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

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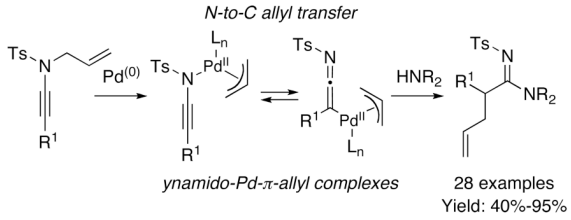
Abstract



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 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.

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].

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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 P d(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 $Pd_2(dba)_3$ 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.

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

Thirdly, 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-P d-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 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 non-allyl transferred amidines **34** after reductive elimination. In addition, this de-allylative pathway is also consistent with the fact that when using the more nucleophilic secondary amines [relative to primary amines][25] and P d $(PPh_3)_4$, non-allyl transferred amine product predominated. Consequently, in all cases, either a controlled amount of HNR_2, or 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 non-allyl 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 keteniminium Pd-complex **35** [Scheme 3]. After addition of the first equivalent of HNR_2, de-allylation 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 non-allyl 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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References

1. (a) Huisgen R. Angew Chem 1963;75:604.Huisgen, R. 1,3-Dipolar Cycloaddition Chemistry. Padwa, A., editor. Oxford: Pergamon Press; 1984. p. 1-176.
2. For leading reviews, see: (a)Meldal M, Tornoe CW. Chem. Rev 2008;108:2952. [PubMed: 18698735] (b)Wu P, Fokin VV. Aldrichimica Acta 2007;40:7. (c)Bock VD, Hiemstra H, Van Maarseveen JH. Eur. J. Org. Chem 2006:51. (d)Katritzky AR, Zhang Y, Singh SK. Heterocycles 2003;60:1225. (e) Abu-Orabi ST. Molecule 2002;7:302. (f)Kolb HC, Finn MG, Sharpless KB. Angew. Chem., Int. Ed 2001;40:2004.
3. For a review on organic azides, see: Bräse S, Gil C, Knepper K, Zimmermann v. Angew. Chem., Int. Ed 2005;44:5188.
4. (a) Zhang X, Li H, You L, Tang Y, Hsung RP. Adv. Syn. Cat 2006;348:2437. (b) Zhang X, Hsung RP, You L. Org. Biomol. Chem 2006;6:2679. [PubMed: 16826290]
5. For reviews on ynamides, see: (a)Zificsak CA, Mulder JA, Hsung RP, Rameshkumar C, Wei L-L. Tetrahedron 2001;57:7575. (b)Mulder JA, Kurtz KCM, Hsung RP. Synlett 2003:1379. (c)Katritzky AR, Jiang R, Singh SK. Heterocycles 2004;63:1455.
6. For chemistry of ynamides in the last two years, see: (a)Couty S, Liegault B, Meyer C, Cossy J. Tetrahedron 2009;65 ASAP. (b)Deweerdt K, Birkedal H, Ruhland T, Skrydstrup T. Org. Lett 2009;11:221. [PubMed: 19035838] (c)Dooleweerdt K, Birkedal H, Ruhland T, Skrydstrup T. J. Org. Chem 2008;73:9447. (d)Saito N, Katayama T, Sato Y. Org. Lett 2008;10:3829. [PubMed: 18681448] (e)Yasui H, Yorimitsu H, Oshima K. Bull. Chem. Soc. Jpn 2008;81:373. (f)Yasui H, Yorimitsu H, Oshima K. Chem. Lett 2008;37:40. (g)Istrate FM, Buzas AK, Jurberg ID, Odabachian Y, Gagosz F. Org. Lett 2008;10:925. [PubMed: 18247498] (h)Martínez-Esperón MF, Rodríguez D, Castedo L, Saá C. Tetrahedron 2008;64:3674. (i)Hamada T, Ye X, Stahl SS. J. Am. Chem. Soc 2008;130:833. [PubMed: 18166058] (j)Yavari I, Sabbaghan M, Hosseini N, Hossaini Z. Synlett 2007;20:3172. (k) Hashimi ASK, Salathe R, Frey W. Synlett 2007:1763. (l)Rodríguez D, Martínez-Esperón MF, Castedo L, Saá C. Synlett 2007:1963. (m)Couty S, Meyer C, Cossy J. Synlett 2007:2819. (n)Movassaghi M, Hill MD, Ahmad OK. J. Am. Chem. Soc 2007;129:10096. [PubMed: 17663557] (o)Tanaka K, Takeishi K. Synthesis 2007:2920. (p)Kohnen AL, Dunetz JR, Danheiser RL. Organic Syn 2007;84:88.
7. (a) Al-Rashid ZF, Johnson WL, Hsung RP, Wei Y, Yao P-Y, Liu R, Zhao K. J. Org. Chem 2008;73:8780. [PubMed: 18937407] (b) Yao P-Y, Zhang Y, Hsung RP, Zhao K. Org. Lett 2008;10:4275. [PubMed: 18754591] (c) Zhang X, Hsung RP, Li H, Zhang Y, Johnson WL, Figueroa R. Org. Lett 2008;10:3477. [PubMed: 18613692] (d) Al-Rashid ZF, Hsung RP. Org. Lett 2008;10:661. [PubMed: 18198881] (e) Oppenheimer J, Hsung RP, Figueroa R, Johnson WL. Org. Lett 2007;9:3969. [PubMed: 17764192] (f) You L, Al-Rashid ZF, Figueroa R, Ghosh SK, Li G, Lu T, Hsung RP. Synlett 2007:1656. (g) Li H, You L, Zhang X, Johnson WL, Figueroa R, Hsung RP. Heterocycles 2007;74:553. (h) Sagamanova IK, Kurtz KCM, Hsung RP. Organic Syn 2007;84:359. (i) Oppenheimer J, Johnson WL, Tracey MR, Hsung RP, Yao P-Y, Liu R, Zhao K. Org. Lett 2007;9:2361. [PubMed: 17489599]
8. Wu P, Feldman AK, Nugent AK, Hawker CJ, Scheel A, Voit B, Pyun J, Frechet JMJ, Sharpless KB, Fokin VV. Angew. Chem., Int. Ed 2004;43:3928.
9. Zhang X, Hsung RP, Li H. Chem. Commun 2007:2420.

10. For related studies on these triazolyl copper intermediates, see: (a)Gerard B, Ryan J, Beeler AB, Porco JA Jr. Tetrahedron 2006;62:6405. (b)Wu YM, Deng J, Li Y, Chen Q-Y. Synthesis 2005:1314. (c) Cassidy MP, Raushel J, Fokin VV. Angew. Chem., Int. Ed 2006;45:3154. see footnote 11.
11. For intermolecular additions, see: (a)Bae I, Han H, Chang S. J. Am. Soc. Chem 2005;127:2038. (b) Cho SH, Yoo EJ, Bae I, Chang S. J. Am. Chem. Soc 2005;127:16046. [PubMed: 16287290] (c)Yoo EJ, Bae I, Cho SH, Han H, Chang S. Org. Lett 2006;8:1347. [PubMed: 16562888] (d)Kim SH, Jung DY, Chang S. J. Org. Chem 2007;72:9769. [PubMed: 17979288] (e)Cho SH, Chang S. Angew. Chem., Int. Ed 2008;47:2836. (f)Kim J, Lee SY, Lee J, Do Y, Chang S. J. Org. Chem 2008;73:9454. (g)Yoo EJ, Ahlquist M, Bae I, Sharpless KB, Fokin VV, Chang S. J. Org. Chem 2008;73:5520. [PubMed: 18557650]
12. For an intramolecular addition, see: Chang S, Lee M, Jung DY, Yoo EJ, Cho SH, Han SK. J. Am. Soc. Chem 2006;128:12366.
13. For a study using ynamides, see: Kim JY, Kim SH, Chang S. Tetrahedron Lett 2008;49:1745.
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. [PubMed: 16986939] (b)Xu X, Cheng D, Li J, Guo H, Yan J. Org. Lett 2007;9:1585. [PubMed: 17381100] (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. [PubMed: 17979278] (e)Cui S-L, Wang J, Wang Y-G. Org. Lett 2008;10:1267. [PubMed: 18284250] For an earlier study on trapping of ynamido-lithium complexes, see: (f)Fromont C, Masson S. Tetrahedron 1999;55:5405.
15. Greenhill JV, Lue P. Prog. Med. Chem 1993;30:203. [PubMed: 7905649]
16. For a leading review on amidine derivatives serving as selective muscarinic agonists in the treatment of Alzheimer's diseases, see: Messer WS Jr, Dunbar PG. Muscarinic Agonists and the Treatment of Alzheimer's Disease 1996:131–153.153
17. Dunn, PJ. Compreh. Org. Funct. Group Transform. II. Katritzky, Alan R.; Taylor, Richard JK., editors. Vol. Vol. 5. Sandwich, UK: Amidines and N-Substituted Amidines. Pfizer Global Research and Development; 2005. p. 655-699.
18. For recent examples of amidine synthesis, see: (a)Yu RT, Rovis T. J. Am. Chem. Soc 2008;130:3262. [PubMed: 18302377] (b)Wang J, Xu F, Cai T, Shen Q. Org. Lett 2008;10:445. [PubMed: 18173276] (c)Malik H, Frederic B, Alexandre M, Jean-Jacques B. Org. Biom. Chem 2006;4:3142. (d)Katritzky AR, Cai C, Singh SK. J. Org. Chem 2006;71:3375. [PubMed: 16626116] (e)Kumagai N, Matsunaga S, Shibasaki M. Angew. Chem., Int. Ed 2004;43:478.
19. See Supporting Information. Based on NOE experiments [see Supporting Information for details], these amidines adopt an *E*-geometry with respect to the C=N bond.
20. For a leading reference on xantphos, see: Kranenburg M, van der Burgt YEM, Kamer PCJ, van Leeuwen PWNM. Organometallics 1995;14:3081.
21. For leading references on X-phos, see: (a)Huang X, Anderson KW, Zim D, Jiang L, Klapars A, Buchwald SL. J. Am. Chem. Soc 2003;125:6653. [PubMed: 12769573] (b)Barder TE, Buchwald SL. J. Am. Chem. Soc 2007;129:12003. [PubMed: 17850080]
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 °C to 80 °C in THF, the reaction was sluggish and slow. For a recent account on a related thermal transformation using ynol ethers, see: Sosa JR, Tudjarian AA, Minehan TG. Org. Lett 2008;10:5091. [PubMed: 18847213]
23. For leading reviews on Claisen rearrangements, see: (a)Hill RK. Morrison JD. Asymmetric Synthesis. 1984New YorkAcademic Press (b)Wipf P. Trost BM, Fleming I. Comprehensive Organic Synthesis 1991;Vol. 5OxfordPergamon Press:827.
24. Because of their basicity, polarity, and/or volatility, the respective allyl amine byproducts [R_2N-$CH_2CH{=}CH_2$] 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 YC, Mayr H. J. Org. Chem 2007;72:3679. [PubMed: 17411095]
26. Hartwig observed that in comparison with mono-dentate 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 MM, Incarvito CD, Hartwig JF. J. Am. Chem. Soc 2006;128:9044. [PubMed: 16834372]

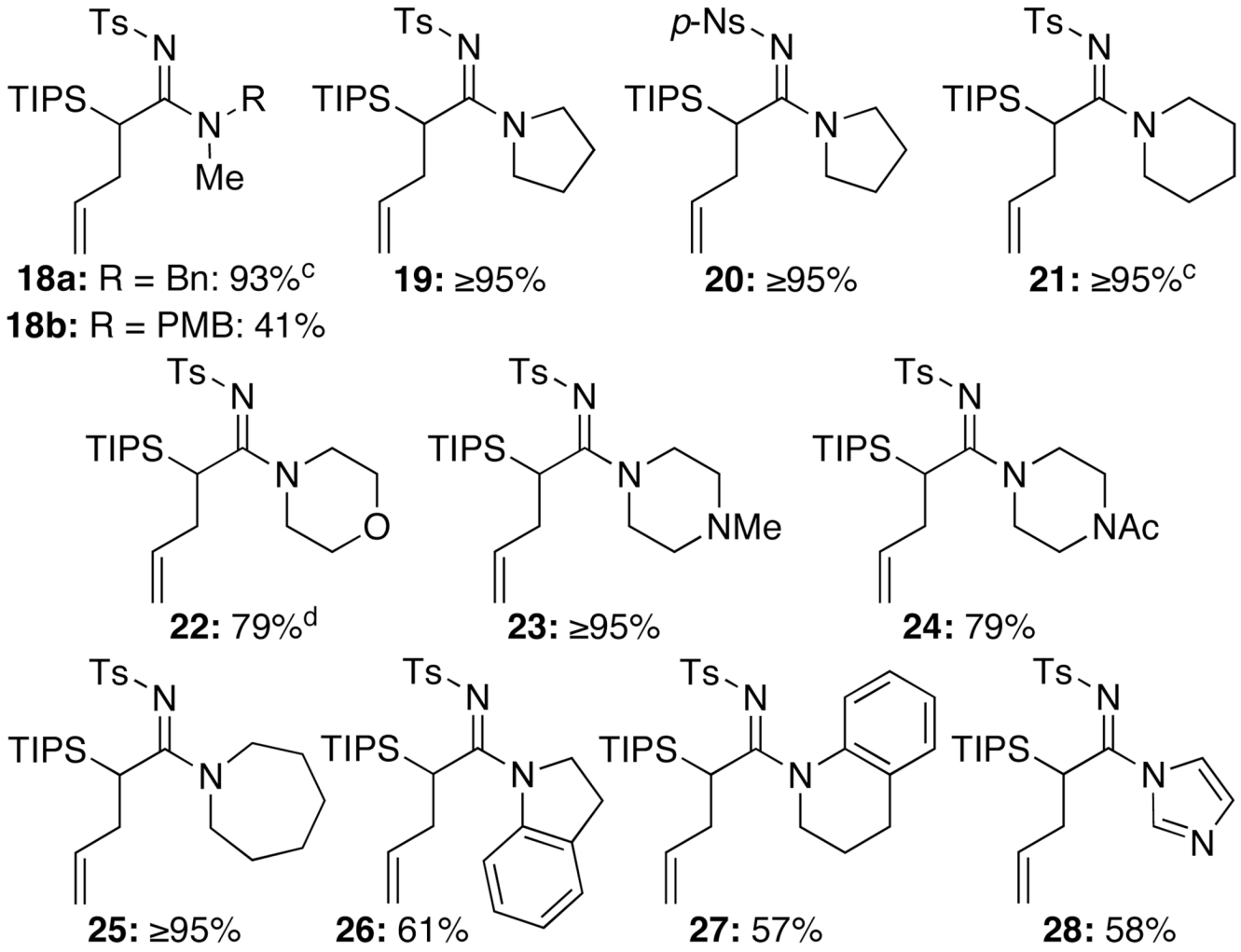
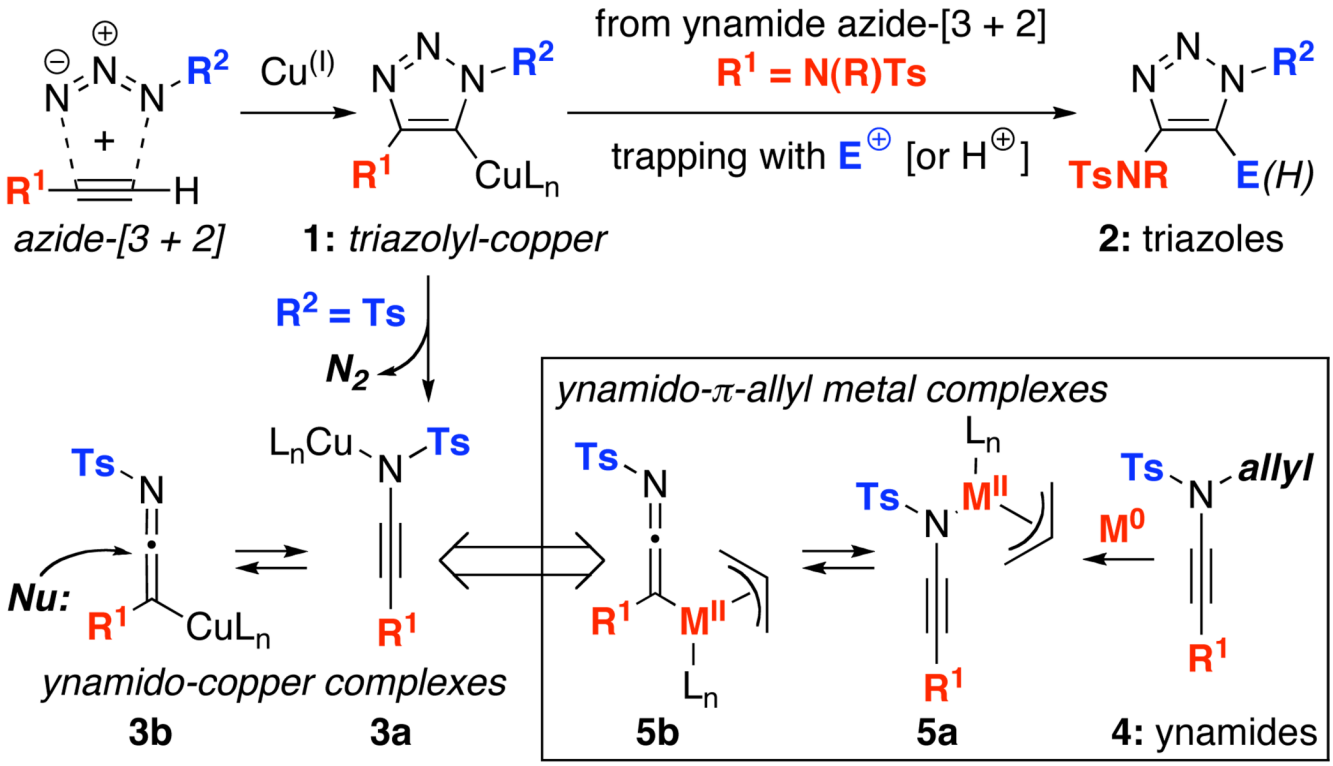


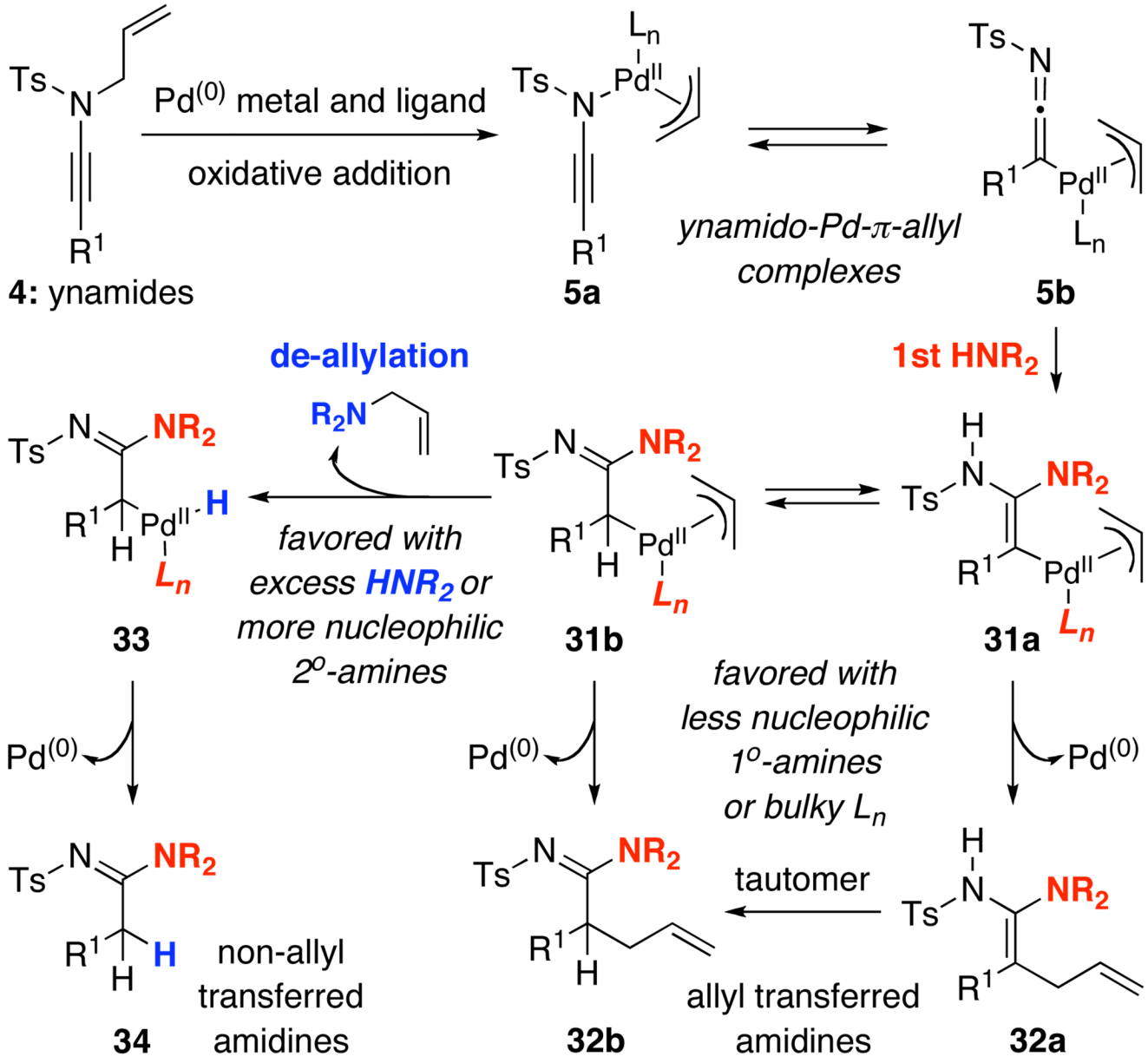
Figure 1.

Secondary Amines in the Amidine Synthesis.a,b

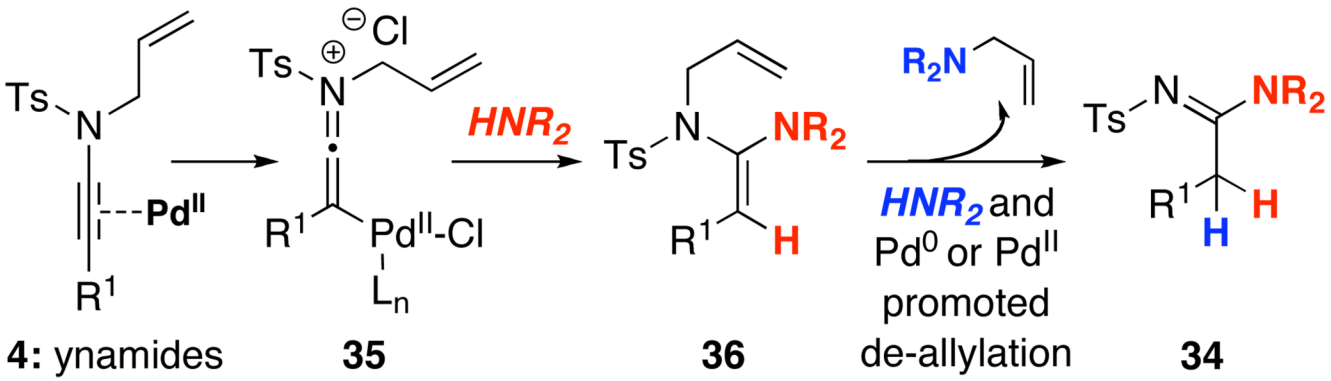
a. Reaction conditions: 5.0 mol % $Pd_2(dba)_3$, 10.0 mol % of xantphos, 1.0 equiv K_2CO_3, 3.0 equiv R_2NH, THF [*conc* = 0.05 *M*], 65 °C, 1.5–6 h. **b.** Isolated yields. **c.** 10.0 mol % $Pd_2(dba)$ **3**, 20.0 mol% of xantphos, and 5.0 equiv R_2NH were used. **d.** The only successful example in using 5.0 mol % $Pd(PPh_3)_4$.



Scheme 1.
Generating Ynamido-Metal Complexes.



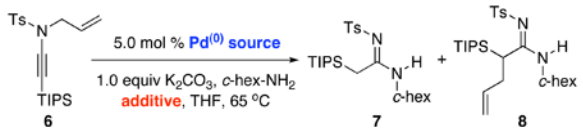
Scheme 2.
A Proposed Mechanistic Model.



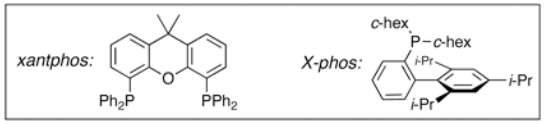
Scheme 3.
Pd(II) Versus Pd(0) Source.

Table 1

Effect of Equivalents of Amines and Pd(0) Sources.



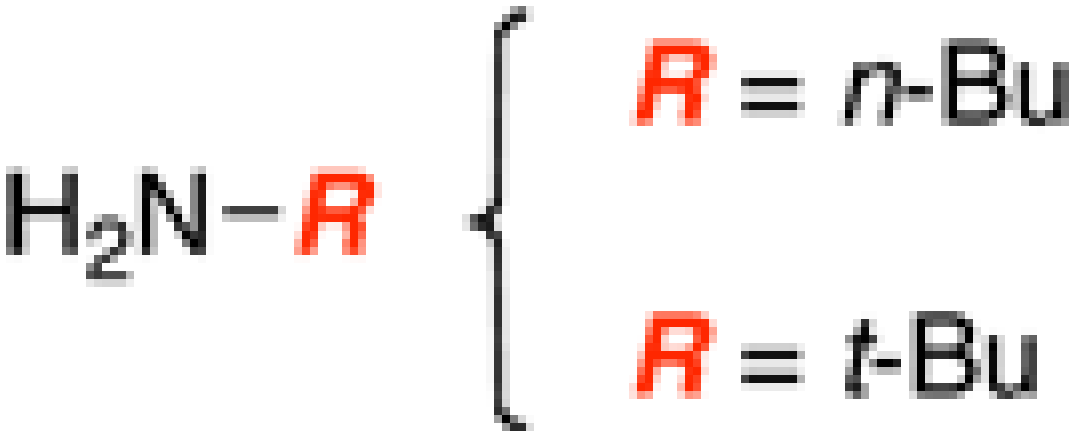
entry	Pd(0)	additive [mol %]	amine equiv	time [h]	yield [%][a]	7	8
1	$Pd(PPh_3)_2Cl_2$	--	5.0	2		92	5
2		--	3.0	2		63	24
3		--	1.0	2		44	45
4		--	1.0: syringe pump addition	2		11	73
5	$Pd(PPh_3)_4$	--	3.0	3		0	≥95
6	$Pd(dppe)Cl_2$	--	3.0	48		30	<5
7	$Pd(dppf)Cl_2$	--	3.0	24		95	0
8	$Pd_2(dba)_3$	BINAP [10.0]	3.0	24		40	59
9	Pd2(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.

Table 2

Amidine Synthesis Using Primary Amines.[a]

entry	primary amines
1	
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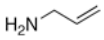
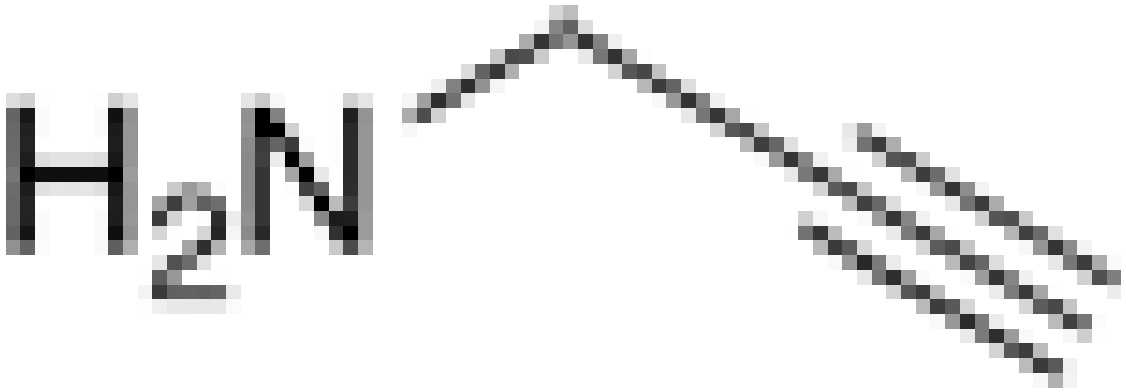
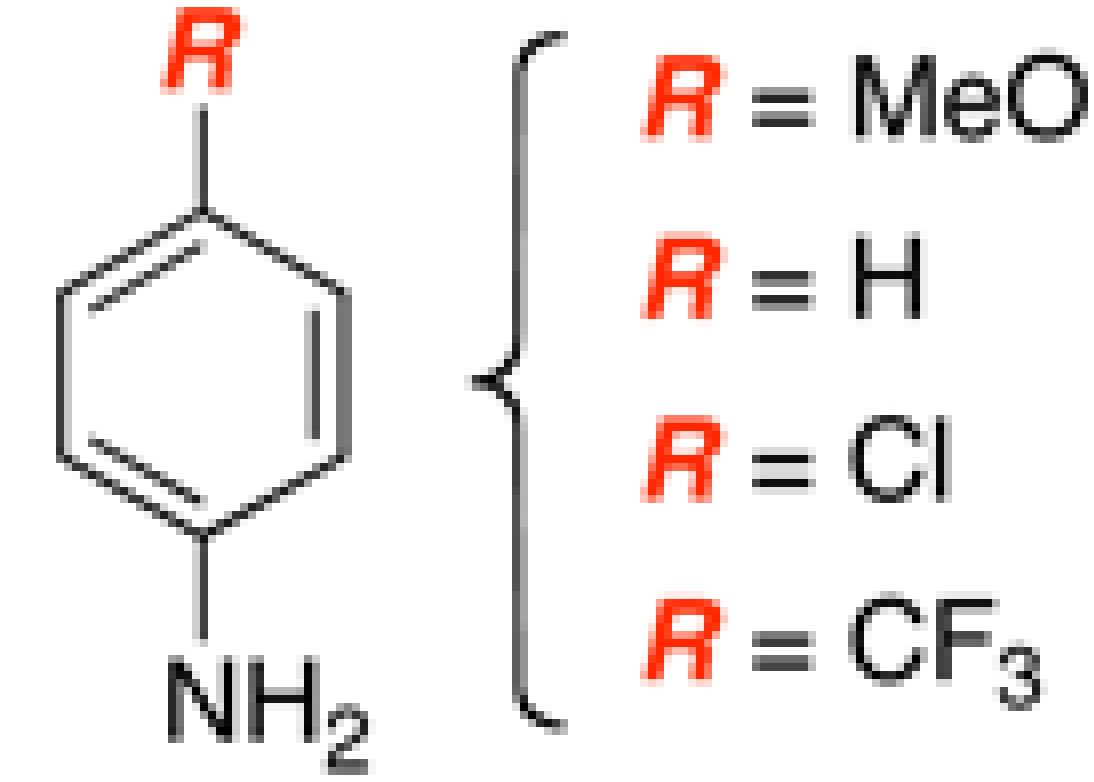
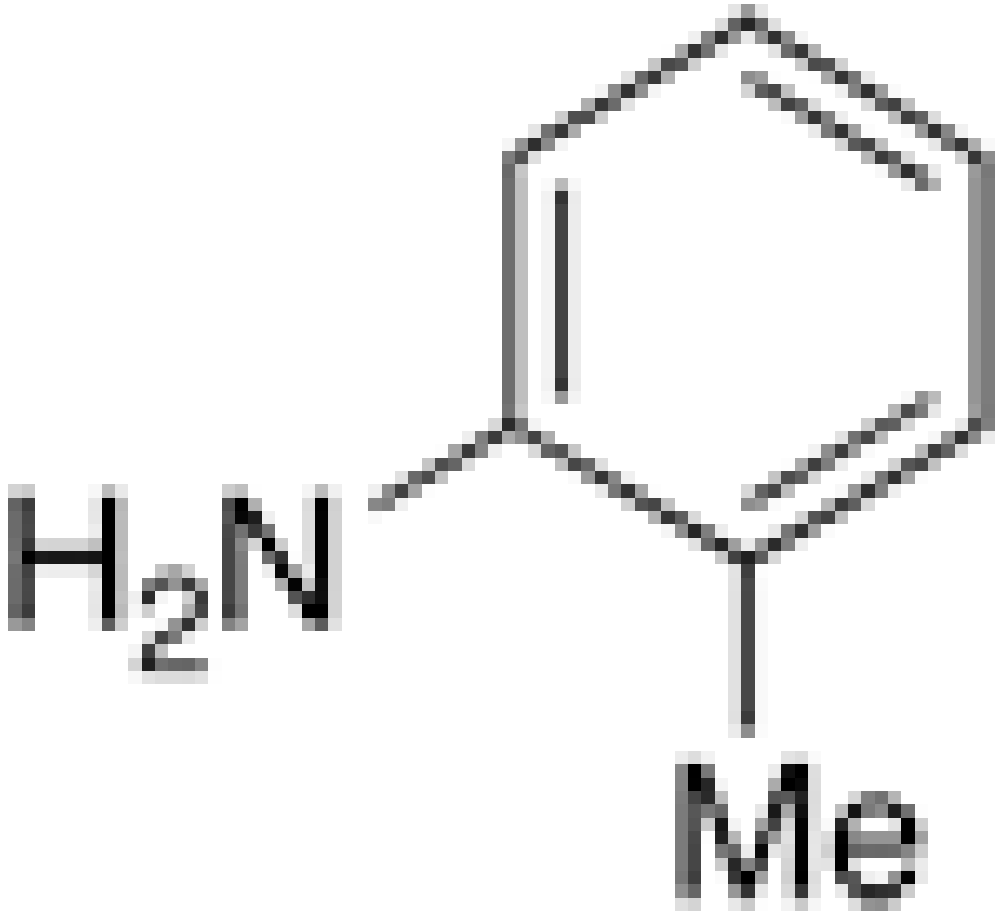
3	

entry	primary amines
4	
5	
6	
7	
8	

entry	primary amines
9	

[a] All reactions utilized ynamide **6**, 5.0 mol % $Pd(PPh_3)_4$, 1.0 equiv K_2CO_3, 3.0 equiv RNH_2, THF [*conc* = 0.05 *M*], 65 °C, 5–8 h.

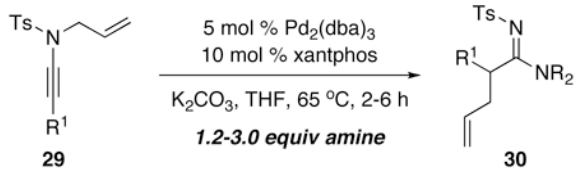
[b] Isolated yields.

[c] 1.0 equiv of amine was used.

[d] Reaction time was 24 h.

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