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A Sequential Metal-Catalyzed C−N Bond Formation in the Synthesis of 2-Amido-indoles

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ABSTRACT

A sequential metal-catalyzed C−N bond formation employing *ortho*-haloaryl acetylenic bromides is described. The initial amidation is highly selective for C^{sp}−N bond formation, leading to *o*-haloaryl-substituted ynamides that can be useful building blocks, while the overall sequence provides a facile construction of 2-amido-indoles.

Given the importance of heterocyclic manifolds,[1] we have been developing synthetic methods that feature ynamides[2,3] en route to various heterocycles.[4] These efforts led us to examine a possible entry for constructing amide-substituted indoles.[5−7] Specifically, as shown in Scheme 1, this pathway would commence with *ortho*-haloaryl acetylenic bromides **1** and adopt a consecutive metal-catalyzed C−N bond

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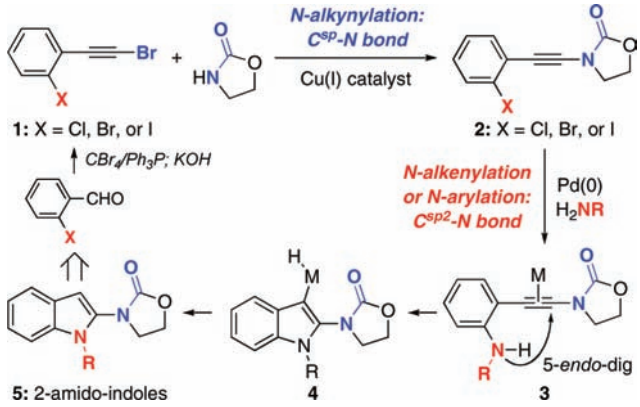
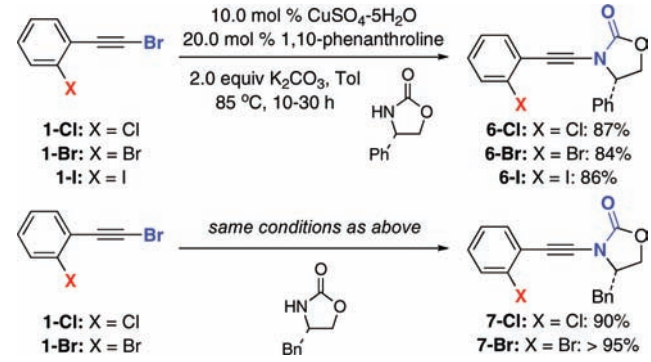
Scheme 1



formation[8] with the first involving the sp-hybridized carbon[9−13] in an N-alkynylation manner and the second one pertaining to an sp^2-hybridized carbon in a N-arylation manner.[8,14] The second C−N bond formation can also occur in a tandem manner with the ensuing indole formation promoted by the metal[15,16] in a 5-*endo*-dig cyclization mode via **3**. While copper can be employed to catalyze the C^{sp}−N formation,[9−13] we intend to utilize palladium for the C^{sp2}−N formation.[15] If this sequential C−N bond formation is selective, it would constitute a facile entry to de novo 2-amido-indoles[17,18] **5** from *ortho*-haloaryl acetylenes **1**, which can be readily derived from aromatic aldehydes in two steps.[19] We report here the synthesis of 2-amido-indoles via a sequential metal-catalyzed C−N bond formation.

A selective amidative cross-coupling of *ortho*-haloaryl acetylenic bromides **1**[20] could be readily established as shown in Scheme 2. By employing 10 mol % of $CuSO_4$·$5H_2O$ and

Scheme 2



20 mol % of 1,10-phenanthroline,[13] ynamide **6-Cl** was attained in 87% yield from **1-Cl**. The amidation remained selective when using **1-Br** and even **1-I**, leading to **6-Br** and **6-I** in 84% and 86% yield, respectively. Under the same conditions, ynamides **7-Cl** and **7-Br** were obtained also via a highly selective C^{sp}−N formation.

A diverse array of *ortho*-haloaryl acetylenic bromides could be subjected to this selective amidation to give ynamides **8**−**16** (Figure 1). Moreover, a range of cyclic and acyclic amides including sulfonamides could be employed for the N-alkynylation to afford ynamides **17**−**23** in good yields.

Having established this selective amidation, we recognized that we have an excellent protocol to access *o*-haloaryl-

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(20) See Supporting Information.

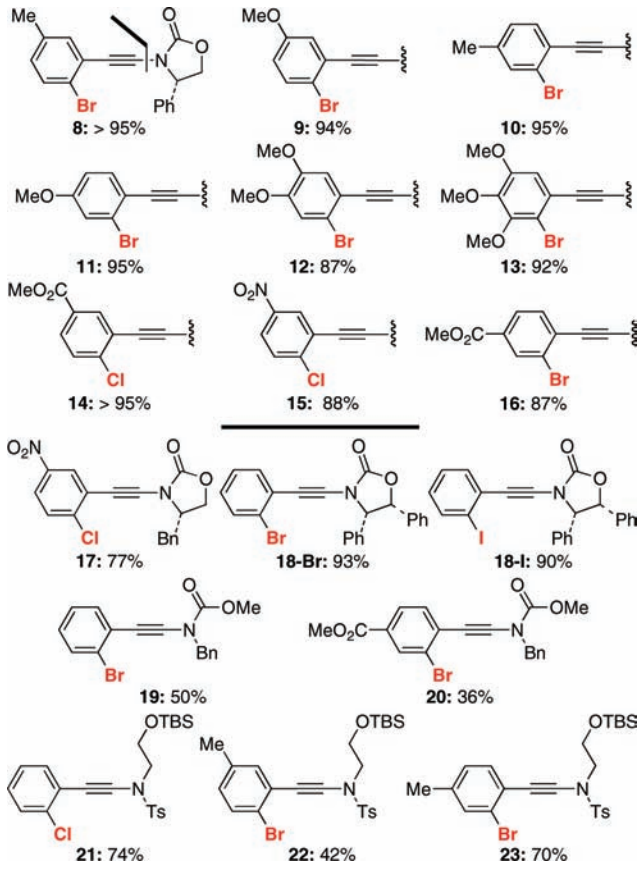


Figure 1. *N*-Alkynylation products. Reaction conditions are the same as those in Scheme 2. All are isolated yields.

substituted ynamides **6**−**23**, which represent a new class of functionally rich building blocks that could be utilized in a number of transformations involving either the *o*-haloaryl or ynamido motif (Figure 2), leading to rapid assembly of structural complexity.

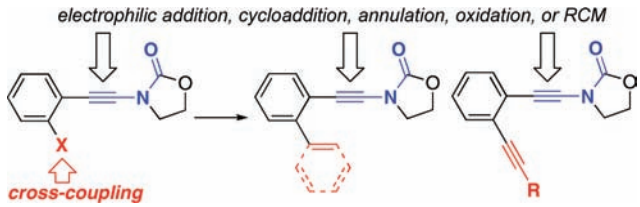
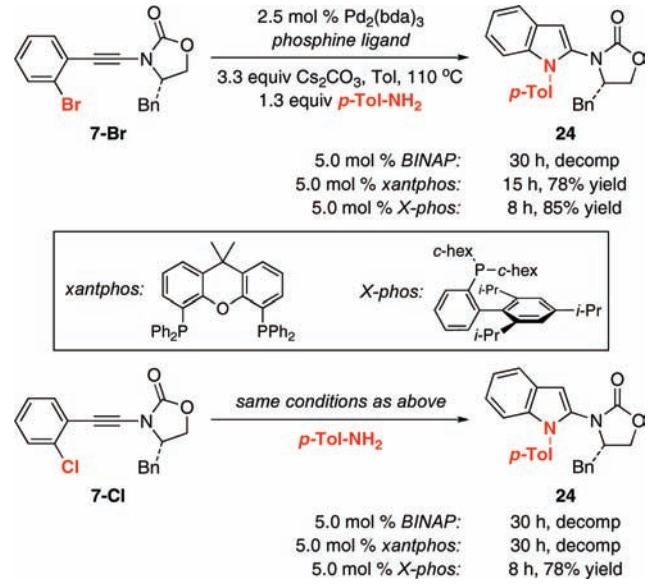


Figure 2. Synthetic potential of *o*-haloaryl ynamides.

To illustrate such synthetic potential, we chose to pursue aminative cross-coupling of aryl halides[8,14] to access 2-acetylenic anilines en route to 2-amido-indoles via metal-promoted 5-*endo*-dig cyclization.[15−19,21] As shown in Scheme 3, when ynamide **7-Br** was subjected to amination conditions employing 2.5 mol % of $Pd_2(dba)_3$ and *p*-Tol-NH_2, 2-amido-indole **24** was obtained in good yields when using either

Scheme 3



5.0 mol % of van Leeuwen's xantphos[22] or Buchwald's X-phos as ligands.[23] Intriguingly, the use of X-phos appears to shorten the reaction time relative to xantphos, while BINAP was not useful. On the other hand, amination of **7-Cl** led to **24** in 78% yield only when using X-phos. It is noteworthy that amination of **6-I** gave only 26% yield of the corresponding indole (not shown), thereby suggesting that aryl chlorides and bromides are better suited in this operation than aryl iodides.

The generality of this tandem amination-5-*endo*-dig cyclization is shown in Table 1, featuring a range of different amines and *o*-chloroaryl- or *o*-bromoaryl-substituted ynamides in excellent yields for their respective reactions. X-ray crystallographic analysis of 2-amido-indole **28** reveals unique orthogonality of three planes: 2-oxazolidone, the indole ring, and the *para*-tolyl ring (Figure 3). Structures with related orthogonality have been shown[24] to possess inhibitory

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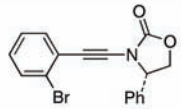
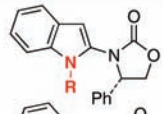
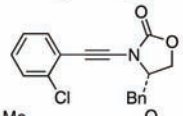
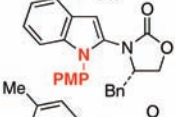
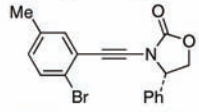
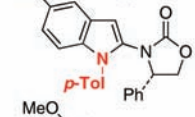
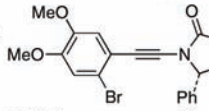
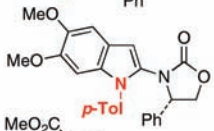
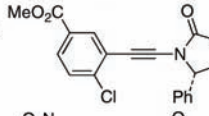
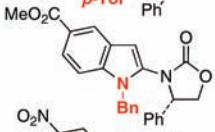
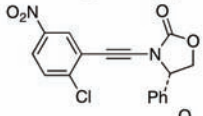
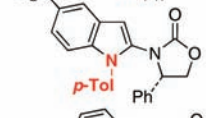
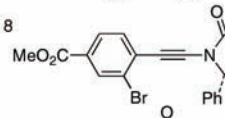
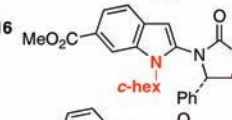
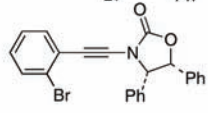
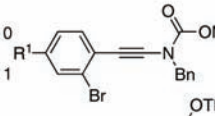
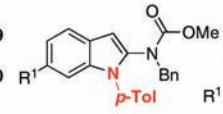
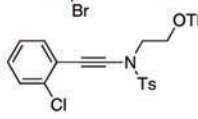
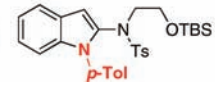
Table 1. N-Alkenylation in the 2-Amido-indole Synthesis

entry	ynamides[a,b]		2-amido-indoles		yield [%][c]
1		6-Br		25: R = *p*-Tol	91
2		6-Br		26: R = *o*-Tol	82
3		7-Cl		27[d]	91
4		8		28	65
5		12		29	60
6		14		30	72
7		15		31	64
8		16		32	80
9		18-Br		33	71
10		19		34: R^1 = H	82
11		20		35: R^1 = CO_2Me	75
12		21		36	88

[a] Reaction conditions: 2.5 mol % of $Pd_2(bda)_3$, 5.0 mol % of X-phos, 3.3 equiv of Cs_2CO_3, 1.3 equiv of R-NH_2, 110 °C, 8−24 h. [b] Toluene was used as solvent in entries 4, 5, 7, and 9, and dioxane was used in entries 1−3, 6, 8, and 10−12. [c] Isolated yields. [d] PMP = *para*-methoxy-phenyl.

activities against human peptidyl prolyl *cis*/*trans* isomerase [PPI] Pin-1,[25] which catalyzes the isomerization of prolyl peptides from *cis* to *trans*[26,27] and accommodates such orthogonality at its active site. We are currently investigating such potential biological activity.

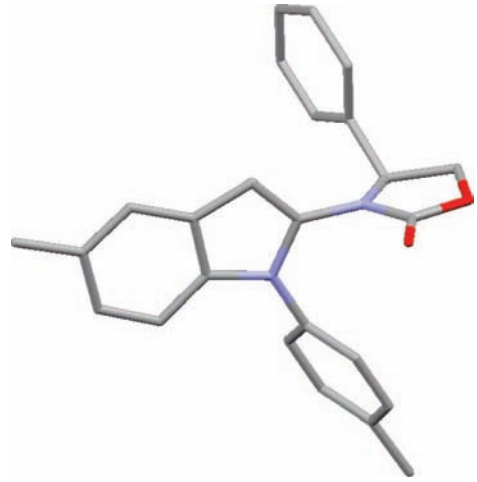


Figure 3. X-Ray structure of 2-amido-indole **28**.

We have described here a sequential metal-catalyzed C−N bond formation employing *ortho*-haloaryl acetylenic bromides. The initial amidation is highly selective for the C^{sp}−N bond, leading to *o*-haloaryl-substituted ynamides that can be useful building blocks. The overall sequence provides a facile construction of 2-amido-indoles possessing a unique structural manifold.

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Supporting Information Available: Experimental procedures as well as NMR spectra, characterizations, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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