Synthetic Methods

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Aerobic Synthesis of Pyrroles and Dihydropyrroles from Imines: Palladium(II)-Catalyzed Intramolecular C–H Dehydrogenative Cyclization**

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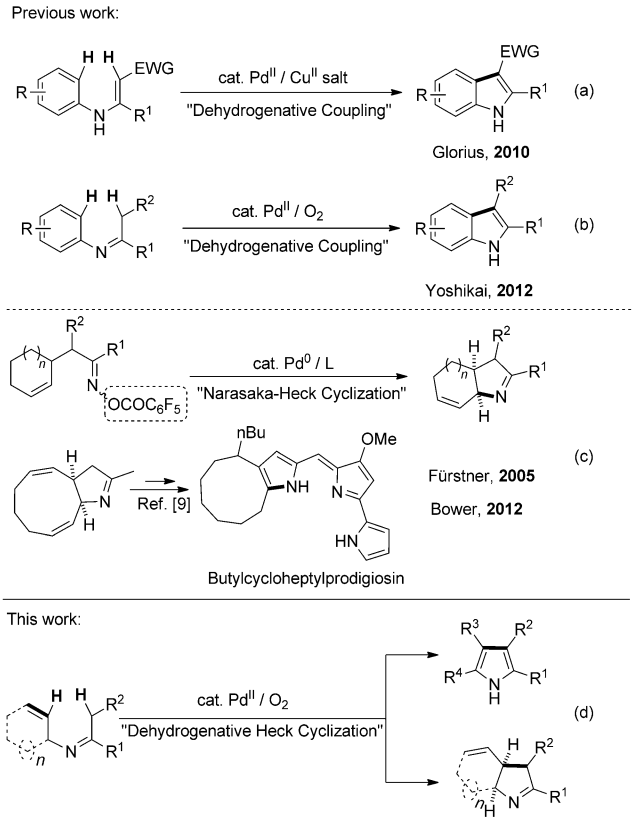
Imines and enamines are useful building blocks in organic synthesis, and especially in the synthesis of nitrogen heterocycles, such as in the Bischler indole, Hantzsch, or Paal–Knorr pyrrole synthesis.[1] During the past years, C–H functionalization has emerged as an attractive and powerful strategy for the generation of C–C and carbon–heteratom bonds in a step- and atom-economical fashion.[2] Among these, a number of novel C–H functionalization strategies for the synthesis of azaheterocycles using imines and enamines as starting materials have been reported.[3] In 2008, a Pd^{II}-catalyzed oxidative cyclization of *N*-aryl enamines was developed (Scheme 1 a).[4] The mechanism starts with the attack of the enamine onto the Pd^{2+} catalyst (electrophilic substitution) and proceeds with an intramolecular C–H activation of the aniline ring, affording the corresponding indoles. Recently, the group of Yoshikai made a significant breakthrough for indole synthesis by Pd^{II}-catalyzed oxidative cyclization of common *N*-aryl imines under mild conditions (Scheme 1 b).[5] In contrast to previous reports, this process works with imine substrates and thus possesses a broader scope.

The pyrrole-based scaffold is one of the most abundant and relevant units in natural products and pharmaceuticals.[6] The Pd-catalyzed cyclization of oxime esters (usually *O*-perfluorobenzoyl oximes) with olefins was first reported by Narasaka et al. and provides an efficient approach to (dihydro)pyrroles by Heck-type reactions.[7] The "Narasaka–Heck" method has been applied to natural product synthesis, such as in the synthesis of butylcycloheptylprodigiosin by Fürstner et al.[8] Very recently, Faulkner and Bower reported a highly efficient Pd-catalyzed "Narasaka–Heck" cyclization using $(3,5\text{-}(CF_3)_2C_6H_3)_3P$ as ligand (Scheme 1 c).[9] In view of the importance of pyrroles and related scaffolds, we were prompted to consider an effective and direct route to construct pyrroles from imine substrates. We hypothesized that *N*-allylimines prepared by condensation of the corresponding allylamines and ketones may undergo intramolecular C–H dehydrogenative cyclization[10,11] to form the (dihydro)pyrroles in an atom-economical approach (Scheme 1 d).

The initial reaction of (*E*)-*N*-(1-phenylethylidene)prop-2-en-1-amine **3a** was carried out in the presence of 10 mol% $Pd(OAc)_2$ as the catalyst at 80 °C under an O_2 atmosphere in DMSO. Interestingly, the desired pyrrole product **4a** was observed in 15% yield and was accompanied by an unexpected pyridine product **4a′** in 33% yield (Table 1, entry 1).[12]



Scheme 1. a,b) Palladium(II)-catalyzed synthesis of indoles from enamines and imines; c) palladium(0)-catalyzed "Narasaka–Heck" reactions; d) Palladium(II)-catalyzed synthesis of (dihydro)pyrroles from imines by C–H dehydrogenative cyclization.

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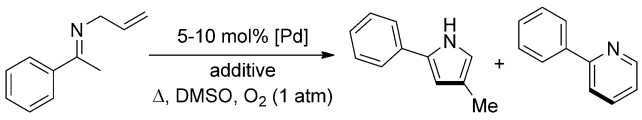
Table 1: Reaction development.[a]

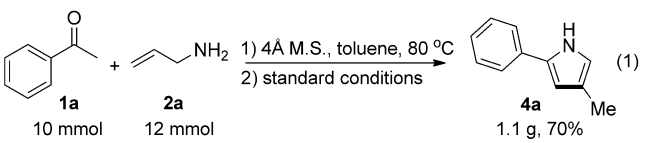


3a **4a** **4a'**

Entry	Pd source (equiv)	Additive (equiv)	*T* [°C]	Yield [%][b]	
				4a	**4a'**
1	$Pd(OAc)_2$ (0.1)	–	80	15	33
2	$Pd(OTFA)_2$ (0.1)	–	80	6	27
3	$Pd(acac)_2$ (0.1)	–	80	8	18
4	$Pd(OAc)_2$ (0.1)	–	60	26	8
5	$Pd(OAc)_2$ (0.1)	–	30	46	8
6	$Pd(OAc)_2$ (0.1)	1,10-Phen (0.1)	30	51	10
7	$Pd(OAc)_2$ (0.1)	Diazafluoreno (0.1)	30	56	15
8	$Pd(OAc)_2$ (0.1)	TBAB (2.0)	30	66	0
9	$Pd(OAc)_2$ (0.1)	TBAB (2.0) + 4 Å MS	30	82	0
10	$Pd(OAc)_2$ (0.05)	**TBAB (2.0) + 4 Å M.S.**	**30**	**85 (83)**	**0**
11	$Pd(OAc)_2$ (0.05)	TEAB (2.0) + 4 Å M.S.	30	82	0
12	$Pd(OAc)_2$ (0.05)	TMAB (2.0) + 4 Å M.S.	30	60	0
13[c]	$Pd(OAc)_2$ (0.05)	TBAB (2.0) + 4 Å M.S.	30	21	0
14	–	TBAB (2.0) + 4 Å M.S.	30	0	0

[a] Conditions: **3a** (0.2 mmol), 10.0 mol% $Pd(OAc)_2$, dry solvent (1.0 mL), 24 h, under O_2 (1 atm). TBAB = nBu_4NBr, TEAB = Et_4NBr, TMAB = Me_4NBr. [b] Determined by GC using an internal standard; value in parentheses indicate yield of isolated product. [c] Using DCE (1,2-dichloroethane) as solvent.

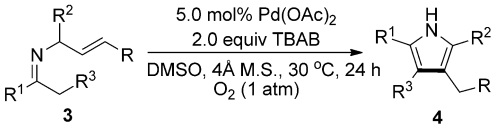
The efficiency of several palladium sources was tested, and $Pd(OAc)_2$ was found to be the best for this cyclization (entries 2 and 3). Lowering the reaction temperature improved the conversion into the pyrrole product (entries 4 and 5), with 30 °C being optimum. We explored different *N*-based ligands in this aerobic palladium-catalyzed system, and observed that diazafluoreno was the most efficient ligand, affording **4a** in 56% (entries 6 and 7). When using 2.0 equiv of TBAB instead of the ligand, **4a** was increased to 66%, and the pyridine by-product was completely inhibited (entry 8).[13] The yield of **4a** was further improved by the addition of 4 Å M.S. molecular sieves (entry 9). Under these conditions, when $Pd(OAc)_2$ was decreased to 5 mol%, a slightly higher yield of 83% was observed (entry 10). Note that freshly activated, powdered 4 Å M.S. and TBAB stored in a glovebox were found to be key for obtaining optimal results. Besides TBAB, TEAB also showed a similar effect, though TMAB gave the reduced yield (entries 11 and 12). The choice of DMSO as solvent is crucial for the success of the present catalytic reaction,[14] and of other solvents, only DCE gave some product (entry 13). Control reactions confirmed that the transformation does not occur in the absence of the $Pd(OAc)_2$ (entry 14). Furthermore, to simplify the operations, this pyrrole synthesis could be easily started directly from acetophenone (**1a**) and allylamine (**2a**) and scaled up to gram quantity without difficulty [Eq. (1)].



1a 10 mmol + **2a** 12 mmol → **4a** 1.1 g, 70% (1)

With a set of optimized conditions in hand, we examined the scope of this dehydrogenative cyclization process (Table 2). The effect of substituents on the arene undergoing the cyclization reaction was first examined. This aromatic ring was found to be tolerant of both electron-rich groups, such as methyl (**4b**, **4j** and **4l**) and methoxy (**4c**), and electron-deficient groups, such as trifluoromethyl (**4d** and **4k**), cyano (**4h**), and nitro (**4i**). Notably, the halogen-containing motifs, such as F (**4e**), Cl (**4f**), and even I (**4g**) work well in this transformation. The naphthaldehyde substrate **3m** can be

Table 2: Palladium(II)-catalyzed cyclization of imines to pyrroles.[a]



3 **4**

Entry	Substrates	Products	Yield (%)[b]
1		**3b**	R^1 = Me, **4b**, 65%
2		**3c**	R^1 = OMe, **4c**, 63%
3		**3d**	R^1 = CF_3, **4d**, 82%
4[c]		**3e**	R^1 = F, **4e**, 78%
5		**3f**	R^1 = Cl, **4f**, 77%
6		**3g**	R^1 = I, **4g**, 43%
7		**3h**	R^1 = CN, **4h**, 71%
8		**3i**	R^1 = NO_2, **4i**, 59%
9		**3j**	R^1 = Me, **4j**, 65%
10		**3k**	R^1 = CF_3, **4k**, 70%
11[c]		**3l**	**4l**, 80%
12		**3m**	**4m**: 76%
13		**3n**	**4n**: 41%
14		**3o**	**4o**: 30%
15		**3p**	**4p**: 71%
16		**3q**	R^2 = Me, **4q**, 76%
17		**3r**	R^2 = Ph, **4r**, 72%
18		**3s**	R^3 = Me, R = H **4s**,n.d
19		**3t**	R^3 = H, R = Ph **4t**, n.d
20[c]		**3u**	**4u**, 46%

[a] Reaction conditions: **3** (0.2–1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), TBAB (2.0 equiv), 4 Å M.S. (0.2–1.0 g), in DMSO (1.0–5.0 mL) at 30 °C for 24 h under O_2 (1 atm). [b] Yield of isolated product. [c] At 60 °C.

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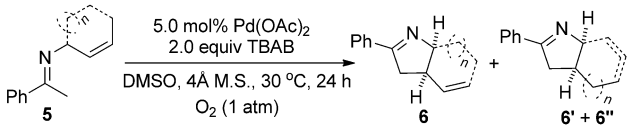
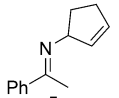
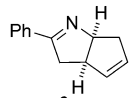
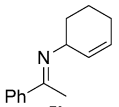
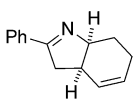
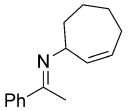
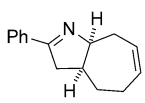
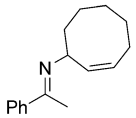
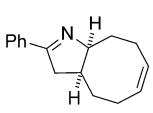
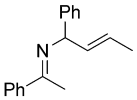
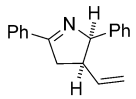
Table 3: Palladium(II)-catalyzed cyclization of imines to dihydropyrroles.[a]



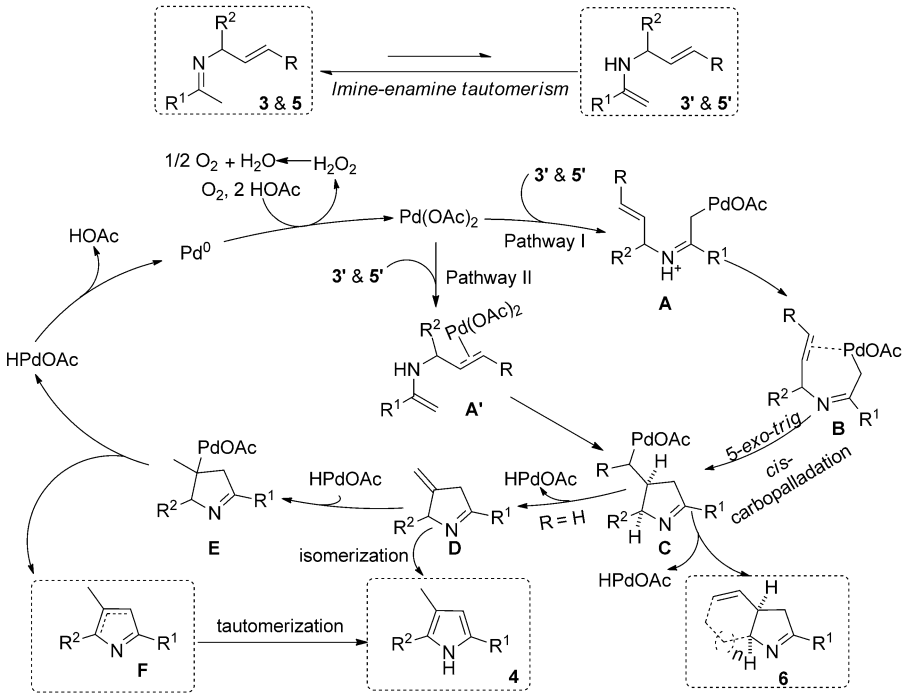
Entry	Substrates	Major products	Yield (**6** + **6'** + **6''**)[b]
1	 **5a**	 **6a**	61%, **6a** + **6a'** (10 : 1)
2	 **5b**	 **6b**	81%, **6b** + **6b'** (5 : 1)
3	 **5c**	 **6c''**	78%, **6c''** + two isomers[c] (1 : 1)
4	 **5d**	 **6d''**	71%, **6d''** + two isomers[c] (5 : 1)
5	 **5e**	 **6e**	87%

[a] Reaction conditions: **5** (0.2 mmol), $Pd(OAc)_2$ (5.0 mol%), TBAB (2.0 equiv), 4 Å M.S. (0.2 g), in DMSO (1.0 mL) at 30°C for 24 h under O_2 (1 atm). [b] The reaction mixture analyzed by ^1H NMR to determine the ratio of regioisomers; yield of isolated product. [c] These isomers are difficult to distinguish by NMR spectroscopy.

converted into the desired product in 76% yield. Heteroaryl groups, such as 2-furyl and 4-pyridyl groups, could also be tolerated to give the biheteroaryl products in moderate yield (**4n** and **4o**). 2-*tert*-Butyl-pyrrole (**4p**) was also obtained in good yields from the alkyl substituted imine. Next, the effect of the substituents on the allyl moiety in the synthesis of the corresponding imines using acetophenone (**1a**) as partner was examined. The reaction of imines **3q** and **3r** under the standard reaction conditions afforded the tri-substituted pyrroles **4q** and **4r** in good yield. However, the imines **3s** and **3t** failed to afford the corresponding products **3s** and **4t**. Enamines proved to be less reactive than imines in this transformation; under higher temperature, the present method can be applicable to the enamines such as ethyl 3-allylamino-3-phenylacrylate (**3u**), resulting in the formation of ethyl 4-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate (**4w**) in 46% yield.

Further exploration into substrate scope revealed that imines derived from acetophenone (**1a**) and cyclic allylamines were selectively proceeding as a 5-*exo* cyclization to form dihydropyrroles (Table 3). Cyclization of **5a** and **5b**, which involves a five- and six-membered-ring allylamine, generated the dihydropyrroles **6a** and **6b** in good yield with a small amount of olefin isomerization byproduct by chain walk.[15] Seven-membered-ring substrate **5c** generated a mixture of cyclization products with poor selectivity. Interestingly, eight-membered-ring substrate **5d** selectively afforded **6d''** as the major product. It is important to note that, besides cyclic allylamines, imine substrates bearing γ-substituents (containing H) on the allyl group such as imine **5e** can also deliver dihydropyrrole products in good yield (such as **6e**; entry 5). The rigid N-heterobicyclic products arising from this transformation can easily be accessed in good yield, suggesting that this method might open up a convenient entry to the core of some scaffolds such as prodigiosin[16] and the aeruginosin skeleton.[17]

On the basis of these results, a mechanistic proposal is outlined in Scheme 2. The transformation begins with an electrophilic palladation of the nucleophilic enamine **3'**, which is generated in situ by tautomerization of imine **3**. The resulting palladium complex **A** is followed by olefin activation, olefin insertion to form **C**. At this stage, when R is the H atom, subsequent β-H elimination gives the intermediate **D**. On the other hand, in case with the alkyl groups (containing β-H) on R, β-H elimination from R is a preferable way to form the dihydropyrrole product **6**. Subsequent isomerization



Scheme 2. Plausible reaction mechanism.

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and aromatization of **D** affords pyrrole product **4**, and another possible way for this step involving olefin insertion into the Pd–H bond affording **E** followed by β-H elimination gives the imine **F** or **F′**, which can tautomerize quickly to **4**. The Pd^0 complex that can be reoxidized to the Pd^{II} complex by O_2 and HOAc (pathway I).[18] An alternative Wacker-type process,[19] involving Pd^{II}-catalyzed olefin activation and subsequent attack by the nucleophilic enamine, cannot be ruled out at the present (pathway II).[20]

In summary, we have developed a remarkably mild oxidative cyclization of imines to (dihydro)pyrroles that relies on C–H functionalization and uses molecular oxygen as the sole stoichiometric oxidant. This method is attractive because inexpensive starting materials are used under mild reaction conditions, leading to the formation of valuable products.

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[1] a) M. F. Shortt, E. J. Thomas, *Science of Synthesis*, *Vol. 10* (Ed.: J. A. Joule), Georg Thieme, Stuttgart, **2000**; b) R. J. Sundberg in *Comprehensive Heterocyclic Chemistry II*, *Vol. 2* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, pp. 119–206; c) H. Fan, J. Peng, M. T. Hamann, J.-F. Hu, *Chem. Rev.* **2008**, *108*, 264; d) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079; e) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; f) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873.

[2] For recent reviews on C–H activation, see: a) S. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318; b) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949; c) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; d) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; e) M. Lautens, P. Thansandote, *Chem. Eur. J.* **2009**, *15*, 5874; f) T. Kitamura, *Eur. J. Org. Chem.* **2009**, 1111; g) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242; h) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; i) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654; j) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; k) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; l) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212; m) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; n) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; o) T. Newhouse, P. S. Baran, *Angew. Chem.* **2011**, *123*, 3422; *Angew. Chem. Int. Ed.* **2011**, *50*, 3362; p) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; q) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885; r) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; s) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; t) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31; u) M. C. White, *Science* **2012**, *335*, 807; v) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; w) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; x) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936; y) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; z) J. Wencel-Delord, F. Glorius, *Nature Chem.* **2013**, DOI: 10.1038/nchem.1607.

[3] a) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585; b) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326; c) M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem.* **2011**, *123*, 1374; *Angew. Chem. Int. Ed.* **2011**, *50*, 1338; d) K. K. Toh, Y.-F. Wang, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 13942; e) J. Barluenga, A. Jiménez-Aquino, F. Aznar, C. Valdés, *J. Am. Chem. Soc.* **2009**, *131*, 4031; f) J. Barluenga, A. Jiménez-Aquino, F. Aznar, C. Valdés, *Chem. Eur. J.* **2010**, *16*, 11707; g) R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, *Angew. Chem.* **2009**, *121*, 8222; *Angew. Chem. Int. Ed.* **2009**, *48*, 8078; h) L. Zhang, G. Y. Ang, S. Chiaba, *Org. Lett.* **2010**, *12*, 3682; i) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 4642; *Angew. Chem. Int. Ed.* **2009**, *48*, 4572; j) Z.-H. Guan, Z.-Y. Yan, Z.-H. Ren, X.-Y. Liu, Y.-M. Liang, *Chem. Commun.* **2010**, *46*, 2823–2825; k) R. Yan, J. Luo, C. Wang, C. Ma, G. Huang, Y. Liang, *J. Org. Chem.* **2010**, *75*, 5395.

[4] a) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, F. Glorius, *Angew. Chem.* **2008**, *120*, 7340; *Angew. Chem. Int. Ed.* **2008**, *47*, 7230; b) J. J. Neumann, S. Rakshit, T. Dröge, S. Würtz, F. Glorius, *Chem. Eur. J.* **2011**, *17*, 7298.

[5] a) Y. Wei, I. Deb, N. Yoshikai, *J. Am. Chem. Soc.* **2012**, *134*, 9098; for a Highlight on this work, see: b) Z. Shi, F. Glorius, *Angew. Chem.* **2012**, *124*, 9354; *Angew. Chem. Int. Ed.* **2012**, *51*, 9220.

[6] For the latest reports on pyrrole synthesis by Ru- and Ir-catalyzed cyclizations, see: a) M. Zhang, H. Neumann, M. Beller, *Angew. Chem.* **2013**, *125*, 625; *Angew. Chem. Int. Ed.* **2013**, *52*, 597; b) S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140.

[7] For reviews, see: a) M. Kitamura, K. Narasaka, *Chem. Rec.* **2002**, *2*, 268; b) K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, 4505.

[8] a) A. Fürstner, K. Radkowski, H. Peters, *Angew. Chem.* **2005**, *117*, 2837; *Angew. Chem. Int. Ed.* **2005**, *44*, 2777; b) A. Fürstner, K. Radkowski, H. Peters, G. Seidel, C. Wirtz, R. Mynott, C. W. Lehmann, *Chem. Eur. J.* **2007**, *13*, 1929.

[9] A. Faulkner, J. F. Bower, *Angew. Chem.* **2012**, *124*, 1707; *Angew. Chem. Int. Ed.* **2012**, *51*, 1675.

[10] For pioneering work on Pd^{II}-catalyzed olefination of Csp^3–H bonds, see: a) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680; for the carbopalladation of the Csp^3–H bond of α-ketones and imines, see: b) Y. Izawa, D. Pun, S. S. Stahl, *Science* **2011**, *333*, 209; c) T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 14566; d) T. Diao, T. J. Wadzinski, S. S. Stahl, *Chem. Sci.* **2012**, *3*, 887; e) W. Gao, Z. He, Y. Qian, J. Zhao, Y. Huang, *Chem. Sci.* **2012**, *3*, 883; f) N. Chernyak, S. I. Gorelsky, V. Gevorgyan, *Angew. Chem.* **2011**, *123*, 2390; *Angew. Chem. Int. Ed.* **2011**, *50*, 2342; g) A. Hajra, Y. Wei, N. Yoshikai, *Org. Lett.* **2012**, *14*, 5488; h) S. A. Girard, X. Hu, T. Knauber, F. Zhou, M. Simon, G.-J. Deng, C.-J. Li, *Org. Lett.* **2012**, *14*, 5606.

[11] For reviews on transition-metal-catalyzed DHR, see: a) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170; b) E. M. Ferreira, H. Zhang, B. M. Stoltz, *Tetrahedron* **2008**, *64*, 5987; for selected examples of transition-metal-catalyzed DHR, see: c) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem.* **2005**, *117*, 3185; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125; d) E. M. Beck, N. P. Grimster, R. Hatley, M. J. Gaunt, *J. Am. Chem. Soc.* **2006**, *128*, 2528; e) G. Cai, Y. Fu, Y. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 7666; f) E. M. Beck, R. Hatley, M. J. Gaunt, *Angew. Chem.* **2008**, *120*, 3046; *Angew. Chem. Int. Ed.* **2008**, *47*, 3004; g) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072; h) A. García-Rubia, R. G. Arrayás, J. C. Carretero, *Angew. Chem.* **2009**, *121*, 6633; *Angew. Chem. Int. Ed.* **2009**, *48*, 6511; i) J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 13888; j) D.-H. Wang, K. M.

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Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315; k) K. M. Engle, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 14137; l) K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2010**, *122*, 6305; *Angew. Chem. Int. Ed.* **2010**, *49*, 6169; m) Y. Lu, D.-H. Wang, K. M. Engle, J-.Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 5916; n) B.-F. Shi, Y.-H. Zhang, J. K. Lam, D.-H. Wang, J-.Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 460; o) F. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9982; p) M. Ye, G.-L. Gao, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 6964; q) D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 5767; r) S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350; s) T. Besset, N. Kuhl, F. Patureau, F. Glorius, *Chem. Eur. J.* **2011**, *17*, 7167; t) F. Patureau, T. Besset, F. Glorius, *Angew. Chem.* **2011**, *123*, 1096; *Angew. Chem. Int. Ed.* **2011**, *50*, 1064; u) N. Schröder, T. Besset, F. Glorius, *Adv. Synth. Catal.* **2012**, *354*, 579; v) Z. Shi, N. Schröder, F. Glorius, *Angew. Chem.* **2012**, *124*, 8216; *Angew. Chem. Int. Ed.* **2012**, *51*, 8092; w) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518.

[12] Two pathways can be considered for the formation of **4a′**, involving Pd^{II}-catalyzed 6-*endo* cyclization of **3a′** or dehydrogenation of **3a′** to form an azatriene, which then undergoes 6π cyclization.

[13] TBAB may play a role in stabilizing Pd^0 complexes from forming Pd^0 aggregates or it might promote the reoxidation to Pd^{II}; see: a) V. Calò, A. Nacci, A. Monopoli, L. Lopez, A. di Cosmo, *Tetrahedron* **2001**, *57*, 6071; b) T. Jeffery, *Tetrahedron* **1996**, *52*, 10113; c) N. T. S. Phan, M. V. D. Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609; see also Ref. [5] and [10g].

[14] DMSO has been widely used in Pd^{II}-mediated oxidation systems to promote reoxidation of Pd^0 with O_2: a) M. S. Chen, M. C. White, *J. Am. Chem. Soc.* **2004**, *126*, 1346; b) B. A. Steinhoff, S. R. Fix, S. S. Stahl, *J. Am. Chem. Soc.* **2002**, *124*, 766; c) H. Grennberg, A. Gogoll, J.-E. Bäckvall, *J. Org. Chem.* **1991**, *56*, 5808.

[15] T. Kochi, T. Hamasaki, Y. Aoyama, J. Kawasaki, F. Kakiuchi, *J. Am. Chem. Soc.* **2012**, *134*, 16544.

[16] a) A. Fürstner, *Angew. Chem.* **2003**, *115*, 3706; *Angew. Chem. Int. Ed.* **2003**, *42*, 3582.

[17] B. M. Trost, T. Kaneko, N. G. Andersen, C. Tappertzhofen, B. Fahr, *J. Am. Chem. Soc.* **2012**, *134*, 18944.

[18] For selected reviews on Pd^{II}-catalyzed reactions using molecular oxygen as the sole oxidant, see: a) A. N. Campbell, S. S. Stahl, *Acc. Chem. Res.* **2012**, *45*, 851; b) Z. Shi, C. Zhang, Y. Cui, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3381; c) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780; d) S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400; see also Ref. [2r].

[19] R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981.

[20] For a detailed mechanistic discussion, see the Supporting Information.

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