Homogeneous Catalysis

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Transition-Metal-Catalyzed Diamination of Olefins

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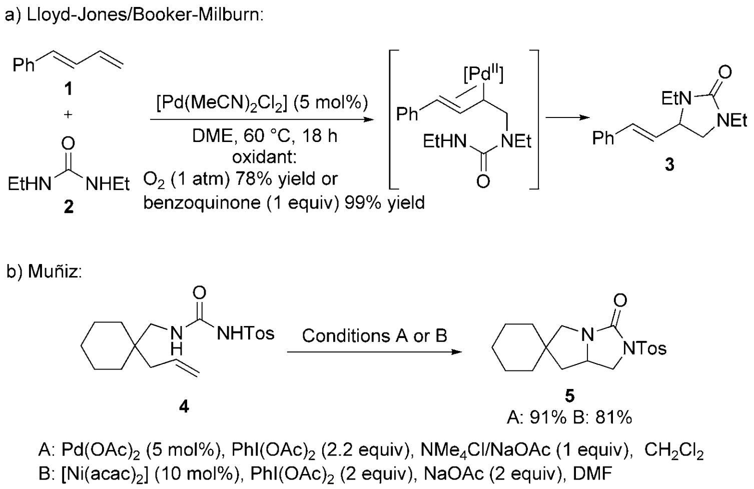
Vicinal diamines constitute important functional moieties which are present in a broad variety of natural products, various biologically active molecules, and are also used as ligands or catalysts in organo- and transition-metal-catalyzed asymmetric reactions.[1] Despite their extensive utility, the development of new methods allowing efficient preparation of 1,2-diamines remains a stimulating challenge.[1,2] Among the methods usually employed to generate such scaffolds, the direct oxidative alkene diamination presents an attractive strategy. Moreover, although catalytic enantioselective epoxidation, dihydroxylation, and aminohydroxylation reactions have been developed and found a wide success in synthetic organic chemistry, little attention has been paid to the corresponding diamination process, and until 2005, catalytic approaches for these reactions were unprecedented.[3] It should be noted that the development of an efficient route for catalytic alkenes diamination is usually confronted by the problem of the high reactivity of diamines in the presence of transition metals, which leads to metal coordination and, consequently, its deactivation. Thus, attempts to devise catalytic approaches must overcome this hurdle. This Highlight underscores major developments, published in the last three years, concerning transition-metal-catalyzed olefin diamination.



Scheme 1. First transition-metal-catalyzed diamination of olefins. DME = dimethoxyethane, acac = 2,4-pentanedione, OAc = acetoxy, Tos = tosyl.

In 2005, Lloyd-Jones, Booker-Milburn, and Bar[4] and Muñiz et al.[5,6] independently published the palladium(II)-catalyzed intermolecular and intramolecular diamination of olefins via an aza-Wacker-type process (Scheme 1).

By employing 1,3-butadienes and alkyl ureas the conversion of conjugated dienes to vinylic cyclic ureas was devised by Lloyd-Jones, Booker-Milburn, and Bar[4] (Scheme 1 a). 1,3-butadienes were chosen as an efficient source of electrophilic π-allyl palladium species since they are not prone to β-hydride elimination. Alkyl ureas are less reactive than their parent amines and, in addition, they can direct the second amination step toward 1,2-regioselectivity. Concerning the mechanistic pathway, the reaction with cyclic dienes is consistent with an initial *anti*-aminopalladation step (palladium(II)-assisted aza-Wacker-type process), since no nucleophilic substitution on the π-allyl complex would be detected with a *syn*-aminopalladation.[7]

Palladium-catalyzed intramolecular diaminations, have independently been investigated by Muñiz and co-workers (Scheme 1 b).[5] Preliminary work relied on the utilization of ω-alkenyl-substituted ureas which allows a vicinal aminopalladation. Iodobenzene diacetate is used as a stoichiometric reoxidant to make formation of the second C–N bond possible via palladium(II)-oxidation/nucleophilic displacement.[6] Although this method experienced great success compared to the few other methods available for such transformation, it lacks product diversification, good reaction rates, and chemoselectivity. In 2007, the scope of palladium-catalyzed diamination of alkenes could be extended by replacing Pd(OAc)$_2$ by nickel salts.[8] Contrary to the Pd^{II}/PhI(OAc)$_2$-system, the reaction takes place in the presence of sulfamide, urea, and guanidine substrates.

Recently, this method was further improved by using CuBr$_2$[9] instead of PhI(OAc)$_2$.[10,11] Using this approach, terminal and internal alkenes are transformed in high yields, thus broadening the substrate scope. The synthetic applicability of Muñiz's work has been demonstrated in the synthesis of bisindoline[12] and bicyclic guanidines[13] and,

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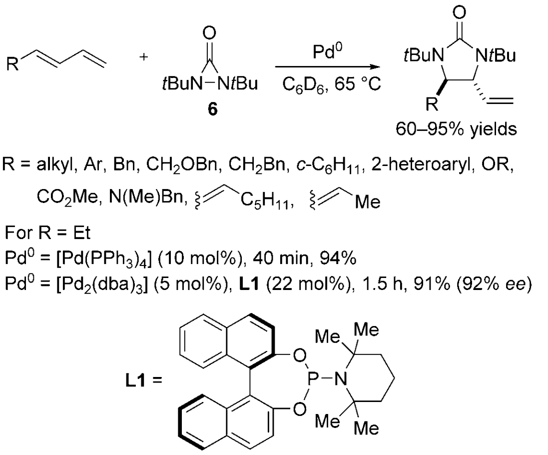
more recently, in the synthesis of the natural alkaloid absouline.[11]

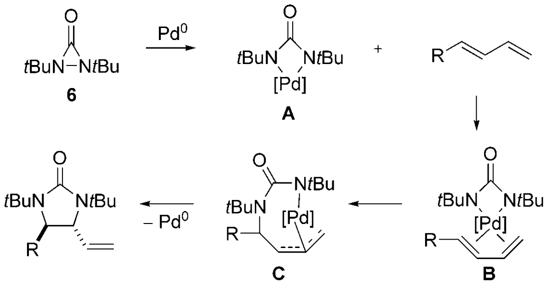
The more recent palladium(0)- and copper(I)-catalyzed intermolecular diamination reported by Shi and co-workers represents a real breakthrough in this area.[14,15] Choosing di-*tert*-butyldiaziridinone (**6**) as a nitrogen source, Shi and co-workers have described the first palladium(0)-catalyzed diamination of conjugated dienes and trienes (Scheme 2).[14,15]



Scheme 2. Diamination of conjugated dienes and trienes by palladium(0) catalysis. Bn = benzyl, dba = dibenzylideneacetone.

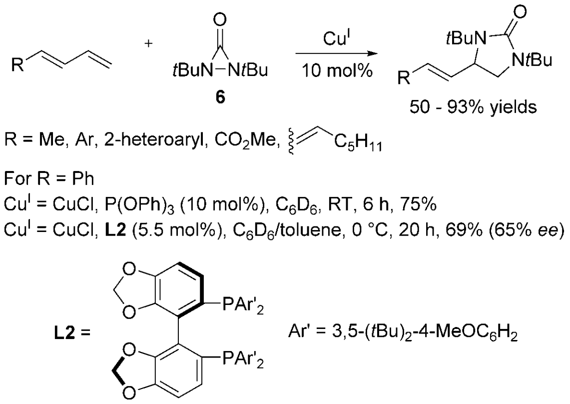
A broad variety of substrates are suitable including both electron-rich and electron-deficient dienes containing trisubstituted double bonds, and dienes containing geminal disubstituted double bonds. Preliminary results showed that $[Pd(PPh_3)_4]$ catalyzes the transformation in very high regio- (only the internal double bond reacts) and stereoselectivities.[14] When conjugated trienes are submitted to the reaction conditions the diamination takes place at the central double bond. In the same year, an asymmetric version of this study was described. It proceeds through a chiral monophosphine-based system to afford various optically active cyclic ureas in high yields and enantioselectivities (up to 95% *ee*).[15] This is the first catalytic asymmetric diamination process for olefins and the reaction requires only 5 mol% of $[Pd_2(dba)_3]$ and 22 mol% of phosphoramidite ligand **L1** (scheme 2).

Although more studies have to be carried out concerning the mechanism, Shi et al. consider that the first step is the addition of Pd^0 into the N–N bond of the diaziridinone **6** to give rise to the intermediate **A** (Scheme 3). After coordination with the diene and a migratory insertion, the π-allyl palladium complex **C** formed is converted into the desired product via a reductive elimination to regenerate the Pd^0 catalytic species. Since different regioselectivities are obtained with Pd^{II} (see Scheme 1a) and Pd^0 catalysts, a distinct pathway for each case is assumed. Moving to N-heterocyclic carbene ligands requires a lower catalyst loading (5 mol%) and very good enantioselectivities are reached (up to 91% *ee*), although longer reaction times (12 h) are needed.[16,17]



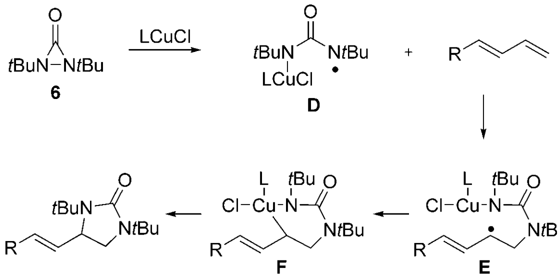
Scheme 3. Mechanism proposed for palladium(0)-catalyzed diamination.

In their search for new catalytic systems, Shi et al. have devised a copper(I)-catalyzed approach (Scheme 4).[18–20] In this case, the diamination occurs at the terminal double bond of a wide number of conjugated dienes providing complementary regioselectivity to the Pd^0-process. The optimal reaction conditions require 10 mol% of $CuCl/P(OPh)_3$ (1:1). Generally, very high regioselectivities and good yields are obtained. Very recently, the synthetic efficacy of such cheaper and milder conditions has been further improved with the development of an asymmetric version.[19] In the presence of 10 mol% of CuCl and 5.5 mol% of ligand (*R*)-dtbm-segphos (**L2**; Scheme 4) a variety of conjugated dienes and a triene could be regio- and enantioselectively diaminated at the terminal double bond in good yields (up to 93%) with 62–74% *ee*.[21] The substrate scope of the reaction was further enlarged by the copper(I)-catalyzed intermolecular diamination[22] of activated terminal olefins and cycloguanidination[23] of trienes, dienes, and terminal olefins. These reactions are highly regioselective as only the terminal double bonds are diaminated and cycloguanidinated.



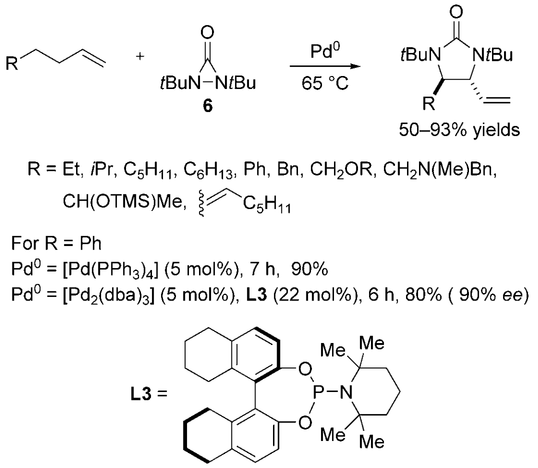
Scheme 4. Copper(I)-catalyzed diamination of conjugated dienes and trienes.

Concerning the mechanism,[18,19] Shi et al. presume a transition-metal-catalyzed radical process in which the CuCl reduction of the N–N bond of the nitrogen donor forms a radical species **D** (Scheme 5). Addition of **D** to the double bond gives rise to intermediate **F** which undergoes homolytic Cu–N cleavage to generate the new C_{sp3}–N bond.



Scheme 5. Catalytic cycle proposed for copper(I)-catalyzed diamination.

Having made major achievements in palladium(0)- and copper(I)-catalyzed diamination of olefins, Shi and co-workers then developed the first asymmetric homoallylic and allylic diamination of alkenes via a C–H functionalization step (Scheme 6).[24,25] In the reaction di-*tert*-butyldiaziridinone (**6**) is used as a nitrogen source and the catalyst is generated from $[Pd_2(dba)_3]$ and ligand **L3** (Scheme 6). Good yields and high diastereo-, regio-, and enantioselectivities (up to 94% *ee*) are obtained. In addition, a broad variety of terminal alkenes, mono-, and 1,1-disubstituted olefins are suitable for this transformation. Notably, bisdiamination of terminal diolefins can also proceed stereoselectively in one step (one diastereoisomer, 95% *ee*; Scheme 7). The same reaction using a diene strategy (see Scheme 2) would require the synthesis of sensitive tetraenes.

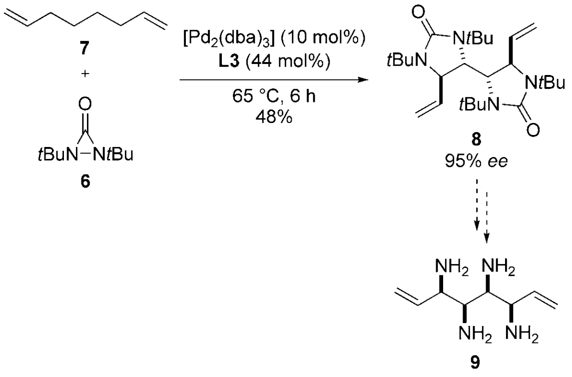


R = Et, *i*Pr, C_5H_{11}, C_6H_{13}, Ph, Bn, CH_2OR, $CH_2N(Me)Bn$, CH(OTMS)Me, C_5H_{11}

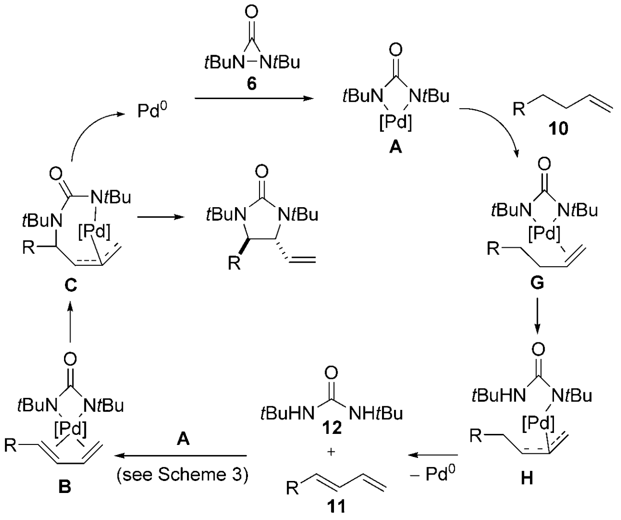
For R = Ph
$Pd^0 = [Pd(PPh_3)_4]$ (5 mol%), 7 h, 90%
$Pd^0 = [Pd_2(dba)_3]$ (5 mol%), **L3** (22 mol%), 6 h, 80% (90% *ee*)

Scheme 6. Catalytic asymmetric allylic/homoallylic C–H diamination of terminal olefins. TMS = trimethylsilyl.

Although the mechanism requires further studies, Shi and co-workers have proposed a plausible catalytic cycle which is depicted in Scheme 8. The opening of the strained N–N bond of **6** with Pd^0 gives rise to a four-membered Pd^{II} species **A** which complexes with olefin **10** to afford intermediate **G**. The formation of diene **11** takes place upon removal of the allylic hydrogen from **G** allowing a π-allyl Pd complex **H** which at the same time regenerates the Pd^0 catalyst after β-hydrogen elimination. The intermediate **B** is then obtained through the reaction of diene **11** with **A** which is, after migratory insertion, converted into π-allyl palladium complex **C**. Finally, **C** undergoes reductive elimination and the final product is then obtained together with the palladium(0) catalyst.



Scheme 7. Catalytic asymmetric allylic/homoallylic C–H diamination of 1,7-octadiene.



Scheme 8. Catalytic cycle proposed for allylic/homoallylic C–H diamination.

In conclusion, these studies on the transition-metal-catalyzed diamination of olefins are very significant. The examples presented herein show breakthroughs in this research that are important, not only because it is the first time that such a desired transformation has been realized, but also because asymmetric versions have been developed in which high levels of asymmetric induction has been achieved. Diaminations reported by Lloyd-Jones/Booker-Milburn and Muñiz involve a palladium(II)-catalyzed aza-Wacker-type process and asymmetric versions have not yet been developed. The palladium(0)- and copper(I)-catalyzed diamination described by Shi and co-workers provides a completely new approach to diamination. They were also the first group to devise catalytic and asymmetric diamination processes. Notably, they have assigned the possibility to address the regioselectivity of diene diamination by simply switching the catalytic system. Impressive high regio- and enantioselectivities are obtained and, generally, the cyclic ureas are isolated in excellent yields. Even more impressive, Shi and co-workers' allylic/homoallylic diamination of alkenes via a C—H functionalization represents a real step forward in this field. The efficiency of this catalytic system lies on the conversion of simple terminal alkenes into conjugated dienes in situ besides being highly enantioselective. Undoubtedly, this intriguing transformation is among the most useful recent discoveries in synthetic organic chemistry. Such reactions have become a valuable tool for C—N bond formation which will have a major impact on future work including transition-metal catalysis. Thus, it can be expected that such results will stimulate their application in synthetic strategies for elaboration of more complex molecules bearing the 1,2-diamine moiety.

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[1] For reviews of 1,2-diamines, see: a) J. E. G. Kemp in *Comprehensive Organic Synthesis, Vol. 7* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 469; b) D. Lucet, T. L. Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580; c) M. S. Mortensen, G. A. O'Doherty, *Chemtracts: Org. Chem.* **2005**, *18*, 555; d) S. R. S. Saibabu Kotti, C. Timmons, G. Li, *Chem. Biol. Drug Des.* **2006**, *67*, 101.

[2] K. Muñiz, *New J. Chem.* **2005**, *29*, 1371.

[3] For stoichiometric 1,2-diamination of alkenes, see: a) J.-E. Bäckvall, *Tetrahedron Lett.* **1975**, *16*, 2225; b) J.-E. Bäckvall, *Tetrahedron Lett.* **1978**, *19*, 163; c) V. G. Aranda, J. Barluenga, F. Aznar, *Synthesis* **1974**, 504; d) J. Barluenga, L. Alonso-Cires, G. Asensio, *Synthesis* **1979**, 962; e) J. Barluenga, F. Aznar, M. C. S. de Mattos, W. B. Kover, S. Garcia-Granda, E. Pérez-Carreño, *J. Org. Chem.* **1991**, *56*, 2930; f) A. O. Chong, K. Oshima, K. B. Sharpless, *J. Am. Chem. Soc.* **1977**, *99*, 3420; g) P. N. Becker, M. A. White, R. G. Bergman, *J. Am. Chem. Soc.* **1980**, *102*, 5676; h) P. N. Becker, R. G. Bergman, *Organometallics* **1983**, *2*, 787; i) S. Ghomi, D. E. Orr, *Chem. Ind.* **1983**, 928; j) W. E. Fristad, T. A. Brandvold, J. R. Peterson, S. R. Thompson, *J. Org. Chem.* **1985**, *50*, 3647; k) W. Pei, C. Timmons, X. Xu, H.-X. Wei, G. Li, *Org. Biomol. Chem.* **2003**, *1*, 2919; l) K. Muñiz, A. Iesato, M. Nieger, *Chem. Eur. J.* **2003**, *9*, 5581; m) K. I. Booker-Milburn, D. J. Guly, B. Cox, P. A. Procopiou, *Org. Lett.* **2003**, *5*, 3313.

[4] G. L. J. Bar, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2005**, *127*, 7308.

[5] J. Streuff, C. H. Hövelmann, M. Nieger, K. Muñiz, *J. Am. Chem. Soc.* **2005**, *127*, 14586.

[6] For mechanistic insights, see: K. Muñiz, C. H. Hövelmann, J. Streuff, *J. Am. Chem. Soc.* **2008**, *130*, 763.

[7] On comparing their diamination method with the oxidative dehydroamination conditions described by Stahl and co-workers with 5 mol% of $Pd(OAc)_2$ in the presence of styrene, contrasting regioselectivities were observed: J. L. Brice, J. E. Harang, V. I. Timokhin, N. R. Anastasi, S. S. Stahl, *J. Am. Chem. Soc.* **2005**, *127*, 2868.

[8] K. Muñiz, J. Streuff, C. H. Hövelmann, A. Núñez, *Angew. Chem.* **2007**, *119*, 7255; *Angew. Chem. Int. Ed.* **2007**, *46*, 7125.

[9] It should be emphasized that no diamination is observed with $Cu(OAc)_2$ and $CuCl_2$.

[10] K. Muñiz, C. H. Hövelmann, E. Campos-Gómez, J. Barluenga, J. M. González, J. Streuff, M. Nieger, *Chem. Asian J.* **2008**, *3*, 776.

[11] K. Muñiz, J. Streuff, P. Chávez, C. H. Hövelmann, *Chem. Asian J.* **2008**, *3*, 1248.

[12] K. Muñiz, *J. Am. Chem. Soc.* **2007**, *129*, 14542.

[13] C. H. Hövelmann, J. Streuff, L. Brelot, K. Muñiz, *Chem. Commun.* **2008**, 2334.

[14] H. Du, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 762.

[15] H. Du, W. Yuan, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 11688.

[16] L. Xu, H. Du, Y. Shi, *J. Org. Chem.* **2007**, *72*, 7038.

[17] L. Xu, Y. Shi, *J. Org. Chem.* **2008**, *73*, 749.

[18] W. Yuan, H. Du, B. Zhao, Y. Shi, *Org. Lett.* **2007**, *9*, 2589.

[19] H. Du, B. Zhao, W. Yuan, Y. Shi, *Org. Lett.* **2008**, *10*, 4231.

[20] For stoichiometric Cu^{II} intramolecular diamination of dienes, see: a) T. P. Zabawa, D. Kasi, S. R. Chemler, *J. Am. Chem. Soc.* **2005**, *127*, 11250; b) T. P. Zabawa, S. R. Chemler, *Org. Lett.* **2007**, *9*, 2035.

[21] Steric effects and radical stability are very important factors for the enantioselectivity since the asymmetric diamination of *trans*-1-phenyl-3-methylbutadiene afforded the desired product in 90% yield with only 23% *ee*.

[22] B. Zhao, W. Yuan, H. Du, Y. Shi, *Org. Lett.* **2007**, *9*, 4943.

[23] B. Zhao, H. Du, Y. Shi, *Org. Lett.* **2008**, *10*, 1087.

[24] H. Du, W. Yuan, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 7496.

[25] H. Du, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 8590.