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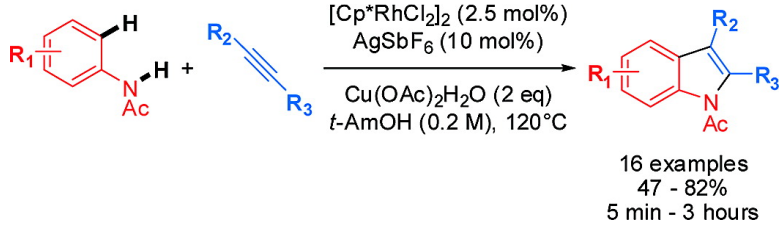

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Indole Synthesis via Rhodium Catalyzed Oxidative Coupling of Acetanilides and Internal Alkynes

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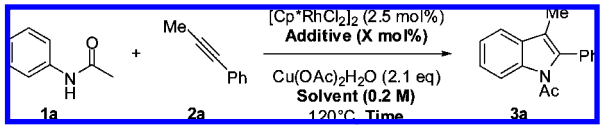
The prevalence of indoles in bioactive molecules[1] has prompted the development of many useful methods for their preparation.[2] Despite advances, most of these techniques rely heavily on substrate preactivation, and very few employ readily available anilines as starting materials.[3] Transition metal catalyzed processes are illustrative,[4] commonly requiring *ortho*-halogenated anilines as starting materials thus adding cost[5] and reducing the breadth of readily available starting materials. A major advance in the minimization of substrate preactivation in indole synthesis was recently described by Glorius involving the condensation of simple anilines with 1,3-dicarbonyl compounds followed by Pd(II)-catalyzed oxidative cyclization.[4m] Similarly, Gagné, Lloyde-Jones, and Booker-Milburn have described an efficient indoline synthesis via Pd(II) catalyzed coupling of *N*-arylureas with activated dienes.[6] Herein we describe the realization of a different approach, namely a rhodium catalyzed oxidative coupling of *N*-acetyl anilines and alkynes, as well as preliminary mechanistic studies.

Based on the known ability of *N*-acetyl anilines to undergo *ortho*-metalation,[7] and the ease with which *N*-acetyl indoles may be deprotected, *N*-acetylaniline **1a** was selected along with 1-phenyl-1-propyne **2a** for reaction development. Extensive experimentation with a variety of Pd(II) catalysts[8] failed to produce indole **3a**, instead giving small amounts of Heck and multiple Heck-type additions. Similarly, Wilkinson's catalyst, which has been shown to induce similar reactivity with 1,2-diaryldiazines,[9] gave none of the desired product. A low but promising outcome was obtained, however, with $[Rh(Cp^*)Cl_2]_2$ in conjunction with a stoichiometric Cu(II) oxidant, a catalyst system recently employed by Satoh and Miura[10] and by Jones[11] for other reactions initiated via cyclometalation.[12] Under these conditions, small amounts of **3a** (~3% yield) could be detected by GCMS analysis of the crude reaction mixture (Table 1, entry 1). Continued optimization revealed that the presence/absence of chloride anions and the choice of solvent exert a dramatic impact on reaction outcome.[13] For example, the addition of silver triflate to sequester the chloride ligands increases the yield 5-fold (entry 2). A solvent screen revealed that the yield could be further increased to 55% by using *tert*-amyl alcohol (1,1-dimethylpropanol) (entry 6), and a second assay of silver salts revealed that, with 10 mol% silver hexafluoroantimonate, a 79% isolated yield of **3a** could be obtained as one regioisomer[14] (entry 9). The reaction time could also be significantly shortened since **3a** can be isolated in 69% yield even after 5 min of reaction (entry 10). Conversely, if 1 equiv of LiCl is added to the reaction mixture, product formation is completely inhibited, adding additional weight to the observation that chloride anions exert a negative role on catalyst activity (Table 1, entry 11).

Table 1. Reaction Development[a]

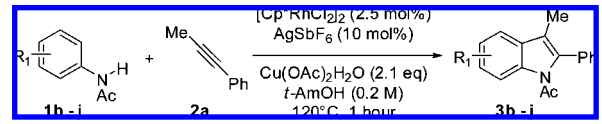


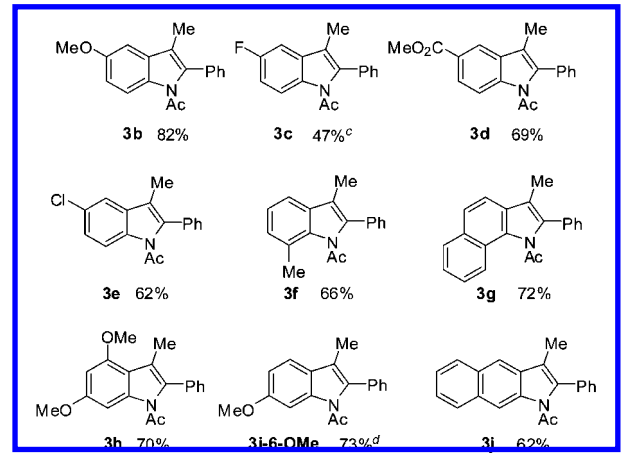
entry	additive (mol%)	solvent	time (h)	GCMS yield (%)
1	none	DMF	16	3
2	AgOTf(10)	DMF	16	15
3	AgOTf(10)	DMA	16	18
4	AgOTf(10)	NMP	16	0
5	AgOTf(10)	mesitylene	16	40
6	AgOTf(10)	*t*-AmOH	16	55
7	$AgBF_4$(10)	*t*-AmOH	16	53
8	$AgSbF_6$(10)	*t*-AmOH	16	74
9	$AgSbF_6$(10)	*t*-AmOH	1	86, 79[b]
10	$AgSbF_6$(10)	*t*-AmOH	0.1	65[b]
11	LiCl(100)	*t*-AmOH	16	<1%

[a] Conditions: Acetanilide (1 equiv), alkyne (1.1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol%), additive, $Cu(OAc)_2 \cdot H_2O$ (2.1 equiv), solvent (0.2 M), 120 °C, specified time. [b] Isolated yield.

Both electron-rich (**3b**, **3h**, and **3i**) and -deficient (**3c** and **3d**) acetanilides participate in good yield (Table 2). A chloride substituent is tolerated (**3e**), as are *ortho*-substituents (**3f** and **3g**). When a *meta*-substituent is present, reaction is preferred at the more sterically accessible position (**3i** and **3j**). A variety of other internal alkynes may also be employed including symmetrically substituted compounds (aryl: **3k**; alkyl: **3l**) (Table 3). When two different alkyl groups are present

Table 2. Acetanilide Scope in the Rhodium Catalyzed Oxidative Indole Synthesis[a,b]





[a] Conditions: Acetanilide (1 equiv), alkyne (1.1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2 \cdot H_2O$ (2.1 equiv), *t*-AmOH (0.2 M), 120 °C, 1 h. [b] Isolated yields are reported above. [c] Allowed to react for 3 h. [d] Minor isomer 1-acetyl-4-methoxy-3-methyl-2-phenylindole was isolated in 9% yield (see Supporting Information).

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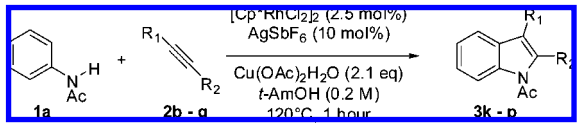
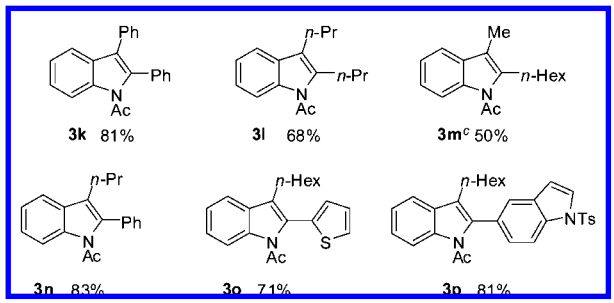
Table 3. Alkyne Scope in the Rhodium Catalyzed Oxidative Indole Synthesis[a,b]



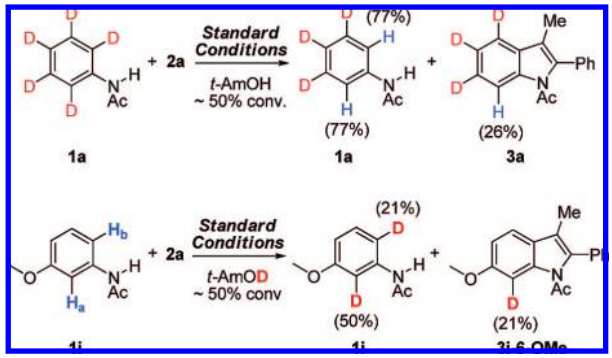


[a] Conditions: Acetanilide (1 equiv), alkyne (1.1 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2 \cdot H_2O$ (2.1 equiv), *t*-AmOH (0.2 M), 120 °C, 1 h. [b] Isolated yields are reported above. [c] Minor isomer 3-*n*-hexyl-2-methylindole was isolated in 28% yield (see Supporting Information).

as in the reaction of 2-nonyne, a 2:1 regioselectivity is observed for the formation of **3m** where the larger *n*-hexyl substituent is situated at C2. As observed with **2a**, other aryl−alkyl disubstituted alkynes also react with high regioselectivity (**3n**, **3o**, and **3p**). Heterocyclic substituents, such as a thiophene (**3o**) and an indole (**3p**), may also be present. Important from a potential application perspective, we have verified that the acetyl moiety is very easily removed under mild conditions (KOH or K_2CO_3 in MeOH/DCM at room temperature) to provide the free N−H indole.[15]

To probe the reaction mechanism, d_5-acetanilide **1a** was subjected to the standard reaction conditions and the reaction was stopped at low conversion to reveal significant deuterium loss at the *ortho*-positions of the unreacted **1a** as well as on the product **3a** (Scheme 1). In the absence of Rh catalyst, no reaction and no loss in deuterium

Scheme 1. Mechanistic Studies



are observed. This may arise from a fast and reversible arene metalation/proto(deutero)demetalation step prior to cross-coupling with the alkyne. Interestingly, when nonsymmetrical aniline **1i** (which undergoes indolization at the more sterically accessible *ortho*-position) is allowed to react in d_1-*tert*-amyl alcohol as the solvent and stopped at early conversions, more deuteration is actually observed at the more sterically hindered *ortho*-position (50%) than at the eventual site of indole formation (21%). This may indicate that the regioselectivity is controlled not by the site of aniline rhodation but by the ease with which the two potential metallated aniline regioisomers undergo subsequent indolization. These observations as well as a more detailed mechanistic evaluation and a greater evaluation of scope are underway.

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Supporting Information Available: Detailed experimental procedures, characterization data for all new compounds, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) All yields for deacetylation were equal to or greater than 90%, and reaction times were between 15 min to 1 h. Please see Supporting Information for specific conditions and representative examples.

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