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Palladium-Catalyzed Aerobic Oxidative Dehydrogenation of Cyclohexenes to Substituted Arene Derivatives

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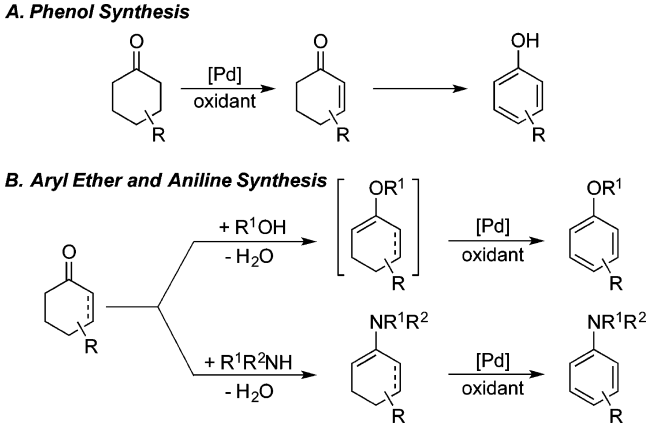
Supporting Information

ABSTRACT: A palladium(II) catalyst system has been identified for aerobic dehydrogenation of substituted cyclohexenes to the corresponding arene derivatives. Use of sodium anthraquinone-2-sulfonate (AMS) as a cocatalyst enhances the product yields. A wide range of functional groups are tolerated in the reactions, and the scope and limitations of the method are described. The catalytic dehydrogenation of cyclohexenes is showcased in an efficient route to a phthalimide-based TRPA1 activity modulator.

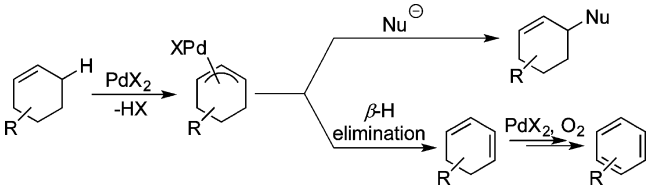
Aromatic rings are ubiquitous in industrial chemicals, ranging from commodities to pharmaceuticals. New reactions for the preparation of substituted aromatic molecules, particularly those that access selectivity patterns different from existing methods, could have a major impact on organic chemical synthesis.[1] The synthesis of substituted aromatic molecules is often achieved via sequential introduction of substituents around the periphery of the aromatic ring. Common synthetic methods include classical nucleo- and electrophilic substitution reactions, catalytic cross-coupling reactions, and modern C−H functionalization methods.[2] Recently, we have pursued a complementary strategy, involving oxidative dehydrogenation of (partially) saturated carbocycles to afford substituted aromatic compounds.[3] This concept was recently illustrated in Pd-catalyzed methods for dehydrogenation of cyclohexanones to phenols (Scheme 1A).[3a,b,4] Analogous approaches have been used to access other aromatic compounds, such as aryl ethers[5] and aniline derivatives[6,7] (Scheme 1B). Many of these methods utilize cyclohexanone and -hexenone derivatives as starting materials (cf. Scheme 1). Substituted cyclohexenes represent another appealing class of precursors to arenes. Cyclohexenes are readily available through a variety of methods, such as Diels−Alder cycloadditions, that install diverse substituent patterns around six-membered carbon rings.

The dehydrogenation of cyclohexenes could proceed by Pd^{II}-mediated activation of an allylic C−H bond, followed by β-hydrogen elimination from the resulting Pd^{II}-allyl intermediate (Scheme 2, bottom pathway).[8] The latter step differs from the more established reactivity of π-allyl-Pd^{II} species with nucleophiles (Scheme 2, top pathway).[9] Previous studies of allylic C−H oxidation of cyclohexene have observed formation of benzene as a side product.[10] Development of the latter oxidative dehydrogenation chemistry as a synthetically useful method has received very little attention, however, with precedents typically limited to cyclohexene or similarly simple precursors.[11] One exception is a recent study by Kandukuri and Oestrich, who observed aromatization of a cyclohexene substituent in the study of intramolecular oxidative C−C coupling reactions with indole substrates.[12] Earlier studies were often complicated by competing disproportionation of the cyclohexene into cyclohexane and benzene (eq 1; i.e., with cyclohexene serving as the hydrogen acceptor).[11a,b,f] The present study describes an effective Pd^{II}-catalyzed method for aerobic dehydrogenation of diverse cyclohexenes to substituted aromatics, without competing disproportionation.[13] The results illustrate important new dehydrogenative reactions that use O_2 as the terminal oxidant, which provide the basis for replacement of undesirable, yet

Scheme 1. Oxidative Dehydrogenation of Cyclic Ketones To Access Aromatic Compounds



Scheme 2. Pd-Catalyzed Reactions of Cyclohexene: Allylic C−H Oxidation or Oxidative Dehydrogenation



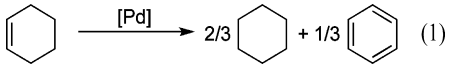


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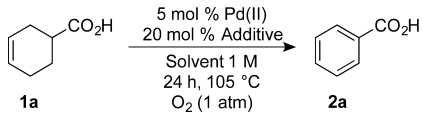
Table 1. Optimization of Reaction Conditions[a]



1a 2a

entry	Pd(II)	solvent	additive	yield (conv.)[b]
1	$PdCl_2$	mesitylene	–	0 (21)
2	$Pd(OAc)_2$	mesitylene	–	30 (82)
3	$Pd(TFA)_2$	mesitylene	–	32 (98)
4	$Pd(TFA)_2$	diglyme	–	62 (100)
5	$Pd(TFA)_2$	DMSO	–	4 (29)
6	$Pd(TFA)_2$	PhCl	–	71 (93)
7	$Pd(TFA)_2$	PhCl	$Cu(TFA)_2$	5 (100)
8	$Pd(TFA)_2$	PhCl	AgTFA	3 (27)
9	$Pd(TFA)_2$	PhCl	benzoquinone	36 (64)
10	$Pd(TFA)_2$	PhCl	anthraquinone	92 (100)
11	**$Pd(TFA)_2$**	**PhCl**	**AMS[c]**	**99 (100)**
12[d]	$Pd(TFA)_2$	PhCl	AMS[c]	89 (100)
13	$Pd(TFA)_2$	$PhCF_3$	AMS[c]	89 (100)
14[e]	$Pd(TFA)_2$	PhCl	AMS[c]	85 (100)

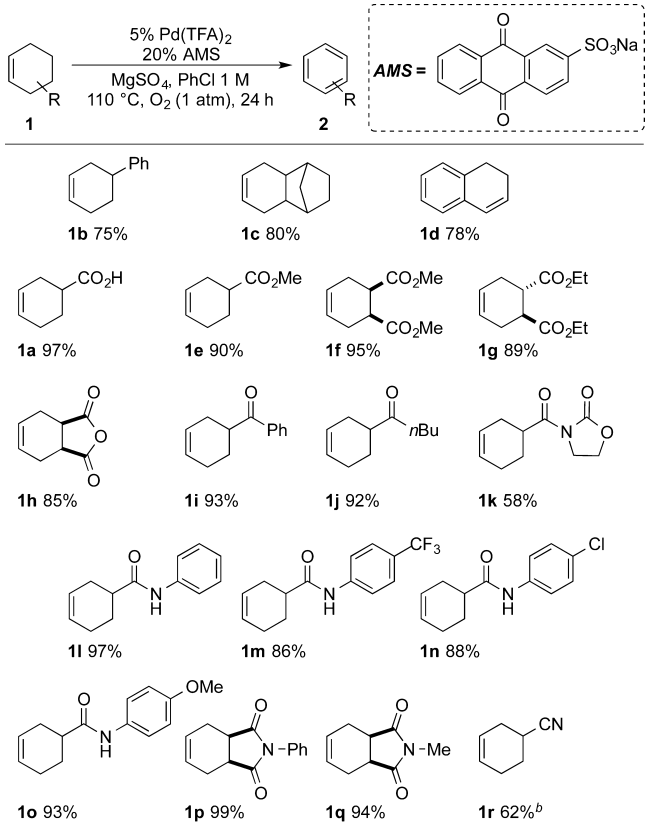
[a]Conditions: **1a** (0.25 mmol), 1 atm of O_2, orbital mixing, 105 °C. [b]% Determined by ^{1}H NMR using a standard. [c]AMS = sodium anthraquinone-2-sulfonate. [d]Reaction performed on 10 mmol scale; isolated yield. [e]Reaction performed with 1 mol % $Pd(TFA)_2$ and 4 mol % AMS.

widely used, stoichiometric oxidants such as DDQ[14] and Mn oxides.[15]

A cyclohexene bearing a remote carboxylic acid (**1a**, Table 1) was used in our initial evaluation of oxidative dehydrogenation conditions with $PdCl_2$, $Pd(OAc)_2$, and $Pd(TFA)_2$ (TFA = trifluoroacetate) at 5 mol % loading (see Table S1 in the Supporting Information for full screening data). $Pd(TFA)_2$ led to complete conversion of the substrate and a slightly higher yield than $Pd(OAc)_2$, and it was evaluated under additional reaction conditions. Significantly improved yields were observed with diglyme (62%) and chlorobenzene (71%) as solvents. Use of Cu^{II} and Ag^{I} cocatalysts led to a significant reduction in yield, and the use of benzoquinone also had an inhibitory effect. A notable improvement was observed, however, with cocatalytic quantities of anthraquinone (entry 10). The best result was obtained with sodium anthraquinone-2-sulfonate (AMS), a quinone cocatalyst previously used by Sheldon to avoid disproportionation in the dehydrogenation of the parent cyclohexene.[11b] These conditions were successfully implemented on a larger scale (10 mmol, entry 12). Use of $PhCF_3$ rather than chlorobenzene as the solvent led to similarly good results (entry 13), and a high product yield was possible even with a 1 mol % Pd catalyst loading (entry 14).

With these conditions in hand, we evaluated a number of readily available cyclohexenes containing diverse functional groups, mainly in the 4- and 5-position of the cyclohexene ring (Table 2).[16] Aromatic and alkyl substituents are well tolerated (**1b–d**), and dehydrogenation of substrates containing ester, diester, cyclic anhydride, ketone, and imide functionalities also proceed well under the standard reaction conditions (**1e–k**). The relative stereochemistry of the ester functionalities in **1f** and **1g** did not have an effect on the reaction yield. *N*-Aryl amides with $-CF_3$, $-Cl$, and $-OMe$ groups on the aryl moiety, as well as a nitrile, were well tolerated (**1l–k**, **1r**). *N*-Substituted imides were also successfully dehydrogenated to the corresponding phthalimides (**1p, q**). In all cases, the competing cyclohexane disproportionation product was not observed. Overall, the

Table 2. Dehydrogenation of Various Cyclohexenes to the Corresponding Arene Derivatives[a]

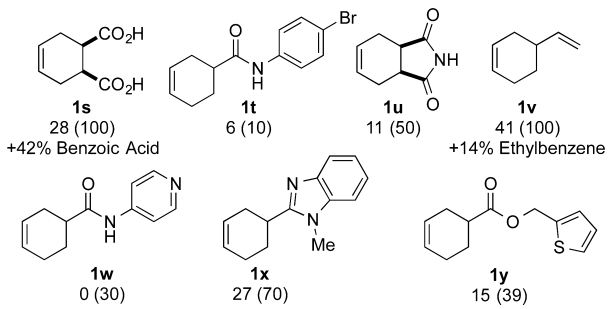


[a]Conditions: Substrate (1.0 mmol), magnetic stirring, 110 °C. Yield represents amount of isolated product. [b]Low yield due to volatility of the product.

reactions are consistent with the allylic C–H activation pathway shown in Scheme 2; however, initiation of the reaction by activation of an acidic C–H bond adjacent to a carbonyl group cannot be excluded with a number of the substrates.

During the course of this study, several less successful substrates were identified (Chart 1). For the diacid **1s**, only a 28% yield of *o*-phthalic acid was obtained, together with significant amounts of the decarboxylation product, benzoic acid. The *N*-aryl amide bearing a bromide substituent **1t** and the cyclohexenyl imide with a free N–H group **1u** proceed in very low yield, accompanied by unidentified side products.[17]

Chart 1. Less Successful Dehydrogenation Substrates[a]



[a]Conditions: Cyclohexene (0.25 mmol), $Pd(TFA)_2$ (5%), AMS (20%), PhCl (1 M), 1 atm of O_2, orbital mixing, 105 °C. Yield (Conversion) determined by ^{1}H NMR using a standard.

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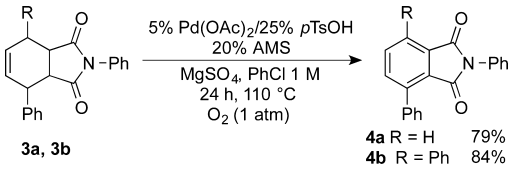
Dehydrogenation of 4-vinyl cyclohexene **1v** (a dimer of 1,3-butadiene) leads to a mixture of styrene and ethylbenzene. The latter reactivity has been observed previously with other Pd-based catalyst systems and presumably arises from isomerization of the exocyclic double bond into the ring prior to dehydrogenation.[11c,g] Additional substrates bearing *N*-heterocycles, such as pyridine (**1w**) and benzimidazole (**1x**), as well as a thiophene containing substrate (**1y**) were also tested under the reaction conditions, but provided low yields of product.

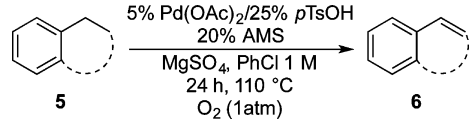
The *N*-phenylsuccinimide substrates **3a** and **3b** derived from Diels–Alder cycloadditions of *N*-phenylmaleimide (Scheme 3) also led to relatively poor product yields with the parent catalyst system (≤45%). The lower reactivity of these substrates, with substituents adjacent to the alkene, seemed likely to be associated with steric effects. We reasoned that this complication could potentially be overcome with a more electrophilic catalyst that has higher affinity for the alkene. Addition of *p*TsOH to $Pd(OAc)_2$ forms $Pd(OTs)_2$ in situ,[18] and the $Pd(OAc)_2$/*p*TsOH combination proved to be effective for dehydrogenation of the cyclohexene precursors to phthalimides **4a** and **4b** (79% and 84% yields, respectively).

Scheme 3. Synthesis of Tri- and Tetrasubstituted Phthalimide Derivatives



Pd^{II}-mediated benzylic C–H bond activation has less precedent and is more challenging than allylic C–H activation.[19] A preliminary effort to achieve dehydrogenation of 1,2,3,4-tetrahydronaphthalene, 9,10-dihydrophenanthrene, and 2,3-dihydrobenzofuran as prototypical substrates reveals that the initial $Pd(TFA)_2$ catalyst system was ineffective. The $Pd(OAc)_2$/*p*TsOH catalyst system showed promising results (Table 3). Although product yields from these reactions are modest, they represent a good starting point for future catalyst development efforts and show marked improvement over a previously attempted Pd^{II}-catalyzed aerobic dehydrogenation of tetrahydronaphthalene, which exhibited only stoichiometric reactivity with respect to Pd^{II} (i.e., 2 equiv).[11f]

Table 3. Dehydrogenation at Benzylic Positions[a]

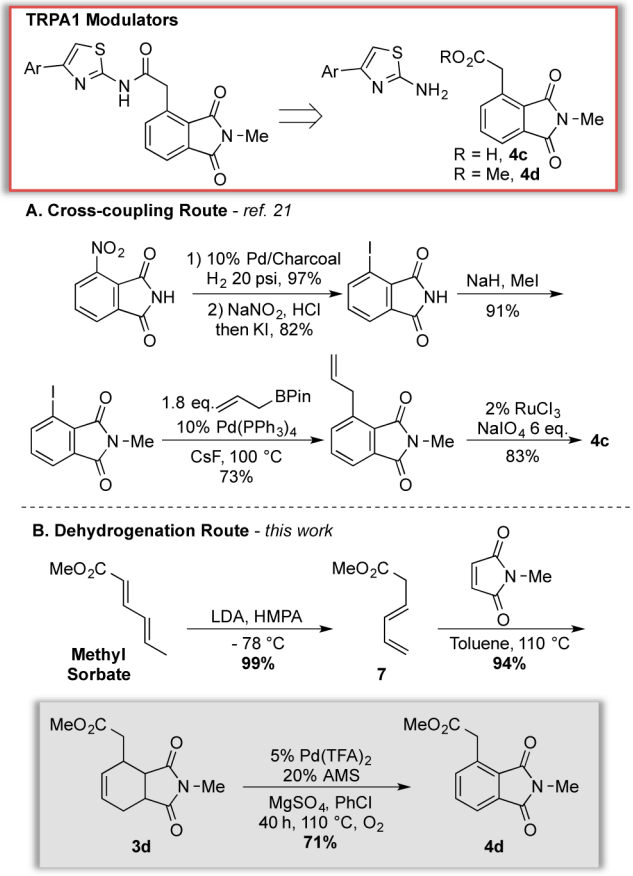


Substrate	Product	Yield (Conv.)
5a	**6a**	31 (34)
5b	**6b**	53 (61)
5c	**6c**	62 (100)

[a]Conditions: Substrate (0.25 mmol), orbital stirring, 110 °C. Yield (Conversion) determined by ^{1}H NMR using a standard.

The dehydrogenation reactions described above present unique opportunities to access substituted aromatics via more convergent synthetic routes. Phthalimides are featured in a number of important biologically active compounds, such as modulators of TRPA1 (Transient Receptor Potential subfamily A1) activity, which are peripheral damage receptors involved in prolonged pain responses.[20] Scheme 4A highlights a patented cross-coupling route to the substituted phthalimide fragment in one of these TRPA1 modulators (**4c**).[21] The nitro group of 3-nitrophthalimide is converted to the 3-iodophthalimide cross-coupling partner via high-pressure hydrogenation of the nitro group, diazotization of the resulting aniline, and nucleophilic aromatic substitution by iodide. The desired carboxymethyl substituent is then introduced via Pd-catalyzed cross-coupling of the aryl iodide with allyl-BPin using 10 mol % $Pd(PPh_3)_4$, followed by oxidative cleavage of the double bond. In contrast, the dehydrogenation route in Scheme 4B accesses the desired substitution pattern in a single step via Diels–Alder cycloaddition of *N*-methylmaleimide and a methyl sorbate derived diene.[22] The starting materials used in this route are very inexpensive and access the substituted phthalimide precursor **3d** in excellent yield. The $Pd(TFA)_2$/AMS catalyst system then mediates dehydrogenation of **3d** to the desired phthalimide product **4d** in 71% yield. This route illustrates how aerobic

Scheme 4. Synthesis of a Precursor to a TRPA1 Modulator via Oxidative Dehydrogenation



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dehydrogenation of cyclohexenes, like the previous dehydrogenation of cyclohexanones and related derivatives,[3−7] offers complementary appeal or significant advantages relative to cross-coupling reactions in the preparation of substituted aromatics. The dehydrogenation methods exploit classical organic transformations, such as Diels−Alder cycloadditions (to access cyclohexenes) and Robinson annulations (to access cyclohexenones[3a]), as versatile and efficient routes to core structures that are excellent precursors to selectively substituted aromatic compounds.

In conclusion, we have identified new Pd catalyst systems for the oxidative dehydrogenation of cyclohexenes. The method enables efficient synthesis of substituted arene derivatives and shows good functional group tolerance. Use of this method in the preparation of a substituted phthalimide showcases the strategic opportunity to use this transformation in the synthesis of biologically active compounds.

■ ASSOCIATED CONTENT

Supporting Information

Additional catalyst screening data, experimental procedures, compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) For the 1-mmol-scale reactions, use of $MgSO_4$ was found to enhance the yields by 5−10%, presumably by serving as a drying agent. See Supporting Information for the experimental procedure.

(17) ^{1}H NMR analysis of the crude reaction mixture with **1t** reveals new alkene peaks, possibly arising from a Heck reaction product, but we were not successful in isolating the byproducts. Peaks associated with the independently prepared hydrodebromination products of **1t**/**2t** are not observed.

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