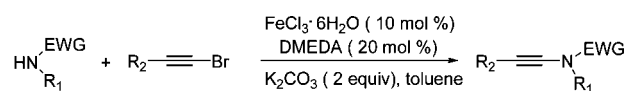# Iron-Catalyzed Amidation of Alkynyl Bromides: A Facile Route for the Preparation of Ynamides

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A facile route to obtain ynamides in high yields was described. The products were achieved through the iron-catalyzed C−N coupling reaction of amides with alkynyl bromides in the presence of 20 mol % of *N,N′*-dimethyl-ethane-1,2-diamine (DMEDA).

Ynamides are useful building blocks and have been widely used in synthetic chemistry.[1] Besides their application in pericyclic reactions,[2] ynamides have shown excellent activity for the reactions of tandem RCM,[3] Co- or Fe-mediated Pauson−Khand reaction,[4] Ficini−Claisen rearrangements,[5] Saucy−Marbet rearrangements,[6] and Kinugasa reaction.[7] Most recently, ynamides have been successfully used in the synthesis

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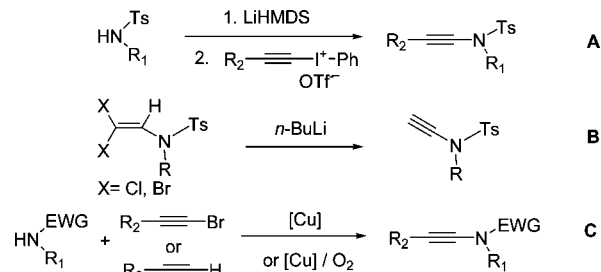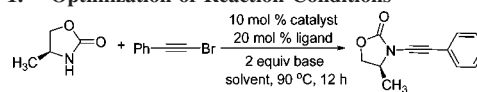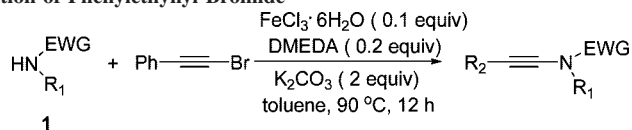
SCHEME 1

TABLE 1. Optimization of Reaction Conditions[a]

entry	catalyst	ligand[b]	base	solvent	yields (%)
1	FeCl₃·6H₂O	DMEDA	K₂CO₃	toluene	96
2	FeCl₂	DMEDA	K₂CO₃	toluene	89
3	FeCl₃	DMEDA	K₂CO₃	toluene	94
4	Fe₂O₃	DMEDA	K₂CO₃	toluene	trace
5	FeCl₃·6H₂O	DMEDA	K₃PO₄	toluene	76
6	FeCl₃·6H₂O	DMEDA	Na₂CO₃	toluene	trace
7	FeCl₃·6H₂O	DMEDA	KOH	toluene	30
8	FeCl₃·6H₂O	DMEDA	Et₃N	toluene	trace
9	FeCl₃·6H₂O	DMEDA	K₂CO₃	DMF	trace
10	FeCl₃·6H₂O	DMEDA	K₂CO₃	dioxane	74
11	FeCl₃·6H₂O	DMEDA	K₂CO₃	DMSO	trace
12	FeCl₃·6H₂O	— —	K₂CO₃	toluene	trace
13	FeCl₃·6H₂O	PN	K₂CO₃	toluene	trace
14	FeCl₃·6H₂O	TMEDA	K₂CO₃	toluene	18
15	FeCl₃·6H₂O	L-proline	K₂CO₃	toluene	trace
16	FeCl₃·6H₂O	acac	K₂CO₃	toluene	trace
17	FeCl₃·6H₂O	DMEDA	K₂CO₃	toluene	81[c]
18	FeCl₃·6H₂O	DMEDA	K₂CO₃	toluene	85[d]

[a] Reaction conditions: (S)-4-methyloxazolidin-2-one (1 mmol), phenylethynyl bromide (1.2 mmol), base (2 mmol), iron catalyst (0.1 mmol), ligand (0.2 mmol), solvent (5 mL), air, 90 °C, 12 h. *[b]* Ligands: DMEDA = *N,N′*-dimethylethane-1,2-diamine; acac = acetateacetone; TMEDA = *N,N,N′,N′*-tetramethylethane-1,2-diamine; PN = 1,10-phenanthroline. *[c]* Iron catalyst (0.05 mmol), ligand (0.1 mmol). *[d]* The reaction was scaled up to 10 mmol.

of indoles and benzofurans.[8] As a consequence, the development of efficient methods for preparation of ynamides has gained attention and several methods have been reported.[9] For example, Feldman and co-workers synthesized the chiral ynamides from the ethynylation of amides with ethynyliodonium triflate in the presence of strong bases (Scheme 1, eq A).[10] The elimination of (Z)-bromoenamides was employed for the preparation of achiral ynamides (Scheme 1, eq B).[11] However, these approaches often involved several steps and suffered from disadvantages such as narrow substrate limitation and harsh reaction conditions. In 2003, Hsung and co-workers explored the CuCN-catalyzed N-alkynylation of amine derivatives with

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TABLE 2. Iron-Catalyzed N-Alkylation of Phenylethynyl Bromide[a]

$$\text{HN} \overset{EWG}{\underset{R_1}{\diagup}} \quad + \quad Ph \!\!-\!\!\equiv\!\!-\!\! Br \quad \xrightarrow[\substack{\text{K}_2\text{CO}_3\ (\ 2\ \text{equiv}) \\ \text{toluene, }90\ ^\circ\text{C, }12\ \text{h}}]{\substack{\text{FeCl}_3 \cdot 6\text{H}_2\text{O}\ (\ 0.1\ \text{equiv}) \\ \text{DMEDA}\ (\ 0.2\ \text{equiv})}} \quad R_2 \!\!-\!\!\equiv\!\!-\!\! N \overset{EWG}{\underset{R_1}{\diagdown}}$$

1

entry	substrate **1**	product	yield (%)	entry	substrate **1**	product	yield (%)
1	**1a**		94	10			94
2			90	11			96
3	**1b**		96	12			93
4			89	13			95
5			93	14			81
6	**1c**		95	15			97
7			97	16			70
8			96	17			57
9	**1d**		96				

[a] Reaction conditions: substrate **1** (1 mmol), phenylethynyl bromide (1.2 mmol), K$_2$CO$_3$ (2 mmol), FeCl$_3$·6H$_2$O (0.1 mmol), DMEDA (0.2 mmol), toluene (5 mL), air, 90 °C, 12 h.

alkynyl bromides,[12] and they improved their reaction conditions later by using CuSO$_4$·5H$_2$O as the catalyst at lower temperatures.[13] At the same time, Danheiser reported that the stoichiometric amount of copper along with the strong base allowed the reaction to occur at room temperature.[14] Very recently, the copper-catalyzed aerobic oxidative amidation of terminal alkynes

for the preparation of ynamides was reported by Stahl and coworkers.[15] These copper systems provide the facile direct routes for the preparation of ynamides (Scheme 1, eq C).[16] On the other hand, massive effort has been made currently to develop catalytic systems that are inexpensive and environmentally safe. As a cheap and environmentally benign metal, iron complexes have been exploited as catalysts,[17] and some significant achievements have already appeared in the literature.[18] For instance, iron-catalyzed N-arylation has been reported by Bolm[19] and others,[20] which provided the promising alternative for the construction of C(sp^2)−N bonds. Herein, we report an efficient

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method for the preparation of ynamides from amides and alkynyl bromides in the presence of an iron catalyst. This is the first example of iron-catalyzed formation of C(sp)−N bonds.

Initially, we optimized the reaction conditions using phenylethynyl bromide and (S)-4-methyloxazolidin-2-one as model substrate, and the selected results are listed in Table 1. No reaction took place in the absence of catalyst. $FeCl_3$, $FeCl_2$, and $FeCl_3·6H_2O$ showed high catalytic activity, while Fe_2O_3 was almost inactive (Table 1, entries 1−4). A variety of bases were evaluated, and K_2CO_3 showed the best efficiency (Table 1, entries 1 and 5−8). Among the solvents tested, toluene was found to be superior to DMF, DMSO, and 1,4-dioxane (Table 1, entries 1 and 9−11). Ligands had a pronounced impact on the coupling reaction (Table 1, entries 1 and 12−16). Ligands that are routinely used for copper coupling reactions such as 1,10-phenanthroline, N,N,N′,N′-tetramethylethane-1,2-diamine (TMEDA), and L-proline exerted a poor effect on the reaction (Table 1, entries 13−15), and only a trace of the product was observed without the use of ligand (Table 1, entry 12). The use of N,N′-dimethylethane-1,2-diamine (DMEDA) substantially accelerated the reaction, and a 96% isolated yield was obtained (Table 1, entry 1). The dioxygenated ligands such as acetateacetone did not lead to efficient catalysis (Table 1, entry 16). The reaction could be scaled up to 10 mmol with the combination of 5 mol % of $FeCl_3·6H_2O$ and 10 mol % of DMEDA to give an 85% yield (Table 1, entry 18).

We next examined the scope and generality of the coupling reaction with various nitrogen nucleophiles under the optimized conditions (Table 1, entry 1). Notably, both oxazolidinones and sulfonamides underwent N-alkynylation in good yields (Table 2). We noticed that oxazolidinones bearing different substituents such as CH_3−, Ph−, Bn−, and i-Pr− worked well and afforded the corresponding ynamides in good to high yields (Table 2, entries 1−5). Acyclic carbamates were almost inactive under the reaction conditions. Both alkylsulfonamides and arylsulfonamides were compatible with the reaction conditions (Table 2, entries 6−17). In the cases of arylsulfonamides, the electronic properties of the substituents in the aryl ring presented little impact to the reactions

and high yields were obtained (Table 2, entries 6−8). Methylsulfonamide readily coupled with phenylethynyl bromide to give a 96% yield (Table 2, entry 9). N-Benzyl and N-alkyl-substituted sulfonamides afforded the desired products in high yields (Table 2, entries 6−14). However, the reactivity of N-phenyl-substituted sulfonamides was slightly decreased (Table 2, entry 14). It should be noted that the free hydroxy group tolerated the reaction conditions (Table 2, entry 15). As mentioned, with significant pharmaceutical indole cycles, a 70% yield was obtained after the coupling with indole-5-carbonitrile (Table 2, entry 16). At the same time, pyrrolidin-2-one was transferred to its corresponding ynamide in 57% yield (Table 2, entry 17).

The reaction scope was also studied with respect to alkynyl bromides, and the results are summarized in Table 3. The catalytic system enabled a variety of alkynyl bromides to couple with the N-nucleophiles smoothly to give the desired ynamides. In the case of arylalkynyl bromides, either electron-donating or electron-withdrawing groups in the aryl ring tolerated the reaction to give the corresponding ynamides in high yields (Table 3, entries 1−12). The alkyl alkynyl bromides were also coupled smoothly with oxazolidinones and sulfonamides to give good yields under the reaction conditions (Table 3, entries 13−16). The reaction was able to be performed by using (3-bromoprop-2-ynyl)triisopropylsilane (TIPS) and 3-bromoprop-2-yn-1-ol as the substrates but with relatively lower yields (Table 3, entries 17−20).

The reusability of iron catalyst was tested in the coupling reaction of phenylethynyl bromide and (S)-4-methyloxazolidin-2-one using 10 mol % of $FeCl_3·6H_2O$. The product was isolated by filtration. The residue was washed with diethyl ether (3 × 15 mL) and subjected to the second run by charging with the same substrate, 0.2 mmol DMEDA, 1 mmol K_2CO_3, and 5 mL of toluene. The catalytic system showed high efficiency of reusability and could be recycled nine times only with a small decrease in activities without the need for addition of catalyst (Scheme 2).

SCHEME 2

Cycles	1	2	3	4	5	6	7	8	9
Yield (%)	96	95	95	93	90	87	86	86	81
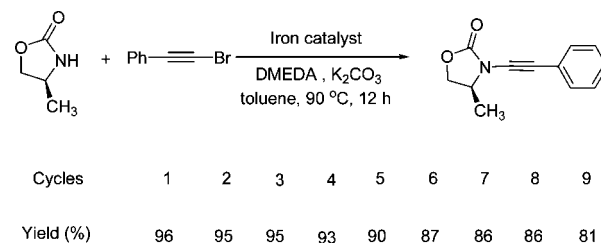
In conclusion, we have developed an efficient and convenient method for the preparation of ynamides by $FeCl_3·6H_2O$-catalyzed coupling reaction of alkynyl bromides and N-nucleophiles. For the first time, the C(sp)−N bond was formed directly by using inexpensive, easy-to-handle, and environmentally benign $FeCl_3·6H_2O$ in combination with DMEDA, which provided a practical and straightforward approach toward ynamides.

Experimental Section

Alkynyl bromides (1.2 mmol) and DMEDA (0.2 mmol) were added to a stirred solution of N-nucleophiles (1 mmol), K_2CO_3 (2.0 mmol), $FeCl_3·6H_2O$ (0.1 mmol), and toluene (5 mL) under air, and the resulting mixture was stirred at 90 °C for 12 h. The suspension was

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TABLE 3. Iron-Catalyzed Formation of Ynamides[a]

entry	1	R$_2$	ynamide	yield (%)	entry	1	R$_2$	ynamide	yield (%)
1	1a	p-CH$_3$C$_6$H$_4$		94	11	1c	p-ClC$_6$H$_4$		86
2	1b	p-CH$_3$C$_6$H$_4$		93	12	1d	p-ClC$_6$H$_4$		89
3	1c	p-CH$_3$C$_6$H$_4$		96	13	1a	n-hexyl		85
4	1d	p-CH$_3$C$_6$H$_4$		96	14	1b	n-hexyl		83
5	1a	p-CH$_3$OC$_6$H$_4$		92	15	1c	n-hexyl		76
6	1b	p-CH$_3$OC$_6$H$_4$		95	16	1d	n-hexyl		78
7	1c	p-CH$_3$OC$_6$H$_4$		94	17	1b	TIPS		63
8	1d	p-CH$_3$OC$_6$H$_4$		93	18	1c	TIPS		69
9	1a	p-ClC$_6$H$_4$		84	19	1d	TIPS		67
10	1b	p-ClC$_6$H$_4$		83	20	1c	CH$_2$OH		62

[a] Reaction conditions: substrate 1 (1 mmol), alkynyl bromide (1.2 mmol), K$_2$CO$_3$ (2 mmol), FeCl$_3$·6H$_2$O (0.1 mmol), DMEDA (0.2 mmol), toluene (5 mL), air, 90 °C, 12 h.

filtered, and the residue was washed with diethyl ether (3 × 15 mL). In the recycling experiments, the residue was subjected to the second run by charging with the same substrates, 0.2 mmol DMEDA, 1 mmol K$_2$CO$_3$, and 5 mL of toluene. The purification of products was achieved by flash chromatography on a silica gel column with ethyl acetate (EA) and petroleum ether (Pet) as eluent.

(S)-4-Methyl-3-(2-phenylethynyl)oxazolidin-2-one (Table 2, entry 1). Prepared according to the general procedure using a solution of EA/Pet = 1/3 as eluent (189 mg, 96%): white solid; mp 82−83 °C; [α]$^{20}_D$ +38.6 (c 1.00, CH$_2$Cl$_2$); ^{1}H NMR (CDCl$_3$, 400 MHz, TMS) δ 7.44−7.46 (m, 2 H), 7.30−7.33 (m, 3 H), 4.55−4.59 (t, J = 8.4 Hz, 1 H), 4.19−4.25 (m, 1 H), 4.00−4.03 (dd, J = 8.4, 8.8 Hz, 1 H), 1.49−1.50 (d, J = 6.4 Hz, 3 H) ppm; ^{13}C NMR (CDCl$_3$, 100 MHz, TMS) δ 156.1, 132.1, 128.8, 128.7,

122.8, 78.3, 73.1, 70.7, 54.6, 18.6 ppm; MS (ESI) m/z 224.1 ([M + Na]$^+$); HRMS (EI) calcd for 201.0790, found 201.0795.

Supporting Information Available: Experimental procedure and spectroscopic data (^{1}H NMR, ^{13}C NMR, MS, and HRMS) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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