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Synthesis of Amidines Using *N*-Allyl Ynamides. A Palladium-Catalyzed Allyl Transfer through an Ynamido−π-Allyl Complex

Yu Zhang, Kyle A. DeKorver, Andrew G. Lohse, Yan-Shi Zhang, Jian Huang, and Richard P. Hsung*

Division of Pharmaceutical Sciences and Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53705

rhsung@wisc.edu

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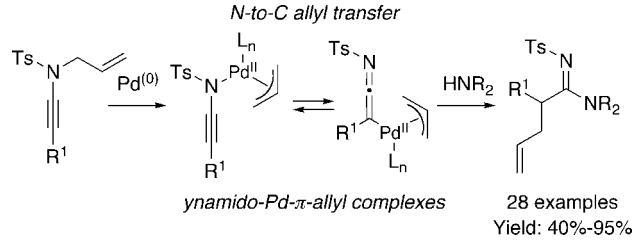
ABSTRACT



A de novo transformation of *N*-allyl-*N*-sulfonyl ynamides to amidines is described featuring a palladium-catalyzed *N*-to-*C* allyl transfer via ynamido−palladium−π-allyl complexes.

Our involvement in the studies of Huisgen's azide-[3 + 2][1−3] cycloadditions employing ynamides[4−7] led us to an exciting possibility. As shown in Scheme 1, under copper(I)-catalyzed conditions,[8] while triazolyl copper intermediates **1** could be trapped with electrophiles other than proton to afford more substituted triazoles **2**,[9,10] when R^2 = Ts, it could also readily lose N_2 in a retro-[3 + 2] manner to give ynamido−copper complexes **3a** in equilibrium with ketenimine−copper complexes **3b**. A series of elegant studies have since appeared reporting nucleophilic trappings of **3** in both inter- and intramolecular fashion, leading to amidines and amidates.[11−14] The potential of harvesting new reactivities from

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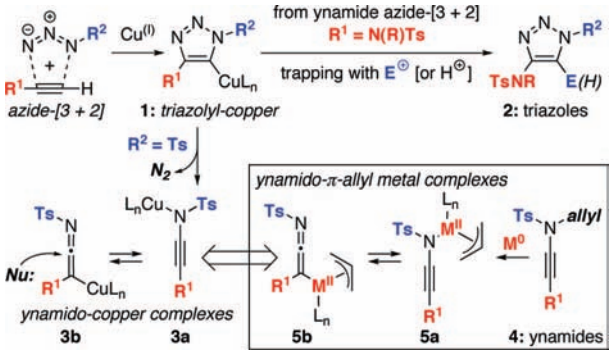
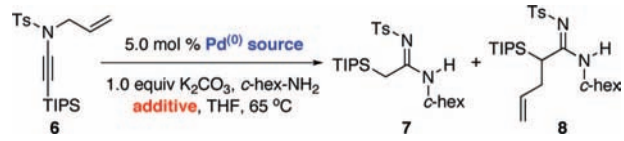
Scheme 1. Generating Ynamido−Metal Complexes

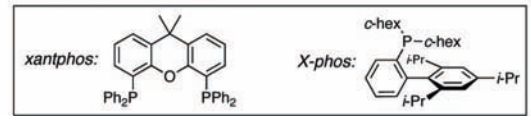


ynamido−metal complexes captured our attention. Consequently, we examined a different pathway that can provide general access to ynamido−metal π-allyl complexes **5a** and **5b** from *N*-allyl-*N*-sulfonyl ynamides **4**. We report here a de novo synthesis of pharmacologically useful amidines[15−18] from ynamides featuring a palladium-catalyzed *N*-to-*C* allyl transfer through ynamido−π-allyl complexes.

Table 1. Effect of Equivalents of Amine and Pd(0) Sources



entry	Pd(0)	additive [mol %]	amine equiv	time [h]	yield [%][a] 7	8
1	$Pd(PPh_3)_2Cl_2$	--	5.0	2	92	5
2		--	3.0	2	63	24
3		--	1.0	2	44	45
4		--	1.0: syringe pump addition	2	11	73
5	$Pd(PPh_3)_4$	--	3.0	3	0	≥95
6	$Pd(dppe)Cl_2$	--	3.0	48	30	<5
7	$Pd(dppf)Cl_2$	--	3.0	24	95	0
8	$Pd_2(dba)_3$	BINAP [10.0]	3.0	24	40	59
9	$Pd_2(dba)_3$	xantphos [10.0]	3.0	3	0	≥95
10	$Pd_2(dba)_3$	X-phos [10.0]	3.0	24	<5	95



[a] All are isolated yields.

While identifying a suitable palladium catalyst for our intended reaction pathway was not difficult, we found two amidine products. As shown in Table 1, when treating *N*-allyl-*N*-sulfonyl ynamide **6** with 5 mol % of $Pd(PPh_3)_2Cl_2$ in the presence of *c*-hex-NH_2 in THF at 65 °C, both amidines **7** and **8** were observed.[19] Intriguingly, the ratio of **7** and **8** depended upon the amount of *c*-hex-NH_2 that was used. A greater amount of *c*-hex-NH_2 (3−5 equiv) predominantly led to the formation of **7** in which the allyl group is lost (entries 1 and 2), while 1.0 equiv of *c*-hex-NH_2 and/or addition with the use of syringe pump began to favor the formation of **8** in which the allyl group had undergone an *N*-to-*C* transfer (entries 3 and 4).

Moreover, a quick screening of palladium sources revealed that the allyl transfer is catalyst dependent (Table 1). At 3.0 equiv of *c*-hex-NH_2 in comparison with $Pd(PPh_3)_2Cl_2$ (see entry 1), $Pd(PPh_3)_4$ gave exclusively allyl-transferred amidine **8** (entry 5), while $Pd(dppe)Cl_2$ and $Pd(dppf)Cl_2$ (entries 6 and 7) reverted back to favor amidine **7** with $Pd(dppf)Cl_2$ giving a better yield (entry 7). Sensing that these contrasts could be due to the differences either in the initial oxidation state of the palladium metal or, more likely, their respective ligands, we examined

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(11) For intermolecular additions, see: (a) Bae, I.; Han, H.; Chang, S. *J. Am. Soc. Chem.* **2005**, *127*, 2038. (b) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046. (c) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347. (d) Kim, S. H.; Jung, D. Y.; Chang, S. *J. Org. Chem.* **2007**, *72*, 9769. (e) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2836. (f) Kim, J.; Lee, S. Y.; Lee, J.; Do, Y.; Chang, S. *J. Org. Chem.* **2008**, *73*, 9454. (g) Yoo, E. J.; Ahlquist, M.; Bae, I.; Sharpless, K. B.; Fokin, V. V.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520.

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(14) For other leading examples of trapping complexes such as **3**, see: (a) Cui, S.-L.; Lin, X.-F.; Wang, Y.-G. *Org. Lett.* **2006**, *8*, 4517. (b) Xu, X.; Cheng, D.; Li, J.; Guo, H.; Yan, J. *Org. Lett.* **2007**, *9*, 1585. (c) Jin, Y.; Fu, H.; Yin, Y.; Jiang, Y.; Zhao, Y. *Synlett* **2007**, 901. (d) Cui, S.-L.; Wang, J.; Wang, Y.-G. *Org. Lett.* **2007**, *9*, 5023. (e) Cui, S.-L.; Wang, J.; Wang, Y.-G. *Org. Lett.* **2008**, *10*, 1267. (f) For an earlier study on trapping of ynamido-lithium complexes, see: Fromont, C.; Masson, S. *Tetrahedron* **1999**, *55*, 5405.

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(19) See the Supporting Information. On the basis of NOE experiments (see the Supporting Information for details), these amidines adopt an *E*-geometry with respect to the *C*═N bond.

Table 2. Amidine Synthesis Using Primary Amines[a]

entry	primary amines	4-pentenyl-amidines		yield [%][b]
1	H_2N–*R*, *R* = *n*-Bu	*R* = *n*-Bu	9	≥95
2	H_2N–*R*, *R* = *t*-Bu	*R* = *t*-Bu	10	90
3	H_2N		11	73
4	H_2N		12	76
5	*R* = MeO	*R* = MeO	13	67
6	*R* = H	*R* = H	14	85[c]
7	*R* = Cl	*R* = Cl	15	78[d]
8	*R* = CF_3	*R* = CF_3	16	54
9	H_2N, Me	Me	17	52

[a] All reactions utilized ynamide **6**, 5.0 mol % of $Pd(PPh_3)_4$, 1.0 equiv of K_2CO_3, 3.0 equiv of RNH_2, and THF [conc = 0.05 M], 65 °C, 5−8 h. [b] Isolated yields. [c] 1.0 equiv of amine was used. [d] Reaction time was 24 h.

$Pd_2(dba)_3$ along with 10 mol % of various phosphine ligands. While BINAP was not useful (entry 8, potential ee was not analyzed), we found that both xantphos[20] and X-phos[21] (entries 9 and 10) represent excellent ligand systems for promoting the allyl transfer, with the former phosphine ligand (see entry 9) providing a much faster reaction.

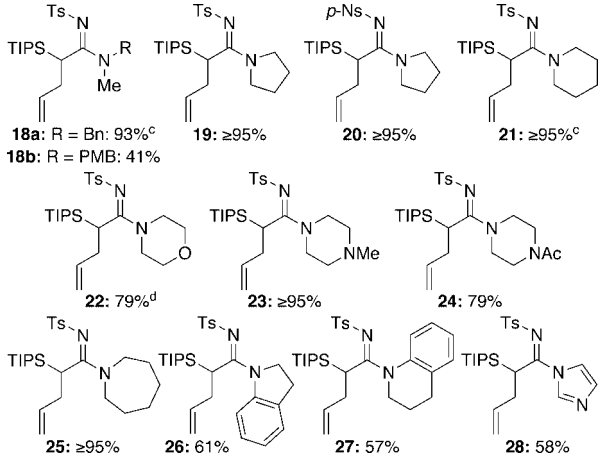
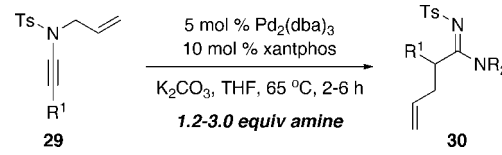


Figure 1. Amine synthesis using secondary amines. (a) Reaction conditions: 5.0 mol % of $Pd_2(dba)_3$, 10.0 mol % of xantphos, 1.0 equiv of K_2CO_3, 3.0 equiv of R_2NH, THF (conc = 0.05 M), 65 °C, 1.5−6 h. (b) Isolated yields. (c) 10.0 mol % of $Pd_2(dba)_3$, 20.0 mol % of xantphos, and 5.0 equiv of R_2NH were used. (d) The only successful example in using 5.0 mol % of $Pd(PPh_3)_4$.

The generality of this allyl transfer could be established very quickly via three perspectives, leading to the synthesis

Table 3. Ynamide Substituent Effect



entry	ynamides	R^1	amidines	NR_2	isolated yield (%)
1	**29a**	TBDPS	**30a**	pyrrolidinyl	95
2	**29b**	TBS	**30b**	pyrrolidinyl	94
3	**29c**	TES	**30c**	pyrrolidinyl	87
4	**29d**	$(CH_2)_3$OTBS	**30d**	*c*-hex-NH	41
5	**29e**	*c*-hex	**30e**	pyrrolidinyl	54
6	**29e**	*c*-hex	**30f**	*c*-hex-NH	69

of a diverse array of amidines. First, we employed a range of primary amines including allyl amine (entry 3 in Table 2), propargyl amine (entry 4), and anilines (entries 5−9). Second, we examined a series of secondary amines including the use of *p*-Ns-substituted ynamide (see **20** in Figure 1), indoline (see **26**), tetrahydroquinoline (see **27**), and imidazole (see **28**).

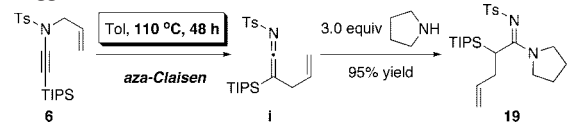
Third, we explored ynamides **29a**−**e** with variations on the acetylenic substituent (Table 3). It is noteworthy that while $Pd(PPh_3)_4$ was effective in promoting allyl transfer when using primary amines, it was not useful for secondary amines (with the exception of **22**), and only the usage of $Pd_2(dba)_3$ and xantphos led to allyl-transferred amidines.

A proposed model consistent with our observations is shown in Scheme 2. While all evidence points toward the presence of ynamido−Pd−π-allyl complexes **5a** in equilibrium with the ketenimine complex **5b** through an oxidative addition,[22,23] the pathway clearly diverged thereafter depending upon the concentration of the amine HNR_2 and the nature of the ligand. We believe the first equivalent of HNR_2 effectively gave the amidinyl Pd−π-allyl complexes **31a** and **31b** via nucleophilic addition to **5b**. An ensuing reductive elimination of **31a** and/or **31b** would lead to respective allyl

(20) For a leading reference on xantphos, see: Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.

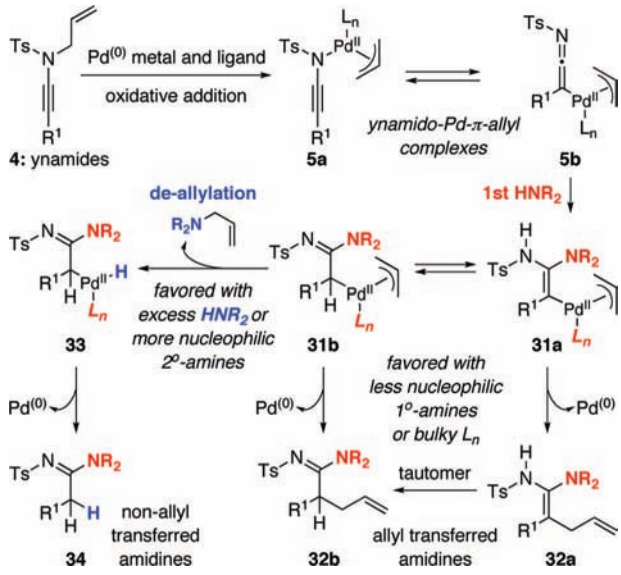
(21) For leading references on X-phos, see: (a) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (b) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 12003.

(22) As shown below, a non-palladium-involved pathway would entail an aza-Claisen type of rearrangement followed by trapping of the allylketenimine intermediate **i** with an external amine. However, while this pathway is indeed a possibility, it requires much higher temperature and longer reaction time. When carried out at 65−80 °C in THF, the reaction was sluggish and slow.



For a recent account on a related thermal transformation using ynol ethers, see: Sosa, J. R.; Tudjarian, A. A.; Minehan, T. G. *Org. Lett.* **2008**, *10*, 5091.

Scheme 2. Proposed Mechanistic Model



transferred amidines **32a** and **32b**, and **32a** appears to tautomerize favorably to **32b**.

However, this reductive elimination step appears to be less favored when an excess of amine was used. Consequently, Pd complexes **33** could be attained likely through a direct nucleophilic attack on the Pd−π-allyl motif, thereby leading to the loss of the respective allyl amines[24] and, ultimately, the formation of the nonallyl-transferred amidines **34** after reductive elimination. In addition, this deallylative pathway is also consistent with the fact that when using the more nucleophilic secondary amines (relative to primary amines)[25] and $Pd(PPh_3)_4$, nonallyl-transferred amine product predominated. Consequently, in all cases, either a controlled amount of HNR_2, a slow addition of HNR_2, or more bulky ligands such as X-phos[21] and/or bidentate ligands with unique bite angles such as xantphos[20,26] that presumably promote reductive elimination could be employed to favor the formation of allyl-transferred amidines **32b**.

Finally, the efficacy of oxidative addition likely plays a role in the distribution between nonallyl- and allyl-transferred amidines because the choice of Pd(0) source appears to be critical. Specifically, a Pd(II) source could also serve as π-Lewis acid to activate the ynamide, leading to keten-iminium Pd complex **35** (Scheme 3). After addition of the first equivalent of HNR_2, deallylation of the resulting *N*-allyl enamide **36** could take place with a second equivalent of HNR_2. This process could be promoted by either Pd(0) or Pd(II), with the former initiating an oxidative addition while the latter again serving to activate the ketene-aminal motif. This assessment is consistent with the observation that nonallyl transferred amidines **34** were the major product when using Pd(II) sources.

We have described here a de novo transformation of *N*-allyl-*N*-sulfonyl ynamides to a diverse array of amidines featuring a palladium-catalyzed *N*-to-*C* allyl transfer via ynamido−palladium−π-allyl complexes. Efforts in further developing synthetic methods involving these ynamido−palladium−π-allyl complexes are underway.

Acknowledgment. We thank the NIH (GM066055) for funding.

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.

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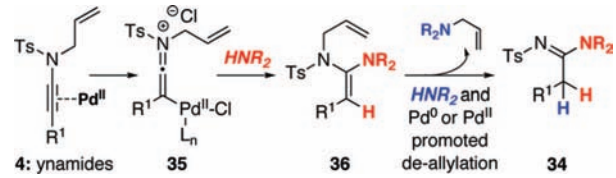
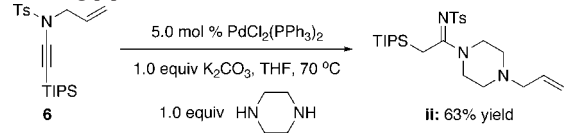
Scheme 3. Pd(II) versus Pd(0) Source



(23) For leading reviews on Claisen rearrangements, see: (a) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984. (b) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 827.

(24) Because of their basicity, polarity, and/or volatility, the respective allyl amine byproducts [$R_2NCH_2CH{=}CH_2$] from de-allylation were difficult to isolate. However, we were able to isolate the following allylated amine **ii** when using piperizine.



(25) For a leading reference on relative nucleophilicity of amines, see: Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679.

(26) Hartwig observed that in comparison with monodentate phosphine ligands, the usage of bidentate ligands such as xantphos leads to a much faster amidative cross-coupling. This is presumably due to the ability of amido-type carbonyl groups to engage in tight complexation with the palladium metal. As a result, when using xantphos, its unique bite angle promotes reductive elimination. See: Fujita, K.-I.; Yamashita, M.; Puschmann, F.; Alvarez-Falcon, M. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9044.