Tetrahedron Letters 50 (2009) 7293–7296

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper-catalyzed C–N coupling of amides and nitrogen-containing heterocycles in the presence of cesium fluoride

Dean P. Phillips *, Xue-Feng Zhu, Thomas L. Lau, Xiaohui He, Kunyong Yang, Hong Liu

Department of Medicinal Chemistry, Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121, United States

ARTICLE INFO

Article history:
Received 20 April 2009
Revised 6 October 2009
Accepted 8 October 2009
Available online 15 October 2009

ABSTRACT

The copper-catalyzed C–N coupling of amides to aryl halides usually requires the use of strong alkali metal bases, such as K_2CO_3, K_3PO_4, and Cs_2CO_3, at high temperature. We discovered that CsF is sufficiently basic to promote the cross-coupling of amides and carbamates with aryl halides. Most aryl iodides coupled in high yield at room temperature. This alternative base may be a suitable replacement for substrates that are incompatible with high temperature and strongly basic conditions and can further enhance the chemoselectivity of this reaction.

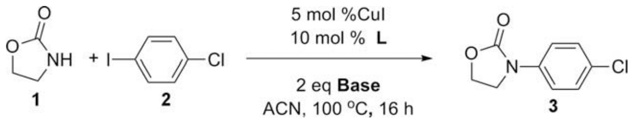
In recent years, new catalytic methods have been introduced that have enabled the coupling of most nitrogen-containing functional groups to sp^2-halides. New variants of the Goldberg reaction have received significant attention.[1,2] These new methods have been employed in early drug discovery research and in the large scale synthesis of active pharmaceutical substances.[1d] In some instances, however, high reaction temperatures (⩾100 °C), long reaction times (⩾24 h), and strongly basic conditions may lead to undesired side products. Therefore, additional methods with improved reactivity, broader reaction scope, and substrate tolerance are still in demand. Improved reaction rates and broader scope have been achieved with a variety of new copper ligands.[1,2] Still, in these instances, mostly strong alkali bases (K_2CO_3, K_3PO_4, and Cs_2CO_3) have been reported. In instances where substrates are incompatible with these bases, milder and less basic conditions would be useful.

Our group had been employing conditions described by Buchwald and co-workers[2a] for the construction of several small molecules; however, we encountered substrates that were incompatible with K_2CO_3, K_3PO_4, and Cs_2CO_3. At the time, precedent for employing weaker bases for this cross-coupling was limited to a few examples.[3c,4] Several bases were screened for the coupling of **1** with **2** and we found that $KHCO_3$, KOAc, or CsF each gave acceptable yields at 100 °C (Table 1). Interestingly, in the presence of CsF, the reaction proceeded to near completion within 2 h whereas the other bases required 18 h. Since it has been reported that CsF can accelerate some transition metal-coupling reactions,[5,6] we decided to test the CsF conditions at room temperature and were very pleased to observe high yields after 18 h. Herein, we describe the scope and limitations of the copper-catalyzed C–N coupling of amides and nitrogen-containing heterocycles in the presence of CsF.

During the course of our investigation, we screened the reaction conditions in our model system (Table 1) and found that acetonitrile, THF, and ethyl acetate provided excellent results. Upon screening equivalents of the base, we determined that a minimum of 2–2.5 equiv of CsF was required. Since CsF demonstrated an effect to promote the CuI-catalyzed reaction in this model system, we next determined the scope of the reaction.

The results of cross-coupling several amides with various aryl iodides are detailed in Table 2.[7] These reactions were performed at 1 mmol scale with 2.5 equiv of CsF, 5 mol % of CuI, and 10 mmol % of *N,N'*-dimethylethylenediamine in either THF, EtOAc, or acetonitrile for 18–24 h. We found that most amides and carbamates coupled very efficiently to aryl iodides with *p*- or *m*-substituents at 25 °C (Table 2). The efficiency of these conditions on 10 mmol scale was demonstrated at 60 °C with example **4b**, illus-

Table 1
Modified Buchwald couplings with weak bases[a]



Entry	Base	Yield[b]
1	$KHCO_3$	89
2	CsF	81[c]
3	KOAc	80
4	CsOAc	31
5	$NaHCO_3$	10

[a] Conditions: 1.2 mmol **1**, 1.0 mmol **2**, 2 mL ACN.
[b] % Isolated yield.
[c] No further change after 2 h.

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* Corresponding author. Tel.: +1 858 332 4433; fax: +1 858 812 1648.
E-mail address: dphillips@gnf.org (D.P. Phillips).

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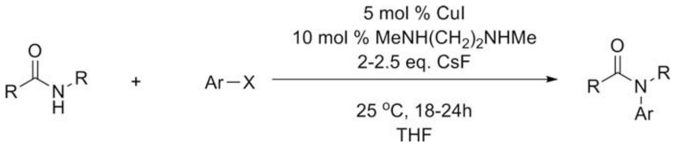
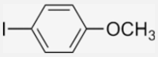
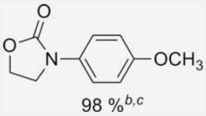
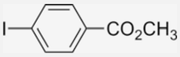
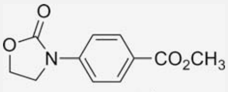
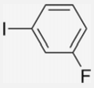
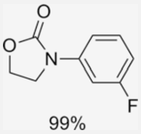
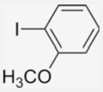
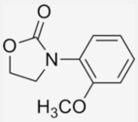
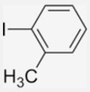
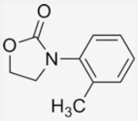
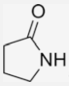
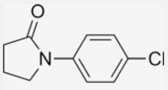
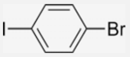
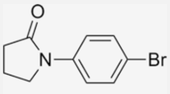
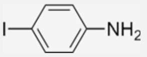
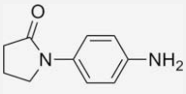
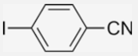
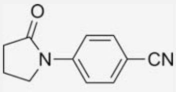
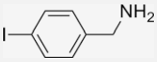
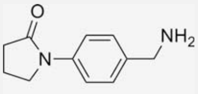
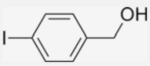
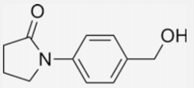
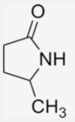
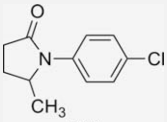
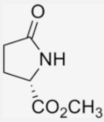
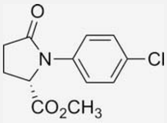
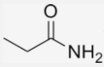
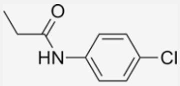
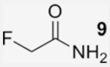
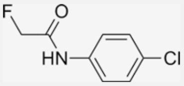
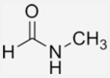
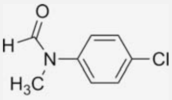
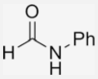
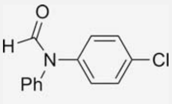
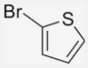
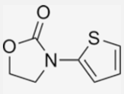
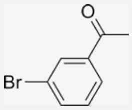
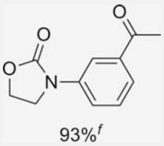
doi:10.1016/j.tetlet.2009.10.041

Table 2
CuI-catalyzed amidations with CsF at 25 °C[a]



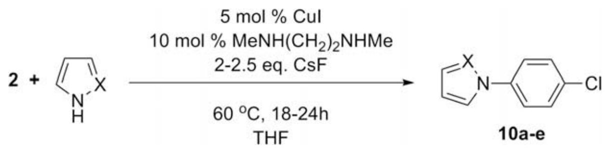
Entry	Amide	Ar–X	Product
4a	**1**		 98 %[b,c]
4b	**1**		 92 %[c,d]
4c	**1**		 99%
4d	**1**		 99%[e]
4e	**1**		 92%[f]
4f	 **5**	**2**	 99%[g]
4g	**5**		 99%[g]
4h	**5**		 99%
4i	**5**		 89%
4j	**5**		 93 %
4k	**5**		 95%
4l	 **6**	**2**	 83%
4m	 **7**	**2**	 99%[h]
4n	 **8**	**2**	 94 %
4o	 **9**	**2**	
4p		**2**	 86%
4q		**2**	 98%
4r	**1**		 97%[f]
4s	**1**		 93%[f]

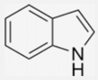
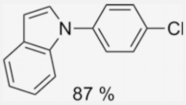
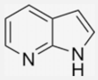
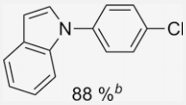
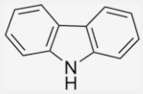
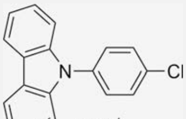
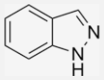
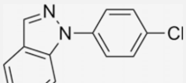
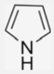
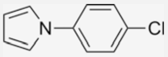
[a] Yields refer to isolated yields.
[b] 83% at 25 °C.
[c] 60 °C.
[d] 10 mmol scale.
[e] In ACN at 85 °C.
[f] In ACN at 100 °C.
[g] In EtOAc.
[h] 91% ee.[7]

trating the potential for scalability. Electron-poor and electron-rich aryl halides coupled with near equal efficiency under these conditions. Overall, excellent substrate tolerance and selectivity were observed.

Several examples from Table 2 are worth highlighting. We observed exclusive coupling of the iodide under the CsF room temperature conditions for entry **4g**; at higher temperature and in the presence of stronger bases, selectivity for the iodide displacement was greatly reduced. The reaction conditions also tolerated other XH-containing functional groups, as in examples **4h**, **4j**, and **4k**. For entry **4m**, the product was obtained in high yield and with no observable racemization or hydrolysis. We observed significant racemization with the conditions reported in the literature.[8] The higher yield of **4m** relative to **4l** can be explained by the favorable

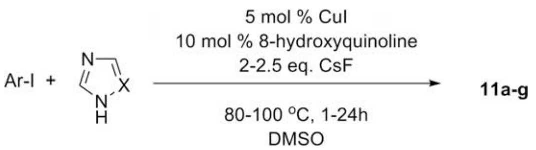
Table 3
CuI-catalyzed arylations of indoles, indazole, and pyrrole with CsF[a]

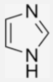
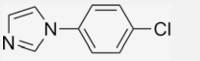
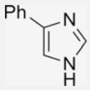
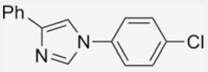
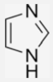
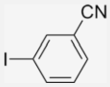
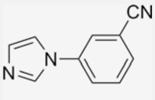
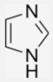
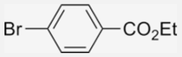
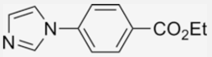
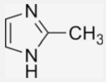
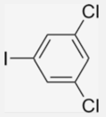
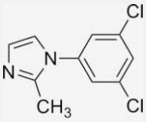
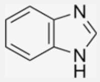
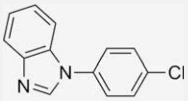
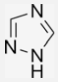
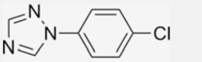


Entry	Heterocycle	Product
10a		 87 %
10b		 88 %[b]
10c		 88 %[b]
10d		 88%
10e		 82 %

[a] Yields refer to isolated yields.
[b] 25 °C.

Table 4
CuI-catalyzed arylation of nitrogen heterocycles[a]



Entry	Heterocycle	Ar–I	Product
11a		**2**	 87 %[b]
11b		**2**	 99%[c]
11c			 85 %[d]
11d			 65 %[e]
11e			 78 %
11f		**2**	 88%
11g		**2**	 77%[f]

[a] Yields refer to isolated yields.
[b] 1 h.
[c] 5 h.
[d] 80 °C, 4 h.
[e] ArBr, 4 h.
[f] 7 h.

formation of the Cu-coordinated intermediate, whereas the 2-methyl lacks the same Cu-coordinated intermediate and furthermore, may hinder the formation of the C–N bond, leading to a slightly lower yield for that substrate. The reaction of aryl bromides with CsF did proceed at room temperature, but heating to 100 °C (Table 2, **4r**, **4s**) gave excellent and comparable yields to those reported in the literature for similar couplings.

The coupling of nitrogen-containing heterocycles using high temperature and strong alkali metal bases has been reported.[1,3] Heterocyclic substrates such as indoles, pyrroles, and indazoles have been shown to couple under the Buchwald-type conditions, and we found that these substrates coupled very efficiently in the presence of CsF at 60 °C (Table 3, **10a**–**e**).

Next, we sought to demonstrate the utility of the CsF as the base with other copper ligands. Liu et al. reported that 8-hydroxyquinoline was an excellent copper ligand for the N-arylation of imidazoles and benzimidazoles in the presence of the soluble base TEAC in DMSO.[3c] The coupling of imidazoles, benzimidazoles, and triazoles proceeded in high yield with CsF and with shorter reaction times than those reported previously[3c] (Table 4). Imidazole and phenylimidazole coupled to **2** in high yield (**11a,b**).[7] The CsF-promoted conditions also gave an acceptable yield for the coupling of imidazole with ethyl 4-bromobenzoate after just 5 h, which, to the best of our knowledge, is the first reported instance of an imidazole coupling to an ester-containing aryl halide (**11d**). In accordance with our earlier observation, steric hindrance on the nucleophilic coupling partner did not significantly inhibit the reaction (e.g., **11e**). Finally, both benzimidazole and 1,2,4-triazole coupled efficiently under the same conditions to give **11f** and **11g**, respectively.

In summary, N-arylation of several amides, carbamates, and nitrogen heterocycles was reported in the presence of CsF. We showed that these are compatible with numerous substrates and effect the N-arylation of several aryl iodides at room temperature. To our knowledge, this report is the first instance of employing CsF in copper-catalyzed N-arylation reactions. We showed that CsF is as effective as the stronger alkali metal bases such as K_2CO_3, K_3PO_4, and Cs_2CO_3, and can be used in instances where base-promoted side reactions need to be avoided.

Acknowledgments

We thank the analytical chemistry and NMR groups for their assistance.

Supplementary data

Supplementary data (General experimental and accompanying spectropscopic data for the compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.041.

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7. *General procedure*: Into a reaction tube were placed cesium fluoride (380 mg, 2.50 mmol), copper(I) iodide (10 mg, 0.05 mmol), aryl halide (1.0 mmol), amide or heterocycle (1.2 mmol), and *N*,*N*′-dimethylethylene diamine or 8-hydroxyquinoline (0.1 mmol). The tube was sealed, evacuated, and back-filled with nitrogen 2–3 times, and then the vessel was charged with 2.0 mL of solvent. The vessel was evacuated and back-filled with nitrogen twice more, then allowed to stir at the requisite temperature (generally room temperature) until completion. The reaction mixture was diluted with EtOAc (2 mL) and the reaction was quenched with saturated ammonium chloride (2 mL). The aqueous layer was removed and 3 × 2 mL EtOAc was extracted. The combined organics were washed with brine, then dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography on an Isco CombiFlash purification system with a 12 g RediSep® flash cartridge using an EtOAc/hexanes gradient (0–100%, 10–12 min).
8. When this substrate was subjected to copper-catalyzed conditions in the presence of K_3PO_4, we obtained a lower yield (59%) and lower ee (84%). Employing Pd and Xantphos, the yield (20%)as well as ee (59%) was lower.