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A NEW APPROACH TO THE SYNTHESIS OF SUBSTITUTED PHENAZINES VIA PALLADIUM-CATALYZED ARYL LIGATION[i]

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Abstract

A new method for the "ligation" of two aromatic rings has been achieved via synthesis of functionalized phenazines by double Buchwald-Hartwig cyclization of a variety of substituted bromoanilines.

The ligation of aromatic rings represents an important tool for the synthesis of molecules of increasing complexity,[ii] with important applications in the synthesis of natural and unnatural products. We describe here the implementation of such a strategy for the preparation of substituted phenazines,[iii] leading to the synthesis of disubstituted heterocycles that cannot be otherwise prepared with comparable levels of efficiency (Figure 1).

Previous efforts by Beifuss[iv] and Senanayake[v] have suggested that such a process should be possible, although with only single examples in unoptimized yields, both of which employ the highly pyrophoric ligand tri-*t*-butyl phosphine. We report herein the optimization of this process and its implementation as a method of choice for the synthesis of unsymmetrically disubstituted phenazines. We further describe the application of this reaction sequence to the aryl ligation of two molecules of tryptophan to generate the previously unreported heterocyclic ring system 1,7-dihydrodipyrrolo-[2,3-*b*:2′,3′-*i*]phenazine, a highly fluorescent pentacyclic ring system.

We report herein that a series of bromoanilines that are substituted with either electron-donating or electron-withdrawing groups can be regioselectively converted to the corresponding disubstituted phenazines in good yields using BINAP or other crystalline phosphine ligands in lieu of tri-*t*-butyl phosphine (Table 1). Using the Buchwald C-N Ligand Kit available from Strem Chemicals, a series of phosphines were surveyed, and the two ligands that afforded the highest yields are presented in the Table for each substrate, illustrating the absence of a single optimal phosphine ligand in this reaction. Similar results were observed with the 2-chloroaniline (64% yield) although the corresponding triflates resulted only in oxygen to nitrogen triflate migration in lieu of the desired coupling reaction. The last entry in Table 1 is particularly notable as, even though the observed yield is moderate, none of the desired phenazine product was observed with BINAP.[vi]

We next examined the reaction of more complex aminoaromatics derived from amino acid precursors, as outlined in Figure 2. Aryl ligation of tryptophan using this strategy could lead to the previously undescribed dihydrodipyrrolophenazine ring system shown in **13**. Toward that end, dimerization of **10**,[vii] leads to the formation of the corresponding phenazine in 51%

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yield. However, all attempts to convert **11** to the ring-opened product under the reaction conditions described by Hino and coworkers[7] led to none of the desired product **13**. Direct dimerization of the N-Boc tryptophan **12** produced the desired ring system **15** in 49% yield. The UV spectrum of **13** was notable for a λ_{max} of 406 nm, and the fluorescence spectrum of **13** featured a λ_{em} of 538 nm, with a Stokes' shift of 132.

The analogous reaction of the phenylalanine-derived substrate **14** afforded the corresponding phenazine **15** in 63% yield. A further example of the regiochemical control that is possible with this phenazine construction strategy is the formation of **17**, albeit in 40% yield, from **16**, without formation of the corresponding dibenzo[a,j]phenazine, a result that would not be possible using the more classical approaches to the synthesis of substituted phenazines.[viii] Finally, we demonstrate that this strategy is not limited to dimerization. By judicious choice of substituents on the aniline ring, i.e., by exploiting the decreased reactivity of anilines substituted with electron-withdrawing groups, we have demonstrated that the reaction of **18** with 2-bromoaniline leads to the formation of **19** in 65% yield. The application of this methodology to the synthesis of diverse substituted phenazines is currently underway in our laboratory and our results will be reported in due course.

Acknowledgments

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References

i. We warmly dedicate this manuscript to our friend and colleague Professor Albert Padwa, in grateful acknowledgement of his lifetime of creative accomplishments in organic chemistry.

ii. For an excellent discussion of increasing molecular complexity, see Corey EJ, Cheng X-M. The Logic of Chemical Synthesis. WileyNew York1995

iii. For an excellent recent review, see Beifuss U, Tietze M. Top Curr Chem. 2005; 244:77.

iv. Reference 3, p. 109.

v. Shen M, Li G, Lu B, Hossain A, Roschangar F, Farina V, Senanayake C. Org Lett. 2004; 6:4129. [PubMed: 15496116]

vi. All compounds were characterized by full spectroscopic (NMR, IR, high resolution MS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials. General experimental procedure: To a solution of bromide (1 equiv) in toluene (0.1 M) was added Cs_2CO_3 (2.0 equiv), phosphine ligand (0.08 equiv), and $Pd(OAc)_2$ (0.05 equiv) at room temperature. The reaction mixture was allowed to stir and warm to 120 °C for 4–4 h. Once the reaction appeared to be complete by consumption of the bromide by TLC analysis, the mixture was allowed to cool to room temperature, diluted with $CHCl_3$, and filtered through celite. The solution was concentrated, loaded on silica gel, and purified by silica gel chromatography. Selected spectral data—**14**: **^{1}H NMR** ($CDCl_3$, 500 MHz): d = 8.91 (bs, 2H), 8.36 (s, 2H), 7.71 (s, 2H), 5.48 (d, *J* = 7.3 Hz, 2H), 4.81–4.88 (m, 2H), 3.77 (s, 6H), 3.71 (s, 6H), 3.30–3.48 (m, 4H), 1.78 (s, 18H). **^{13}C NMR** ($CDCl_3$, 125 MHz): d = 171.9, 156.3, 149.2, 141.2, 139.7, 137.7, 136.3, 130.4, 116.9, 114.8, 112.7, 84.4, 53.6, 52.6, 52.4, 28.2, 27.9. **FTIR** (thin film) 3310, 2954, 1726, 1536, 1425, 1374, 1329, 1254, 1153, 1067, 855 cm^{-1}. $[\alpha]_D25$ = 20.7 (c = 0.33, $CDCl_3$). **HRMS** (ES) Calcd. for $C_{38}H_{44}N_6O_{12}$: 799.2915 ($M+Na^+$), found 799.2934 ($M+Na^+$); **18**: **^{1}H NMR** ($CDCl_3$, 500 MHz): d = 9.49 (d, *J* = 7.8 Hz, 1H), 8.19 (d, *J* = 9.2 Hz, 1H), 8.11 (d, *J* = 9.2 Hz, 1H), 8.00 (d, *J* = 6.9 Hz, 1H), 7.79–7.89 (m, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz): d = 142.1, 141.9, 133.5, 132.4, 131.4, 129.5, 128.4, 127.9, 127.7, 125.3. **FTIR** (thin film) 2919, 2851, 1727, 1458, 1382, 1341, 1258, 1115, 827, 741. **HRMS** (ES) Calcd. for $C_{20}H_{12}N_2$: 281.1079 ($M+H^+$), found 281.1080 ($M+H^+$); **20**: **^{1}H NMR** ($CDCl_3$, 500 MHz): d = 9.11 (d, *J* = 1.9 Hz, 1H), 8.77 (d,

J = 1.9 Hz, 1H), 8.34 (m, 1H), 8.27 (m, 1H), 7.87–7.95 (m, 2H), 4.13 (s, 3H), 4.06 (s, 3H). ^{13}**C NMR** ($CDCl_3$, 125 MHz): d = 166.7, 165.6, 144.7, 144.2, 142.4, 142.3, 136.4, 132.4, 132.2, 131.9, 131.0, 130.7, 130.6, 130.1, 53.1, 53.0. **FTIR** (thin film) 1725, 1600, 1520, 1435, 1329, 1244, 1099, 1030, 755. **HRMS** (ES) Calcd. for $C_{16}H_{12}N_2O_4$: 297.0875 ($M+H^+$), found 297.0873 ($M+H^+$).

vii. Prepared from the known amino compound (Taniguchi M, Gonsho A, Nakagawa M, Hino T. Chem Pharm Bull. 1983; 31:1856.by 1) Boc protection; 2) bromination; and 3) Boc deprotection. For an excellent review on the chemistry of hexahydropyrroloindoles, see Crich D, Banerjee A. Acc Chem Res. 2007; 40:151. [PubMed: 17309195]

viii. For a discussion of the regiochemistry of phenazine formation, see Kosugi Y, Itoho K, Okazaki H, Yanai T. J Org Chem. 1995; 60:5690.

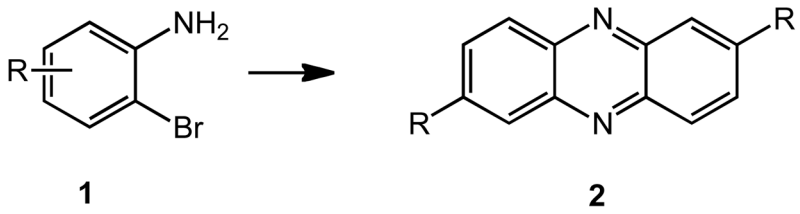


Figure 1.
Regiochemistry of Synthesis of Disubstituted Phenazines

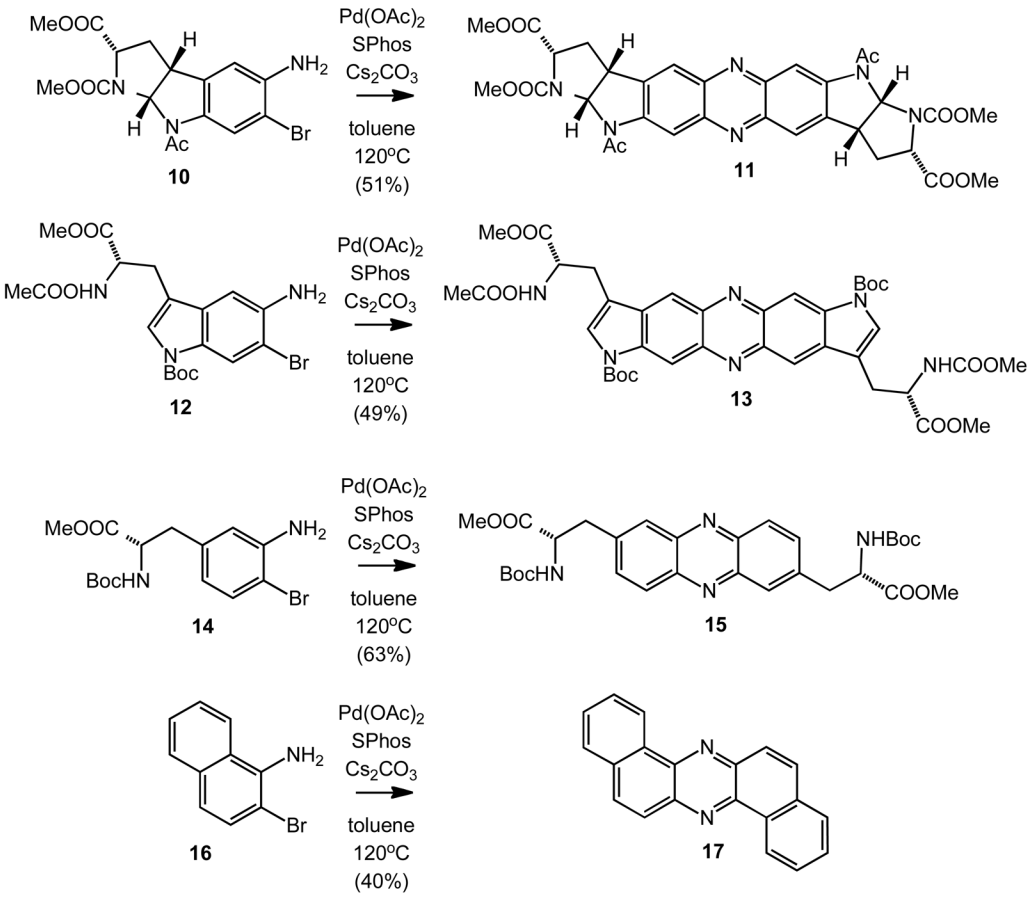


Figure 2.
Synthesis of Complex Phenazines

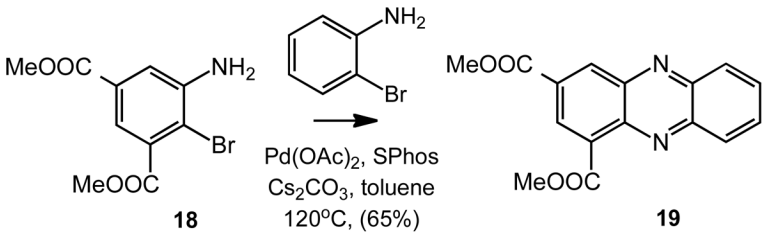
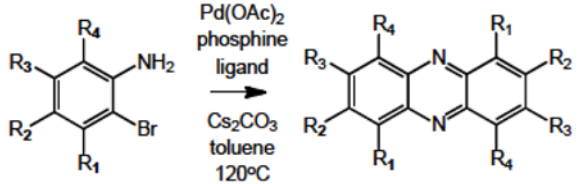


Figure 3.
Synthesis of an Unsymmetrical Phenazine

Table 1

The Effect of Phosphine Ligand on Phenazine Yield



Entry	R_1	R_2	R_3	R_4	Phosphine ligand (Yield)
3	H	H	H	H	SPhos (95%) XPhos (95%)
4	Me	H	H	H	BrettPhos (92%) XPhos (59%)
5	H	H	H	Me	RuPhos (92%) BrettPhos (71%)
6	H	*t*-Bu	H	H	XPhos (55%) SPhos (54%)
7	H	CF_3	H	H	XPhos (80%) RuPhos (56%)
8	OMe	H	H	H	RuPhos (72%) BINAP (56%)
9	H	AcN(Me)−	H	H	XPhos (43%) SPhos (41%)