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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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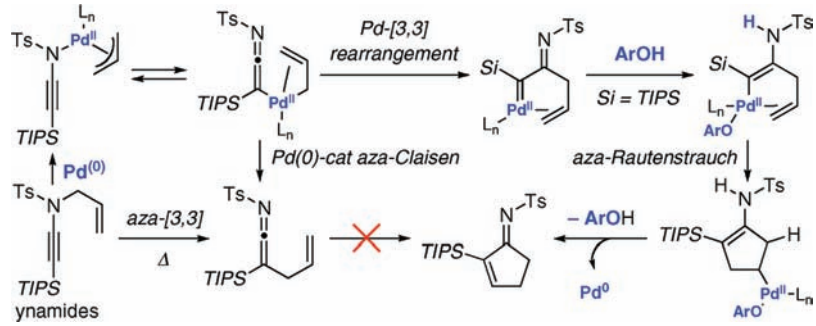
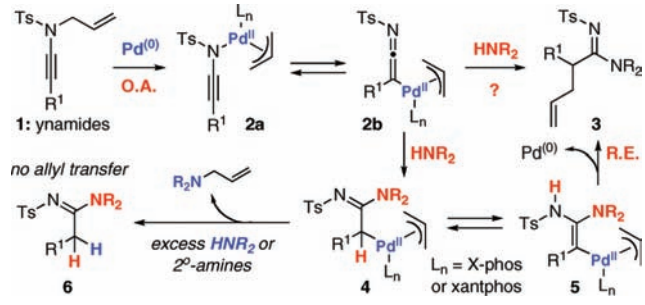
ABSTRACT



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*-allylynamides **1**. Subsequently, after the addition of an amine, the reaction pathway

Scheme 1. Ynamido−Pd−π-Allyl Complexes



(1) Greenhill, J. V.; Lue, P. *Prog. Med. Chem.* **1993**, *30*, 203.
(2) For a leading review on amidine derivatives serving as selective muscarinic agonists in the treatment of Alzheimer's diseases, see: Messer, W. S., Jr.; Dunbar, P. G. *Muscarinic Agonists Treat. Alzheimer's Dis.* **1996**, 131–153.
(3) Dunn, P. J. In *Comprehensive Organic Functional Group Transformations II, Amidines and N-Substituted Amidines*; Katritzky, A. R., Taylor, R. J. K., Eds.; Pfizer Global Research and Development: Sandwich, U.K., 2005; Vol. 5, pp 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, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 3262.
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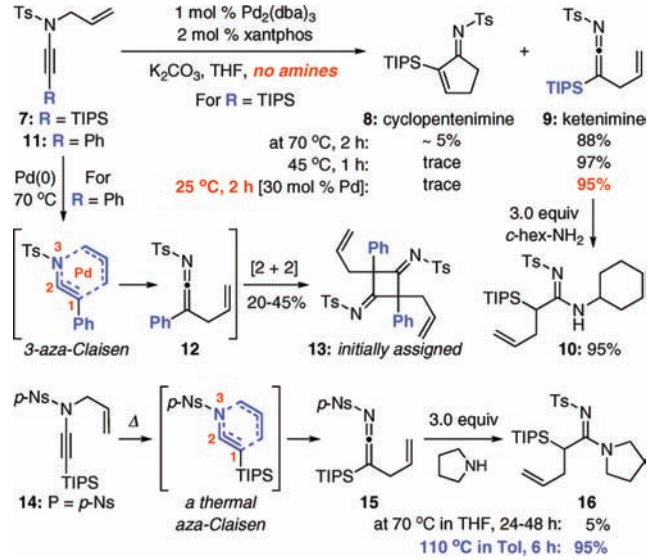
would diverge from **4** or **5** depending upon the concentration of the amine HNR_2 and the nature of the palladium catalyst and ligands. Excess amounts of amines or more nucleophilic secondary amines[8] tend to attack the ynamido−π-allyl complexes **4** (or **5**), leading to deallylated amidines **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 detail 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*-allylynamide **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

Scheme 2. Isolation of a Stable Silyl Ketenimine



via treatment of **9** with *c*-hex-NH_2 solidifies the identification of this novel intermediate.[13]

Despite the potential reactivity of *N*-sulfonylketenimines, 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 on the basis of a 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-aza-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

(6) For efforts in 2009 alone, see: (a) Yao, B.; Liang, Z.; Niu, T.; Zhang, Y. *J. Org. Chem.* **2009**, *74*, 4630. (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. (d) Laroche, C.; Kerwin, M. S. *Tetrahedron Lett.* **2009**, *50*, 5194. (e) Kramer, S.; Dooleweerdt, K.; Lindhardt, A. T.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4208. (f) Das, J. P.; Chechik, H.; Marek, I. *Nature Chem.* **2009**, *1*, 128. (g) Koester, D. C.; Werz, D. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 7971. (h) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802. (i) Gourdet, B.; Rudkin, M. E.; Watts, C. A.; Lam, H. W. *J. Org. Chem.* **2009**, *74*, 7849. (j) Sato, A.; Yorimitsu, H.; Oshima, K. *Synlett* **2009**, 28. (k) Cockburn, N.; Karimi, E.; Tam, W. *J. Org. Chem.* **2009**, *74*, 5762. (l) Riddell, N.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2009**, *74*, 5762. (m) Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem.−Eur. J.* **2009**, *15*, 7026. (n) Buzas, A.; Istrate, F.; Le Goff, X. F.; 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, R. K.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10775. (q) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Tetrahedron* **2009**, *65*, 1889. (r) Dooleweerdt, K.; Ruhland, T.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 221. (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, R. P. *Org. Lett.* **2009**, *11*, 4462. (v) Oppenheimer, J.; Johnson, W. L.; Figueroa, R.; Hayashi, R.; Hsung, R. P. *Tetrahedron* **2009**, *65*, 5001.

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(11) For a rationale on the usage of bidentate xantphos in promoting reductive elimination with its unique bite angle, 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.

(12) See the 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 on display spectroscopically.

(14) For documentation of silicon stabilization of ketenes and ketenimines, see: Brady, W. T.; Saidi, K. *J. Org. Chem.* **1990**, *55*, 4215.

(15) For reviews on chemistry of ketenimines, see: (a) Krow, G. R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 435. (b) Gambaryan, N. P. *Usp. Khim.* **1976**, *45*, 1251. (c) Dondoni, A. *Heterocycles* **1980**, *14*, 1547. (d) Barker, M. W.; McHenry, W. E. In *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley-Interscience: Chichester, UK, 1980; Part 2, pp 701−720. (e) Alajarin, M.; Vidal, A.; Tovar, F. *Targets Heterocycl. Syst.* **2000**, *4*, 293.

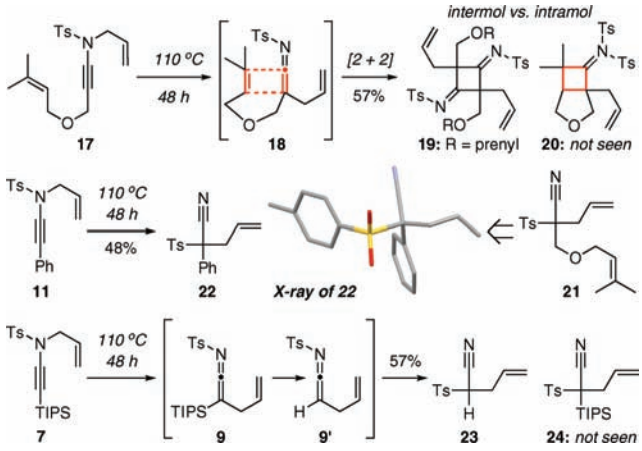
(16) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157.

(17) For leading reviews on aza-Claisen rearrangements, see: (a) Majumdar, K. C.; Bhayyacharyya, T.; Chattopadhyay, B.; Nandi, R. K. *Synthesis* **2009**, 2117. (b) Nubbemeyer, U. *Top. Curr. Chem.* **2005**, *244*, 149.

(18) For general reviews on Claisen rearrangements, see: (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43. (c) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847. (d) Wipf, P. In *Comprehensive Organic Synthesis*; Vol. 5, Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 827.

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 the 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.

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



When heating ynamide **17** at 110 °C led again to 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 the X-ray structure of the aza-Claisen product from **11** and were surprised that it was not the dimer **13** 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.

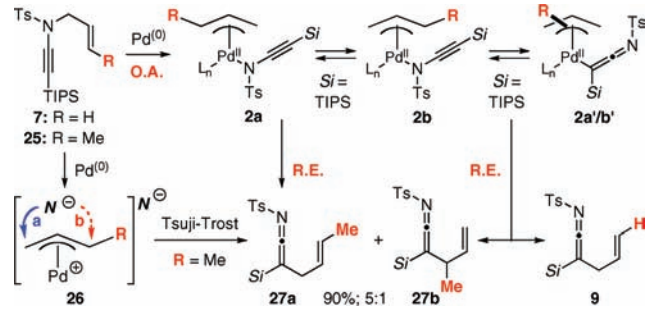
It is noteworthy that these results further accentuate the stability of silyl ketenimine **9**. While thermal rearrangement of **7** took place at 110 °C, 1,3-Ts shift to give TIPS-less nitrile **23** only proceeded after desilylation (**9** → **9′**), thereby suggesting sterics could also be at play.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

(19) For some examples of aza-Claisen rearrangements, see: (a) Majumdar, K. C.; Samanta, S.; Chattopadhyay, B.; Nandi, R. K. *Synthesis* **2010**, 863. (b) Cheung, L. L. W.; Yudin, A. K. *Org. Lett.* **2009**, *11*, 1281. (c) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199. (d) Yasui, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2008**, *37*, 40. (e) Walters, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11618. (f) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 978. For some previous work on palladium-promoted aza-Claisen-type rearrangements using *N*-allylthioamide, allylimidates, or allyl carbamates, see: (g) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (h) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579. (i) Tamaru, Y.; Kagotani, M.; Yoshida, Z. *J. Org. Chem.* **1985**, *50*, 764. (j) Overman, L. E.; Donde, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2933. (k) Lei, A.; Lu, X. *Org. Lett.* **2000**, *2*, 2357.

(20) For a related 1,3-shift, see: Bendikov, M.; Duong, H. M.; Bolanos, E.; Wudl, F. *Org. Lett.* **2005**, *7*, 783. It 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 the 1,3-Ts shift was very fast at 110 °C.

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 address this question, we pursued two experiments.

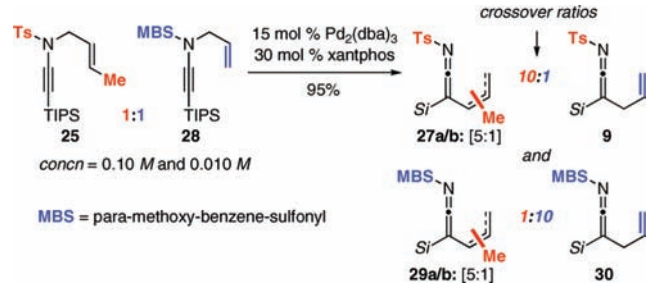
Scheme 4. Pd Model for the Ketenimine Formation



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**$^-$) 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 four sets of ketenimines: **27a/b**, **9**,

Scheme 5. Crossover Experiment



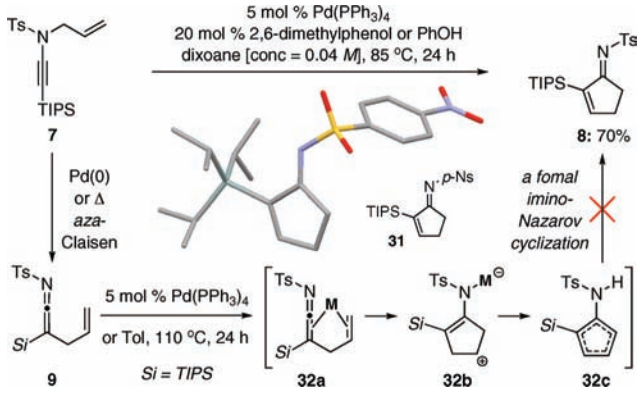
(21) For leading references, see: (a) Fleming, F. F.; Liu, W. *Eur. J. Org. Chem.* **2009**, 699. (b) Fleming, F. F.; Wei, G.; Steward, O. W. *J. Org. Chem.* **2008**, *73*, 3674. (c) Mermerian, A. H.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 949.

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.

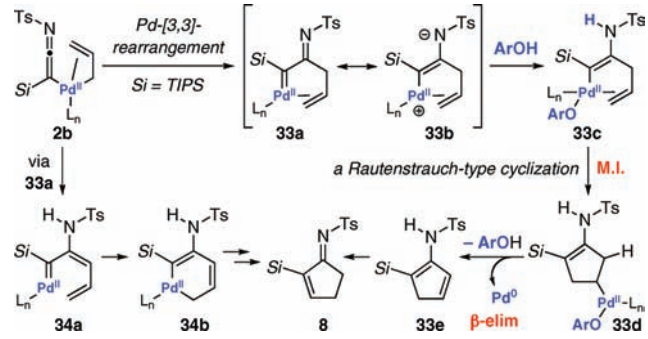
The difference in conditions implied that cyclopentenimine **8** is likely derived from a different mechanistic course for which silyl ketenimine **9** is not an intermediate.[23] This assertion is consistent with the fact that treatment of **9** with either 5 mol % of $Pd(PPh_3)_4$, or by using thermal 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).

Scheme 6. Effective Cyclopentenimine Formation



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 reductively

Scheme 7. Aza-Rautenstrauch-Type Cyclization Pathway



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 there on, one possibility that is consistent with the use of PhOH would entail the formation of enamido−Pd complex **33c**, which 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*-allylynamides, 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.

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

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(22) Some of the conditions explored are as follows. Pd(0) source: $Pd_2(dba)_3$, $Pd(PPh_3)_4$. Ligand: xantphos, X-Phos, $(C_6F_5)_3P$. Solvent: THF, dioxane. Concentration: 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.

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(27) For a leading reference on Rautenstrauch rearrangement, see: Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802.