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A Divergent Mechanistic Course of Pd(0)-Catalyzed *Aza*-Claisen Rearrangement and *Aza*-Rautenstrauch-Type Cyclization of *N*-Allyl-Ynamides

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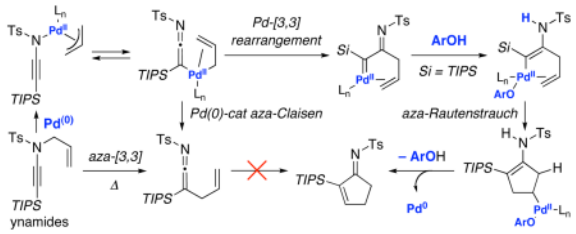
Abstract



A fascinating mechanistic study of ynamido-palladium-π-allyl complexes is described that features isolation of a unique silyl-ketenimine via *aza*-Claisen rearrangement, which can be accompanied by an unusual thermal *N-to-C* 1,3-Ts shift in the formation of tertiary nitriles, and a novel cyclopentenimine formation via a palladium catalyzed *aza*-Rautenstrauch-type cyclization pathway.

We recently reported an account on the synthesis of pharmacologically useful amidines[1–4] from ynamides[5,6] via a Pd(0)-catalyzed *N-to-C* allyl transfer.[7] As shown in Scheme 1, the formation of amidine **3** was proposed to proceed through ynamido-π-allyl complexes **2a** or **2b** after the initial oxidative addition [O.A.] of *N*-allyl-ynamides **1.** Subsequently, after the addition of an amine, the reaction pathway would diverge from **4** or **5** depending upon the concentration of the amine HNR_2 and the nature of the palladium catalyst and ligands. Excess amount of amines or more nucleophilic secondary amines[8] tend to attack the ynamido-π-allyl complexes **4** [or **5**], leading to deallylated-amidines **6,** whereas Pd(0) catalysts such as $Pd_2(dba)_3$ [instead of starting from Pd(II) species], and more bulky ligands such as X-phos[9] and/or bidentate ligands with unique bite angles such as xantphos[10,11] that presumably promote reductive elimination [R.E.] favored the formation of allyl transferred amidines **3**. Given the novelty of these ynamido-metal complexes and the potential of harvesting new reactivities, we examined this reaction in greater details mechanistically and uncovered a unique ketenimine intermediate, a rare 1,3-Ts shift, and an unusual and formally a Nazarov-type pathway leading to cyclopentenimine formation. We report here these findings.

Our initial experiments involved removing the amine nucleophile to suppress amidine formation in an attempt to isolate and/or observe key intermediates. As shown in Scheme 2, in the presence of 1 mol % of $Pd_2(dba)_3$ and 2 mol % of xantphos, heating of *N*-allyl ynamide

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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.

7 at 70 °C afforded two interesting products: Cyclopentenimine **8** and silyl-ketenimine **9** in ~ 5% and 88% yield, respectively.[12] The yield of **9** was improved with the formation of **8** completely impeded when the reaction was run at lower temperatures. While characterizations of **9** were unambiguous given its stability, the formation of amidine **10** in 95% yield via treatment of **9** with *c*-hex-NH_2 solidifies the identification of this novel intermediate.[13]

Despite the potential reactivity of *N*-sulfonyl-ketenimines, the surprising stability of ketenimine **9** is likely unique to the silyl substitution.[14,15] Under similar reaction conditions, ynamide **11** containing a Ph substituent led to a very different product, although in low yields. The product was initially assigned based on literature report[16] as cyclobutane bis-imine **13,** presumably attained through a facile dimerization or [2 + 2] cycloaddition of the less stable ketenimine **12**.

The formation of ketenimines from *N*-allyl ynamides invokes an *aza*-Claisen rearrangement, [17] specifically 3-az-Claisen, although those involving a C1-C2 acetylenic motif are very rare if not unprecedented.[17–19] However, the involvement of the palladium metal in the formation of **9** is distinctly clear, as a non-palladium involved *aza*-Claisen pathway required higher temperatures and longer reaction times [see **14→ 15→ 16** in Scheme 3]. When the *aza*-Claisen rearrangement was carried out at 70 °C, the reaction was sluggish as evident in yield of the trapping of the ketenimine **15** with pyrrolidine, and the usage of Ts or *p*-Ns group was not critical to the reactivity.

When heating ynamide **17** at 110 °C led to again the dimer **19** and not the intended intramolecular cycloadduct **20** [Scheme 3], we sensed a possible mis-assignment because an intermolecular process had just dominated over an intramolecular one. We attained X-ray structure of the *aza*-Claisen product from **11** and were surprised that it was not the dimer **12** but a tertiary nitrile **22.** *Aza*-Claisen rearrangements of ynamides in fact can occur in tandem with a rare *N-to-C* 1,3-Ts shift at 110 °C,[20] leading to nitriles with a quaternary carbon formation.

It is noteworthy that these results further accentuate the stability of silyl-ketenimine **9.** While thermal rearrangement of **7** took place at 110 °C, 1,3-Ts shift to give TIPS-less nitrile **23** only proceeded after desilylation [**9→9′**], thereby suggesting sterics could also be at play. While this unusual 1,3-Ts shift in the formation of tertiary nitriles holds significant merit in synthesis, [21] and that our finding cautions the assignment of possible homo-dimeric products from ketenimines, details of this shift will be examined in another study.

Having established the significance of the palladium metal in this *aza*-Claisen rearrangement, we believe ynamido-π-allyl complexes **2** derived from the oxidative addition of ynamide **7** should be responsible for the formation of ketenimines [Scheme 4]. The question is whether it proceeds through a reductive elimination process via an intramolecular pathway, or a Tsuji-Trost pathway. To addressing this question, we pursued two experiments.

The first experiment involved the use of ynamide **25** containing a crotyl group as shown in Scheme 4. While the reaction temperature had to be higher, new ketenimine **27** was isolated in 90% yield with a regiochemical ratio of 5:1. While this outcome concisely suggests that the crotyl group is scrambled through the oxidative addition, the resulting regiochemical ratio reflects that both pathways are possible with the major isomer **27a** being derived from either reductive elimination of **2a** [or **2a′**: a ketenimine palladium complex], or a favored addition of ynamido anion **[N^{o-}]** to **26** at the less hindered site [blue arrow].

The second study is a revealing crossover experiment as shown in Scheme 5. With a 1:1 mixture of ynamides **25** and **28** containing a crotyl and allyl group, respectively, we were able to concisely assign 4 sets of ketenimines: **27a/b, 9, 29a/b,** and **30.** While the regiochemical ratio

of **27a/b** or **29a/b** is the same at 5:1, the ratios of crossover of 10:1 even when the reaction was run at 0.10 *M* suggest that the ketenimine formation is likely an intramolecular process, and that these are likely tightly bound ynamido-π-allyl complexes shown as **2a** and **2b** [or **2a′**/**2b′**].

While literature precedents[15] suggest that ketenimines represent highly reactive entities for developing useful synthetic methods, the observation of trace amounts of cyclopentenimine **8** and its mechanistic course captured our attention. Although it took much effort to optimize the formation of **8**,[22] it was found that conditions which relatively disfavored reductive elimination [5 mol % of $Pd(PPh_3)_4$] as well as the use of a phenolic substrate as an additive led to cyclopentenimine **8** in 70% yield. Preparation of **31** led to an X-ray structure, allowing an unambiguous assignment.

The difference in conditions implied that cyclopentenimine **8** is likely derived from a different mechanistic course for which silyl-ketenimine **9** is not an intermediate.[23] This assertion is consistent with the fact that treatment of **9** with either 5 mol % of $Pd(PPh_3)_4$, or by using thermal conditions, did not provide any identifiable amount of **8,** thereby ruling out the possibility of a formal imino-Nazarov type cyclization[24,25] involving **32a–c** [Scheme 6].

Instead, a likely mechanistic course would involve an *aza*-variant of a Rautenstrauch-type cyclization [or also formally an *aza*-Nazarov-type cyclization][26,27] as shown in Scheme 7. While the Pd-complex **2b** could readily reductive eliminate to give ketenimine **9,** under conditions in which the reductive elimination is slowed, a Pd-[3,3] sigmatropic rearrangement could occur to give α-imino palladium carbenoid **33a.** While a number of possibilities could take place from thereon, one possibility that is consistent with the use of PhOH would entail the formation of enamido-Pd-Complex **33c** could undergo migratory insertion [M.I.] followed by β-elimination to afford cyclopentenimine **8** after tautomerization of cyclopentadienamide **33e.** An alternative pathway would proceed through dienyl palladium carbenoid **34a** derived from tautomerization of **33a**.

We have uncovered here a fascinating divergent mechanistic pathway consisting of a Pd(0)-catalyzed *aza*-Claisen rearrangement of *N*-allyl ynamides, which can also be accompanied with an *N-to-C* 1,3-Ts shift through the ketenimine intermediate, and an *aza*-Rautenstrauch cyclization. These studies provide insight into the nature of ynamido-π-allyl complexes as well as new reactivities with synthetic potential. Efforts are underway in pursuing synthetic methods involving ketenimines and the *N-to-C* 1,3-Ts shift as well as applications using cyclopentenimines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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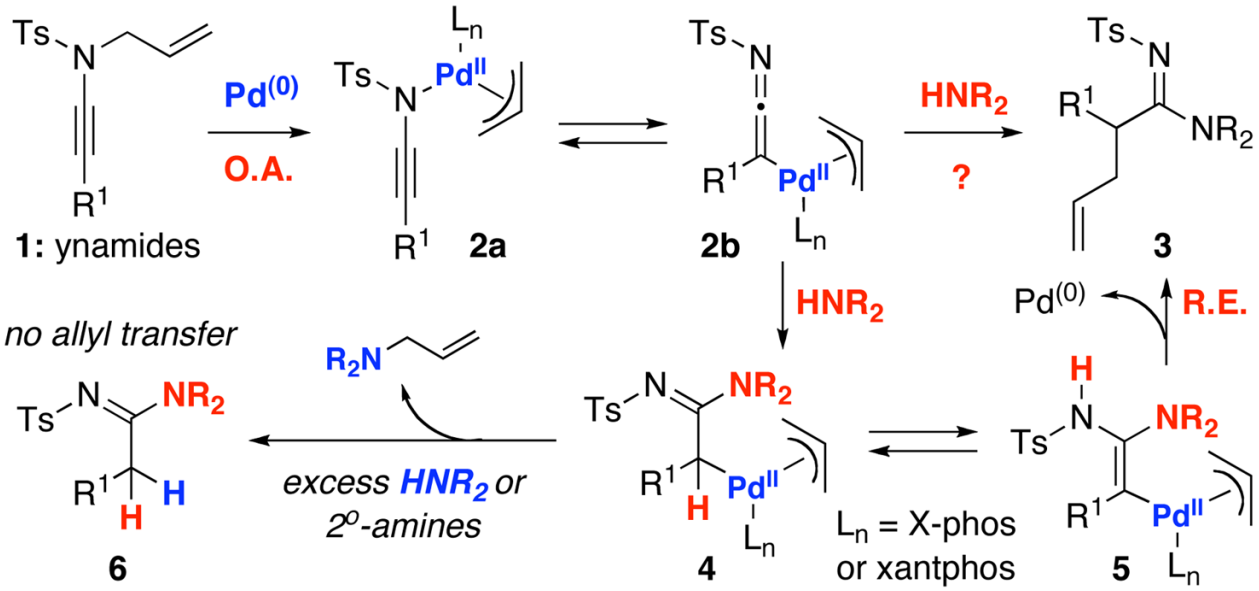
References

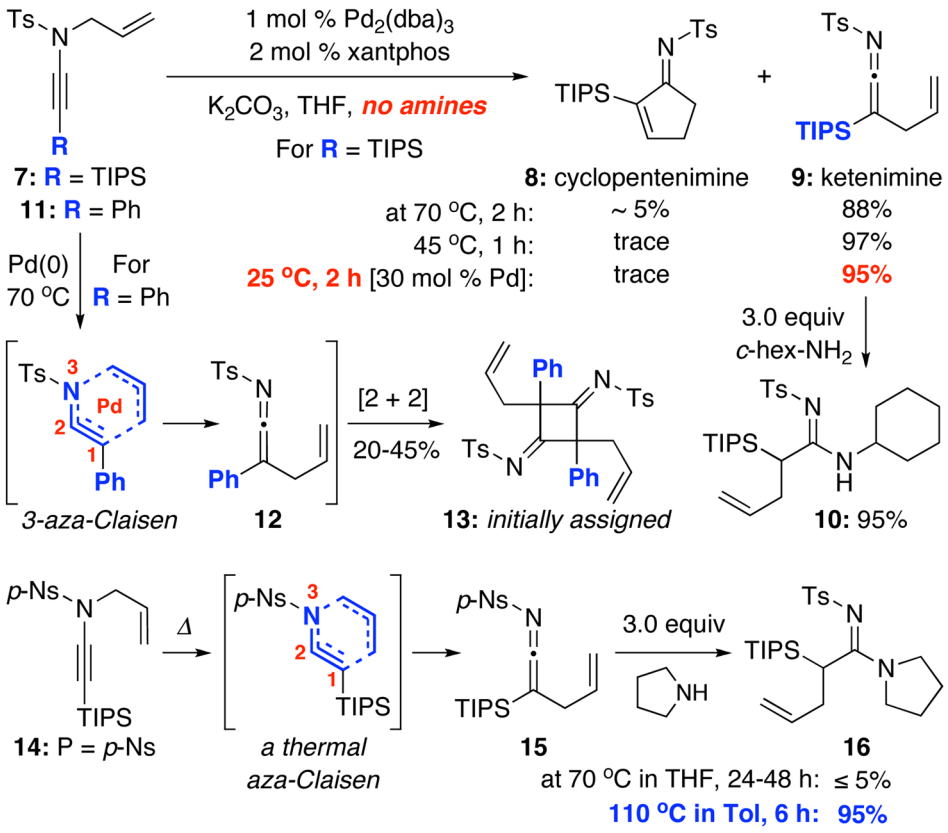
1. Greenhill JV, Lue P. Prog Med Chem 1993;30:203. [PubMed: 7905649]
2. For a leading review on amidine derivatives serving as selective muscarinic agonists in the treatment of Alzheimer’s diseases, see: Messer WS Jr, Dunbar PG. Muscarinic Agonists and the Treatment of Alzheimer’s Disease 1996:131–153.

3. Dunn, PJ. Compreh Org Funct Group Transform II, Amidines and N-Substituted Amidines. Katritzky Alan, R.; Taylor Richard, JK., editors. Vol. 5. Pfizer Global Research and Development; Sandwich, UK: 2005. p. 655-699.
4. For recent examples of amidine synthesis, see: (a) Shang Y, He X, Hu J, Wu J, Zhang M, Yu S, Zhang Q. Adv Synth Catal 2009;351:2709. (b) She J, Jiang Z, Wang Y. Synlett 2009;12:2023. (c) Yu RT, Rovis T. J Am Chem Soc 2008;130:3262. [PubMed: 18302377]
5. For reviews, see: (a) Katritzky AR, Jiang R, Singh SK. Heterocycles 2004;63:1455. (b) Mulder JA, Kurtz KCM, Hsung RP. Synlett 2003:1379. (c) Zificsak CA, Mulder JA, Hsung RP, Rameshkumar C, Wei LL. Tetrahedron 2001;57:7575.
6. For efforts in 2009 alone, see: (a) Yao B, Liang Z, Niu T, Zhang Y. J Org Chem 2009;74:4630. [PubMed: 19453151] (b) Coste A, Karthikeyan G, Couty F, Evano G. Angew Chem Int Ed 2009;48:4381. (c) Coste A, Couty F, Evano G. Org Lett 2009;11:4454. [PubMed: 19775187] (d) Laroche C, Kerwin MS. Tetrahedron Lett 2009;50:5194. (e) Kramer S, Dooleweerdt K, Lindhardt AT, Rottländer M, Skrydstrup T. Org Lett 2009;11:4208. [PubMed: 19697920] (f) Das JP, Chechik H, Marek I. Nature Chem 2009;1:128. (g) Koester DC, Werz DB. Angew Chem Int Ed 2009;48:7971. (h) Gourdet B, Lam HW. J Am Chem Soc 2009;131:3802. [PubMed: 19253939] (i) Gourdet B, Rudkin ME, Watts CA, Lam HW. J Org Chem 2009;74:7849. [PubMed: 19754108] (j) Sato A, Yorimitsu H, Oshima K. Synlett 2009:28. (k) Cockburn N, Karimi E, Tam W. J Org Chem 2009;74:5762. [PubMed: 19572573] (l) Riddell N, Villeneuve K, Tam W. J Org Chem 2009;74:5762. [PubMed: 19572573] (m) Shindoh N, Takemoto Y, Takasu K. Chem Eur J 2009;15:7026. (n) Buzas A, Istrate F, Le Goff XF, Odabachiam Y, Gagosz F. J Organomet Chem 2009;694:515. (o) Garcia P, Moulin S, Miclo Y, Leboeuf D, Gandon V, Aubert C, Malacria M. Chem Eur J 2009;15:2129. (p) Friedman RK, Rovis T. J Am Chem Soc 2009;131:10775. [PubMed: 19569692] (q) Buzas AK, Istrate FM, Gagosz F. Tetrahedron 2009;65:1889. (r) Dooleweerdt K, Ruhland T, Skrydstrup T. Org Lett 2009;11:221. [PubMed: 19035838] (s) Couty S, Meyer C, Cossy J. Tetrahedron 2009;65:1809. (t) Alayrac C, Schollmeyer D, Witulski B. Chem Commun 2009:1464.For our own recent efforts in 2009, see: (u) Li H, Hsung RP. Org Lett 2009;11:4462. [PubMed: 19739617] (v) Oppenheimer J, Johnson WL, Figueroa R, Hayashi R, Hsung RP. Tetrahedron 2009;65:5001. [PubMed: 20161177]
7. Zhang Y, DeKorver KA, Lohse AG, Zhang YS, Huang J, Hsung RP. Org Lett 2009;11:899. [PubMed: 19199763]
8. For a leading reference on relative nucleophilicity of amines, see: Brotzel F, Chu YC, Mayr H. J Org Chem 2007;72:3679. [PubMed: 17411095]
9. 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]
10. For a leading reference on xantphos, see: Kranenburg M, van der Burgt YEM, Kamer PCJ, van Leeuwen PWNM. Organometallics 1995;14:3081.
11. For a rationale on the usage of bidentate xantphos in promoting reductive elimination with its unique bite angle, see: Fujita KI, Yamashita M, Puschmann F, Alvarez-Falcon MM, Incarvito CD, Hartwig JF. J Am Chem Soc 2006;128:9044. [PubMed: 16834372]
12. See Supporting Information.
13. Although attempts were made, these reactions were too fast to allow NMR studies to be revealing of possible ynamido-π-allyl complexes even at 25 °C. Only the starting ynamide **7** and silyl-ketenimine **9** [and amidine **10** if the reaction was run in the presence of an amine] were clearly in display spectroscopically.
14. For documentation of silicon-stabilization of ketenes and ketenimines, see: Brady WT, Saidi K. J Org Chem 1990;55:4215.
15. For reviews on chemistry of ketenimines, see: (a) Krow GR. Angew Chem, Int Ed Engl 1971;10:435. (b) Gambaryan NP. Usp Khim 1976;45:1251. (c) Dondoni A. Heterocycles 1980;14:1547.(d) Barker, MW.; McHenry, WE. The Chemistry of Ketenes, Allenes and Related Compounds. Patai, S., editor. Wiley-Interscience; Chichester, UK: 1980. p. 701-720. (e) Alajarin M, Vidal A, Tovar F. Targets Heterocycl Syst 2000;4:293.
16. Whiting M, Fokin VV. Angew Chem Int Ed 2006;45:3157.

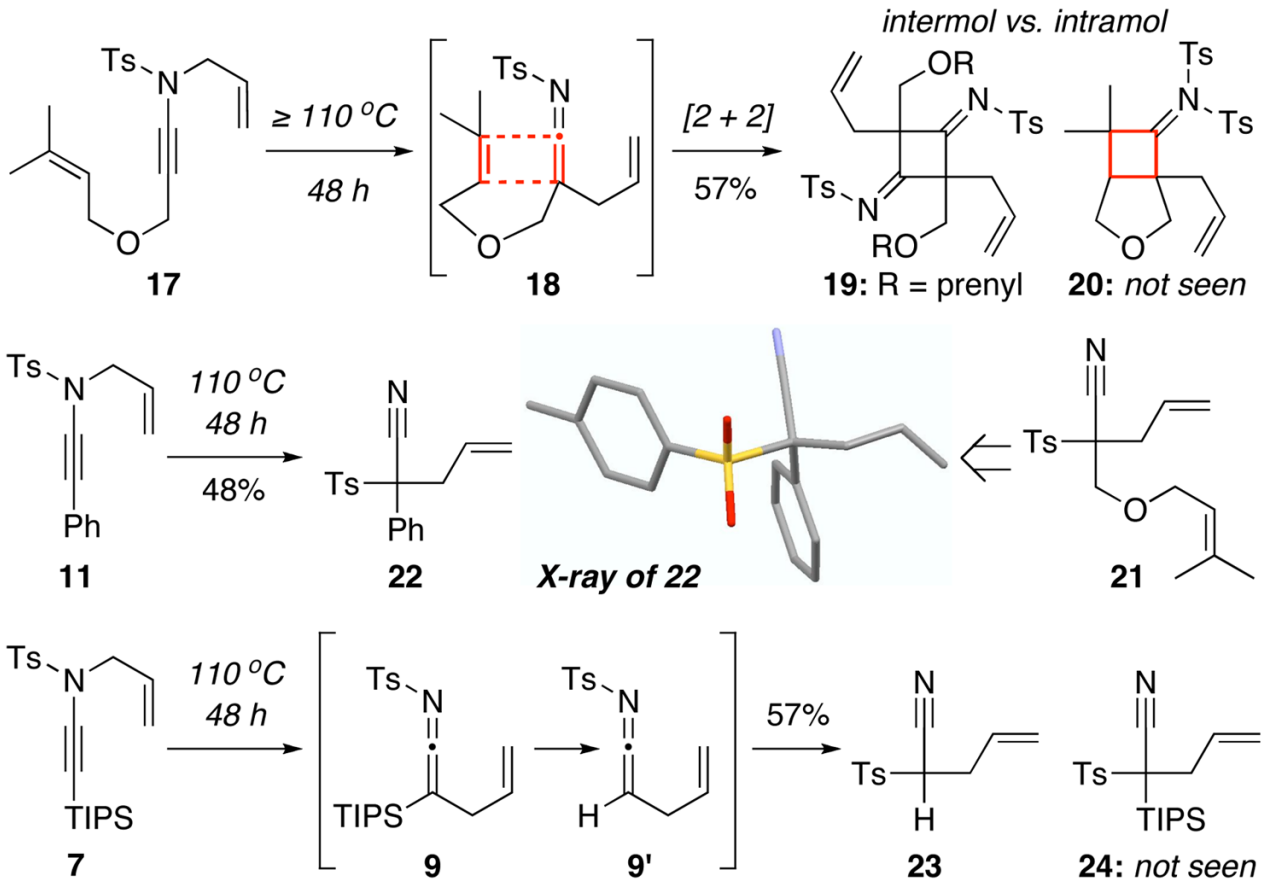
17. For leading reviews on aza-Claisen rearrangements, see: (a) Majumdar KC, Bhayyacharyya T, Chattopadhyay B, Nandi RK. Synthesis 2009:2117. (b) Nubbemeyer U. Top Curr Chem 2005;244:149.
18. For general reviews on Claisen rearrangements, see: (a) Castro AMM. Chem Rev 2004;104:2939. [PubMed: 15186185] (b) Ito H, Taguchi T. Chem Soc Rev 1999;28:43. (c) Enders D, Knopp M, Schiffers R. Tetrahedron Asym 1996;7:1847.(d) Wipf, P. Comprehensive Organic Synthesis. Trost, BM.; Fleming, I., editors. Vol. 5. Pergamon Press; Oxford: 1991. p. 827
19. For some examples of aza-Claisen rearrangements, see: (a) Majumdar KC, Samanta S, Chattopadhyay B, Nandi RK. Synthesis 2010:863. (b) Cheung LLW, Yudin AK. Org Lett 2009;11:1281. [PubMed: 19239262] (c) Cant AA, Bertrand GHV, Henderson JL, Roberts L, Greaney MF. Angew Chem Int Ed 2009;48:5199. (d) Yasui H, Yorimitsu H, Oshima K. Chem Lett 2008;37:40. (e) Walters MA. J Am Chem Soc 1994;116:11618. (f) Jolidon S, Hansen HJ. Helv Chim Acta 1977;60:978.For some earlier work of palladium promoted aza-Claisen-type rearrangements using N-allylthioamide, allylimidates, or allyl carbamates, see: (g) Overman LE. Acc Chem Res 1980;13:218. (h) Overman LE. Angew Chem, Int Ed Engl 1984;23:579. (i) Tamaru Y, Kagotani M, Yoshida Z. J Org Chem 1985;50:764. (j) Overman LE, Donde Y. J Am Chem Soc 1999;121:2933. (k) Lei A, Lu X. Org Lett 2000;2:2357. [PubMed: 10930283]
20. For a related 1,3-shift, see: Bendikov, M.; Duong, HM.; Bolanos, E.; Wudl, F. Org Lett. Vol. 7. 2005. p. 783It is noteworthy that our work distinctly indicates that the *N-to-C* 1,3-Ts shift took place after the *aza*-Claisen rearrangement. Monitoring the thermal *aza*-Claisen rearrangement of **11** using NMR did not reveal any ketenimine **12,** thereby suggesting 1,3-Ts shift was very fast at 110 °C.
21. For leading references, see: (a) Fleming FF, Liu W. Eur J Org Chem 2009:699. (b) Fleming FF, Wei G, Steward OW. J Org Chem 2008;73:3674. [PubMed: 18416532] (c) Mermerian AH, Fu GC. Angew Chem Int Ed 2005;44:949.
22. For some of the conditions explored, see: *Pd(0) source:* $Pd_2(dba)_3$, $Pd(PPh_3)_4$; *ligand:* xantphos, X-Phos, $(C_6F_5)_3P$; *solvent:* THF, Dioxane; *concn* = 0.04–0.10 *M; Lewis acid:* $Zn(OTf)_2$, $Cu(OTf)_2$,$Sc(OTf)_3$, $Ln(OTf)_3$; *base:* K_2CO_3; *additive:* t-BuOH, PhOH, 4-$NO_2C_6H_4OH$, 2,6-dimethylphenol, 2,3-dimethylphenol.
23. Sosa JR, Tudjarian AA, Minehan TG. Org Lett 2008;10:5091. [PubMed: 18847213]
24. For reviews, see: (a) Habermas, KL.; Denmark, SE.; Jones, TK. Organic Reactions. Paquette, LA., editor. Vol. 45. John Wiley & Sons; New York: 1994. p. 1-158.(b) Denmark, SE. Comprehensive Organic Synthesis. Trost, BM.; Fleming, I., editors. Vol. 5. Pergamon; Oxford, U.K: 1991. p. 751-784. (c) Frontier A, Collison C. Tetrahedron 2005;61:7577. (d) Tius MA. Eur J Org Chem 2005:2193. (e) Pellissier H. Tetrahedron 2005;61:6479. (f) Tius MA. Acc Chem Res 2003;36:284. [PubMed: 12693926] (g) Harmata M. Chemtracts 2004;17:416.
25. For examples of imino-Nazarov cyclizations, see: (a) Tius MA, Chu CC, Nieves-Colberg R. Tetrahedron Lett 2001;42:2419. (b) Kim SH, Cha JK. Synthesis 2000:2113. (d) Bow WF, Basak AK, Jolit A, Vicic DA, Tius MA. Org Lett 2010;12:440. [PubMed: 20030316]
26. Rautenstrauch V. J Org Chem 1984;49:950.
27. For a leading reference on Rautenstrauch rearrangement, see: Shi X, Gorin DJ, Toste FD. J Am Chem Soc 2005;127:5802. [PubMed: 15839674]



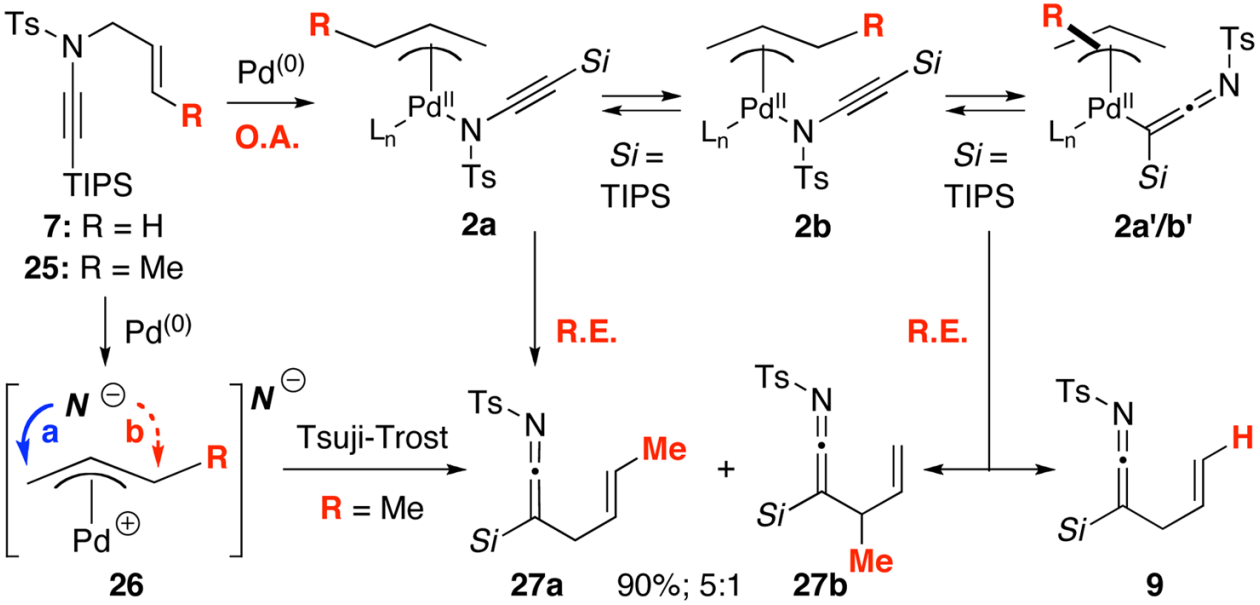
Scheme 1.
Ynamido-Pd-π-Allyl Complexes.



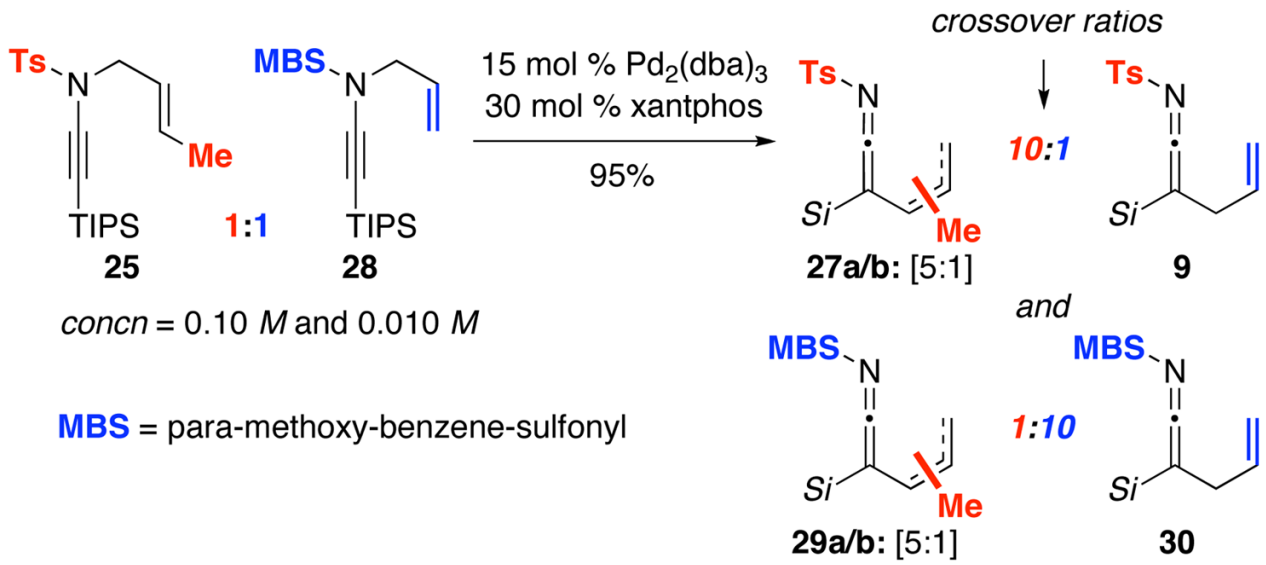
Scheme 2.
Isolation of a Stable Silyl-Ketenimine.



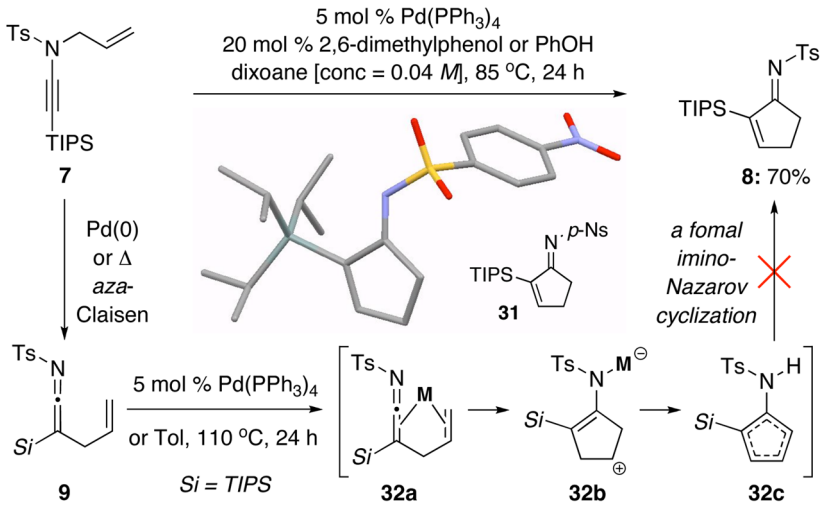
Scheme 3.
An Unusual *N-to-C* 1,3-Ts Shift.



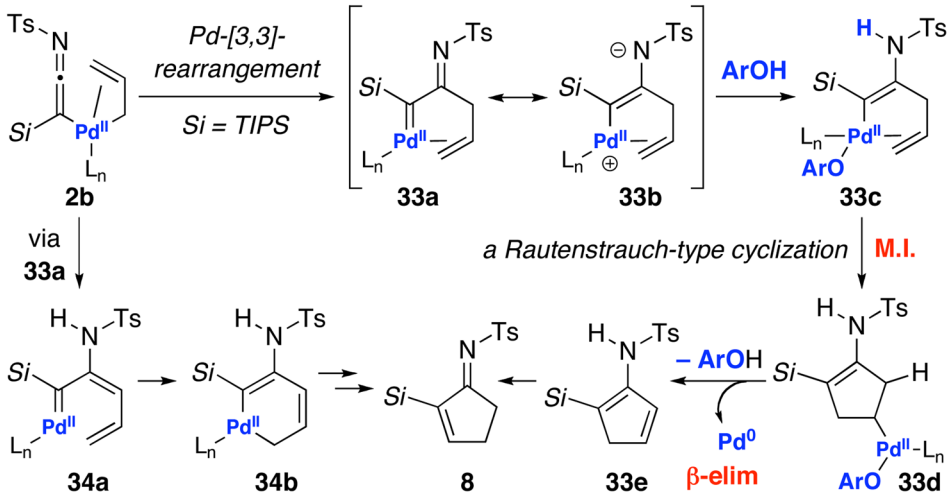
Scheme 4.
A Pd-Model for the Ketenimine Formation.



Scheme 5.
A Crossover Experiment.



Scheme 6.
An Effective Cyclopentenimine Formation.



Scheme 7.
An *Aza*-Rautenstrauch-Type Cyclization Pathway.