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A Copper-Catalyzed C−N Bond Formation Involving sp-Hybridized Carbons. A Direct Entry to Chiral Ynamides via N-Alkynylation of Amides

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The emerging interest in ynamides as useful building blocks in synthetic transformations has become distinctly apparent because of its superior thermal stability over ynamines.[1,2] Despite being known since 1972,[3,4] applications of ynamides in an array of methodologies such as Co or Fe mediated Pauson−Khand,[5−7] Suzuki couplings,[6f] tandem RCM,[8,9a] Ficini−Claisen rearrangements,[9b] and other pericyclic reactions have only been unveiled recently.[9c] However, accessibility of ynamides, an equally if not more important issue than applications, remains unresolved. The limited scope of existing protocols has prohibited a greater synthetic utility of ynamides.[1] Although isomerization of propargyl amides **1** represents a facile entry to ynamides, it either has led to arrested-isomerization to give allenamides[10] or has been substrate-specific when using **2** [Figure 1]. A stepwise alternative via elimination of *Z*-bromoenamides **3**[11] delineates a tedious sequence in which the initial enamide formation under acidic conditions precluded a greater range of functionality in the R^1 group.

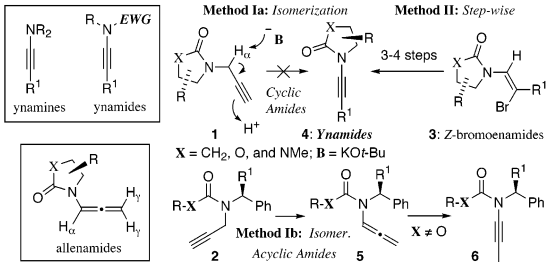


Figure 1.

Inspired initially by the work of Buchwald,[12,13] Hartwig,[12,14] and many others[15] in palladium-catalyzed N-arylation of amines and amides, we recognized that the best entry to ynamides would be a metal mediated coupling of alkynyl halides **7** to amides [Path A in Figure 2].[4b] Furthermore, if the ynamide **8** where $R^1 = H$ could be prepared using such coupling strategy, it would represent a "parent" ynamide ultimately leading to other new ynamides **10** via simple deprotonation and electrophilic substitutions [Path B in Figure 2]. We report here a copper-catalyzed C−N bond formation involving a sp-hybridized carbon and a direct entry to chiral ynamides via N-alkynylation of amides.

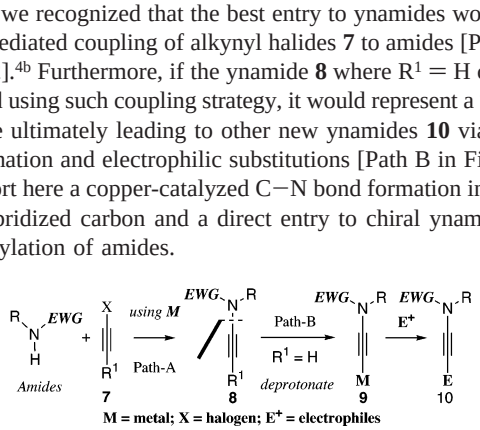
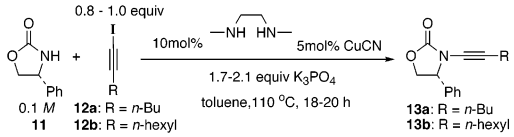


Figure 2.

Our initial work involving palladium-catalyzed conditions did not lead to any desired ynamides when alkynyl halides were coupled with stannylated or other metalated amides or amines. Instead, the dominant pathway was the homocoupling of alkynes.[16] While chances of succeeding in such a coupling strategy appeared to be remote, we became reinvigorated because of recent work in copper-catalyzed N-arylation of amides[17−19] or the Goldberg reaction.[17b]

The work of Buchwald using amine ligands to facilitate N-arylations of amides was particularly encouraging.[18] We investigated in detail the copper-catalyzed coupling of chiral oxazolidinone **11** with alkynyl iodides **12a** and **12b** enroute to ynamides **13a** and **13b**,[20] respectively, with the optimum conditions summarized in Scheme 1.

Scheme 1



Despite the encouraging preliminary results, these reactions remained inconsistent, and homocoupling of the alkynyl iodides continued to compete. It was not until we switched to alkynyl bromides that desired coupling was obtained on a consistent basis, and the scope of this novel N-alkynylation of amides could then be established [Table 1].

There appears to be no significant difference in the outcome when using CuCN and CuI except that CuCN led to more consistent results overall [entries 1−4]. This coupling reaction appears to tolerate various substitutions [2°, 3°, Ph, silyl, and OTBS] for the R^1 group in the alkynyl bromide [entries 5−10]. It is very noteworthy that tri-iso-propylsilylbromoacetylene also withstood reaction conditions and underwent coupling to afford the silyl substituted ynamide **17** in 85% yield [entry 8].

Other oxazolidinone-based amides also gave the desired ynamides **20**−**25** in good yields [entries 11−16], including diphenylmethyl substituted oxazolidinone [entries 13 and 14]. Lactams also yielded ynamides **26**−**28** [entries 17−18].

On the other hand, urea-based auxiliaries such as imidazolidinone appeared to be very slow to give ynamide **29** in 10% yield with less than 20% conversion after prolonged reaction duration [entry 20]. Given the difference between the pK_a's of urethanes and lactams versus those of ureas [slightly less acidic], we speculated that the key to this reaction is to match the appropriate base relative to the pK_a of the amide, given that several sulfonamides and sultam also failed in these couplings. However, stronger bases such as KO*t*-Bu and NaO*t*-Bu did not improve the coupling of urea auxiliary.

Acyclic urethane-based amides did undergo coupling reactions to give ynamides **30**−**32** in good yields based on cleanly recovered starting materials [entries 21−23]. These reactions were also slower, but they could be stopped at less than 50% conversion to avoid decompositions and to still provide pure ynamides in synthetically useful quantities.

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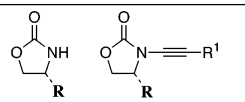
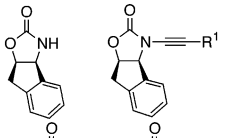
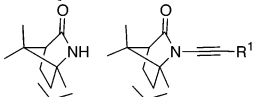
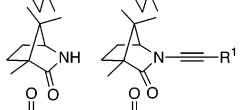
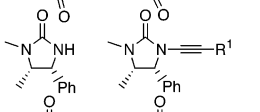
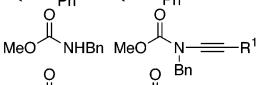
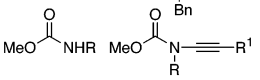
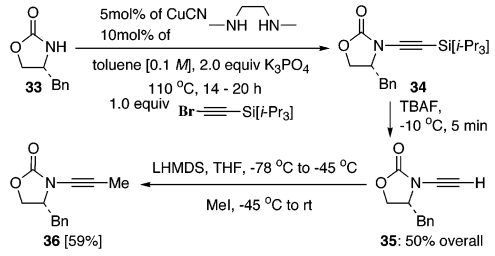
Table 1

entry	amides[a]	product	R =	R^1 =	yield[b]
1			**13a** Ph	*n*-Bu	74%[c]
2			**13a** Ph	*n*-Bu	52
3			**13b** Ph	*n*-hexyl	71[c]
4			**13b** Ph	*n*-hexyl	83
5			**14** Ph	cyclohexyl	70[d]
6			**15** Ph	*t*-Bu	48
7			**16** Ph	Ph	69
8			**17** Ph	*i*-Pr_3Si	85
9			**18** Ph	$(CH_2)_{11}OTBS$	75[d]
10			**19** Ph	CH_2OTBS	20[e]
11			**20** H	*n*-Bu	82
12			**21** Bn	*n*-hexyl	58
13			**22** $CHPh_2$	*n*-hexyl	52[d,f]
14			**23** $CHPh_2$	*i*-Pr_3Si	72[d,f]
15			**24**	Ph	65
16			**25**	*n*-hexyl	55[g]
17			**26**	*n*-hexyl	45[d,f]
18			**27**	*i*-Pr_3Si	20[h]
19			**28**	*n*-Bu	50
20			**29**	*n*-hexyl	10
21			**30**	*n*-hexyl	42[f,h]
22			**31**	*i*-Pr_3Si	36[h]
23			**32**	*i*-Pr_3Si	24[h,i]

R = $(CH_2)_2CH_2CH{=}CH_2$

[a] All reactions are carried out using 5 mol % CuCN [OR: CuI; see note c], 10 mol % *N*,*N*′-dimethylethylenediamine, and 2.0 equiv of K_3PO_4 in toluene [concentrated 0.1 M based on the amide] at 110 °C for 18−30 h. [b] Isolated yields. [c] 5 mol % CuI was used. [d] Xylene was the solvent. [e] An α-haloenamide derived from addition of HBr to the ynamide was found in 50−60% yield. [f] Temperature was at 150 °C. [g] 1 mol % CuI and 3 mol % ligand were used. [h] Isolated yields after reactions were terminated at 30−50% conversion. [i] 1 mol % CuCN.

Scheme 2



Given the similar criteria in our reactions, we believe at this juncture that the course of the catalytic cycle is related to the one proposed by Buchwald for the N-arylation of amides.[18] However, we are examining other mechanistic details of this $C_{sp}-N$ formation because urea or sulfonamide-based amides still do not work as well as urethanes and lactams.

Finally, the chiral oxazolidinones **33** was coupled with 1-bromo-2-tri-iso-propylsilyl ethyne to give ynamide **34** [70% yield with 1−2 mmol scale] [Scheme 2]. The removal of the silyl group using TBAF at −10 °C led to the first preparation of parent ynamide **35** in 50% overall yield for the two steps. Subsequently, the concept of Path B proposed in Figure 2, for the synthesis of new ynamides, was illustrated using LHMDS to successfully deprotonate **35** and MeI as the electrophile to give the ynamide **36** in 59% yield.

We have described here a copper-catalyzed new C−N bond formation involving a sp-hybridized carbon. This route provides a direct entry to chiral ynamides via N-alkynylation of amides and should have a significant impact on the future synthetic utility of ynamides.

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Supporting Information Available: Preliminary screenings of conditions, experimental procedures, ^1H spectra, and characterization data of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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