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Introducing the New Class of *N*-Phosphoryl Ynamides via Cu(I)-Catalyzed Amidations of Alkynyl Bromides

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Abstract

We describe here the first synthesis of *N*-phosphoryl ynamides featuring *C*- and *P*-chirality via copper(I)-catalyzed amidative cross-couplings between phosphoramidates and phosphordiamidates with alkynyl bromides. Also featured is a tandem *aza*-Claisen–hetero-[2+2] cycloaddition for the synthesis of *N*-phosphoryl azetidin-2-imines.

The chemistry of ynamides¹ has continued to blossom, with the number of publications increasing at an astonishing rate.² This surge of new and exciting chemistry is largely a result of the ease of ynamide synthesis using copper-catalyzed cross-coupling reactions³ [Scheme 1]. However, with the exception of Masson's⁴ single example of trapping a lithiated ynamine **5** with diethyl chlorophosphate, all examples of ynamides to date utilize amide, carbamate, urea, sulfonyl, and, only recently, imide⁵ derived electron-withdrawing groups [EWG] to harness the ynamide's reactivity. To the best of our knowledge, the amidative cross-coupling⁶ between an *sp*-C and a phosphoramidate^{7–8} has not been reported. We describe herein the first general synthesis of a novel class of *N*-phosphoryl ynamides capable of containing both *C*- and *P*-chirality. The highly Lewis-basic nature of the phosphoryl moiety as well as the ability to tune its electronegativity make the phosphoryl EWG ideal to further expand the already vast scope of reactions one can accomplish using ynamides. To this effect, we disclose an application towards highly functionalized *N*-phosphoryl azetidin-2-imines through a Staudinger-type ketenimine-imine [2+2] cycloaddition not possible with pre-existing ynamides.

Our initial efforts were in optimizing the copper-catalyzed cross-coupling between phosphoramidate **7a** and alkynyl bromide **8** [Table 1]. It was immediately clear that the strength of the base played a significant role in the reaction, with K₃PO₄ giving the best

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Supporting Information Available: Experimental procedures as well as NMR spectra, and characterizations are available for all new compounds and free of charge via Internet <http://pubs.acs.org>.

yield of ynamide **9** [entries 1–3]. Unfortunately, the stronger KO^t-Bu base led to complete decomposition [entry 4]. Also, the combination of CuSO₄·5H₂O and 1,10-phenanthroline was far more efficient than both CuI and CuCN with DMEDA as the ligand [entry 3 vs. 5 – 6].

With an optimized protocol in hand, our next goal was to access the tolerance of the reaction to functionality on both the phosphoramidates and alkynyl bromides [Table 2].

Phosphoramidate **7a** led smoothly to ynamides **12a** and **12b** in moderate yield [entries 1 and 2]. However with the *N*-allyl phosphoramidate **7b**, a thermal *aza*-Claisen⁹ rearrangement of the ynamide product and ensuing hydrolysis¹⁰ occurred readily at 75 °C leading to a low yield of the desired ynamide **13** [entry 3]. This issue could be overcome using anhydrous coupling conditions [CuTC/DMEDA] and a lower reaction temperature to give *N*-allyl ynamide **14** in 57% yield, with almost complete recovery the unreacted **10a**. In general, cyclic diol-derived phosphoramidates **10b** and **10e** gave ynamides **15** and **17** with higher yields [entries 5–7], likely due to the increased hydrolytic stability¹¹ of both the amides and the ynamide products. Interestingly, these cyclic *N*-phosphoryl ynamides adopt a chair configuration with the *N*-C≡C in an axial orientation such that the nitrogen lone pair is delocalized into the σ*[P=O] [see X-ray of **15b** in Figure 1].

By using a 1:1 diastereomeric mixture of phosphoramidates **11**, ynamides **17-eq** and **17-ax** differing only in the stereochemistry at phosphorous could be obtained in excellent yield and separated by column chromatography [Table 2, entry 8]. X-ray crystallography and nOe analysis was used to determine the conformation of the two diastereomeric ynamides, revealing that **17-ax** adopted a similar configuration to that of **15b**, with the nitrogen atom axial and delocalized into the σ*[P=O] while the two oxygen lone pairs were delocalized into the σ*[P-N] [Figure 2]. Unfortunately, the X-ray of **17-eq** was convoluted by the co-crystallization of both enantiomers in a 90:10 ratio as an example of whole molecule disorder. Regardless, it was evident that **17-eq** adopted a chair configuration with the nitrogen atom equatorial and delocalized into the π*[P=O] with the two oxygen lone pairs delocalized into the σ*[P=O].

Next, we turned our attention to preparing ynamides bearing a chiral phosphoryl group, which is especially exciting as the phosphorous atom directly attached to the nitrogen of the ynamide can itself be chiral. Amino alcohols represent an obvious choice for preparing such chiral auxiliaries. Unfortunately, from the onset it was immediately apparent that the reactivity of 1,2-amino alcohol derived phosphordiamidates was very different from their 1,3-diol counterparts [Scheme 2]. To illustrate this point, the synthesis of ynamide **19a** from *L*-proline derived phosphordiamidate **18** proceeded in a meager 13% yield even after 48 hrs at 110 °C using the previously optimized conditions. Though some starting material could be recovered after the reaction, the majority had decomposed. Unfortunately, anhydrous conditions using CuTC and DMEDA for 1*R*,2*R*-(–)-pseudoephedrine derived amide **20** also resulted in no formation of the desired ynamide **21**, though 70% of the starting material could be recovered.

After much struggle, it was discovered that the addition of 10 equiv of NEt₃ to the reaction mixture allowed for isolation of the desired ynamides **19a** and **19b** in low, but synthetically useful yields under anhydrous conditions [Table 3]. Furthermore, ynamide formation from the two separable diastereomers of **20** led to **23** and **24** in moderate yields. The stereochemistry of phosphordiamidates **18**, **20a**, and **20b** was determined by nOe analysis [see supporting information]. The racemic 1,3-amino alcohol derived phosphoramidate **22** led to ynamides **25a** and **25b** resembling a phosphoryl version of Evan's chiral auxiliary in moderate yields without the addition of NEt₃.

We had set out to investigate this new class of *N*-phosphoryl ynamides to solve a problem we had previously encountered while developing a thermal *aza*-Claisen rearrangement of *N*-sulfonyl, *N*-allyl ynamides, allowing for their use as precursors to ketenimines.⁹ Despite our best efforts, the nucleophilic trapping of the *N*-sulfonyl ketenimines was severely limited due to a very rapid intramolecular 1,3-sulfonyl shift yielding nitriles. Since amide, carbamate, and urea-derived ynamides failed to undergo such an *aza*-Claisen in our hands, we turned our attention to phosphoryl-based electron-withdrawing groups. So, we were delighted to see that during the coupling of *N*-allyl phosphoramidate **7b**, some ketenimine hydrolysis product was isolated.¹⁰ Furthermore, heating of *N*-allyl ynamide **26b** resulted in no formation of nitrile **28b**, meaning the *aza*-Claisen is operational, but a 1,3-phosphoryl shift is not [Scheme 3]. This afforded us the opportunity to use the *in situ* generated ketenimine derived from **26b** in a Staudinger-type ketenimine-imine [2+2] cycloaddition¹² to give azetidin-2-imine¹³ **30** bearing a quaternary carbon center with 4:1 diastereoselectivity, which was confirmed by nOe. While these types of tandem reactions initiated by an *aza*-Claisen rearrangement are the reason we initially undertook this project, they are by no means the only types of transformations possible with these *N*-phosphoryl ynamides.

We have described here the first practical synthesis of a new class of ynamides utilizing a variety of chiral and achiral diol and amino alcohol-derived phosphates as the required electron-withdrawing group. As one example of the type of chemistry one may accomplish with such ynamides, we have demonstrated a diastereoselective Staudinger-type ketenimine-imine [2+2] cycloaddition using *N*-phosphoryl ynamides as the synthetic precursor to give highly functionalized *N*-phosphoryl azetidin-2-imines. Investigations are currently underway to further develop these tandem sequences as well as to explore the use of the *N*-phosphoryl as a chiral auxiliary¹⁴⁻¹⁵ and a temporary tether.¹⁶

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. For current leading reviews on ynamides, see (a) Evano G, Coste A, Jouvin K. *Angew Chem Int Ed.* 2010; 49:2840. (b) DeKorver KA, Li H, Lohse AG, Hayashi R, Lu Z, Zhang Y, Hsung RP. *Chem Rev.* 2010; 110:5064. [PubMed: 20429503]
2. For ynamide papers published in 2011 alone, see: (a) Balieu S, Toutah K, Carro L, Chamoreau L-M, Rouselière H, Courillon C. *Tetrahedron Lett.* 2011; 52:2876. (b) Fadel A, Legrand F, Evano G, Rabasso N. *Adv Synth Catal.* 2011; 353:263. (c) Schotes C, Mezzetti A. *Angew Chem.* 2011; 123:3128. (d) Barbazanges M, Meyer C, Cossy J, Turner P. *Chem-Eur J.* 2011; 17:4480. (e) Pizzetti M, Russo A, Petricci E. *Chem-Eur J.* 2011; 17:4523. (f) Garcia P, Evanno Y, George P, Sevrin M, Ricci G, Malacria M, Aubert C, Gandon V. *Org Lett.* 2011; 13:2030. [PubMed: 21413688] (g) Kramer S, Friis SD, Xin Z, Odabachian Y, Skrydstrup T. *Org Lett.* 2011; 13:1750. [PubMed: 21384821] (h) Li C, Zhang L. *Org Lett.* 2011; 13:1738. [PubMed: 21351760] (i) Wang YP, Danheiser RL. *Tetrahedron Lett.* 2011; 52:2111. [PubMed: 21479121] (j) Mak XY, Crombie AL, Danheiser RL. *J Org Chem.* 2011; 76:1852. [PubMed: 21322545] (k) Davies PW, Cremonesi A, Martin N. *Chem Commun.* 2011:379. (l) Xu C-F, Mei Xu M, Jia YX, Li C-Y. *Org Lett.* 2011; 13:1556. [PubMed: 21332143] (m) Chen Z, Zheng D, Wu J. *Org Lett.* 2011; 13:848. [PubMed: 21299243] (n) Shindoh N, Takemoto Y, Takasu K. *Heterocycles.* 2011; 82:1133. (o) Saito N,

- Katayama T, Saito K. *Heterocycles*. 2011; 82:1181. (p) Kramer S, Odabachian Y, Overgaard J, Rottländer M, Gagosz F, Skrydstrup T. *Angew Chemie*. 2011; 123:5196. (q) Nissen F, Richard V, Alayrac C, Witulski B. *Chem Commun*. 2011; 47:6656. (r) Hashmi ASK, Schuster AM, Zimmer M, Rominger F. *Chem–Eur J*. 2011; 17:5511. (s) Gilboa N, Wang H, Houk KN, Marek I. *Chem–Eur J*. 2011; 17:8000. (t) Chemla F, Dulong F, Ferreira F, Nüllen MP, Pérez-Luna A. *Synthesis*. 2011; 9:1347. (u) Saito N, Saito K, Shiro M, Sato Y. *Org Lett*. 2011; 13:2718. [PubMed: 21510622]
3. For leading reviews on the synthesis of ynamides, see: (a) Tracey MR, Hsung RP, Antoline JA, Kurtz KCM, Shen L, Slafer BW, Zhang Y. *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*. Weinreb, Steve M. Georg Thieme Verlag KG Stuttgart, Germany Chapter 21.42005; (b) Mulder JA, Kurtz KCM, Hsung RP. *Synlett*. 2003:1379.
4. Fromont C, Masson S. *Tetrahedron*. 1999; 55:5405.
5. Sueda T, Oshima A, Teno N. *Org Lett*. 2011; 13:3996. [PubMed: 21710984]
6. For an intramolecular Cu-catalyzed cross-coupling between an sp^2 -C and phosphoramidate, see: Yang T, Lin C, Fu H, Jiang Y, Zhao Y. *Organic Lett*. 2005; 7:4781.
7. For examples of phosphoramidates and phosphordiamidates as pharmaceuticals, see: (a) Jeng AY, De Lombaert S. *Curr Pharm Des*. 1997; 3:597. (b) Colvin OM. *Curr Pharm Des*. 1999; 5:555–8. [PubMed: 10469891]
8. For examples as insecticides, see: (a) Milzner K, Reisser F. CH 554376. 1974 (b) Anderson J, Homeyer B, Kuehle E, Scheinpflug H, Zeck WM, Simonet DE. US 4603214. 1986
9. (a) Zhang Y, DeKorver KA, Lohse AG, Zhang Y-S, Huang J, Hsung RP. *Org Lett*. 2009; 11:899. [PubMed: 19199763] (b) DeKorver KA, Hsung RP, Lohse AG, Zhang Y. *Org Lett*. 2010; 12:1840. [PubMed: 20337418] (c) DeKorver KA, North TD, Hsung RP. *Synlett*. 2010:2397. [PubMed: 21278848] (d) DeKorver KA, Johnson WL, Zhang Y, Hsung RP, Dai H, Deng J, Lohse AG, Zhang Y-S. *J Org Chem*. 2011; 76:5092. [PubMed: 21563776]
10. During the formation of ynamide **i** bearing an *N*-allyl moiety, an ensuing thermal *aza*-Claisen occurred followed by hydrolysis of the resulting ketenimine to give **ii**.

11. For leading references, see: (a) Garrison AW, Boozer CE. *J Am Chem Soc*. 1968; 90:3486. (b) Núñez A, Berroterán D, Núñez O. *Org Biomol Chem*. 2003; 1:2283. [PubMed: 12945698]
12. For a review of ketenimine cycloadditions, see: Alajarin M, Vidal A, Tovar F. *Targets Heterocycl Syst*. 2000; 4:293.
13. (a) Arnold B, Regitz M. *Angew Chem Int Ed*. 1979; 4:320. (b) Van Camp A, Goossens D, Moya-Portuguez M, Marchand-Brynaert J, Ghosez L. *Tetrahedron Lett*. 1980; 21:3081. (c) Alajarin M, Molina P, Vidal A. *Tetrahedron Lett*. 1996; 37:8945. (d) Whiting M, Fokin VV. *Angew Chem Int Ed*. 2006; 45:3157.
14. Molt O, Schrader T. *Synthesis*. 2002:2633.
15. Preliminary efforts at utilizing chiral amino-alcohol derived *N*-phosphoryl ynamides in Lewis acid-catalyzed reactions have been problematic thus far due to instability of the ynamides to acidic conditions. We are currently exploring their use in thermally driven pathways.
16. For leading reviews on utilizing phosphorous as a temporary tether, see: (a) McReynolds MD, Dougherty JM, Hanson PR. *Chem Rev*. 2004; 104:2239. [PubMed: 15137790] (b) Thomas CD, McParland JP, Hanson PR. *Eur J Org Chem*. 2009; 32:5487.

Figure 1.
X-ray of Ynamide **15b**.

Figure 2.
X-rays of Diastereomeric Ynamides **17-eq** and **17-ax**.

N-Amide, Carbamate, Urea, Sulfonyl, and Imide Derived Ynamides: *N*-Phosphoryl Ynamide:

Scheme 1.
Current Ynamide Electron-Withdrawing Groups.

Scheme 2.

Attempts at Ynamide Synthesis from Amino Alcohols.

Scheme 3.
Towards the Synthesis of *N*-Phosphoryl Azetidin-2-imines.

Table 1Optimization of Coupling Conditions.^a

entry	catalyst	ligand	base	yield [%] ^b
1	CuSO ₄ ·5H ₂ O	1,10-phenanthroline	K ₂ CO ₃	38
2	CuSO ₄ ·5H ₂ O	1,10-phenanthroline	Cs ₂ CO ₃	59
3	CuSO₄·5H₂O	1,10-phenanthroline	K₃PO₄	68
4	CuSO ₄ ·5H ₂ O	1,10-phenanthroline	KOt-Bu	–
5	CuI	DMEDA	K ₃ PO ₄	25 ^c
6	CuCN	DMEDA	K ₃ PO ₄	27 ^c

^a Conditions: 15 mol % Cu, 30 mol % ligand, 2 equiv base, toluene (concn = 0.4 M), 95 °C, 24 h.^b Isolated yields.^c Reactions run at 110 °C.

Table 2

Synthesis of *N*-Phosphoryl Ynamides from Diols.^a

entry	phosphoramidate	alkyne	ynamide	yield [%] ^b
1				61
2	7a	R	R = CH₂OTBS 12a R = n-hex 12b	69
3				39
4	7b	TIPS	TIPS	
5				57 ^{c,d}
6	10a	TIPS	TIPS	
5				84 ^d
6	10b	R	R = n-hex 15a R = (CH₂)₂Ph 15b	92 ^d
7				54 ^d
7	10c	n-hex	n-hex	
8				95 ^d
	11 [1:1 dr]	Ph	17-eq 17-ax	

^a Conditions: 15 mol % CuSO₄·5H₂O, 30 mol % 1,10-phenanthroline, 1.3 equiv alkynyl bromide, 2 equiv K₃PO₄, toluene (concn = 0.4 M), 75–100 °C, 24 h.

^b Isolated yields. ^c 20 mol % CuTC, 40 mol % DMEDA, 50 °C, 48 h and 95% based on recovered **10a**. Using conditions from Table 2, yield was 75%. ^d 48 h reaction time.

Table 3

Ynamides from Amino Alcohols.^a

entry	phosphor(di)amidate	alkyne	ynamide	yield ^b
1				38
2				28
3				23
4				24
5				25a
6				25b

^a Conditions: 1.3 equiv alkynyl bromide, 20 mol % CuTC, 40 mol % DMEDA, 3 equiv Cs₂CO₃, 10 equiv NEt₃, dioxane (concn = 0.4 M), 95 °C, 6–24 h.^b Isolated yields.^c Same catalyst, but with 3:1 toluene:EtOAc (concn = 0.4 M), 2 equiv K₃PO₄, 95 °C, 24 h.