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α-Nitrogen activating effect in the room temperature copper-promoted *N*-arylation of heteroarylcarboxamides with phenyl siloxane or *p*-toluylboronic acid

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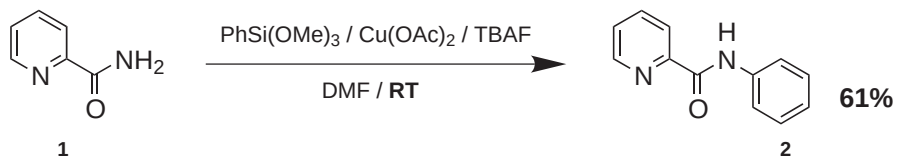
Abstract—Heteroarylcarboxamides containing α-nitrogens undergo copper-promoted *N*-phenylation with hypervalent phenyl trimethylsiloxane at *room temperature*, *in the absence of base and in air*. Arylboronic acid can substitute for phenyl trimethylsiloxane as the organometalloid. The α-heteroatom chelating effect is in the decreasing order of N>O, S. This discovery opens up the possibility of using other α-nitrogen functional groups to direct the *N*-arylation of peptides and simple amides under conditions as mild as that of amide bond formation.

There is a lack of mild (room temperature, no base and air) methodologies for the *N*-arylation of amides using readily available commercial starting materials. Recent elegant work by Buchwald[1] and Shakespeare[2] has demonstrated the palladium catalyzed *N*-arylation of amides with aryl halides. The former occurs at 45–100°C in the presence of cesium carbonate. The latter occurs at 120°C with sodium *tert*-butoxide. Hartwig[3] has also reported an analogous *N*-arylation of carbamates. In the search for a mild *N*-arylation methodology for benzamides, we discovered that hypervalent aryl trimethylsiloxane is an efficient arylating agent for 2-picolinamide **1** in the presence of copper(II) acetate at room temperature[4] (Scheme 1). This is an extension of the copper-promoted C–N/C–O bond cross-coupling with arylboronic acids first reported by Chan, Evans and Lam.[5] Many applications of this new methodology have been reported recently.[6,7] However, in contrast to the initial report,[5d] simple and common amides such as alkylamides[6a] and benzamides (vida infra) do not undergo *N*-arylation. We decided to investigate the reason for the ease of *N*-arylation of 2-picolinamide **1**.

The reaction involves the addition of a stoichiometric amount of tetrabutylammonium fluoride (TBAF) to phenyl trimethylsiloxane in the presence of 2-picolinamide **1** and copper(II) acetate in methylene chloride and is allowed to react at room temperature for 2 days.[8] *N*-Phenyl-2-picolinamide **2** was obtained in 61% yield.

Benzamide **3**, in contrast to compound **1**, gave only 9% yield of **4** upon heating at 70°C (Table 1). 3-Picolinamide **5** and 4-picolinamide **7** are very poor substrates. There appears to be a beneficial chelating effect of the nitrogen alpha to the amide group of 2-picolinamide in the formation of a copper intermediate according to our proposed mechanism of *N*-arylation[4] (Scheme 2).



1 2

Scheme 1. *N*-Phenylation of 2-picolinamide with hypervalent phenyl trimethylsiloxane.

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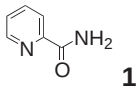
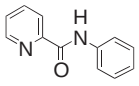
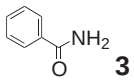
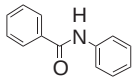
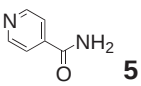
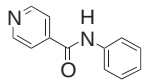
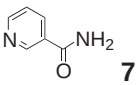
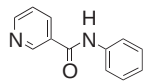
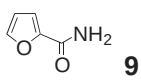
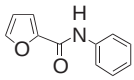
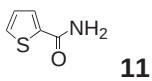
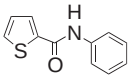
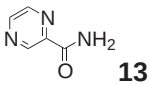
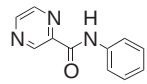
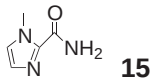
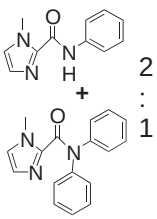
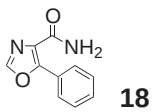
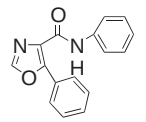
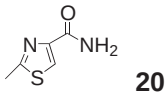
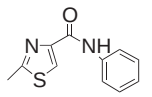
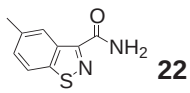
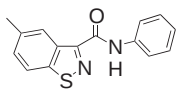
Table 1. Cross-coupling reactions of α-heteroarylcarboxamides with phenyl siloxane

Entry	Substrates	Products	% Isolated Yields
1	 **1**	 **2**	61%
2	 **3**	 **4**	9%[a]
3	 **5**	 **6**	<14%[a]
4	 **7**	 **8**	<12%[a]
5	 **9**	 **10**	36%
6	 **11**	 **12**	22%
7	 **13**	 **14**	52%
8	 **15**	 **16** + **17**	50%
9	 **18**	 **19**	27%
10	 **20**	 **21**	64%
11	 **22**	 **23**	73%

[a]Reaction heated at 70°C

Other heteroatoms were investigated and it was found that 2-furanylcarboxamide **9** and 2-thiophenylcarboxamide **11** gave only 36 and 22% *N*-arylation, respectively. After determining that nitrogen is the best α-heteroatom, we investigated other α-nitrogen-containing heteroarylcarboxamides. 2-Pyrazinecarboxamide **13** yielded 52% of **14**. 2-Imidazoylcarboxamide **15** gave 50% yield of a mixture of **16** and **17** (2:1). 4-Oxazolylcarboxamide **18**, on the other hand, gave only 27% yield of **19**, probably because of the electron-withdrawing oxygen reducing the nitrogen chelating effect. In contrast, 4-thiazolylcarboxamide **20** and 3-isothiazolylcarboxamide **22** gave 64 and 73% yields, respectively.

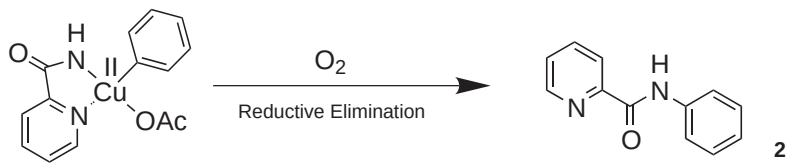
We have previously demonstrated that both arylboronic acids and hypervalent aryl siloxanes are efficient organometalloids for copper-promoted C–N cross-coupling reactions.[4,5] As expected, *p*-toluylboronic acid can replace phenyl trimethylsiloxane to give 44% yield of **24** (Scheme 3).

Instead of stoichiometric $Cu(OAc)_2$, Collman[7c] has recently demonstrated that catalytic $[Cu(OH)\cdot TMEDA]_2Cl_2$ can replace $Cu(OAc)_2$ to promote our C–N bond cross coupling of arylboronic acids and imidazoles under an oxygen atmosphere. By using 10 mol% of $[Cu(OH)\cdot TMEDA]_2Cl_2$ instead of 100 mol% $Cu(OAc)_2$, we found that the cross coupling between phenyl trimethylsiloxane and 2-picolonamide gave 45% yield of **2** in air. An oxygen atmosphere did not appear to increase the yield.

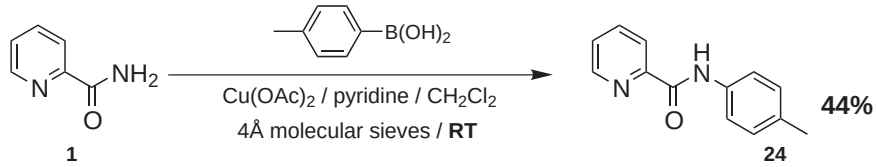
In summary, we have discovered that heteroarylcarboxamides containing α-nitrogen can undergo copper-promoted *N*-phenylation with hypervalent phenyl trimethylsiloxane at *room temperature*, *in the absence of base and in air*. Arylboronic acid can substitute for phenyl trimethylsiloxane as the organometalloid.[9] The α-heteroatom chelating effect is in the decreasing order of N>O, S. This discovery opens up the possibility of using other α-nitrogen functional groups to direct the *N*-arylation of peptides and simple amides under conditions as mild as that of amide bond formation with no risk of racemization as shown in Scheme 4.[10] The key feature is for one to find the optimal activating group A for the α-amino group of peptides. Peptoids thus derived should have interesting biological activities.

Acknowledgements

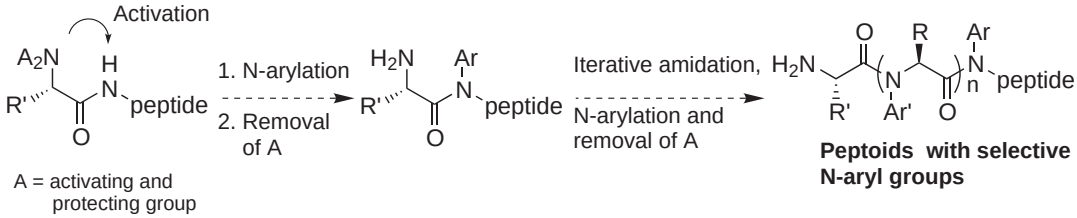
We thank Dr. Paul S. Anderson and Dr. Ruth R. Wexler for their support of this research and Professor Philip DeShong and Professor David A. Evans for helpful discussions.



Scheme 2. α-Nitrogen chelating effect.



Scheme 3. *N*-Arylation of 2-picolinamide with *p*-toluylboronic acid.



Scheme 4. Proposed *N*-arylation of peptides.

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6. For solid-phase version of *N*-arylation see: (a) Combs, A. P.; Rafalski, M. *J. Comb. Chem.* **2000**, *2*, 29–32. (b) Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett.* **1999**, *40*, 1623–1626.
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8. Experimental procedure for thiazolecarboxamide **21**: Oxygen was bubbled into a solution of 2 mL of DMF during 2 min. $PhSi(OMe)_3$ (0.125 mL, 0.667 mmol, 2 equiv.), 2-methylthiazole-4-carboxamide **20** (47.4 mg, 0.333 mmol, 1 equiv.), $Cu(OAc)_2$ (67 mg, 0.367 mmol, 1.1 equiv.) and TBAF (0.67 mL, 0.667 mmol, 2 equiv.) were added in order. The progress of the reaction was monitored by TLC (eluent: 5% $MeOH/CHCl_3$), after a mini-work up of an aliquot. When the reaction was done (48 h), 4 mL of NH_3 in MeOH (2 M) was added, the solution was filtered through glasswool on a pad of Celite® and washed with methanol (6–7 ml) until it was colorless. The solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography. *N*-4-Phenyl-2-methyl-1,3-thiazole-4-carboxamide **21** was isolated (46.2 mg, 64% yield). MS (ES) *m*/*z* 219.2 (80%) $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 9.2 (s, 1H), 8.05 (s, 1H), 7.72 (d, 2H, $J=7.7$ Hz), 7.37 (t, 2H, $J=8$ Hz), 7.14 (t, 1H, $J=7.4$ Hz), 2.76 (s, 3H); HRMS calcd for [M+H] 219.0592, found 219.0587.
9. We recently found that Kang and co-workers have successfully replaced hypervalent aryl siloxanes with hypervalent diaryliodonium salt for *N*-arylation of amines, azoles and amides: Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* **2000**, 1022–1024.
10. The alternative strategy of *N*-arylation before peptide amide bond formation is not efficient due to the low nucleophilicity of the resulting *N*-arylated amine under standard peptide coupling conditions.