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Oxidative C−H Homodimerization of Phenylacetamides

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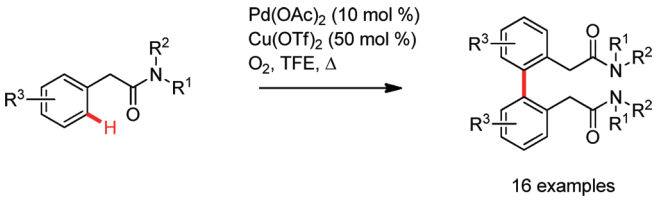
ABSTRACT



A range of secondary and tertiary phenylacetamides undergo oxidative homodimerization to afford biaryls. The reaction proceeds under palladium catalysis in the presence of a copper cocatalyst and oxygen and is most effective for electron-rich substrates.

The biaryl motif is integral to a large number of biologically active molecules, making biaryl synthesis one of the most studied and applied areas of synthetic methodology. Current methods are dominated by transition metal (TM) catalyzed coupling, which has recently expanded to include C−H activation mechanisms. Oxidative biaryl formation, where two C−H bonds react to form the key C−C bond, represents a particularly powerful approach.[1,2] Requiring no prefunctionalization at the inchoate biaryl bond, TM catalysis is used to selectively activate two separate arene C−H bonds. A stoichiometric oxidant is then required to ensure catalyst turnover.

We recently established an oxidative coupling reaction for medium ring synthesis, whereby indole and arene C−H bonds underwent intramolecular coupling to form biaryls tethered with seven- and eight-membered rings.[3] As part of this study, we prepared substrate **1a** as a possible nine-membered ring precursor (Scheme 1). The compound proved recalcitrant to intramolecular cyclization but did afford significant amounts of intermolecular homodimerization product **2**, under Pd/Cu-based oxidative coupling conditions in trifluoroethanol (TFE). Given the current interest in intermolecular C−H oxidative processes, we were interested in examining the scope of this reaction for biaryl synthesis.[4] We

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prepared the truncated phenylacetamide **1b** as a test substrate on which to optimize the reaction.

Scheme 1. Oxidative Dimerization of Phenylacetamides

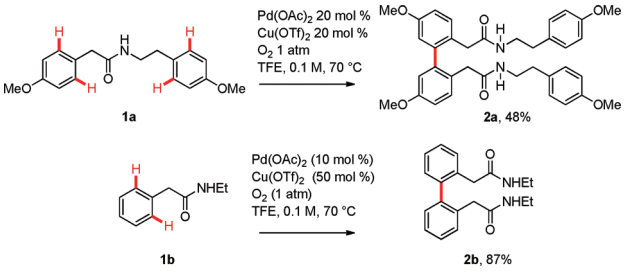

Table 1. Optimization of Homodimerization Conditions

entry	catalyst (mol %)[a]	solvent	temp (°C)	yield (%)[b]
1	copper salt (50)[d] + O_2	TFE	70	n.d. or trace
2	oxidant (300)[c]	TFE	70	n.d.
3	$Cu(OTf)_2$ (20) + O_2 + base (100)[e]	TFE	70	n.d.
4	$Cu(OTf)_2$ (20) + O_2	TFA	70	trace
5	$Cu(OTf)_2$ (20) + O_2	AcOH	90	trace
6	$Cu(OTf)_2$ (20) + O_2	PivOH	110	n.d.
7	$Cu(OTf)_2$ (20) + O_2	toluene	110	n.d.
8	$Cu(OTf)_2$ (20) + O_2	1,4 dioxane	90	n.d.
9	$Cu(OTf)_2$ (20) + O_2	DMA	120	n.d.
10	$Cu(OTf)_2$ (20) + O_2	DMSO	120	n.d.
11	$Cu(OTf)_2$ (20) + O_2	TFE	80	72
12	$Cu(OTf)_2$ (300)	TFE	80	41
13	O_2	TFE	80	n.d.
14	$Cu(OTf)_2$ (20) + air	TFE	80	<72
15	**$Cu(OTf)_2$ (50) + O_2**	**TFE**	**70**	**87**

[a] O_2 balloon at 1 atm. [b] Isolated yields; n.d. = Not determined as no product observed on LC-MS. [c] Copper source: *Cu(I)*: CuBr·Me_2S, CuCl, CuI, Cu_2O; *Cu(II)*: $Cu(Acac)_2$, $Cu(OAc)_2$, CuO, $CuBr_2$, $CuCl_2 \cdot 2H_2O$, $CuSO_4$, $CuCO_3$. [d] Oxidant: $Ce(SO_4)_2$, AgOAc, $Cu(OAc)_2$, BQ, $K_2S_2O_8$, AgTFA, Ag_2CO_3, PIDA, TBHP, TBPB. [e] Base: K_2CO_3, KOAc, Cs_2CO_3, CsOAc, CsPiv, CsF.

The dimerization proved to be quite specific in terms of solvent and oxidant (Table 1) with the reaction only being viable using TFE as solvent in the presence of $Cu(OTf)_2/O_2$. A range of alternative copper salts and oxidants failed to produce any coupling products (entries 1 and 2), and alternative solvents were not effective (entries 4−10). The optimal conditions are shown in entry 15: 10 mol % $Pd(OAc)_2$, 50 mol % $Cu(OTf)_2$ under 1 atm of oxygen at 70 °C for 24 h. Under these conditions dimer **2b** could be isolated in an excellent 87% yield. Notably, basic additives (entry 3) or acidic solvents such as TFA or AcOH (entries 4 and 5) were not tolerated in the reaction.

With an optimized procedure in hand, we moved on to explore the scope of the homodimerization (Figure 1). The dimeric phenylacetamides can display a variety of functionality and have been used as TM ligands[5] and precursors to biologically active biaryls.[6] Existing synthetic routes to these products use classic Ullmann coupling of aryl iodides with copper catalysis.[6,7]

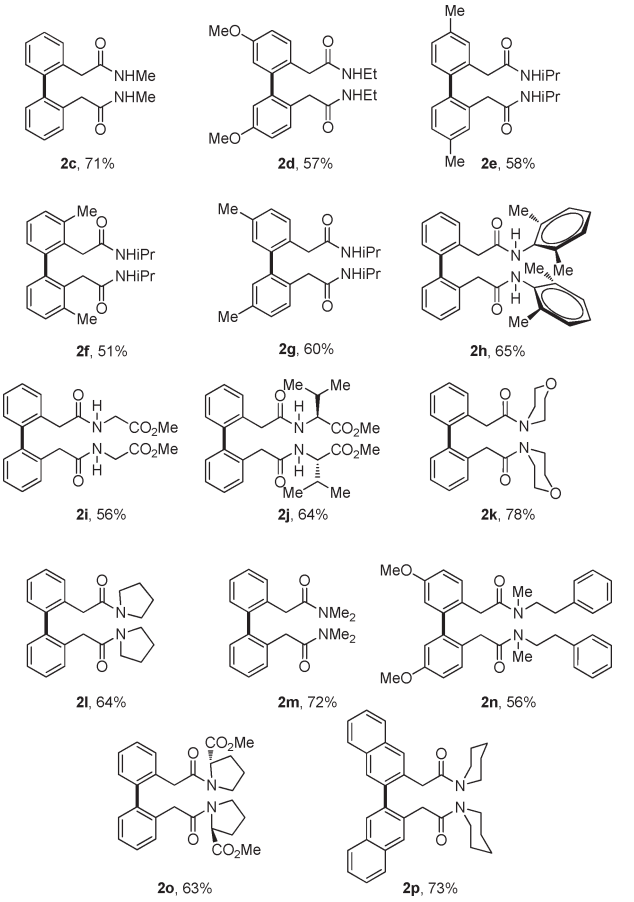

Figure 1. Oxidative dimerization products of secondary and tertiary phenylacetamides.

The reaction proved successful for electron-neutral and -rich arenes, whereas electron-poor substrates were unreactive. The parent (**2b** and **2c**), Me (**2e**, **2f**, and **2g**), and OMe (**2d**) substituted compounds were all formed in moderate to good yields, but *p*-fluoro- and *p*-chlorophenylacetamides were unreactive under the conditions. An *ortho*-Me substituent was tolerated (**2f**), likewise the *meta*-Me arene which gave the expected regioselectivity where C−H activation occurs at the more sterically accessible position (**2e**). The simple anilide substrate ($PhCH_2CONHPh$) was unproductive in the reaction, possiby due to competing cyclopalladation events.[2f] This was supported by the 2,6-dimethylphenyl derivative (where both *ortho* positions are

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blocked on the anilide) undergoing dimerization in good yield to afford **2h**. Steric hindrance around the amide group was tolerated without problem; along with **2h** the dimeric isopropylamides **2e**, **2f**, and **2g** were all successfully formed in 51−60% yield. Functionality on the amide was also viable in the reaction, with the glycine and valine units undergoing successful dimerization (**2i** and **2j**, the latter as a single diastereoisomer). We were pleased to see that tertiary amides were equally effective in the reaction; morpholine, pyrollidine, dimethyl, phenethyl, and proline amides all produced the biaryl dimers in moderate to good yields (**2k**−**2o**). Finally, the electron-rich naphthylacetamide dimer **2p** was formed in good yield as a single regioisomer displaying two piperidine groups.

Mechanistically, a cyclopalladation pathway is likely based on related phenylacetamide C−H activations in the literature. Dong has shown phenylacetamides to be excellent substrates for *ortho*-directed, oxidative cross-coupling with simple arenes such as benzene.[2e,f,8] Using $Na_2S_2O_8$ as oxidant and the arene as solvent, a variety of electron-rich phenylacetamides were arylated in high yield using Pd catalysis in the presence of TFA. While our conditions differ with respect to oxidant and the acidity of solvent, the propensity of electron-neutral and -rich phenylacetamides, but not electron-poor, to undergo C−H activation mirrors the heterocoupling system of Dong. However, the sensitivity of C−H activation mechanisms to changes in reaction conditions was illustrated by adding excess benzene to the dimerization of **1c**. No intermolecular arylation was observed, indicating that the homodimerization pathway is dominant under these conditions. In earlier work, Shi[2a] and Buchwald[2b] have reported the oxidative cross-coupling of anilides with arenes using oxygen as the stoichiometric oxidant. These substrates, where the nitrogen atom is switched to the aniline position, were not productive under our reaction conditions, and no dimer could be isolated.

In conclusion, we have defined a Pd-catalyzed homodimerization pathway for phenylacetamides. The reaction proceeds in the presence of substoichiometric copper(II) and oxygen, affording symmetrical 2,2-disubstituted biaryls that display a wide range of amide functionality. Future work will look to apply this method to the synthesis of biologically active biaryls.

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

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