ORGANIC LETTERS

2011
Vol. 13, No. 18
4862–4865

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

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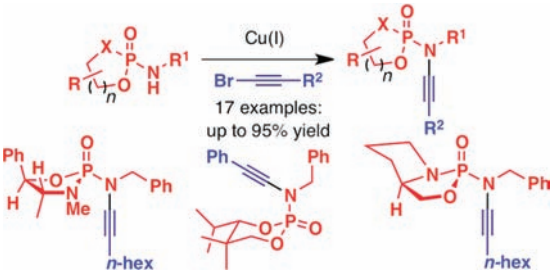
Received July 19, 2011

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 ynamides[1] 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 reactions[3] (Scheme 1). However, with the exception of Masson's[4] single example of trapping lithiated ynamine **5** with diethyl chlorophosphate, all examples of ynamides to date utilize amide, carbamate, urea, sulfonyl, and only recently, imide[5] derived electron-withdrawing groups (EWG) to harness the ynamide's reactivity. To the best of our knowledge, the amidative cross-coupling[6] between an *sp*-C and a phosphoramidate[7,8] has not been reported. We describe herein the first general synthesis of a

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(3) For leading reviews on the synthesis of ynamides, see: (a) Tracey, M. R.; Hsung, R. P.; Antoline, J. A.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: Stuttgart, Germany, 2005; Chapter 21.4. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379.

(4) Fromont, C.; Masson, S. *Tetrahedron* **1999**, *55*, 5405.

(5) Sueda, T.; Oshima, A.; Teno, N. *Org. Lett.* **2011**, *13*, 3996.

(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. *Org. Lett.* **2005**, *7*, 4781.

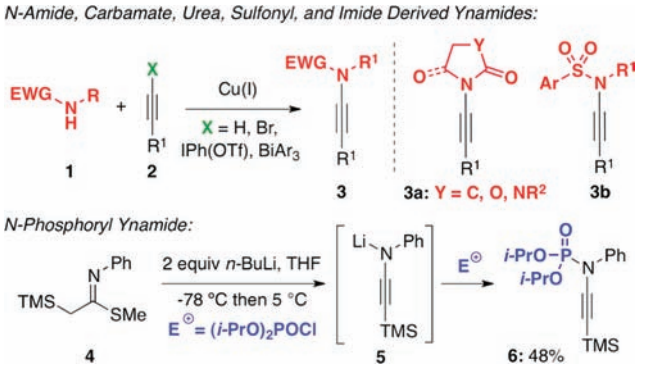
(7) For examples of phosphoramidates and phosphordiamidates as pharmaceuticals, see: (a) Jeng, A. Y.; De Lombaert, S. *Curr. Pharm. Des.* **1997**, *3*, 597. (b) Colvin, O. M. *Curr. Pharm. Des.* **1999**, *5*, 555–8.

(8) For examples as insectides, see: (a) Milzner, K.; Reisser, F. Patent CH 554376, 1974. (b) Anderson, J.; Homeyer, B.; Kuehle, E.; Scheinpflug, H.; Zeck, W. M.; Simonet, D. E. Patent US 4603214, 1986.

10.1021/ol201947b
Published on Web 08/17/2011

novel class of *N*-phosphoryl ynamides capable of containing both *C*- and *P*-chirality. The highly Lewis basic nature of the phosphoryl moiety and the ability to tune its electronegativity make the phosphoryl EWG ideal to further expand

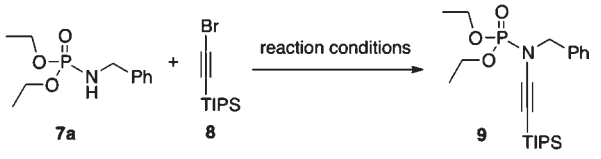
Scheme 1. Current Ynamide Electron-Withdrawing Groups



the already vast scope of reactions one can accomplish using ynamides. To this effect, we disclose an application toward 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 K_3PO_4 giving the best yield of ynamide **9** (entries 1−3). Unfortunately, the stronger KO*t*-Bu base led to complete decomposition (entry 4). Also, the combination of $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline was far more efficient than both CuI and CuCN with DMEDA as the ligand (entry 3 vs 5 and 6).

Table 1. Optimization of Coupling Conditions[a]



entry	catalyst	ligand	base	yield (%)[b]
1	$CuSO_4 \cdot 5H_2O$	1,10-phenanthroline	K_2CO_3	38
2	$CuSO_4 \cdot 5H_2O$	1,10-phenanthroline	Cs_2CO_3	59
3	$CuSO_4 \cdot 5H_2O$	1,10-phenanthroline	K_3PO_4	68
4	$CuSO_4 \cdot 5H_2O$	1,10-phenanthroline	KO*t*-Bu	<5
5	CuI	DMEDA	K_3PO_4	25[c]
6	CuCN	DMEDA	K_3PO_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.

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*-Claisen[9] rearrangement of the ynamide product and ensuing hydrolysis[10] 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 of the unreacted **10a**. In general, cyclic diol-derived phosphoramidates **10b** and **10c** gave ynamides **15** and **16** with higher yields (entries 5−7), likely due to the increased hydrolytic stability[11] 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).

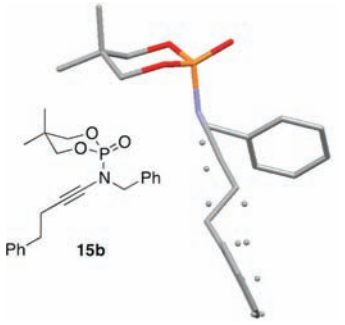
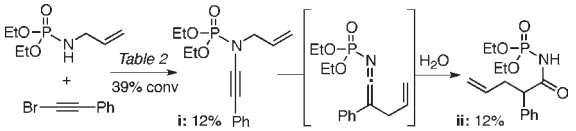


Figure 1. X-ray of ynamide **15b**.

By using a 1:1 diastereomeric mixture of phosphoramidates **11**, ynamides **17-eq** and **17-ax** differing only in the stereochemistry at phosphorus 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 configuration similar 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]

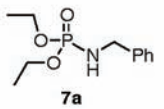
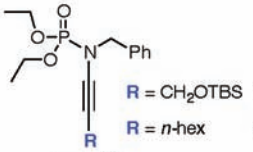
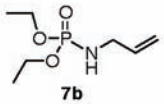
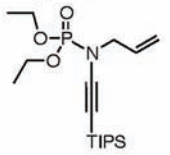
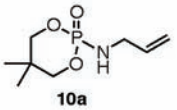
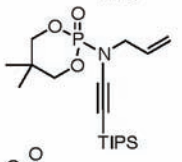
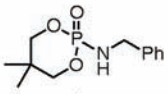
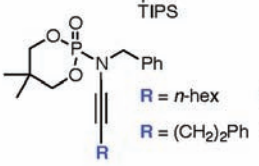
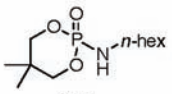
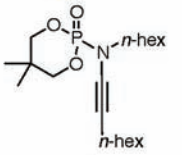
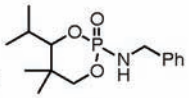
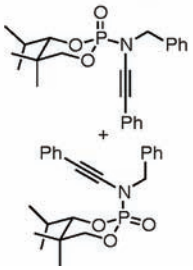
(9) (a) Zhang, Y.; DeKorver, K. A.; Lohse, A. G.; Zhang, Y.-S.; Huang, J.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 899. (b) DeKorver, K. A.; Hsung, R. P.; Lohse, A. G.; Zhang, Y. *Org. Lett.* **2010**, *12*, 1840. (c) DeKorver, K. A.; North, T. D.; Hsung, R. P. *Synlett* **2010**, 2397. (d) DeKorver, K. A.; Johnson, W. L.; Zhang, Y.; Hsung, R. P.; Dai, H.; Deng, J.; Lohse, A. G.; Zhang, Y.-S. *J. Org. Chem.* **2011**, *76*, 5092.

(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, A. W.; Boozer, C. E. *J. Am. Chem. Soc.* **1968**, *90*, 3486. (b) Núñez, A.; Berroterán, D.; Núñez, O. *Org. Biomol. Chem.* **2003**, *1*, 2283.

Table 2. Synthesis of *N*-Phosphoryl Ynamides from Diols[a]

entry	phosphoramidate	alkyne	ynamide		yield [%][b]
1				R = CH_2OTBS	12a	61
2	7a			R = *n*-hex	12b	69
3	 7b				13	39
4	 10a				14	57[c,a]
5				R = *n*-hex	15a	84[d]
6	10b			R = $(CH_2)_2Ph$	15b	92[d]
7	 10c				16	54[d]
8	 11 [1:1 *dr*]				17-eq / 17-ax	95[d]

[a] Conditions: 15 mol % $CuSO_4 \cdot 5H_2O$, 30 mol % 1,10-phenanthroline, 1.3 equiv alkynyl bromide, 2 equiv K_3PO_4, 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.

(Figure 2). Unfortunately, the X-ray of **17-eq** was convoluted by the cocrystallization 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 phosphorus 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

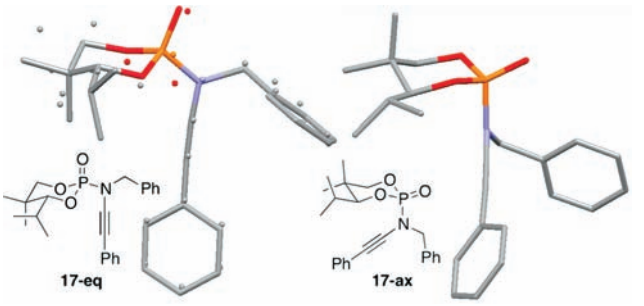
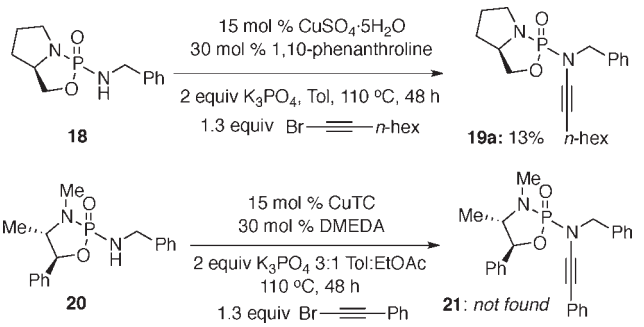


Figure 2. X-rays of diastereomeric ynamides **17-eq** and **17-ax**.

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 h 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.

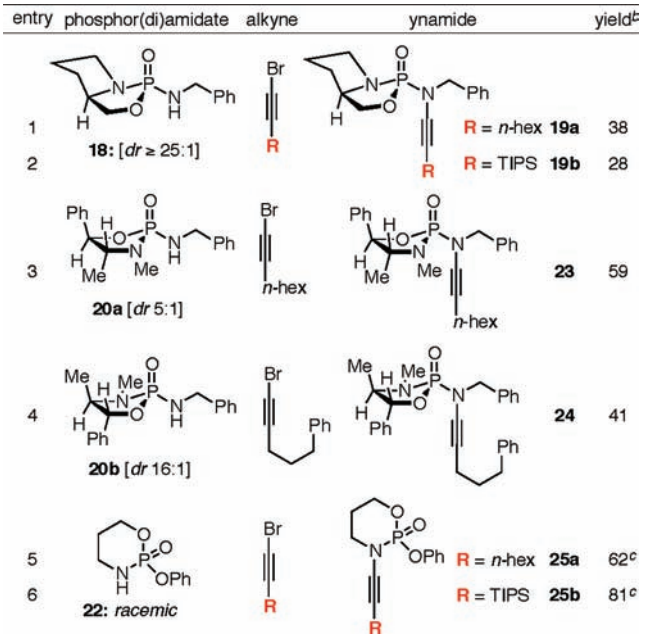
Scheme 2. Attempts at Ynamide Synthesis from Amino Alcohols



After much struggle, it was discovered that the addition of 10 equiv of NEt_3 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 Evans' chiral auxiliary in moderate yields without the addition of NEt_3.

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

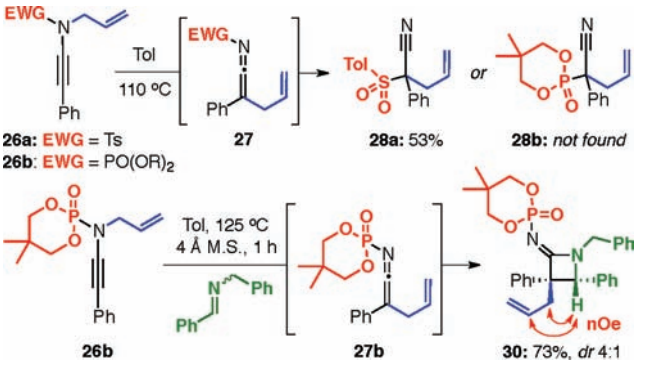
Table 3. Ynamides from Amino Alcohols[a]



[a] Conditions: 1.3 equiv alkynyl bromide, 20 mol % CuTC, 40 mol % DMEDA, 3 equiv Cs_2CO_3, 10 equiv NEt_3, 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 K_3PO_4, 95 °C, 24 h.

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. 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] cycloaddition[12] to give azetidin-2-imine[13] **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.

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



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 auxiliary[14,15] and a temporary tether.[16]

Acknowledgment. We thank NIH (GM066055) for funding. K.A.D. thanks the American Chemical Society for a Division of Medical Chemistry Predoctoral Fellowship. We thank Dr. Vic Young and Mr. Gregory T. Rohde of the University of Minnesota for providing X-ray structural analysis.

Supporting Information Available. Experimental procedures as well as NMR spectra and characterizations for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(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.; Goosens, 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, V. V. *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, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239. (b) Thomas, C. D.; McParland, J. P.; Hanson, P. R. *Eur. J. Org. Chem.* **2009**, *32*, 5487.