Synthetic Methods

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Aerobic Oxidative Heck/Dehydrogenation Reactions of Cyclohexenones: Efficient Access to *meta*-Substituted Phenols**

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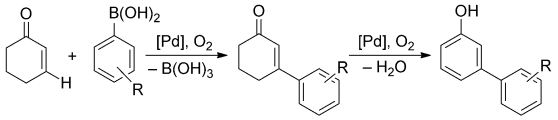
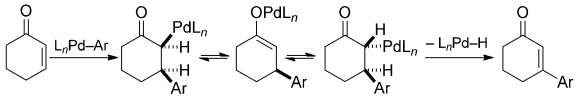
Phenol derivatives are common and important structural motifs in bioactive natural products and pharmaceuticals,[1] and the selective synthesis of substituted phenols is facilated by the strong *ortho*/*para*-directing effect of the hydroxy group. The same directing effect, however, limits access to analogous *meta*-substituted derivatives. In recent years, considerable efforts have targeted C–H functionalization reactions which enable preparation of *meta*-substituted arenes by steric[2] or directing-group[3] control over the site selectivity. The overall efficiency of these methods is often limited by functional-group interconversions or installation and removal of directing groups needed to access the final product.[4] Moreover, in molecules with more than one electronically or sterically active substituent, competition between the directing groups can lead to product mixtures. Following our recent development of palladium-catalyzed aerobic dehydrogenation reactions of ketones,[5–7] we envisioned that *meta*-substituted phenols could be accessed efficiently by an aerobic oxidative Heck/dehydrogenation sequence with cyclohexenone (Scheme 1).[8] Cyclohexenone is a convenient and inexpensive



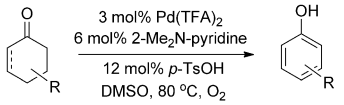
Scheme 1. Strategy for the synthesis of *meta*-substituted phenols.

phenol precursor, and the proposed strategy exploits the intrinsic regioselectivity of additions to electron-deficient alkenes to enable functionalization of the *meta* C–H bond. Herein, we describe a new palladium catalyst and reaction conditions compatible with this sequence, and we showcase their utility in the synthesis of a pharmaceutically active phenol derivative.

The proposed sequence in Scheme 1 faces several challenges. The oxidative Heck reaction must be more facile than the dehydrogenation step to avoid direct conversion of the cyclohexenone starting material into an unsubstituted phenol. Furthermore, while aerobic oxidative Heck reactions have extensive precedent with terminal alkenes,[9,10] analogous reactions with cyclohexenone tend to be more difficult.[11,12] With this substrate, the palladium(II) enolate must isomerize to place the palladium atom on the opposite side of the ring to undergo β-hydride elimination (Scheme 2).[13] Finally, the catalyst and reaction conditions must be compatible with both reactions in the sequence. The only general method for dehydrogenation of cyclohexenones to phenols employs a strong acid additive (*p*-TsOH; Scheme 3),[5a] which interferes with oxidative Heck reactions.[14]



Scheme 2. Mechanistic steps highlighting the requirement for isomerization of the palladium(II) enolate intermediate in Heck reactions of cyclohexenone.



Scheme 3. Previously reported aerobic dehydrogenation conditions for the synthesis of phenols. DMSO = dimethylsulfoxide, TFA = trifluoroacetate, Ts = 4-toluenesulfonyl.

Our initial studies targeted the identification of non-acidic reaction conditions for aerobic dehydrogenation of 3-methylcyclohexenone. Upon screening diverse PdX_2 sources, ligands, additives, and solvents (see the Supporting Information for full screening data), we found that the dicationic palladium(II) complex $[Pd(CH_3CN)_4](BF_4)_2$ was particularly effective as a catalyst (Table 1). Formation of palladium black and gradual loss of catalytic activity during the reaction prompted us to test ancillary ligands to stabilize the catalyst. Most of the ligands tested inhibited the reaction (Table 1 and the Supporting Information). However, 4,5-diazafluorenone (**L4**)[15] and 6,6′-dimethyl-2,2′-bipyridine (**L5**) enabled good product yields to be obtained. While screening of numerous additives, including Brønsted bases, copper(II) and silver(I) salts, and quinones showed little beneficial effect, nearly quantitative yield of the phenol product (95%) was obtained when 9 mol% AMS (anthraquinone-2-sulfonic acid sodium salt) was included in the reaction with the ligand **L5**.[16] The

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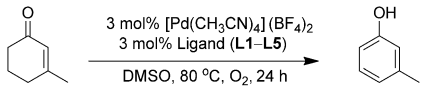
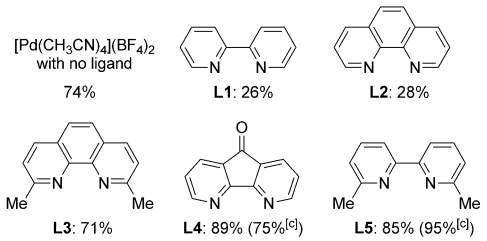
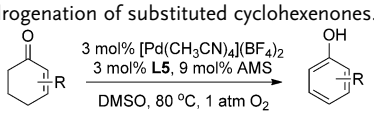
Table 1: Dehydrogenation of 3-cyclohexenones: Screening results.[a,b]

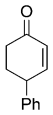
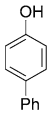
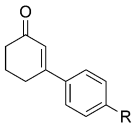
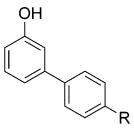




[a] Reactions were performed on a 1.0 mmol scale in DMSO (0.2 mL), 1 atm O_2. [b] Product yield determined by GC analysis. [c] H_2O (0.05 mL) and AMS (0.09 mmol) were added. Reaction time: 6.5 h. See the Supporting Information for details.

Table 2: Dehydrogenation of substituted cyclohexenones.[a]



Entry	Cyclohexenone	Phenol	*t* [h]	Yield [%][b]
1			10	90[c]
2		 R = Ph	10	96[c]
3		R = CH_2(*N*-pip)[d]	36	46
4		R = CH_2CO_2Me	6.5	63
5			10	87
6		 R = Ac	24	77
7		R = CO_2Me	24	73
8		R = CF_3	12	68
9		 R = H	10	89
10		R = CHO	10	52[c]
11		R = OH	10	83

[a] Reactions were performed on a 1.0 mmol scale in DMSO/H_2O (v/v 0.2/0.05 mL). [b] Yield of isolated product. [c] Pd^{II}/**L5**/AMS = 5%/5%/15%. [d] pip = piperidyl.

optimal result was obtained upon addition of water (20 vol%) to enhance the solubility of AMS.

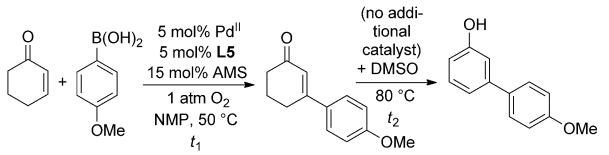
The optimized reaction conditions proved to be effective with a number other substituted cyclohexenones, including those with heteroatom substituents (Table 2). These neutral reaction conditions revealed some advantages over the previously reported reaction conditions in Scheme 3. For example, 6-phenylcyclohexanone underwent dehydrogenation to *o*-phenyl phenol in only 33% yield under the previous reaction conditions, but this product is obtained in excellent yields under the present reaction conditions (entries 1 and 2). The successful reaction of 3-arylcyclohexenones, prepared by oxidative Heck reactions with cyclohexenone (entries 9–11), provided a useful starting point for the investigation of oxidative Heck and tandem oxidative Heck/dehydrogenation reactions.

Preliminary experiments showed that this catalyst was quite effective for the oxidative Heck coupling of 4-methoxyphenylboronic acid and cyclohexenone. Moreover, the reaction could take place at 50°C, a temperature at which no conversion of cyclohexenone into phenol was observed. In DMSO, the oxidative Heck reaction proceeded in 65% yield. Upon heating of this reaction mixture to 80°C, nearly complete in situ conversion into the 3-aryl phenol was observed (i.e., 64% yield of the phenol; Table 3, entry 1). Several other solvents, including *N*,*N*-dimethylformamide (DMF), *N*-methylpyrrolidone (NMP) and 1,4-dioxane, proved to be better for the oxidative Heck reaction (entries 2–7). However, they proved less effective for the tandem sequence (e.g., entry 2). Further studies revealed that an effective one-pot sequence could be achieved by performing the oxidative Heck reaction in NMP at 50°C with subsequent addition of DMSO and heating to 80°C for the dehydrogenation step. This protocol enabled a good yield of the phenol to be obtained (84%, entry 12).

$[Pd(CH_3CN)_4](BF_4)_2$/**L5** proved to be very effective as a stand-alone catalyst for the oxidative Heck reactions with cyclohexenone. Good yields of the 3-arylcyclohexenones were obtained with a variety of arylboronic acids (Table 4). Reactions with the electron-rich arylboronic acids typically led to higher yields than those obtained with electron-deficient substrates, as the latter substrates were more susceptible to the formation of homocoupling products. Halogenated arylboronic acids (X = F, Cl, Br) were tolerated in the oxidative Heck reaction, with yields ranging from 68 to 86% (entries 4–6 and 18). The same arylboronic acids were then employed in the one-pot oxidative Heck/dehydrogenation to afford the 3-substituted phenol derivatives. In most cases, the phenol yields correlate closely with the yields of the 3-aryl cyclohexenones in the independent oxidative Heck reaction.

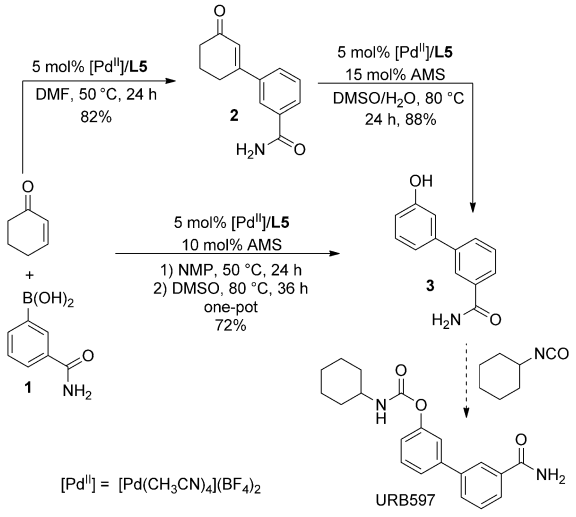
To demonstrate the potential utility of the aerobic oxidative Heck/dehydrogenation sequence and further test its functional-group compatibility, we investigated the synthesis of URB597 from cyclohexenone and the commercially available benzamide-derived boronic acid **1** (Scheme 4). URB597 is a potent inhibitor of fatty acid amide hydrolase (FAAH) and an important focus of efforts to treat pain, anxiety, and depression.[17,18] The phenol intermediate **3** was prepared by a stepwise oxidative Heck coupling of **1** and

Table 3: Optimization of the reaction conditions for the oxidative Heck and one-pot oxidative Heck/dehydrogenation reactions.[a]



Entry	Oxidative Heck				Oxidative Heck/dehydrogenation		
	Solvent	Conc. [M][b]	t_1 [h]	Yield [%][c]	Solvent	t_2 [h]	Yield [%][d]
1	DMSO	1.3	8	65	–	24	64
2	DMF	1.3	3	95	–	24	25[e]
3	NMP	1.3	3	90	–	–	–
4	1,4-dioxane	1.3	3	93	–	–	–
5	CH_3CN	1.3	3	73	–	–	–
6	DMF	2.5	3	96	–	–	–
7	DMF	5.0	3	80	–	–	–
8	DMF	2.5	3	–	DMSO	24	54
9	NMP	2.5	3	–	DMSO	24	72
10	NMP	3.1	3	–	DMSO	24	82
11[f]	NMP	3.1	3	–	DMSO	32	82
12[f,g]	NMP	3.1	4	95	DMSO	32	84

[a] Reaction conditions: Heck reactions [cyclohexenone (0.75 mmol), boronic acid (0.25 mmol), $Pd^{II} = [Pd(CH_3CN)_4](BF_4)_2$, 50 °C, 3-8 h]; dehydrogenation: *T* increased to 80 °C, 24–32 h (for entries 8–12, 0.2 mL DMSO added). [b] Concentration of boronic acid. [c] Yield determined by GC analysis. [d] Yield determined by ^1H NMR spectroscopy. [e] Recovered 65% of Heck product. [f] Used 10% AMS. [g] Used 0.5 mmol cyclohexenone.

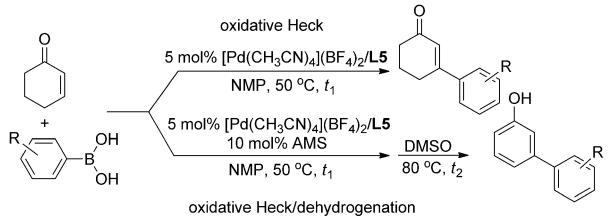


Scheme 4. Application of one-pot oxidative Heck/dehydrogenation reactions in the synthesis of URB597.

cyclohexenone, followed by catalytic dehydrogenation of the isolated intermediate **2**, and in a direct, one-pot process. The $[Pd(CH_3CN)_4](BF_4)_2$/**L5** catalyst was employed for each of these steps, and both pathways led to the phenol product **3** in good yield (ca. 72%, in each case).

The results above highlight a new catalyst system that mediates both aerobic oxidative Heck reactions with cyclohexenone and aerobic dehydrogenation of cyclohexenones. The one-pot sequence developed for these reactions represents an efficient strategy for the preparation of *meta*-substituted of phenols, which should be advantageous or highly competitive with other approaches based on C–H functionalization of an aromatic ring.

Table 4: Oxidative Heck and one-pot oxidative Heck/dehydrogenation reactions to prepare substituted cyclohexenones and phenols.[a]



Entry	R	Oxidative Heck		Oxidative Heck/dehydrogenation	
		t_1 [h]	Yield [%][b]	t_2 [h]	Yield [%][c]
1	*p*-Me	4	97	32	91
2	*p*-*t*Bu	4	98	36	85
3	*p*-MeO	4	94	32	80
4	*p*-Cl	4	85	32	68
5	*p*-Br	4	65	32	41
6	*p*-F	4	86	32	87
7	*p*-OH	4	85	32	64
8	*p*-Ph	13	62	36	63
9	*p*-COOMe	4	86	32	74
10	*p*-CF_3	4	56	32	40
11	*p*-CN	13	41	36	35
12	*p*-H	4	76	32	75
13	*m*-MeO	13	83	36	47
14	*m*-Me	13	89	36	76
15	*m*-NO_2	13	48	36	42
16	*m*-CF_3	4	68	32	60
17	*o*-Me	13	73	36	58
18	*o*-F	13	75	36	66

[a] Reactions conditions: cyclohexenone (0.5 mmol), arylboronic acid (0.25 mmol) in NMP (0.2 mL for Heck and 0.08 mL for one-pot) at 50 °C for Heck reactions. For the one-pot reactions, DMSO was then added and the reactions were continued at 80 °C for 32 or 36 h. See the Supporting Information for details. [b] Yields of the isolated 3-substituted cyclohexenones. [c] Yields of the isolated phenols.

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Communications

Synthetic Methods

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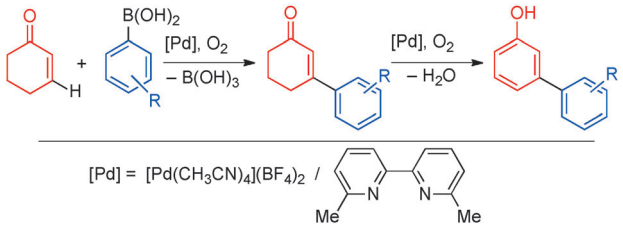
Aerobic Oxidative Heck/Dehydrogenation Reactions of Cyclohexenones: Efficient Access to *meta*-Substituted Phenols



Jockeying for the (*meta*)position: A new dicationic palladium(II) catalyst, employing a 6,6′-dimethyl-2,2′-bipyridine ligand, promotes both the aerobic oxidative Heck coupling and dehydrogenation reactions of cyclohexenones. These reactions may be combined in a one-pot sequence to enable the straightforward synthesis of *meta*-substituted phenols (see scheme).