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Hydrogenolysis of Unstrained Carbon−Carbon σ Bonds: Stereoselective Entry into Benzylic Tertiary Centers

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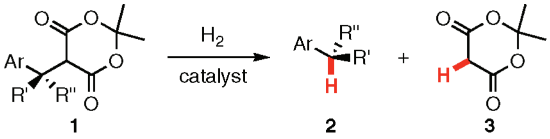
The functionalization or modification of sp^3-hybridized carbon centers by cleavage of unstrained carbon−carbon σ bonds remains unexplored to date.[1] Although hydrogenolysis of C−Z bonds (Z = N, O, S, halogen) is common, hydrogenolysis of C−C bonds under mild reaction conditions is unprecedented.[2] All examples of C−C bond hydrogenolysis reported in the literature necessitate either high temperature/pressure conditions[3] or involve C−C bonds in strained rings, such as cyclopropanes and cyclobutanes, or in activated cyclohexadienones,[4] for which scission is driven by aromatization.[5]

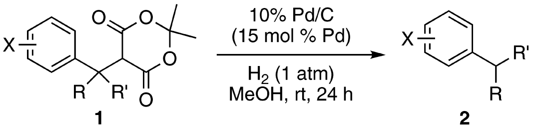
In the course of preparing a series of benzyl Meldrum's acid derivatives,[6,7] we discovered that their exposure to Pd/C in the presence of H_2 induced reductive C−C σ-bond scission to release the corresponding aromatics **2** and Meldrum's acid (**3**) (Scheme 1). This observation provided an opportunity to tackle the synthetic challenge of modifying sp^3-hybridized carbon centers via cleavage of C−C σ bonds. Moreover, we have reported a number of protocols (including enantioselective strategies) for the facile preparation of benzyl Meldrum's acid derivatives **1** bearing an all-carbon benzylic quaternary stereocenter via conjugate addition of organometallic reagents to 5-(1-arylalkylidene) Meldrum's acids.[8] Herein, we document a catalytic hydrogenolysis of C−C bonds in benzyl Meldrum's acid derivatives **1** to access tertiary benzylic stereocenters **2** and Meldrum's acid in good to excellent yields and conversions (Scheme 1). Additionally, some mechanistic aspects of the transformation are discussed.

Scheme 1



When 2,2-dimethyl-5-(2-(4-(octyloxy)phenyl)propan-2-yl)-1,3-dioxane-4,6-dione (**1a**) was subjected to 10% Pd/C (15 mol % Pd) and MeOH at room temperature (rt) under an atmosphere of hydrogen for 24 h, 97% conversion to Meldrum's acid and **2a** was observed, and **2a** was isolated in 76% yield (Table 1, entry 1). In the absence of H_2 or Pd/C, the hydrogenolysis reaction did not proceed. Similar results were obtained with Meldrum's acid derivatives **1b** and **1c** (entries 2 and 3). Important electronic factors were at play, as illustrated by the facile hydrogenolysis of the para and ortho analogues **1a** and **1e** in comparison with the meta-substituted compound **1d** (entries 1, 4, and 5). 2,2-Benzyl Meldrum's acid **1f** afforded cyclohexyl-substituted aromatic **2f** in 91% conversion and 81% yield (entry 6). Replacing one of the methyl groups at the all-carbon quaternary benzylic center with larger primary groups such as Et or *n*-Bu did not affect the reaction, and **2g** and **2h** were obtained in excellent conversions and 86 and 90% yields, respectively (entries 7 and 8). Substitution with an *i*-Pr group hampered the reactivity and led to modest levels of conversion to **2i**. However, when run under stoichiometric conditions, hydrogenolysis of **1i** furnished **2i** in good yield (entry 9). Secondary benzylic Meldrum's acid **1j** was inert toward hydrogenolysis (entry 10), but the analogous diaryl **1k** was fully converted to **2k**, which was isolated in 96% yield (entry 11).

Table 1. Scope of the C−C Hydrogenolysis in Benzyl Meldrum's Acids



entry	X	R; R′	conv. (%)	yield (%)
1	4-(OC_8H_{17})	R = R′ = Me (**1a**)	>95	76 (**2a**)
2	4-Ph	R = R′ = Me (**1b**)	>95	71 (**2b**)
3	H	R = R′ = Me (**1c**)	>95	80 (**2c**)[a]
4	3-(OC_8H_{17})	R = R′ = Me (**1d**)	9	N/A (**2d**)
5	2-(OC_8H_{17})	R = R′ = Me (**1e**)	80 (92)[b]	65 (71) (**2e**)[b]
6	4-(OC_8H_{17})	R−R′ = $(CH_2)_5$ (**1f**)	91	81 (**2f**)
7	4-(OC_8H_{17})	R = Me; R′ = Et (**1g**)	>95	86 (**2g**)
8	4-(OC_8H_{17})	R = Me; R′ = *n*-Bu (**1h**)	>95	90 (**2h**)
9	4-(OC_8H_{17})	R = Me; R′ = *i*-Pr (**1i**)	20 (>95)[c]	N/A (70) (**2i**)[c]
10	4-(OC_8H_{17})	R = H; R′ = Me (**1j**)	<5	N/A (**2j**)
11	4-(OMe)	R = H; R′ = 4-MeOC_6H_4 (**1k**)	>95	96 (**2k**)

[a] Yield for the isolation of Meldrum's acid, as product **2c** was too volatile. [b] The conversion and yield in parentheses were obtained using 20 mol % Pd. [c] The conversion and yield in parentheses were obtained using 100 mol % Pd.

The hydrogenolysis mechanism was investigated first through labeling studies. Subjecting **1a** to 10% Pd/C (15 mol % Pd) and CD_3OD under a hydrogen atmosphere afforded 52% deuterium incorporation at the benzylic position of **2a** (Scheme 2a). Performing the reaction under D_2 with undeuterated methanol provided 32% deuterium incorporation at the benzylic position of **2a** (Scheme 2b). The hydrogenolysis was then performed under deuterium gas with deuterated methanol, which led to full deuterium incorporation at the benzylic position (Scheme 2c). In all three experiments, <5% deuterium incorporation was observed at the methyl position of the isopropyl group.

Further insights into the mechanism were obtained by investigating the hydrogenolysis of enantioenriched benzyl Meldrum's acids. As depicted in Table 2, Meldrum's acids (*R*)-**1g**, (*R*)-**1l**, and (*R*)-**1m** reacted with virtually complete inversion of configuration (92−97%) at the benzylic center to yield products (*S*)-**2g**, (*S*)-**2l**, and (*S*)-**2m**, respectively. The absolute stereochemistry of the products was determined by correlation with the known compound (*S*)-**2l**.[9]

Nearly complete inversion of configuration in the hydrogenolysis of enantioenriched all-carbon quaternary centers strongly suggests that the reductive C−C σ-bond scission reaction proceeds through

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Scheme 2. Labeling Studies

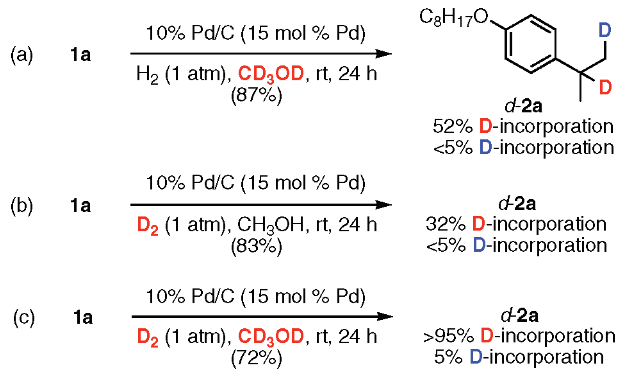
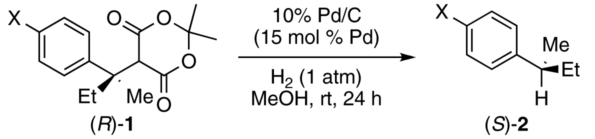


Table 2. Hydrogenolysis of Enantioenriched All-Carbon Quaternary Centers with Inversion of Configuration



entry	X	er of **1** (*R*/*S*)	er of **2** (*S*/*R*)	inv (%)[a]	yield (%)
1	4-(OC_8H_{17}) [(*R*)-**1g**]	98.5:1.5	96:4	97	93 [(*S*)-**2g**]
2	4-(OMe) [(*R*)-**1l**]	98.5:1.5	94.5:5.5	96	72 [(*S*)-**2l**]
3	Ph [(*R*)-**1m**]	98:2	90.5:9.5	92	51 [(*S*)-**2m**]

[a] Inversion of er.

an S_N2 mechanism. Furthermore, an electron-withdrawing group retarded the hydrogenolysis (Table 1, entry 4), and its rate was strongly dependent upon the size of the benzylic substituent (Table 1, entry 9). The lack of reactivity of **1d** and **1j** and the high conversion and yield obtained with **1k** illustrate the "loose" nature of the S_N2 mechanism,[10] in which a significant development of positive charge occurs in the transition state.

In the C−C bond scission process, the Meldrum's acid moiety is directly displaced either by a palladium hydride or Pd(0) to yield a benzylic organopalladium intermediate that undergoes protonation by MeOH. The latter mechanism was proposed Carreira and coworkers[11] in the hydrogenolysis of secondary benzylic nitro groups under similar conditions, on the basis of the observation that the hydrogen atom incorporated into the product originated strictly from the solvent.

In our labeling study, the hydrogen/deuterium incorporation originated from both the solvent and the gas. These observations seem to indicate that nucleophilic attack, either by palladium hydride or by Pd(0), is slower than isotopic dilution, which occurs through exchange on the Pd surface between the reactive palladium species and the acidic proton of the solvent (Scheme 2a,b). The modest level of deuterium incorporation may also be the result of both pathways, operating simultaneously.

The slight erosion of the enantiomeric ratio during the reaction can occur as a result of a competitive S_N1[12] or alkene formation, either by Meldrum's acid or palladium β-hydride elimination followed by olefin hydrogenation (Table 2).[13] This is supported by the <5% incorporation of deuterium at the methyl position of the isopropyl group (Scheme 2a−c).

In summary, we have described the modification of sp^3-hybridized carbon centers through Pd-catalyzed reductive cleavage of unstrained C−C σ bonds. The hydrogenolysis of benzyl Meldrum's acids bearing an all-carbon benzylic quaternary center furnished Meldrum's acid and aromatics substituted with a tertiary benzylic stereocenter in good to excellent yields. Mechanistic studies showed that the reductive cleavage of enantioenriched benzylic quaternary centers proceeds with inversion of configuration, supporting a "loose" S_N2 pathway. We are currently exploring the scope of this transformation with respect to other benzyl Meldrum acids and studying the mechanism thoroughly.

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

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