol (entries 4a and 4b in Table 1) owing to competitive conversion of the aryl iodide to the phenol and, in 2-propanol solvent, the isopropyl aryl ether. When the amino alcohol is used as the limiting reagent,

Table 1. N-Arylation Using Sodium Hydroxide as Base[a]



entry	product	time (h)	% yield[d]
1[e]		16.5	86
2[f]		15	87
3		16.5	88
4a		16	84
b[g]		16	76
5a		16.5	84
b[i]		16.5	77
6a[h]		17	77
b[i]		17	89
7		14.5	63

[a] Conditions: 1 mL of ^{i}PrOH or DMSO/H_2O under N_2 in a sealed tube. [b] Reactions 1−3. [c] Reactions 4−7. [d] Average of two isolated yields; satisfactory combustion analyses were obtained for all compounds. No evidence for the *O*-aryl isomers was seen in the ^{1}H NMR spectra of the isolated products. [e] Temperature = 100 °C. [f] The amino alcohol was used as the HCl salt, requiring 3 mmol of base. [g] The stoichiometries of the aryl iodide and the amino alcohol were reversed. [h] Three equivalents of the amino alcohol and 0.8 mL of ^{i}PrOH were used. [i] Reaction was run in neat amino alcohol.

0−5% of the amino alcohol remains after approximately 16 h. In general, the use of 1.4 equiv of aryl iodide or the use of 10% CuI could eliminate the residual amino alcohol, although no method was completely general. These measures usually led to a reduced N/O ratio and/or increased amounts of diaryl byproducts. Consequently, no significant improvement in yield was realized and the residual amino alcohol was tolerated in our cases since it is easily separated from the *N*-aryl product.[15]

As sodium hydroxide curtails functional group tolerance, the use of mild bases such as K_3PO_4 and Cs_2CO_3 was investigated. The selectivity observed in reactions using mild bases was initially low. Subsequently, in our laboratory, ethylene glycol was identified as a ligand for the Cu-catalyzed arylation of simple aliphatic amines,[14] and so we investigated its use in the arylation of amino alcohols.

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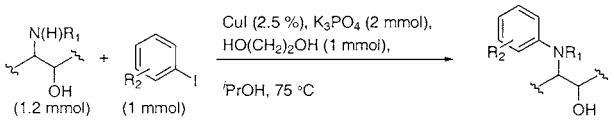
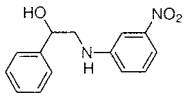
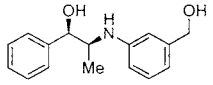
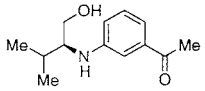
(14) Amides and heterocycles: (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. Amines: (b) Kwang, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. Alcohols: (c) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973. Hydrazines: (d) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.

(15) For example, the compound in entry 2 of Table 1 could be purified by extraction. After concentration, analytically pure material was obtained.

Table 2. N-Arylation Using K_3PO_4 as Base[a]



entry	product	time (h)	% yield[b]
1a		16	73
b[c]		16	66
2[c,d]		16.5	76
3		16.5	75

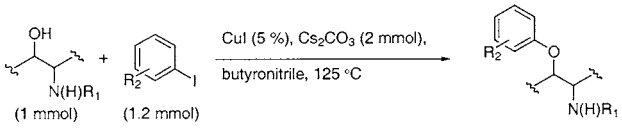
[a] Conditions: 1.1 mL of 2-propanol under N_2 in a sealed tube. [b] Average of two isolated yields; satisfactory combustion analyses were obtained for all products. No evidence of the *O*-aryl isomers was seen in the ^{1}H NMR spectra of the isolated products. [c] The stoichiometries of aryl iodide and amino alcohol were reversed. [d] Temperature = 80 °C

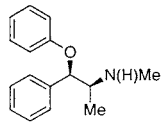
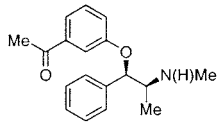
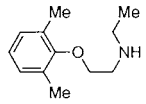
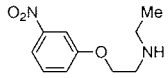
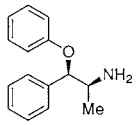
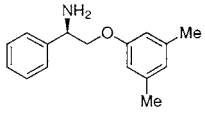
Addition of 1 equiv of ethylene glycol (Table 2) suppresses formation of the *O*-aryl isomer, although the N/O selectivities observed are usually lower than those seen with the hydroxide method. While nitro and ketone functional groups were well-tolerated, low yields were obtained in reactions using ethyl 2-iodobenzoate[16] and 3-iodobenzonitrile. As with the hydroxide method, residual amino alcohol is observed with its use as the limiting reagent in the mild base protocol. However, the use of the aryl iodide as the limiting reagent, in combination with K_3PO_4, results in the better yield (entries 1a and 1b in Table 2).

A trait common to both N-arylation protocols is the diminished reactivity of β-amino alcohols containing a secondary amine (secondary amino alcohols). Although the hydroxide method could effect the N-arylation of 2-(ethylamino)ethanol in acceptable yield, *N*-phenyl ephedrine was obtained in less than 50% yield under the conditions shown in Table 1 owing to the incomplete conversion of ephedrine. These conditions were modified (2 equiv of iodobenzene, 56 h, 100 °C) in an attempt to overcome this difficulty; however, approximately 30% of the ephedrine still remained at the end of the reaction. The reactivity of ephedrine compared with that of the amino alcohols in Table 1 suggests that the presence of α-branching or a secondary amine may be tolerated individually but not together.

Low N/O ratios were obtained in reactions using mild bases and secondary β-amino alcohols. At times, moderately selective O-arylation was observed for these compounds, thus raising the possibility of complementary O-arylation. To assess this possibility, a variety of conditions were screened. Cesium carbonate proved to be the best base for C−O bond formation, consistent with previous experience.[14] The best compromise between selectivity and reaction time was realized using butyronitrile as the solvent, although toluene was better in one case (entry 4 in Table 3). In the reactions

Table 3. O-Arylation of Amino Alcohols[a]



entry	product (as the HCl salt)	time	% yield[b]
1[c]		25	74
2		21	52
3[d]		30	72
4[d,e]		21	54
5		14	53
6		14	47

[a] Conditions: 1 mL of butyronitrile under N_2 in a sealed tube. [b] Average of two isolated yields. Satisfactory combustion analyses were obtained for entries 1−4. Entries 5 and 6 determined to be >95% pure by ^{1}H NMR; water was the chief impurity. No evidence of the *N*-aryl isomers was seen in the ^{1}H NMR spectra of the isolated products. [c] The amount of aryl iodide was 1.5 mmol. [d] Two equivalents of amino alcohol and 1 equiv of aryl iodide were used. [e] Toluene was used as the solvent, and the oil bath temperature was 115 °C.

of 2-(ethylamino)ethanol, the amino alcohol was used in excess since it is extremely cheap and the high water solubility of this amino alcohol simplified the isolation of its *O*-aryl derivatives. In the other examples shown in Table 3, though, the amino alcohol was used as the limiting reagent and was fully consumed, thus allowing isolation of the arylated products by precipitation as their hydrochloride salts.

Reactions of primary β-amino alcohols, such as those used in entries 5 and 6 of Table 3, exhibited higher N/O ratios and/or greater amounts of diaryl byproducts compared to the secondary β-amino alcohols. The complete lack of reactivity of simple alcohols under the conditions of Table 3[17] provides

(16) The reaction was run in ethanol.

(17) Nordmann, G.; Wolter, M.; Job, G. E.; Buchwald, S. L. Unpublished results.

evidence for activation by the neighboring amine group. The yields in Table 3 are better than or similar to those obtained with the competitive routes. For example, the S_NAr displacement of fluoride from arene−$Cr(CO)_3$ complexes has been used to generate, in moderate yields, a series of mexiletine analogues similar to the compound in entry 3 of Table 3.[18] Both the Mitsunobu and Williamson reactions using phenols have been applied to the synthesis of mexiletine analogues, but the highest yield reported was 48%.[19] The opening of a phthalimidoaziridine with phenol, followed by reduction, has been reported to occur in good yield,[20] although the need for a phthalimidoaziridine intermediate somewhat reduces the desirability of this method.

In our study, enantiopure or enantioenriched amino alcohols were used when possible. Valinol, phenylglycinol, norephedrine, and ephedrine were all used in enantiopure form, whereas *trans*-2-amino cyclohexanol was used as the racemate. For all products bearing a single stereocenter, comparison of the product with its racemate or antipode by chiral HPLC[21] demonstrated complete retention of stereochemistry in the coupling reactions. For those products bearing two stereocenters, the lack of evidence for formation of diastereomers, as evidenced by the NMR spectra of the products and the gas chromatographs of the crude reaction mixtures, also demonstrated retention of stereochemistry. These data are consistent with our experience in the Cu-catalyzed arylation of simple amines and alcohols[14] and the Pd-catalyzed arylation of simple amines using bidentate phosphine ligands.[22]

Few enantioselective syntheses of *N*-aryl β-amino alcohols have been reported,[23] while there exist many natural, enantiopure β-amino alcohols and many stereoselective syntheses of β-amino alcohols.[24] Thus, in addition to providing another bond disconnection to consider in a retrosynthetic analysis, our methods provide increased flexibility in planning a stereoselective synthesis. Furthermore, our N-arylation methods enjoy an advantage over epoxide aminolysis. A compound such as that in entry 3 of Table 2 could not be synthesized in good yield by epoxide aminolysis since the regioisomer resulting from attack at the less substituted epoxide carbon is expected to predominate. As for the synthesis of enantiopure *O*-aryl β-amino alcohols, the Williamson reaction can yield an enantiopure compound such as that in entry 1 of Table 3; however, obtaining the necessary enantiopure halide is not trivial. While the Mitsunobu reaction is a viable route to enantiopure *O*-aryl β-amino alcohols, it typically gives no better yield than our O-arylation protocol.

In conclusion, our methods greatly increase both the number of arylated β-amino alcohols reported and the synthetic paths to these compounds. The greatest advantage to our methods, though, lies in their convenience. Commercially available reagents were used without purification and all reagents were weighed and handled in air. Additionally, our protocols make use of widely available, often enantiopure, β-amino alcohols.

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Supporting Information Available: Experimental details and characterization for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Chromatography was performed on an (*R*,*R*)-Whelk-O analytical column. The conditions are described in Supporting Information.

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