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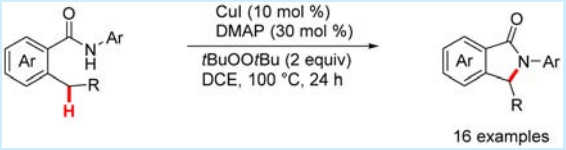
Copper-Catalyzed sp^3 C−H Aminative Cyclization of 2-Alkyl-*N*-arylbenzamides: An Approach for the Synthesis of *N*-Aryl-isoindolinones

Kanako Nozawa-Kumada, Jun Kadokawa, Takehiro Kameyama, and Yoshinori Kondo*

Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3, Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

Supporting Information

ABSTRACT: The synthesis of isoindolinones via copper-catalyzed sp^3 C−H functionalization of 2-alkyl-*N*-substituted benzamides is described. This process does not require the preparation of halogenated substitutes, expensive transition metals, or toxic Sn or CO gas. This method provides an efficient approach to generate various functionalized isoindolinones.



Amination reactions are crucial for synthesizing natural organic and medicinally important compounds. Among the many available amination methods, the direct amination of sp^3 C−H bonds has emerged as an attractive route to prepare sp^3 C−N bonds[1] because it does not require prefunctionalized starting materials. Transition-metal-catalyzed nitrene insertion into C−H bonds is one of the most widely established sp^3 C−H amination procedures.[2] However, this process is limited to the synthesis of secondary amines. Recently, a Kharasch−Sosnovsky type amination reaction[3,4] was developed as an alternative to the metal-nitrene-based strategies. This reaction is an amination of allylic,[3a] benzylic,[3b−e] and aliphatic[3f−h] C−H bonds using peroxide as the oxidant. However, despite its usefulness, there have been no reports of it being applied to intramolecular aminative cyclizations.

Isoindolinones with sp^3 C−N bonds are found in many natural and synthetic drug molecules,[5] for example, indoprofen (an anti-inflammatory),[6] stachybotrin (an anxiolytic),[7] and staurosporine (a protein kinase C inhibitor)[8] (Figure 1). Many methods have been reported for the synthesis of *N*-substituted isoindolinones, such as selective monoreduction of phthalimides,[9] transition-metal-catalyzed cyclization of 2-halobenzamides,[10] olefination of benzoic amides,[11] and Pd-catalyzed cycloaminocarbonylation.[12] However, most of these methods require starting materials that are difficult to prepare, expensive transition metals, or toxic Sn or CO gas. During the course of our present study, Kumar et al. reported the transition-metal-free intramolecular oxidative coupling of 2-alkylbenzamides for preparing isoindolinones.[13] This process employs iodine, potassium carbonate, and di-*tert*-butyl peroxide and provides a route to various *N*-aryl-isoindolinones. Herein, we report a new approach for the synthesis of isoindolinones via Cu-catalyzed sp^3 C−H aminative cyclization of 2-alkyl-*N*-substituted benzamides.

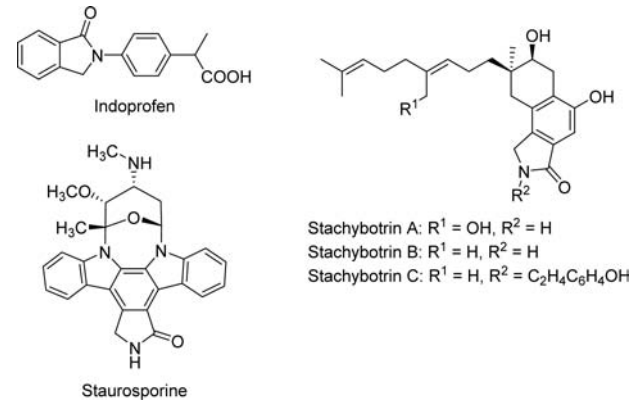


Figure 1. Bioactive and natural isoindolinone derivatives.

We began our investigation using 2-methyl-*N*-phenylbenzamide **1a** as a substrate to optimize the reaction conditions (Table 1). The cyclization of **1a** was first performed in the presence of CuI (20 mol %) and di-*tert*-butyl peroxide (2 equiv) at 100 °C in benzene. Without the addition of ligands, the reaction did not proceed at all (Table 1, entry 1). Ligands play a role in enhancing the overall yield, and it was found that pyridine was the most effective for this reaction (entries 2−4). Of the solvents investigated, DCE was demonstrated to be the best (entry 7). A subsequent screening of Cu(I) and Cu(II) salts revealed that CuI represented the optimum source of copper for the reaction (entries 7−10). When we tested further pyridine derivatives as ligands, we found that electron-donating group substituted pyridines improved the reaction yield (entries 11 and 12 vs 7). Decreasing the amount of copper and ligand did not affect the reaction, and it was found that a high yield of **2a** was still obtained under these conditions (entry 13). Other oxidants, such as *tert*-butyl peroxide and *tert*-butyl peroxyacetate, inhibited the reaction (data not shown).

Having identified the optimum reaction conditions, we explored the range of substrates to which this process can be applied. As shown in Scheme 1, it worked with a wide range of

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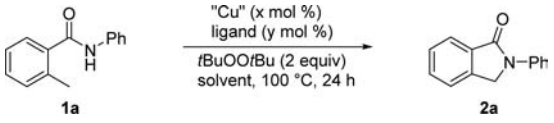
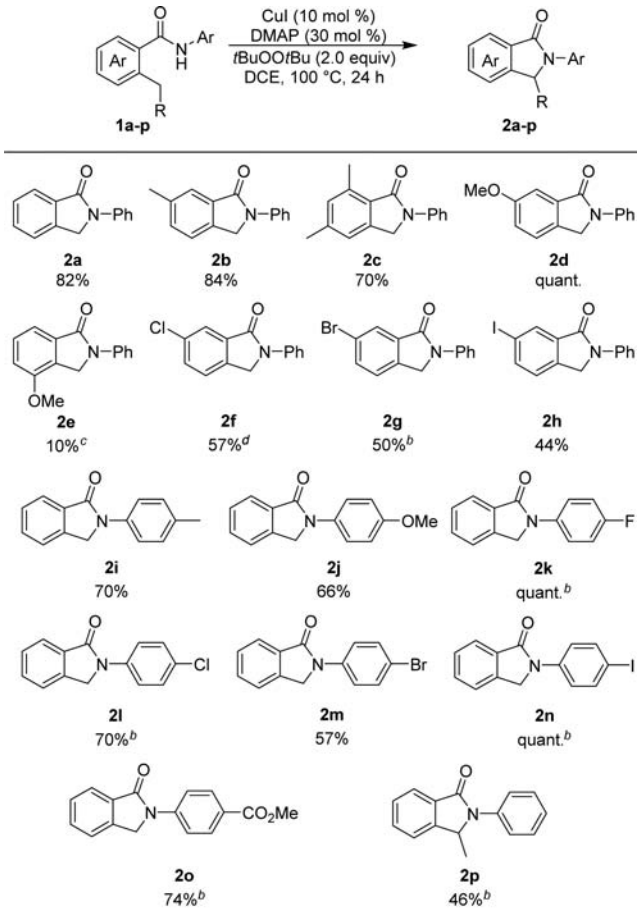
Table 1. Effect of Reaction Parameters



entry	Cu (mol %)	ligand (mol %)	solvent	yield (%)[a]
1	CuI (20)	none	benzene	trace
2	CuI (20)	phen (40)	benzene	15
3	CuI (20)	bipy (40)	benzene	13
4	CuI (20)	pyridine (40)	benzene	17
5	CuI (20)	pyridine (40)	toluene	22
6	CuI (20)	pyridine (40)	DMSO	trace
7	CuI (20)	pyridine (40)	DCE	57
8	$Cu(OAc)_2$ (20)	pyridine (40)	DCE	26
9	$CuBr_2$ (20)	pyridine (40)	DCE	46
10	CuBr (20)	pyridine (40)	DCE	47
11	CuI (20)	4-MeO-Py (40)	DCE	65
12	CuI (20)	DMAP (40)	DCE	86
13	CuI (10)	DMAP (30)	DCE	85 (82)[b]

[a]Determined by ^{1}H NMR using 1,1,2-trichloroethane as an internal standard. [b]Isolated yield in parentheses.

Scheme 1. sp^3 C−H Functionalization of Various 2-Alkyl-*N*-arylbenzamides[a]

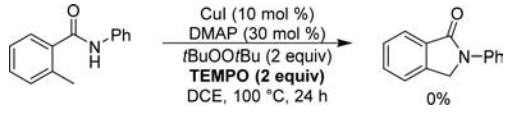


[a]Isolated yield. [b]Reaction was run at 120 °C. [c]Determined by ^{1}H NMR using 1,1,2-trichloroethane as an internal standard. [d]0.3 mmol scale.

functional groups including halogen atoms. Substrates with electron-donating groups in the benzamide ring gave the desired products **2b−d** with good yields, with the exception of 3-substituted-2-methyl-*N*-phenylbenzamide (**1e**). Conversely, substrates containing halogen atoms produced the isoindolinones **2f−h** with slightly reduced yields. Next, we explored substitution in the aniline ring and found that the process yielded moderate amounts of the cyclized products **2i−o** regardless of the electronic properties of the aniline ring. 2-Ethyl-*N*-phenylbenzamide **1p**, which has a secondary benzylic hydrocarbon, reacted to produce a good yield.

To investigate the reaction mechanism, we performed the reaction with the addition of radical scavenger TEMPO (Scheme 2). None of the desired product was detected, indicating that the reaction might proceed via a radical process. Further mechanistic studies are currently underway.

Scheme 2. Radical Scavenger Experiment



In conclusion, the Cu-catalyzed sp^3 C−H aminative cyclization of 2-alkyl-*N*-arylbenzamides has been developed using di-*tert*-butyl peroxide, and various substituted substrates were found to be suitable for the reaction. This process provides a powerful approach to synthesize *N*-aryl-isoindolinones. Further studies to expand the scope of substrates and broaden the synthetic application to other heterocycles are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02235.

Experimental procedures, characterization data, and spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ykondo@m.tohoku.ac.jp.

Notes

The authors declare no competing financial interest.

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