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Cesium Hydroxide-mediated Regio- and Stereoselective Hydroamidation of Internal Aryl Alkynes with Primary Amides

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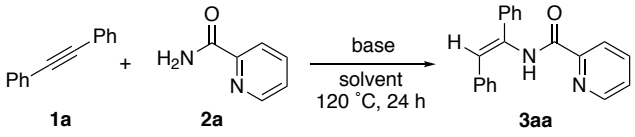
A cesium hydroxide-mediated hydroamidation of internal aryl alkynes with primary amides has been developed. The reaction proceeds with high *anti*-selectivity to deliver the corresponding stereodefined (*Z*)-enamides in good yields. The alkali base-promoted system is also compatible with unsymmetrical aryl alkyl alkynes, and the hydroamidated products are obtained with high regioselectivity as well as stereoselectivity.

Keywords: Cesium, Hydroamidation, Stereoselectivity

The hydroamination reaction of carbon–carbon multiple bonds has recently received significant attention because it can readily convert the relatively simple hydrocarbon materials into the nitrogen-containing organic molecules, which are of great value in pharmaceutical science and material chemistry as well as synthetic organic chemistry. Thus, many synthetic chemists have developed numerous reaction systems including rare-earth metal catalysts, transition metal catalysts, alkali bases, and Brønsted/Lewis acids, for the hydroamination of alkynes, alkenes, and dienes.[1] However, there still remains a challenge for the intermolecular reaction of unactivated internal alkynes[2] with less nucleophilic amides (hydroamidation of internal alkynes). Although Liang and Xu,[3] and Cui[4] developed the ruthenium-catalyzed hydroamidation of internal aryl alkynes, the scope of amides were limited to 6-aryl(dihydro)pyridazinones and *N*-benzylamides bearing a specially designed directing group, respectively. Kondo also reported the hydroamidation of internal alkyne in the presence of a strongly basic P4-*t*-Bu phosphazene catalyst, but only one example of diphenylacetylene with *N*-methylacetamide was shown.[5] Thus, further development of hydroamidation reaction for internal alkynes with more general amides is greatly appealing from the synthetic point of view. During our continuous interest in the hydroamination chemistry,[6] we have now found a cesium hydroxide-mediated hydroamidation of internal aryl alkynes with primary amides: the reaction proceeds with high *anti*-selectivity to afford the corresponding (*Z*)-enamides in good yields. Additionally, the alkali base system accommodates unsymmetrical aryl alkyl alkynes, and the corresponding enamides are formed regioselectively and stereoselectively. Detailed optimization studies and substrate scope are reported herein.

Our optimization studies commenced with diphenylacetylene (**1a**; 0.25 mmol) and picolinamide (**2a**; 0.25 mmol) by screening hydroamidation promotors (Table 1). We initially focused on transition metal catalysts such as ruthenium and gold, but any desired hydroamidated products were not detected at all. Although some Lewis acid catalysts were also tested, no promising result was obtained.[7] We thus paid attention to alkali bases. Knochel reported the cesium hydroxide-catalyzed addition of alcohol, anilines, and azoles to terminal alkynes.[8,9] On the basis of the above seminal work, the reaction was conducted with 0.20 equiv of $CsOH{\bullet}OH_2$ in NMP at 120 °C. Gratifyingly, the (*Z*)-enamide **3aa** was formed albeit in 10% GC yield (Entry 1). The structure and stereochemistry of **3aa** were determined by ^1H NMR, ^{13}C NMR, NOESY, HRMS, and finally X-ray crystallographic analysis.[10] Although the posphazene P4-*t*-Bu [5] promoted the reaction with comparable efficiency (Entry 2), we identified $CsOH{\bullet}OH_2$ to be a better promotor in view of the cost.[11] A quick survey of solvent (Entries 3–5) revealed that DMSO increased the yield to 22% GC yield (Entry 4). An increase in amount of $CsOH{\bullet}OH_2$ to 1.0 equiv further improved the reaction efficiency, and we isolated **3aa** in 66% yield (Entry 6). Other alkali metal hydroxides including RbOH, KOH, NaOH, and LiOH also mediated the reaction to some extent (Entries 7–10), but CsOH proved to be much better. On the other hand, Cs_2CO_3, CsOPiv, and CsF were much less effective (Entries 11–13).

Table 1. Optimization studies for hydroamidation of diphenylacetylene (**1a**) with picolinamide (**2a**).[a]



1a **2a** **3aa**

Entry	Base (equiv)	Solvent	Yield[b]/%
1	$CsOH{\bullet}OH_2$ (0.20)	NMP	10
2	P4-*t*-Bu[c] (0.20)	NMP	15
3	$CsOH{\bullet}OH_2$ (0.20)	DMF	trace
4	$CsOH{\bullet}OH_2$ (0.20)	DMSO	22
5	$CsOH{\bullet}OH_2$ (0.20)	DMI	14
6	$CsOH{\bullet}OH_2$ (1.0)	DMSO	70 (66)
7	$RbOH{\bullet}xOH_2$ (1.0)	DMSO	56
8	KOH (1.0)	DMSO	64
9	NaOH (1.0)	DMSO	42
10	LiOH (1.0)	DMSO	12
11	Cs_2CO_3 (1.0)	DMSO	4
12	CsOPiv (1.0)	DMSO	0
13	CsF (1.0)	DMSO	3

[a]Conditions: base, **1a** (0.25 mmol), **2a** (0.25 mmol), solvent (1.0 mL), 120 °C, 24 h, N_2. [b]Estimated by GC method. Isolated yield is in parentheses. [c]0.8 M hexane solution.

Unfortunately, we could not optimize conditions catalytic in cesium[7] but examined the scope of amides **2** with diphenylacetylene (**1a**) under conditions of Entry 6 in Table 1 (Table 2). In addition to the picolinamide (**2a**; Entry 1), the simple benzamide (**2b**) also reacted with **1a** smoothly to

furnish **3ab** in 74% (Entry 2). Both electron-donating methoxy (**2c**) and electron-withdrawing trifluoromethyl (**2d**) groups were equally tolerated under the standard conditions (Entries 3 and 4). Aliphatic pivalamide (**2e**) was also the viable substrate (Entry 5). Regardless of steric and electronic nature of amides, the corresponding enamides were uniformly formed with excellent (*Z*)-selectivity. Additionally, the reaction could be easily scaled up (2.5 mmol), and the desired **3aa** and **3ab** were obtained in 61% and 71% yields, respectively (Entries 1 and 2). On the other hand, secondary benzamide (e.g., *N*-phenylbenzamide and *N*-methylbenzamide) and tosylamide were reluctant to the present hydroamidation (< 5% GC yield, data not shown).

Table 2. Cesium hydroxide-mediated hydroamidation of diphenylacetylene (**1a**) with several benzamides **2a**.[a]

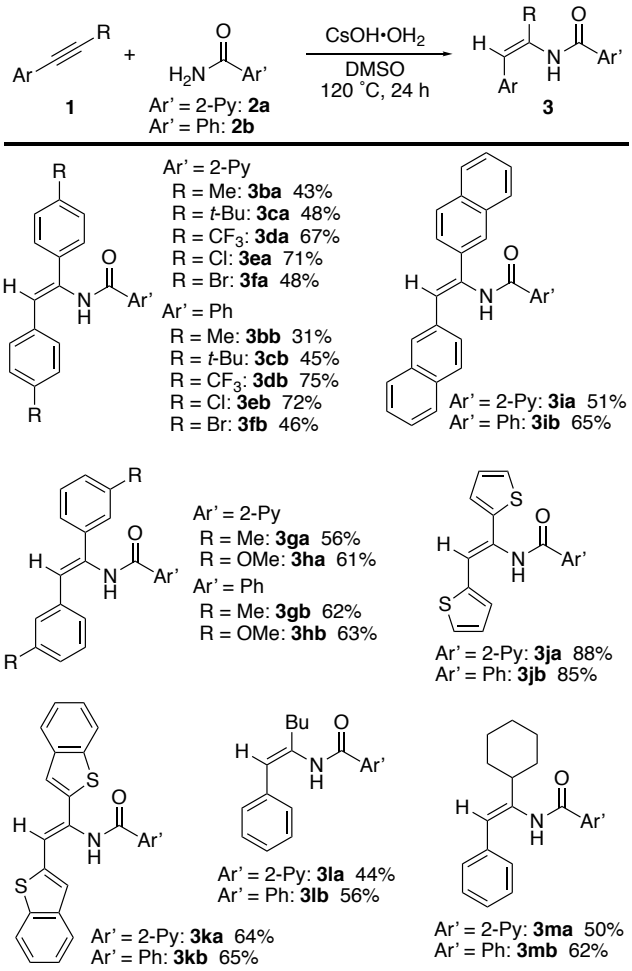
1a **2** **3**

Entry	R (**2**)	**3**, Yield[b]/%
1	2-Pyridyl (**2a**)	**3aa**, 66 (61)[c]
2	Ph (**2b**)	**3ab**, 74 (71)[c]
3	4-$MeOC_6H_4$ (**2c**)	**3ac**, 58
4	4-$CF_3C_6H_4$ (**2d**)	**3ad**, 63
5	*t*-Bu (**2e**)	**3ae**, 45

[a]Conditions: $CsOH•OH_2$ (0.25 mmol), **1a** (0.25 mmol), **2** (0.25 mmol), DMSO (1.0 mL), 120 ˚C, 24 h, N_2. [b]Isolated yield. [c]2.5 mmol scale.

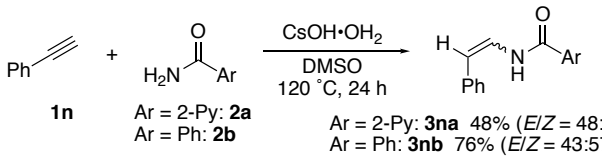
We then evaluated the scope of alkynes with picolinamide (**2a**) and benzamide (**2b**). Representative products are illustrated in Scheme 1. The cesium-mediated hydroamidation reaction accommodated electronically diverse diarylacetylenes containing methyl, *tert*-butyl, trifluoromethyl, and chloro substituents, but electron-deficient substrates (**3da**, **3ea**, **3db**, **3eb**) generally showed better reactivity than electron-rich acetylenes (**3ba**, **3ca**, **3bb**, **3cb**). Additionally notable is the compatibility with the bromo function (**3fa**, **3fb**), which can provide an opportunity for further manipulations of enamide product. *Meta*-substituted diarylacetylenes (**3ga**, **3ha**, **3gb**, **3hb**) and bulky di(2-naphthyl)acetylene (**3ia**, **3ib**) could also be employed under identical conditions. Moreover, the present conditions was applicable to the thienyl- and benzothienyl-substituted acetylenes, and the corresponding enamides were formed in good yields (**3ja**, **3jb**, **3ka**, **3kb**). In the case of unsymmetrical aryl alkyl alkyne, 1-phenylhexyne, the reaction occurred regioselectively: the nitrogen atom was selectively incorporated at the position β to the phenyl group (**3la**, **3lb**). The same trend was observed in the reaction of cyclohexyl-substituted phenylacetylene (**3ma**, **3mb**). Again, all enamides were obtained as the exclusive (*Z*)-stereoisomer.[12] On the other hand, the reaction of terminal alkyne, phenylacetylene (**1n**) with either amide gave a nearly 1:1 mixture of *E*/*Z* isomers (Scheme 2), which is consistent with Knochel's original report.[8]

Although the detailed reaction pathway is unclear at present, on the basis of literature information[1h,9d] it can include 1) generation of cesium amide by proton abstraction of amide NH with CsOH, 2) nucleophilic *anti*-addition to alkyne, and 3) protonation of the resulting vinyl cesium species. The nucleophilic, aza-Michael addition-type mechanism can explain the uniformly observed high *anti*-selectivity and regioselectivity in the case of unsymmetrical aryl alkyl alkynes (**3la**, **3lb**, **3ma**, **3mb** in Scheme 1); the same trend was often observed in related base-promoted hydroamination of internal and terminal aryl alkynes,[1d,5,8] where the aryl substituent can serve as an electron-withdrawing group. The poor stereoselectivity with terminal alkyne **1n** may result from in-situ *E*/*Z* isomerization of the product; indeed when the independently prepared isomerically pure (*Z*)-**3nb** was subjected to the standard conditions (1.0 equiv CsOH, DMSO, 120 ˚C, 10 h), a 63:37 mixture of *E*/*Z* isomers was detected by ^{1}H NMR analysis. Although the exact reason for no catalytic turnover of cesium remains to be elucidated, the formed NH enamide could be deprotonated again by CsOH to generate a stable but nonreactive secondary cesium amide; actually, secondary amides including *N*-phenylbenzamide and *N*-methylbenzamide were hardly reactive under identical conditions (vide supra), and a doubly hydroaminated product, namely *N,N*-divinylamide, was not observed in all cases. Further efforts are essential for development of the catalytic variant.



Scheme 1. Cesium hydroxide-mediated hydroamidation of various internal alkynes **1** with picolinamide (**2a**) or benzamide (**2b**). Isolated yields are shown.

3



Scheme 2. Cesium hydroxide-mediated hydroamidation of phenylacetylene (**1n**) with picolinamide (**2a**) or benzamide (**2b**).

In conclusion, we have developed a cesium hydroxide-mediated intermolecular hydroamidation of internal aryl alkynes with primary amides. The reaction proceeds with high *anti*-selectivity to deliver the corresponding (*Z*)-enamides in good yields. Additionally, unsymmetrical aryl alkyl alkynes undergo the hydroamidation stereoselectively and regioselectively to form the single isomer under identical conditions. Ongoing work seeks to develop catalytic conditions in cesium and transform the enamide products to more valuable nitrogen-containing organic molecules.

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Supporting Information is available on http://dx.doi.org/xxxx.

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10 Crystallographic data for the structure of **3aa** has been deposited with the Cambridge Crystallographic Data Centre (CCDC 1539967). See the Supporting Information for details. The stereochemistry of other enamides was tentatively assigned by analogy.

11 $CsOH•OH_2$ (7.5 JPY/mmol) vs P4-*t*-Bu (9180 JPY/mmol) (Sigma-Aldrich, April, 2017).

12 Dialkylacetylenes such as 4-octyne did not produce any hydroamidated products at all.