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Molecular Complexity via C−H Activation: A Dehydrogenative Diels−Alder Reaction

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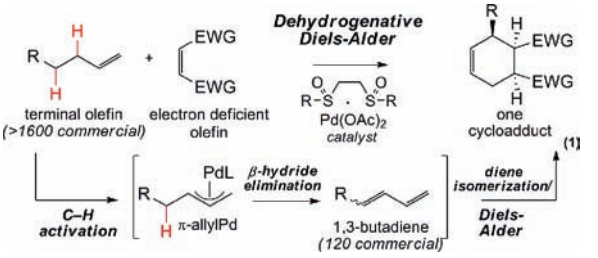
Supporting Information

ABSTRACT: Traditionally, C−H oxidation reactions install oxidized functionality onto a preformed molecular skeleton, resulting in a local molecular change. The use of C−H activation chemistry to construct complex molecular scaffolds is a new area with tremendous potential in synthesis. We report a Pd(II)/bis-sulfoxide-catalyzed dehydrogenative Diels−Alder reaction that converts simple terminal olefins into complex cycloadducts in a single operation.

Selective transformation of inert C−H bonds into more reactive functionality is a challenging problem that also presents great opportunities for streamlining the synthesis of complex molecules.[1,2] While C−H oxidation reactions have been primarily used to install functional groups onto established carbon frameworks, they also hold tremendous promise for directly accessing reactive intermediates that can be coupled to productive secondary reactions to forge new carbon frameworks. In this regard, transition metal-catalyzed dehydrogenation reactions may be particularly powerful.[3−5] Although extremely rare, preparatively useful hydrocarbon dehydrogenation processes have utilized a secondary reaction to generate valuable, stable products while avoiding undesired side reactions and reactive intermediate isolations.[5a,6] We questioned whether a dehydrogenation reaction could be developed that would convert simple terminal olefins into reactive 1,3-diene intermediates[6] capable of participating in a wide range of complexity-generating transformations[7] (e.g., cycloadditions,[8] 1,2- and 1,4-additions,[9] and cycloisomerizations[10]). Performing such a sequence in tandem would enable the rapid construction of diverse molecular skeletons from topologically simple starting materials.[11] Herein, we report the first dehydrogenative Diels−Alder (DA) reaction that proceeds with simple terminal olefins to furnish complex cyclohexenyl rings.

In recent years, our laboratory has introduced electrophilic Pd(II)/sulfoxide catalysis as a general platform for allylic C−H activation that enables direct allylic esterification,[12] amination,[13] and alkylation[14] of terminal olefins through the intermediacy of a π-allylPd species. We hypothesized that a dehydrogenation reaction of terminal olefins could also be developed using this reaction manifold by promoting β-hydride elimination from the π-allylPd intermediate, in the absence of nucleophile.[15] Given the abundance of bulk commodity terminal olefins (>1600 commercial) versus the relative scarcity of commercial terminal dienes (120) along with inefficient synthetic routes required for their construction (*vide infra*), we anticipated that such a dehydrogenation transformation would provide a significant synthetic advantage. Moreover, because 1,3-dienes are typically used as synthetic building blocks, ideally this dehydrogenation reaction could be directly



coupled to a desirable secondary reaction. However, in addition to general difficulties associated with dehydrogenation chemistry (e.g., thermodynamically uphill), generating 1,3-butadienes from terminal olefin substrates poses unique challenges: (1) dienes are reactive intermediates prone to isomerizations and olefin oxidations, and (2) the electrophilic catalysts needed for the C−H activation step often catalyze diene oligomer- and polymerization processes.[16] We therefore sought to generate low concentrations of the reactive (*E*)-1,3-butadiene intermediate in the presence of high concentrations of a reactive component capable of furnishing a stable product. Of the possible secondary transformations, the DA reaction would be particularly enabling, as it remains one of the most powerful complexity-generating reactions in organic chemistry.[8] Herein, we describe the first dehydrogenative DA reaction, which has been achieved using Pd(II)/sulfoxide-catalyzed allylic C−H activation /β-hydride elimination followed by a dynamic diene isomerization.

We began our study by examining the viability of the dehydrogenation step in the absence of dienophile, using limiting amounts of α-olefin **3** under standard allylic C−H activation conditions (Table 1). Although 1,4-benzoquinone is typically used as an oxidant for such allylic C−H functionalization processes, bulky 2,6-dimethyl-1,4-benzoquinone (2,6-Me_2BQ) was used here, both to prevent a possible quinone DA reaction with the diene products[17] and to prevent functionalization of the intermediate π-allylPd species with the acetate counterion.[12b,13d] While the use of $Pd(OAc)_2$ resulted in only recovered starting material (entry 1), Pd(II)/phenylbis-sulfoxide catalyst **1** provided initial dehydrogenation reactivity, albeit in low yield (6% yield of **3a**, entry 2). After a survey of ligands, it was found that 10 mol % of the Pd(II)/benzylbis-sulfoxide catalyst **2**[12a,14b,c] resulted in higher catalytic turnover, leading to 28% diene product (4:1 *E*:*Z* selectivity, entry 3). Longer reaction times led to significantly diminished yields, indicating that the 1,3-butadiene product was not stable to the reaction conditions. As further evidence of this, when authentic (*E*)-diene **3a** was

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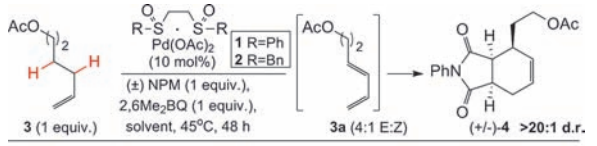
Table 1. Development of the Tandem Dehydrogenation/Diels–Alder Reaction



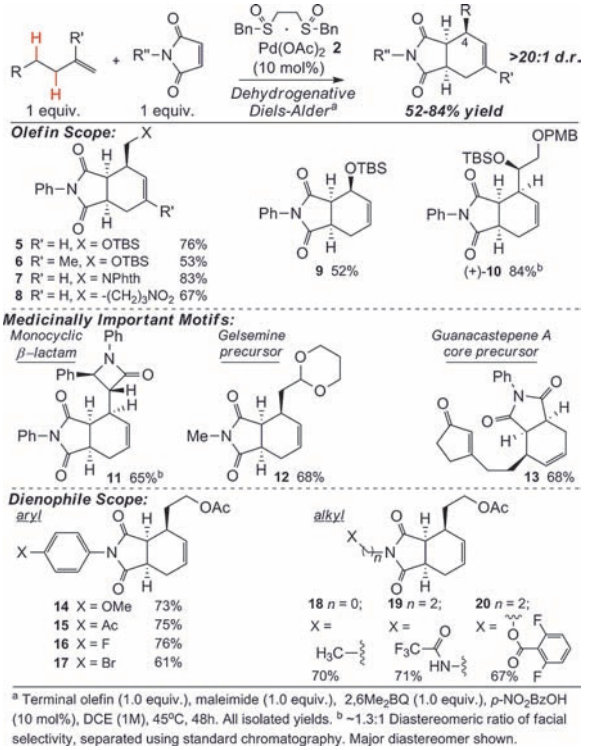
entry	catalyst[a]	solvent	additive[f]	dienophile[e]	yield diene[b]	yield cycloadduct[c]
1	$Pd(OAc)_2$	dioxane	---	---	<1[d]	---
2	**1**	dioxane	---	---	6	---
3	**2**	dioxane	---	---	28	---
4	**2**	dioxane	---	NPM	<1[d]	33
5	**2**	DCE	---	NPM	<1[d]	52
6	**2**	DCE	*p*-NO_2BzOH	NPM	<1[d]	74
7	**2**	DCE	*p*-NO_2BzOH	---	35	---

[a] 10 mol% catalyst [b] Isolated after 24 hr as a 4:1 mixture of E/Z isomers along with rSM [c] isolated yield [d] Determined by GC analysis [e] NPM = N-phenylmaleimide (1.0 equiv.) [f] 10 mol%

subjected to the electrophilic Pd(II) conditions, significant conversion occurred after 24 h (75%), likely due to polymerization. In the hopes of generating the desired DA adduct, 1 equiv of the reactive *N*-phenylmaleimide (NPM) dienophile was included in the dehydrogenation reaction to trap the unstable diene intermediate. Gratifyingly, the dehydrogenative DA adduct **4** was furnished in encouraging yield (33%) and as a single diastereomer (>20:1 dr, entry 4). Switching solvents to 1,2-dichloroethane (DCE) dramatically improved the tandem yield to 52% (entry 5). The yield was increased further to 74% upon the addition of 10 mol % *p*-NO_2BzOH, which likely aids Pd(0) → Pd(II) catalyst reoxidation[18] (entry 6). For all tandem dehydrogenation/DA reactions, very little diene (<1%) could be detected by GC analysis. Maintaining low concentrations of diene is thought to be critical for retarding polymerization pathways and enabling the use of limiting olefin starting material. Consistent with this, when NPM was excluded from the optimized reaction conditions, the diene was isolated in only 35% yield (24 h, entry 7), suggesting that diene decomposition pathways were still operative.

Experiments to probe the scope of both the terminal olefin and maleimide components are summarized in Scheme 1. A wide range of polar groups that can serve as synthetic handles for further elaboration are well-tolerated in terminal olefin dehydrogenations: silyl (**5**, **6**, **9**, **10**) and benzyl ethers (**10**), phthalimide (Phth)-protected amines (**7**), nitro functionality (**8**), amides (**11**), acid-sensitive acetals (**12**), and α,β-unsaturated enones (**13**). Although 1,1-disubstituted olefins and terminal olefins that form 1-oxy-1,3-butadienes are less reactive dehydrogenation substrates, they furnish the DA adducts in synthetically useful yields (**6** and **9**, respectively). Terminal olefins containing stereogenic branching elements undergo facile tandem dehydrogenation/DA cycloaddition without epimerization of the preexisting stereogenic center (**10**, **11**). While the DA reaction still proceeds with exclusive endo selectivity, the chiral substituent displays little control over diastereofacial selectivity (~1:1 dr), as expected for maleimide dienophiles.[19] Access to these functionalized dienes traditionally requires differentiation of bifunctional starting materials using lengthy protecting group manipulation sequences. Alternatively, this dehydrogenation manifold provides direct access to 1,3-diene intermediates from monofunctional terminal olefins, the majority of which are generated in one step from commercial starting materials.[20]

Scheme 1

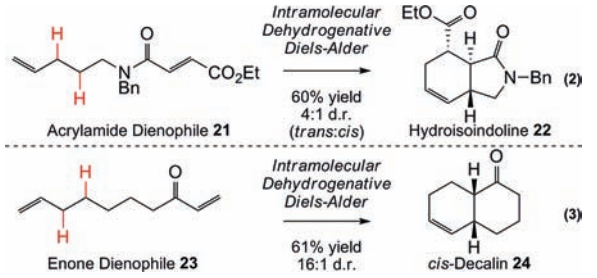


[a] Terminal olefin (1.0 equiv.), maleimide (1.0 equiv.), 2,6Me_2BQ (1.0 equiv.), *p*-NO_2BzOH (10 mol%), DCE (1M), 45°C, 48h. All isolated yields. [b] ~1.3:1 Diastereomeric ratio of facial selectivity, separated using standard chromatography. Major diastereomer shown.

The high functional group tolerance of the dehydrogenative DA reaction enables rapid access to functionally dense motifs found in biologically active molecules. For example, cycloadducts containing monocyclic β-lactams, known to furnish antibiotics with activity against Gram-negative organisms, can be generated in just three steps using this methodology (**11**).[21] Furthermore, adduct **12** (two steps from commercial materials) contains the core structure needed for the synthesis of gelsemine,[22] an alkaloid that possesses anxiolytic and analgesic properties.[23] Because of the high reactivity of maleimides in the DA reaction, other potentially reactive dienophiles are tolerated on the diene precursors (e.g., α,β-unsaturated enones, **13**). Cycloadduct **13** provides an expedient route to intermediates used to construct the [5-7-6] tricyclic core of Guanacastepene A, an active antibiotic against methicillin- and vancomycin-resistant bacteria.[24]

The dehydrogenative DA reaction was also examined with a series of maleimide dienophile substrates. Both electron-donating (**14**) and -withdrawing (**15**, **16**) *N*-aryl substituents are well-tolerated, including functionalities that can be further elaborated using Pd(0) catalysis (i.e., **17**, Scheme 1). In addition to *N*-methyl- (**12**, **18**), densely functionalized *N*-alkylmaleimides also undergo dehydrogenative DA reactions with good yields and selectivities. These substituents provide additional opportunities for synthetic elaboration (e.g., *N*-ethylamine derivatives can cyclize to furnish imidazolines,[25] **19**) and amide diversification (i.e., pharmacophoric esters,[26] **20**; see Scheme 2).

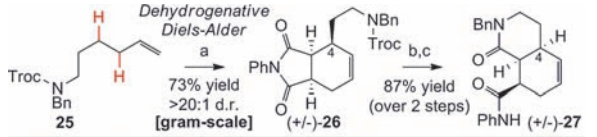
Maleimides proved to be superior dienophiles for trapping the reactive 1,3-diene intermediates under these mild dehydrogenation conditions. Less reactive dienophiles, such as α,β-unsaturated esters and quinones, exhibit low reactivity under the current intermolecular conditions, although the dehydrogenation step is still operative. This is a common limitation of non-Lewis acid-catalyzed DA cycloadditions of



unactivated dienes under mild conditions.[8b] However, tethering terminal olefin functionality to the dienophile reaction partner led to significant rate enhancements of the DA cycloaddition. Under such intramolecular cyclization conditions, the dienophile scope could be expanded to include acrylamides (**21**, eq 2) and enones (**23**, eq 3), providing expedient access[27] to medicinally important hydroisoindolines (**22**) and *cis*-decalin (**24**) frameworks, respectively.

Maleimide-based cycloadducts containing synthetic handles at the C-4 and nitrogen positions are powerful synthetic intermediates that can be readily elaborated to a wide range of alkaloid frameworks. Toward this end, we incorporated an amine nucleophile onto the α-olefin component for an ultimate intramolecular cyclization onto the succinimide moiety of the cycloadduct. Subjecting Troc-protected hexenamine **25** to the dehydrogenative DA reaction gave cycloadduct **26** in 73% yield and >20:1 dr (Scheme 2). This operationally simple reaction can be conducted on a gram scale, with no precautions taken to exclude moisture. Removal of the Troc protecting group with zinc dust, followed by thermally promoted imide acylation, provided the hydroisoquinoline heterocycle **27** in 87% yield over two steps. This tandem dehydrogenation/DA reaction provides an expedient route to such substituted hydroisoquinolines,[28] which are common structural elements found in a variety of alkaloid natural products.[28b,c]

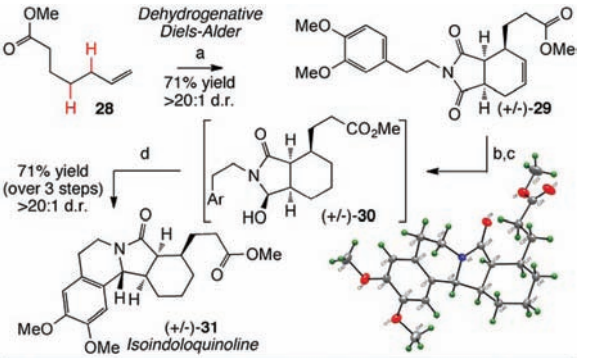
Scheme 2



a) **2** (10 mol%), **25** (1 equiv.), NPM (1 equiv.), 2,6Me$_2$BQ (1 equiv.), *p*-NO$_2$BzOH (10 mol%), DCE (1M), 45°C, 73%, >20:1 d.r. b) Zn, AcOH c) PhMe, 80°C, 87% (over 2 steps)

We next incorporated a nucleophilic phenethyl moiety onto the dienophile for an ultimate cyclization onto the succinimide group. One equivalent of 3,4-dimethoxyphenethyl maleimide was coupled to commercially available methyl 6-heptenoate (**28**) using the tandem dehydrogenation/DA reaction, providing adduct **29** in 71% yield and >20:1 dr (Scheme 3). We next sought to differentiate the two imide carbonyls as a prelude to regioselective intramolecular cyclization. It had been previously shown on related hexahydrophthalimide compounds that the imide carbonyl distal to the pendant side chain could be monoreduced with $NaBH_4$ in >95:5 selectivity.[29] In accord with these results, following olefin hydrogenation, a regioselective monoreduction with $NaBH_4$ afforded a single hydroxylactam (**30**), with hydride addition occurring solely at the carbonyl farthest from the methyl ester side chain. With the 3,4-dimethoxyphenyl moiety acting as the nucleophile, **30** underwent stereoselective

Scheme 3

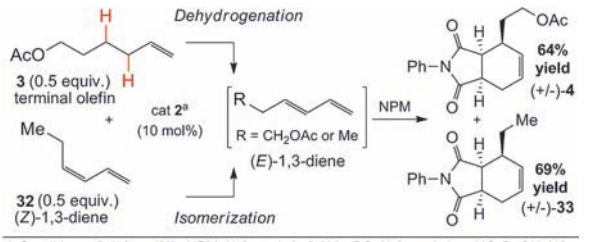


a) **2** (10 mol%), **28** (1 equiv.), N-(3,4-dimethoxy)phenethyl maleimide (1 equiv.), 2,6Me$_2$BQ (1 equiv.), *p*-NO$_2$BzOH (10 mol%), DCE (1M), 45°C, 71%, >20:1 d.r. b) Pd/C (cat.), H_2 (1 atm) c) $NaBH_4$, H_2SO_4 d) CSA, PhMe, 80°C, 71% (over 3 steps), >20:1 d.r.

(>20:1 dr) cyclization under typical *N*-acyliminium ion conditions,[30] to afford the isoindoloquinoline polycycle **31** as a single diastereomer in 71% yield (over three steps). This isoindoloquinoline skeleton is found in several alkaloids, such as jamtine, which displays significant antihyperglycemic activity.[31] In total, this stereochemically dense azapolycyclic architecture was constructed in just four steps from commercially available terminal olefin **28**.

In all achiral substrates examined, the maleimide-based products were isolated with >20:1 diastereoselectivities, resulting from cycloadditions of (*E*)-1,3-dienes with maleimide dienophiles. However, the dehydrogenation step produced a mixture (4:1 *E*:*Z*) of diene isomers. Based on the low reactivity of (*Z*)-1,3-dienes in the DA reaction at these temperatures, this isomer was likely either reacting in nonproductive pathways (e.g., polymerization) or isomerizing under the reaction conditions to yield the DA-capable (*E*)-1,3-diene. To determine the fate of the (*Z*)-1,3-diene, we performed a crossover experiment utilizing 0.5 equiv of terminal olefin **3** and 0.5 equiv of (*Z*)-1,3-diene **32** (Scheme 4). Under these reaction conditions, the dehydrogenation cycloadduct **4**, derived from **3**, was formed in 64% yield (>20:1 dr). Cycloadduct **33**, derived from isomerization of **32** to the (*E*)-isomer, was formed in good yield (69%) and >20:1 dr. Interestingly, when pure **32** was reacted with NPM and catalyst **2**, **33** was formed in >20:1 dr, suggesting that diene isomerization is Pd(II)-promoted. In the absence of Pd(II), **32** is fully recovered (Supporting Information). These results support a Pd(II)-catalyzed dynamic diene isomerization pathway in which both the (*E*)- and (*Z*)-diene isomers generated during the dehydrogenation step are funneled to the desired cycloadducts *in situ*. Consequently, this dehydrogenation

Scheme 4



a) Conditions: **2** (10 mol%), NPM (1.0 equiv.), 2,6Me$_2$BQ (1.0 equiv.), *p*-NO$_2$BzOH (10 mol%), DCE (1M), 45°C, 48 hr. Both cycloadducts were isolated as single diastereomers.

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chemistry circumvents the need for geometrically predefined diene starting materials.

In summary, a novel approach to stereochemically dense cyclohexenyl rings from terminal olefins has been achieved using Pd(II)/sulfoxide C−H activation catalysis. This dehydrogenative Diels−Alder reaction underscores the power of coupling transition-metal-catalyzed C−H activation to complexity-generating transformations for the rapid synthesis of complex molecular skeletons from topologically simple starting materials. Further investigations are focused on expanding the scope of this transformation with respect to both the olefin class and dienophile, and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org

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