Highlight Review

Palladium Catalyzed Aerobic Dehydrogenation: From Alcohols to Indoles and Asymmetric Catalysis

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Abstract

Catalytic aerobic dehydrogenation of organic substrates is going through a Renaissance. Recent advances in this area have led to the discovery of palladium-catalyzed alcohol dehydrogenations and oxidative hetero- and carbocyclizations. The development of asymmetric catalytic dehydrogenations is the latest advance in a long line of catalytic asymmetric oxidation reactions.

♦ Introduction

Asymmetric catalytic oxidation chemistry has profoundly impacted organic synthesis.[1] Some reactions of particular consequence are shown in Figure 1 and include the Katsuki-Sharpless asymmetric epoxidation (KSAE) and dihydroxylation, the Katsuki–Jacobsen and Shi epoxidations, and the Evans and Jacobsen aziridinations. There is no doubt that the KSAE reaction not only paved the way for future directions in enantioselective oxidation chemistry, but also opened the door to a wide range of other catalytic asymmetric reactions.[2] Moreover, the introduction of the KSAE and the other reactions listed in Figure 1 led to innumerable advances in the construction of complex molecules by de novo asymmetric synthesis. All of the reactions shown in Figure 1 are examples of oxidations by virtue of heteroatom transfer. As a result, these reactions may be classified in a simplistic sense as belonging to a family of similar oxidations characterized by the stylized reaction in Figure 2.

In contrast, asymmetric oxidation chemistry that *does not* involve heteroatom transfer has been relatively less explored

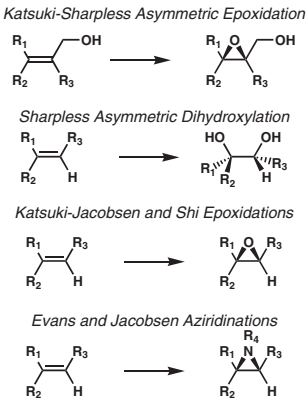

Figure 1. Heteroatom transfer asymmetric oxidation reactions.

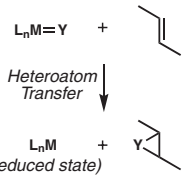

Figure 2. General heteroatom transfer mechanism.

(e.g., the dehydrogenations shown in Figure 3). Until recently, few methods existed for catalytic asymmetric dehydrogenation chemistry, despite the ubiquity of such processes in nature (e.g., oxidases and dehydrogenases) and for racemic scenarios in the chemistry laboratory (e.g., alkane → alkene and alcohol → carbonyl). For instance, seminal contributions for the asymmetric dehydrogenation of alcohols were provided by Rychnovsky[3] and Noyori[4] only in the last decade.[5]

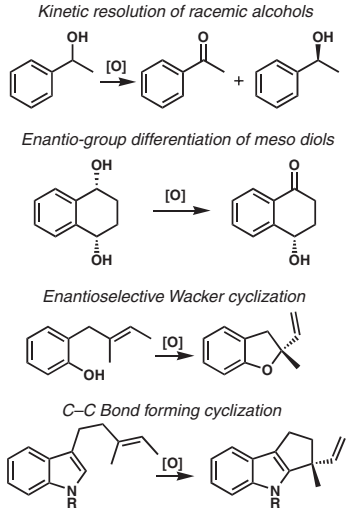

Figure 3. Non heteroatom transfer oxidations.

In part, it may be possible to understand the relatively slow nature with which developments along these lines have proceeded, by the subtle nature of the problem. Dehydrogenation is, by definition, a complexity-minimizing event. Thus, in the case of an enantioselective oxidation of a secondary alcohol, the product ketone arises by *destruction* of the asymmetric center (as opposed to asymmetric *induction*). Recently, increasing interest in the use of palladium catalyzed aerobic dehydrogenation chemistry as a broad platform for asymmetric oxidation has surfaced. This highlight review will focus on these developments,

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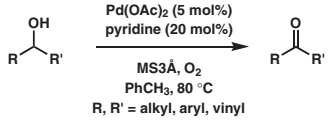
which set the stage for a promising future in enantioselective aerobic non-heteroatom transfer oxidation chemistry.

♦ *Palladium Catalyzed Aerobic Oxidation: The Oxidative Kinetic Resolution of Secondary Alcohols*

Palladium catalyzed aerobic oxidation processes date back nearly a century to Wieland's discovery that the noble metal could catalyze the oxidation of primary alcohols to aldehydes in aqueous media.[6] In 1977, Schwartz and Blackburn described the use of $Pd(OAc)_2$ and NaOAc for the aerobic oxidation of alcohols to carbonyl compounds.[7] Since that time, a number of advances toward more efficient catalysis have ensued, including a "ligandless" system in DMSO solvent pioneered by Hiemstra, Bäckvall, and Larock.[8] Additionally, a modern catalyst for aerobic oxidations in water has been developed by Sheldon.[9]

A major breakthrough was disclosed in 1998 by the Uemura group in Kyoto that set the stage for important developments in asymmetric catalysis.[10] Uemura discovered that a catalyst comprised of $Pd(OAc)_2$ and pyridine promotes the aerobic oxidation of a wide array of primary and secondary alcohols to the corresponding carbonyl derivatives in the non-coordinating solvent toluene (Scheme 1). Importantly, the reaction did not occur in the absence of the pyridine.



Scheme 1. The Uemura oxidation.

The recognition that the pyridine ligand was serving as a rate accelerant, or at the very least an on/off switch for the Uemura reaction, led to the notion that asymmetric catalysis could be possible without suffering from deleterious racemic background oxidation. In 2001, the groups of Stoltz[11] and Sigman[12] simultaneously reported nearly identical systems for the oxidative kinetic resolution of secondary alcohols using a modification of the Uemura system. The Stoltz group reported the use of $Pd(nbd)Cl_2$ in conjunction with (−)-sparteine and molecular oxygen resulted in highly enantioselective oxidations of secondary benzylic and allylic alcohols in toluene at 80 °C (Table 1).[13]

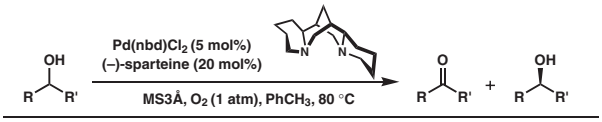
This asymmetric oxidation could be applied to kinetic resolution or to *meso* diol desymmetrization (i.e., Scheme 2, **1** → **2**). Importantly, the stoichiometric major product of the kinetic resolution (i.e., the prochiral ketone) could be trivially reduced to racemic alcohol and resolved again to give a greater than 50% yield of enantiopure alcohol after two cycles (i.e., **3** → **4** → **3**, etc.)[11]

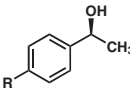
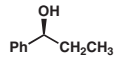
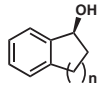
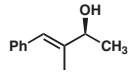
Alternatively, Sigman reported that a catalyst comprised of $Pd(OAc)_2$ and (−)-sparteine produced similar results in dichloroethane (Table 2).[12]

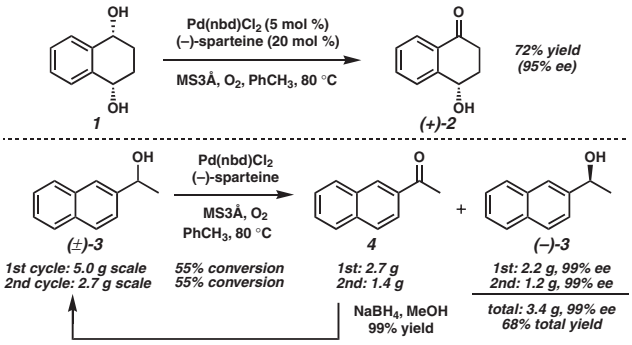
Despite the potential utility of this system for the preparation of optically pure secondary alcohols, the original conditions developed for asymmetric oxidation were rather sluggish. In certain cases (e.g., Table 1, entry 7), resolution to high enantiomeric excess was prohibitively slow for practical purposes. It was known that amounts of sparteine in excess of the moles of Pd were needed for competent catalysis. Prompted by this mechanistic clue, stoichiometric base promotion was investigated as a potential accelerant to counter this problem. In the event, Stoltz found that a mixture of Cs_2CO_3 and *t*-BuOH led to an increase in the reaction rate that enabled resolutions to be performed on a more practical timescale (Table 3).[14]

Although the accelerating effect of Cs_2CO_3 supports a base promoted reaction, the role of the *t*-BuOH was not obvious. In fact, the Sigman group subsequently reported that *t*-BuOH was

Table 1. Stoltz's aerobic oxidative kinetic resolution of secondary alcohols

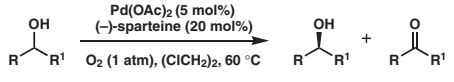


Entry	Unreacted alcohol, major enantiomer		Time/h	C/%	Isolated yield of alcohol(total)/%	ee ROH/%	s
1.		R = H	96	59.9	37 (93)	98.7	23.1
2.		R = OMe	96	66.6	32 (96)	98.1	12.3
3.		R = F	54	63.3	32 (88)	97.4	14.4
4.		Ar = 1-Naph	192	55.9	43 (97)	78.4	9.8
5.		Ar = 2-Naph	112	55.2	44 (99)	99.0	47.1
6.		Ar = *o*-tolyl	144	48.4	49 (95)	68.7	13.1
7.			192	59.3	40 (98)	93.1	14.8
8.		n = 1	54@60 °C	67.5	30 (93)	93.4	8.3
9.		n = 2	40	68.6	31 (99)	99.8	15.8
10.			120	70.4	29 (99)	91.8	6.6



Scheme 2. *Meso* diol desymmetrization and ketone recycling.

Table 2. Sigman's aerobic oxidative kinetic resolution of secondary alcohols



Entry	R	R^1	C/% (ee/%)	s
1.	C_6H_5	CH_3	65.9 (98.2)	13.0
2.	C_6H_5	CH_3CH_2	59.4 (82.0)	8.7
3.	*p*-$CH_3OC_6H_4$	CH_3	67.2 (99.0)	15.1
4.	*p*-$CH_3C_6H_4$	CH_3	60.8 (96.6)	14.0
5.	*p*-$CF_3C_6H_4$	CH_3	59.4 (83.2)	9.1
6.	*m*-$CH_3OC_6H_4$	CH_3	66.7 (98.4)	12.9
7.	*p*-FC_6H_4	CH_3	52.9 (80.7)	12.2
8.	*t*-Bu	CH_3	58.5 (77.8)	7.6

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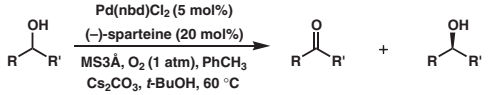
a reasonable solvent for oxidative kinetic resolution of a range of substrates, even for certain unactivated secondary alcohols.[15] Sigman's success in this regard, coupled with the rate acceleration observed by Stoltz with the Cs_2CO_3/*t*-BuOH combination led to the hypothesis that a more thorough solvent screen was needed in order to fully optimize the reaction. Of particular importance were those solvents imparting characteristics of *t*-BuOH believed to be beneficial, i.e., the ability to serve as a hydrogen bond donor and the ability to solvate charged intermediates and halide counteranions. To this end, Stoltz investigated a wide array of solvents and found that $CHCl_3$ was uniquely effective as a solvent for the oxidative kinetic resolution (Table 4).[16] Excellent selectivities were observed by employing $CHCl_3$ as the solvent. Furthermore, the solvent change allows these resolutions to be performed for the first time at 23 °C and under reduced pressures of molecular oxygen (i.e., ambient air). Under these improved conditions, alcohols are resolved with as little as a 5% O_2 in N_2.

Table 3. Stoltz's rate-accelerated oxidative kinetic resolution



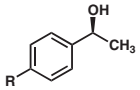
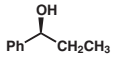
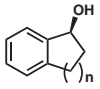
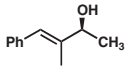
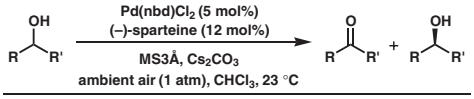
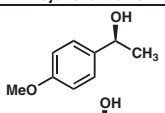
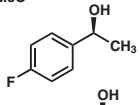
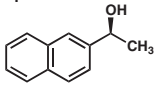
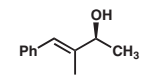
Entry	Unreacted alcohol, major enantiomer		Time/h	C/%	ee ROH/%	s
1.		R = H	12.5	63.9	99.6	20.0
2.		R = OMe	9.5	67.4	99.5	14.9
3.		R = F	12.5	65.7	97.4	12.1
4.			4.5@80 °C	62.8	98.0	16.1
5.		n = 1	12@40 °C	74.0	99.5	10.1
6.		n = 2	12	61.5	99.0	20.9
7.			12	65.1	87.9	7.5

Table 4. Stoltz's room temperature/ambient air oxidative kinetic resolution in $CHCl_3$



Entry	Unreacted alcohol, major enantiomer	Time/h	C/%	ee ROH/%	s
1.		24	62.3	99.8	25.4
2.		24	56.7	93.0	19.5
3.		24	55.5	98.0	37.3
4.		16	60.2	99.6	28.0
5.		44	64.7	98.9	15.7

Stoltz has demonstrated the use of the oxidative kinetic resolution for the asymmetric preparation of intermediates in the synthesis of a number of pharmaceutical substances (Figure 4).[17] Of particular note is the high selectivity observed in the kinetic resolution of the cyclopentenol useful for the preparation of Merck's h-NK1 receptor antagonist.

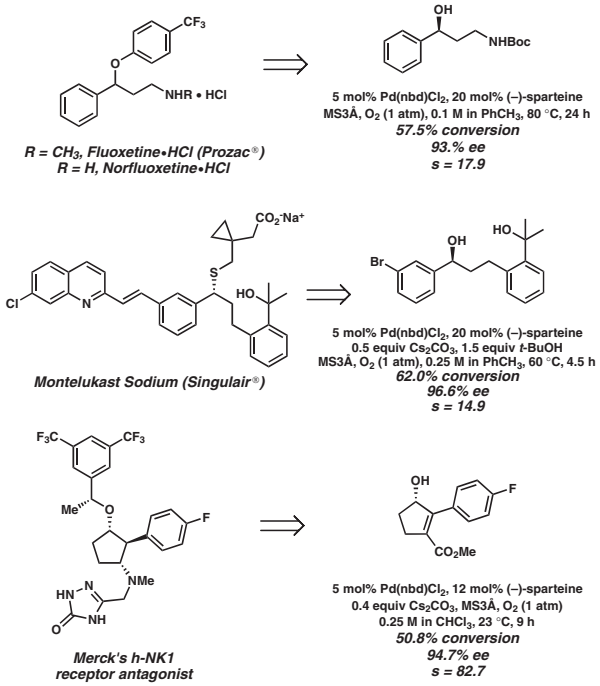


Figure 4. Oxidative kinetic resolution of pharmaceutical intermediates.

The mechanism for the palladium catalyzed oxidation of secondary alcohols presumably involves the base promoted substitution of an alkoxide for the anionic ligand of the precatalyst complex L_nPdX_2 (i.e., X = Cl^- or AcO^-) followed by β-hydride elimination.[18] In the case of the Uemura oxidation where monodentate pyridine is the ligand, this elimination presumably proceeds via a neutral Pd^{II} intermediate. By contrast, in the case of the bidentate ligand sparteine, β-hydride elimination is likely to proceed via a higher energy cationic Pd^{II}. This may account for the fact that reaction rates are much slower with bidentate ligands. Stoltz observed a marked counterion effect, with Cl^- serving as the optimal anionic ligand for Pd in the kinetic resolution.[11] Careful kinetic analyses by Stahl[19] and Sigman[20] confirmed that the rate limiting step in the both the pyridine and sparteine mediated processes is β-hydride elimination. In contrast, Stahl has found that in the DMSO-based systems oxidation of Pd^0 is rate limiting.[21] Furthermore, Sigman discovered an interesting dependence of the rate-determining step on sparteine stoichiometry.[22] While β-hydride elimination is rate determining at high sparteine concentration, at low sparteine levels, deprotonation of an intermediate alcohol complex becomes rate determining. This data corroborates the earlier observation that in the absence of additional base, the reaction does not proceed. This dual role of sparteine may be obviated by utilizing exogenous bases in the oxidative kinetic resolution.[23]

Other mechanistic work by the Stahl group has focused on the catalyst turnover steps that follow β-hydride elimination. By using a bulky bathocuproine (bc) ligand, Stahl oxidized a

(bc)Pd^0 complex to the peroxo derivative (**5**, Figure 5) with dioxygen.[24] Upon treatment of **5** with acetic acid, (bc)$Pd(OAc)_2$ is formed quantitatively, suggesting the intermediacy of such peroxo compounds in direct dioxygen coupled aerobic oxidations of Pd. A similar peroxo palladium was proposed by Larock for the DMSO based system,[25] and this mechanism has also been adopted by Sheldon for the aqueous aerobic oxidation system.[26] Alternatively, a direct insertion of O_2 into a Pd^{II}–H has been proposed by Uemura, avoiding Pd^0 altogether.[10]

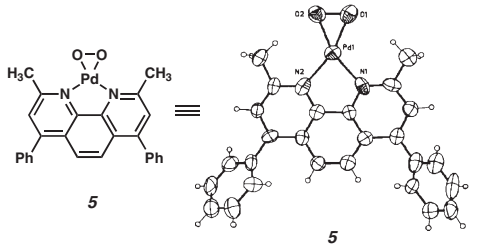


Figure 5. Stahl's peroxopalladium species **5**. (reproduced from the *J. Am. Chem. Soc.*)[24]

♦ Beyond Alcohol Oxidation: Aerobic Dehydrogenative Bond Formation, Bond Cleavage, and Ring Opening Reactions

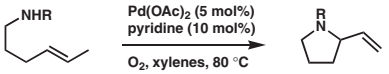
There has been considerable interest in using the previously described aerobic oxidation catalysts to perform oxidative bond forming chemistry. The classical example of such a reaction is the Wacker process, which involves Pd^{II}, an olefin (ethylene), a nucleophile (H_2O), and an oxidant (Cu^{II}/O_2). For the purposes of this *Highlight Review*, we will focus exclusively on those dehydrogenations that utilize direct dioxygen coupled catalysis in the absence of other co-oxidants.[27] Much of this work has focused on oxidative cyclization chemistry. Seminal examples by Hiemstra, Bäckvall, Andersson, and Larock took advantage of the $Pd/DMSO/O_2$ system for the oxidative cyclization of nitrogen and oxygen nucleophiles for the synthesis of a range of heterocycles.[8]

Carbon-Heteroatom Bond Formation

Recently, Stahl demonstrated that the Uemura system ($Pd(OAc)_2$, pyridine, O_2) was capable of performing oxidative amination with high catalyst activity (i.e., high turnover numbers and frequencies).[28] Recently, Stahl has implemented a similar strategy for intermolecular amination.[29]

Stoltz showed that a modified system using $Pd(TFA)_2$/pyridine/Na_2CO_3/O_2 could be applied to a variety of heterocyclization reactions of unsaturated phenolic, carboxylic acid, and alcohol derivatives (Table 6).[30] As in the oxidative kinetic resolution, a strong counteranion effect was observed, with trifluoroacetate (TFA) performing most effectively.

Table 5. Stahl's aerobic oxidative amination



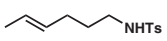
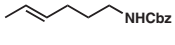
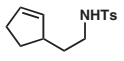
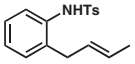
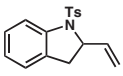
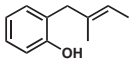
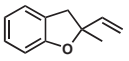
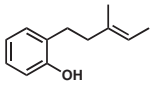
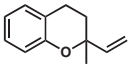
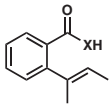
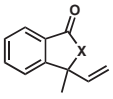
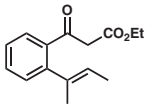
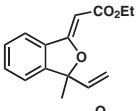
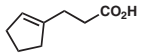
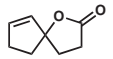
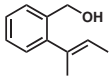
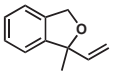
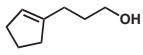
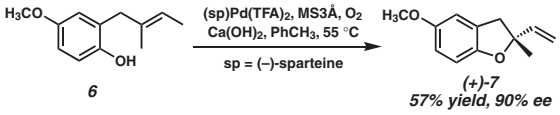
Entry	Substrate	Time/h	Product	Yield/%
1.		2		87
2.		48		76
3.		2		91
4.		1.5		91

Table 6. Stoltz's aerobic oxidative cyclizations[a]

Entry	Substrate	Product		Time, Yield/%
1.				*20 min, 95*
2.				*75 min, 85*
3.			X = O	*8 h, 90[b]*
4.			X = NTs	*8 h, 88[b]*
5.			X = NOBn	*4 h, 82[b]*
6.				*48 h, 63[c,d]*
7.				*48 h, 62[e]*
8.				*3 h, 87*
9.				*10 h, 93*

[a] 5 mol % $Pd(TFA)_2$, 20 mol % pyridine, 2 equiv. Na_2CO_3, MS3Å, 1 atm O_2, $PhCH_3$, 80 °C. [b] no added Na_2CO_3. [c] 10 mol % $Pd(TFA)_2$, 40 mol % pyridine, 2 equiv. LiOAc. [d] 3:1 Z:E. [e] 10 mol % $Pd(TFA)_2$, 40 mol % pyridine.

As an important proof-of-principle, Stoltz demonstrated that high levels of enantioselectivity were achievable under the dehydrogenative cyclization conditions by substituting sparteine for pyridine in the optimized case (Scheme 3).[30] Further studies in the area of asymmetric aerobic dehydrogenative heterocyclizations are certain to continue.

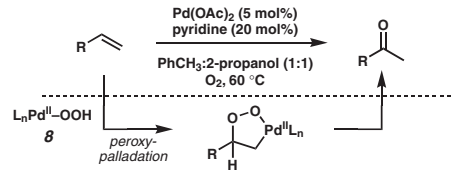


Scheme 3. Stoltz's enantioselective aerobic oxidative etherification.

Shortly after Uemura's initial report on the aerobic oxidation of alcohols, three additional applications of this catalyst system were reported by the same group. The first, in 2000, is an interesting Wacker-type oxidation of terminal alkenes (Scheme 4). Presumably, this reaction takes advantage of the palladium(II) hydroperoxide intermediate (**8**) to carry out an intermolecular peroxypalladation reaction followed by rearrangement.[31] The Pd–OOH is generated by dehydrogenation of a sacrificial alcohol (2-propanol).

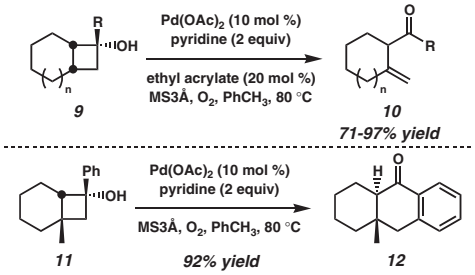
Carbon–Carbon Bond Cleavage

Uemura's second application of his oxidation system in-



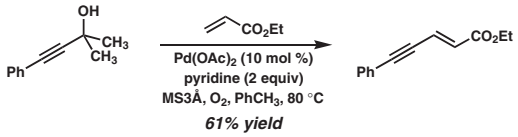
Scheme 4. Uemura's aerobic Wacker oxidation.

volves C–C bond scission.[32] Treatment of *tert*-cyclobutanols (e.g., **9**) under slightly modified conditions leads to the formation of dehydrogenative ring opened products **10**. In the case of arylated cyclobutanols (**11**), a subsequent cyclization occurs to form tricyclic products **12**.



Scheme 5. Uemura's aerobic *tert*-cyclobutanol cleavage.

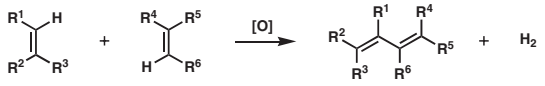
Along these lines, Uemura recently reported the oxidative C–C scission of 2-propynyl alcohols to afford enyne product by addition of a proposed Pd–acetylide to a variety of olefins followed by β-hydride elimination.[33]



Scheme 6. Uemura's aerobic 2-propynyl alcohol C–C scission.

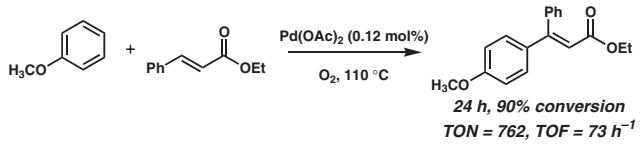
Carbon–Carbon Bond Formation

Palladium catalyzed reductive bond coupling chemistry has revolutionized organic synthetic chemistry. Conversely, palladium catalyzed aerobic dehydrogenative C–C bond forming reactions have seen relatively little investigation, although recently have been under intense study. These reactions result in the functionalization of two C–H bonds and the formation of a new C–C single bond (Scheme 7).



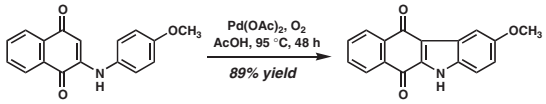
Scheme 7. Dehydrogenative C–C coupling.

Seminal contributions to olefin arylation chemistry involving stoichiometric palladium were made by Fujiwara and Heck.[34] The first report of an aerobic palladium catalyzed C–C coupling was contributed by Shue of the Phillips Petroleum Company in 1971, wherein he described the reaction of benzene and styrene to form stilbene using $Pd(OAc)_2$ and 300 psi O_2 at 100 °C.[35] Under these conditions up to 110 turnovers could be observed. Recently, Jacobs has re-investigated this coupling chemistry with a number of benzene derivatives and activated olefins, with impressive results (Scheme 8).[36] The addition of benzoic acid results in turnover numbers exceeding 750, as well as turnover frequencies of $>70\,h^{-1}$ at 90 °C.



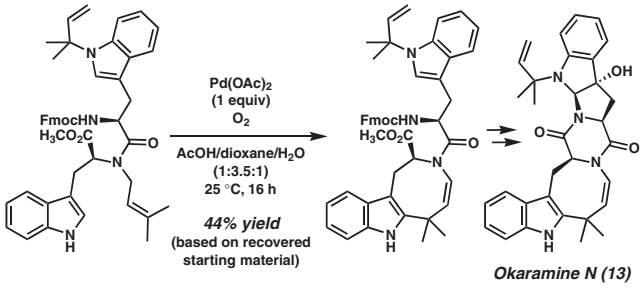
Scheme 8. Jacobs's oxidative coupling.

In the late 1970s and early 1980s Itahara extensively broadened the scope of the arylation reaction, although he obtained only modest results using O_2 as the sole stoichiometric oxidant.[37] Importantly, Itahara established the feasibility of using heterocycles, and especially indoles, as substrates in such transformations by converting *N*-acyl indoles to 3-alkenyl-*N*-acyl indoles by intermolecular and intramolecular coupling chemistry. In 1999 Åkermark reported the oxidative cyclization of arylaminoquinones shown in Scheme 9.[38] The products of these cyclizations resemble a number of natural product scaffolds (e.g., ellipticine, murrayquinone A, and kinamycin A).



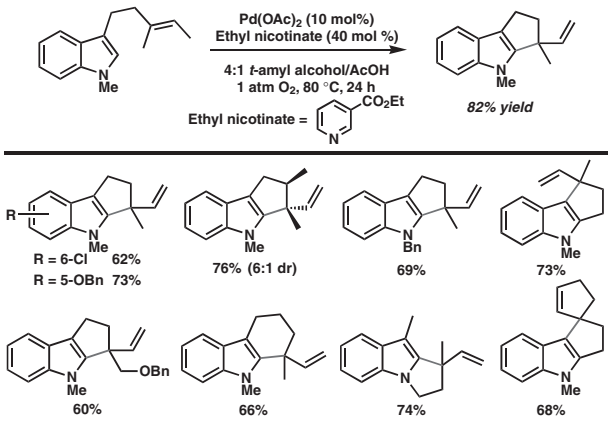
Scheme 9. Åkermark's arylaminoquinone cyclization.

Corey has utilized a palladium/dioxygen mediated oxidative cyclization strategy for the synthesis of a number of natural products, exemplified by Okaramine N (**13**).[39] Despite extensive efforts, substoichiometric quantities of palladium were not effective for the key cyclizations. Nonetheless, the preparation of highly functionalized dihydroindoloazocines by direct dehydrogenative coupling is an impressive advance in the area.

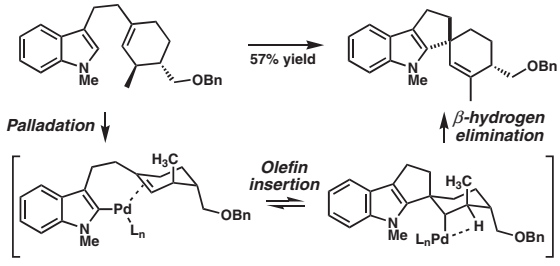


Scheme 10. Corey's Okaramine N synthesis.

In 2003, Stoltz reported the intramolecular dehydrogenative cyclization of indole derivatives using direct dioxygen coupled palladium catalysis.[40] For the first time, good yields of annulated indole products were obtained using catalytic quantities of palladium. In order to overcome a deleterious background oxidative decomposition pathway, the reaction was performed in an unusual solvent mixture of *tert*-pentyl alcohol and AcOH (4:1). Furthermore, 3-ethyl nicotinate was found to be the optimal ligand for $Pd(OAc)_2$ in the process (Scheme 11). Again, a strong counterion effect was observed in that AcO^- was uniquely effective, and all other counterions tested produced little, if any, carbocyclized products. Finally, the stereochemical outcome of the reaction indicates that the reaction proceeds via indole pallada-



Scheme 11. Stoltz's aerobic indole annulation. The bond formed in the cyclization is highlighted in red.



Scheme 12. Mechanism for the aerobic indole annulation.

tion (C–H bond functionalization) followed by olefin insertion and β-hydride elimination (Scheme 12). The implications of this mechanism for other C–C bond coupling reactions are the subject of current investigations.

♦ Conclusions

The direct dioxygen coupled palladium catalyzed dehydrogenation of organic molecules is currently a subject of intense study. Recent use of N-based ligands for palladium have paved the way for a number of advances in this broad area of non-heteroatom transfer oxidation chemistry. The prospects for asymmetric induction appear to be good, and have been demonstrated in the cases of the alcohol oxidative kinetic resolution, the oxidative desymmetrization of *meso* diols, and the dehydrogenative cyclization of unsaturated phenols. Given the ubiquity of dehydrogenation as a general organic transformation, it is certain that further advances await discovery.

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References and Notes

1 a) R. A. Johnson and K. B. Sharpless, in "Catalytic Asymmetric Synthesis," ed. by I. Ojima, Wiley & Sons, New York (2000), p 231. b) T. Katsuki, in "Catalytic Asymmetric Synthesis," ed. by I. Ojima, Wiley & Sons, New York (2000), p 287.
2 T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980).
3 S. D. Rychnovsky, T. L. McLernon, and H. Rajapakse, *J. Org. Chem.*, **61**, 1194 (1996).
4 S. Hashiguchi, A. Fujii, K.-J. Haack, K. Matsumura, T. Ikariya, and R. Noyori, *Angew. Chem., Int. Ed. Engl.*, **36**, 288 (1997).
5 Recently, other approaches have emerged, see: a) K. Masutani, T. Uchida, R. Irie, and T. Katsuki, *Tetrahedron Lett.*, **41**, 5119 (2000). b) Y. Nishibayashi, A. Yamauchi, G. Onodera, and S. Uemura, *J. Org. Chem.*, **68**, 5875 (2003). c) W. Sun, H. Wang, C. Xia, J. Li, and P. Zhao, *Angew. Chem., Int. Ed.*, **42**, 1042 (2003).
6 H. Wieland, *Ber.*, **45**, 484 (1912).
7 T. F. Blackburn and J. Schwartz, *J. Chem. Soc., Chem. Commun.*, **1977**, 157.
8 a) R. A. T. M. van Benthem, H. Hiemstra, and W. N. Speckamp, *J. Org. Chem.*, **57**, 6083 (1992). b) M. Rönn, J.-E. Bäckvall, and P. G. Andersson, *Tetrahedron Lett.*, **36**, 7749 (1995). c) R. C. Larock, T. R. Hightower, L. A. Hasvold, and K. P. Peterson, *J. Org. Chem.*, **61**, 3584 (1996).
9 G.-J. ten Brink, I. W. C. E. Arends, and R. A. Sheldon, *Science*, **287**, 1636 (2000).
10 a) T. Nishimura, T. Onoue, K. Ohe, and S. Uemura, *Tetrahedron Lett.*, **39**, 6011 (1998). b) T. Nishimura, T. Onoue, K. Ohe, and S. Uemura, *J. Org. Chem.*, **64**, 6750 (1999).
11 E. M. Ferreira and B. M. Stoltz, *J. Am. Chem. Soc.*, **123**, 7725 (2001).
12 D. R. Jensen, J. S. Pugsley, and M. S. Sigman, *J. Am. Chem. Soc.*, **123**, 7475 (2001).
13 The selectivity factor (s) was determined using the equation: $s = k_{rel(fast/slow)} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion. See: H. B. Kagan and J. C. Fiaud, in "Topics in Stereochemistry," ed. by E. L. Eliel, Wiley & Sons, New York (1988), Vol. 18, p 249.
14 J. T. Bagdanoff, E. M. Ferreira, and B. M. Stoltz, *Org. Lett.*, **5**, 835 (2003).
15 S. K. Mandal, D. R. Jensen, J. S. Pugsley, and M. S. Sigman, *J. Org. Chem.*, **68**, 4600 (2003).
16 J. T. Bagdanoff and B. M. Stoltz, *Angew. Chem., Int. Ed.*, **43**, 353 (2004).
17 D. D. Caspi, D. C. Ebner, J. T. Bagdanoff, and B. M. Stoltz, *Adv. Synth. Catal.*, **346**, in press (2004).
18 R. A. Sheldon and I. W. C. E. Arends, in "Advances in Catalytic Activation of Dioxygen by Metal Complexes," ed. by L. I. Simándi, Kluwer, Dordrecht (2003), Vol. 26, Chap. 3, p 123.
19 B. A. Steinhoff and S. S. Stahl, *Org. Lett.*, **4**, 4179 (2002).
20 J. A. Mueller and M. S. Sigman, *J. Am. Chem. Soc.*, **125**, 7005 (2003).
21 B. A. Steinhoff, S. R. Fix, and S. S. Stahl, *J. Am. Chem. Soc.*, **124**, 766 (2002).
22 a) J. A. Mueller, D. R. Jensen, and M. S. Sigman, *J. Am. Chem. Soc.*, **124**, 8202 (2002). b) D. R. Jensen and M. S. Sigman, *Org. Lett.*, **5**, 63 (2003).
23 a) see ref 14. b) S. K. Mandal and M. S. Sigman, *J. Org. Chem.*, **68**, 7535 (2003).
24 S. S. Stahl, J. L. Thorman, R. C. Nelson, and M. A. Kozee, *J. Am. Chem. Soc.*, **123**, 7188 (2001).
25 R. C. Larock, T. R. Hightower, G. A. Kraus, P. Hahn, and D. Zheng, *Tetrahedron Lett.*, **36**, 2423 (1995).
26 G.-J. ten Brink, I. W. C. E. Arends, M. Hoogenraad, G. Verspui, and R. A. Sheldon, *Adv. Synth. Catal.*, **345**, 497 (2003).
27 Hosokawa and Hayashi have extensively studied non-aerobic enantioselective palladium catalyzed oxidative cyclizations, see: a) T. Hosokawa, T. Uno, S. Inui, and S.-I. Murahashi, *J. Am. Chem. Soc.*, **103**, 2318 (1981). b) Y. Uozumi, K. Kato, and T. Hayashi, *J. Org. Chem.*, **63**, 5071 (1998).
28 S. R. Fix, J. L. Brice, and S. S. Stahl, *Angew. Chem., Int. Ed.*, **41**, 164 (2002).
29 V. I. Timokhin, N. R. Anastasi, and S. S. Stahl, *J. Am. Chem. Soc.*, **125**, 12996 (2003).
30 R. M. Trend, Y. K. Ramtohul, E. M. Ferreira, and B. M. Stoltz, *Angew. Chem., Int. Ed.*, **42**, 2892 (2003).
31 T. Nishimura, N. Kakiuchi, T. Onoue, K. Ohe, and S. Uemura, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1915.
32 a) T. Nishimura, K. Ohe, and S. Uemura, *J. Am. Chem. Soc.*, **121**, 2645 (1999). b) T. Nishimura, K. Ohe, and S. Uemura, *J. Org. Chem.*, **66**, 1455 (2001).
33 T. Nishimura, H. Araki, Y. Maeda, and S. Uemura, *Org. Lett.*, **5**, 2997 (2003).
34 a) Y. Fujiwara, I. Moritani, M. Matsuda, and S. Teranishi, *Tetrahedron Lett.*, **1968**, 3863. b) R. F. Heck, *J. Am. Chem. Soc.*, **90**, 5518 (1968).
35 R. S. Shue, *J. Chem. Soc., Chem. Commun.*, **1971**, 1510.
36 M. Dams, D. E. De Vos, S. Celen, and P. A. Jacobs, *Angew. Chem., Int. Ed.*, **42**, 3512 (2003).
37 T. Itahara, M. Ikeda, and T. Sakakibara, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1361.
38 H. Hagelin, J. D. Oslob, and B. Åkermark, *Chem.—Eur. J.*, **5**, 2413 (1999).
39 P. S. Baran, C. A. Guerrero, and E. J. Corey, *J. Am. Chem. Soc.*, **125**, 5628 (2003).
40 E. M. Ferreira and B. M. Stoltz, *J. Am. Chem. Soc.*, **125**, 9578 (2003).