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Chemo- and Regioselective Synthesis of Acyl-Cyclohexenes by a Tandem Acceptorless Dehydrogenation-[1,5]-Hydride Shift Cascade

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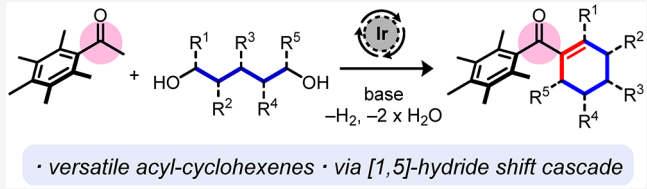
ABSTRACT: An atom-economical methodology to access substituted acyl-cyclohexenes from pentamethylacetophenone and 1,5-diols is described. This process is catalyzed by an iridium(I) catalyst in conjunction with a bulky electron rich phosphine ligand (CataCXium A) which favors acceptorless dehydrogenation over conjugate reduction to the corresponding cyclohexane. The reaction produces water and hydrogen gas as the sole byproducts and a wide range of functionalized acyl-cyclohexene products can be synthesized using this method in very high yields. A series of control experiments were carried out, which revealed that the process is initiated by acceptorless dehydrogenation of the diol followed by a redox-neutral cascade process, which is independent of the iridium catalyst. Deuterium labeling studies established that the key step of this cascade involves a novel base-mediated [1,5]-hydride shift. The cyclohexenyl ketone products could readily be cleaved under mildly acidic conditions to access a range of valuable substituted cyclohexene derivatives.



1. INTRODUCTION

The synthesis of cyclohexenes in a regio- and stereocontrolled manner is of fundamental importance in the preparation of natural products, functional materials, and medicinally relevant compounds.[1] As a testament to this, the Diels−Alder cycloaddition reaction remains the premier method for the construction of the cyclohexene core (Scheme 1A).[2] However, in order to achieve high regioselectivity in intermolecular Diels−Alder reactions, it is often necessary to rely upon sterically or electronically biased substrates, which means only cyclohexenes bearing certain substitution patterns can be accessed.[3] Several catalytic approaches to cyclohexene synthesis have also been developed, such as ring closing metathesis (RCM) and catalytic cyclotrimerization.[4,5] However, these approaches are best expressed in intramolecular reactions and depend on the accessibility of appropriately substituted precursors. Intermolecular reactions used to synthesize sterically demanding, multisubstituted cyclohexenes are much less well documented, and therefore, new methods for cyclohexene synthesis that complement the Diels−Alder approach are highly desirable.

We recently reported that pentamethylphenyl (Ph*) ketones can be directly alkylated with alcohols via hydrogen borrowing catalysis.[6,7] We subsequently showed that this approach could be extended to an iridium catalyzed synthesis of cyclohexanes by double alkylation of pentamethylacetophenone with 1,5-diols (Scheme 1B).[8,9] Mechanistically, it was proposed that this process operated via two sequential hydrogen borrowing catalytic cycles (cycles 1 and 2). The first cycle would begin with oxidation of the 1,5-diol to the corresponding hydroxyaldehyde along with concomitant formation of iridium hydride. Aldol condensation with Ph*COMe would generate an acyclic enone which could then be reduced by iridium hydride to release a hydroxyketone intermediate and close cycle 1. This intermediate could then enter cycle 2 in which oxidation of the remaining alcohol, followed by condensation, would generate a cyclic enone intermediate which could finally undergo reduction to form the corresponding cyclohexane product. We were intrigued by the acyl-cyclohexenes formed as the penultimate intermediates in this sequence and speculated that if the final reduction step in cycle 2 could be interrupted, it might be possible to selectively isolate these compounds and thereby develop an unprecedented intermolecular (5 + 1) strategy for cyclohexene synthesis. However, in order to accomplish this goal, we would have to solve the challenging chemoselectivity issue of achieving complete reduction of the acyclic enone intermediate in cycle 1 while fully suppressing reduction of the cyclic enone products in cycle 2. We aimed to achieve this goal by a combination of two approaches: (i) by addition of a hydrogen acceptor, which could competitively intercept and recycle iridium hydride;[10] (ii) by employing α-substituted diol starting materials to target sterically hindered tetrasubstituted enones as the final product, which would be less prone to over reduction.[11] Here we describe how we were ultimately able to address these challenges to develop a remarkably general and operationally simple synthesis of acyl

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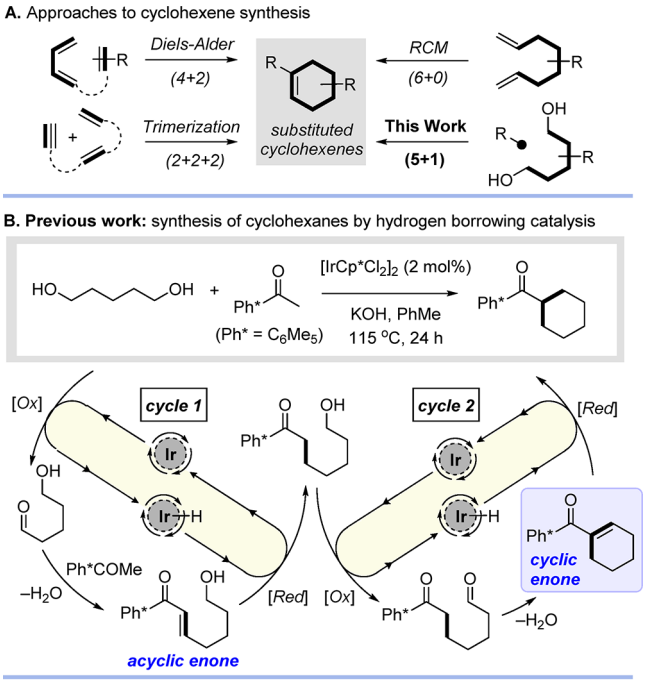
Scheme 1. Previous Work and Strategy for Formation of Acyl-Cyclohexenes by Interrupted Hydrogen Borrowing Catalysis



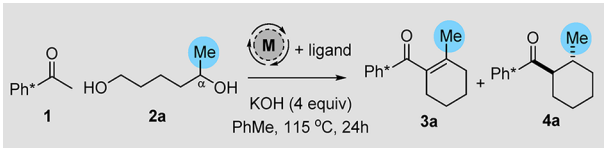
cyclohexenes and how a detailed study of the mechanism of the process has led us to revise our understanding of the annulation chemistry more generally.

2. RESULTS AND DISCUSSION

We commenced our study by investigating the formation of tetrasubstituted cyclohexene **3a** from pentamethylacetophenone (**1**) and 1,5-hexane diol (**2a**). Applying our previously reported conditions for cyclohexane synthesis, we found that the major product was the over-reduced cyclohexane **4a** which was formed in 71% yield along with a small amount (7% yield) of the desired acyl-cyclohexene **3a** (Table 1, entry 1). Using this result as a benchmark, we investigated the effect of adding norbornene which has been reported to be an effective hydrogen acceptor in a variety of iridium and rhodium catalyzed processes.[12] We were delighted to find that addition of 2 equiv of norbornene resulted in a dramatic improvement and cyclohexene **3a** was formed in 51% yield (Table 1, entry 2). At this point, we embarked upon an extensive program of optimization exploring the stoichiometry of norbornene (for full details of the optimization, see the Supporting Information). However, ultimately, we discovered that the beneficial result observed with norbornene was simply due to increased dilution; in fact, the hydrogen acceptor could be removed entirely, and by decreasing the concentration in toluene to 0.25 M enone **3a** could be obtained in up to 54% yield (Table 1, entries 3–5). A further decrease in concentration to 0.1 M resulted in lower conversion (Table 1, entry 6). Several other catalysts reported for hydrogen borrowing were tested but were found to be less effective (Table 1, entries 7 and 8). However, we found that switching to an Ir(I) precatalyst with PPh_3 led to a further increase in selectivity, providing **3** in 65% yield along with only a trace of the corresponding over-reduced cyclohexane **4a** (Table 1, entry 9). Pleasingly, the loading of iridium could be reduced to 1 mol % (0.5 mol % dimer) with no reduction in efficiency (Table 1, entry 10). Finally, we found that a further improvement was obtained with bulky alkyl phosphine ligand CataCXium A ($PAd_2{}^nBu$), enabling isolation of cyclohexene **3a** in 79% yield with no over reduction observed at all (Table 1, entry 11). Notably, **3a** was formed as a single regioisomer, which suggests that the first C–C bond formation (in cycle 1) takes place exclusively with the primary alcohol end of the diol rather than the secondary site. Analysis of the reaction headspace by gas chromatography with a thermal conductivity detector (GC-TCD) qualitatively indicated the formation of H_2 gas, which suggests that the process proceeds via acceptorless dehydrogenation and explains why the reaction can proceed efficiently in the absence of a hydrogen acceptor.[13] This hypothesis is also in good agreement with studies by Beller and co-workers, who have reported that CataCXium A is particularly effective at promoting acceptorless dehydrogenation processes.[14] Our working hypothesis is that switching from $[Cp^*IrCl_2]_2$ to a more sterically bulky Ir(I)-CataCXium system favors protonation of Ir–H rather than conjugate reduction of the enone. Increased dilution is also predicted to retard the reduction step and therefore favors formation of the desired acyl-cyclohexene.

As expected, a control experiment conducted in the absence of iridium catalyst returned only unreacted starting material (Table 1, entry 12). Furthermore, when we replaced ketone **1**

Table 1. Optimization of Reaction Conditions[a]



entry	metal precatalyst (mol %)[b]	ligand (mol %)	[1] (M)	yield 3a/4a (%[c])
1	$[IrCp^*Cl_2]_2$(4)	-	4	7/71
2[d]	$[IrCp^*Cl_2]_2$(4)	-	4	51/25
3	$[IrCp^*Cl_2]_2$(4)	-	2	16/61
4	$[IrCp^*Cl_2]_2$(4)	-	1	36/40
5	$[IrCp^*Cl_2]_2$(4)	-	0.25	54/7
6	$[IrCp^*Cl_2]_2$(4)	-	0.1	35/2
7	$[RhCp^*Cl_2]_2$ (4)	-	0.25	52/2
8	$[Ru(Cp^*)Cl_2]_n$(4)	-	0.25	18/1
9	$[Ir(cod)Cl]_2$(4)	PPh_3(8)	0.25	65/2
10	$[Ir(cod)Cl]_2$(1)	PPh_3(2)	0.25	67/0
11	$[Ir(cod)Cl]_2$(1)	$PAd_2{}^nBu$ (2)	0.25	75(79)/0
12	-	-	0.25	<5
13[e]	$[Ir(cod)Cl]_2$(1)	$PAd_2{}^nBu$ (2)	0.25	<5

[a]Reaction conditions: aryl ketone **1** (1 equiv), diol **2a** (2 equiv), KOH (4 equiv) PhMe, 115 °C, 24 h. [b]Loading refers to stoichiometry of monomeric metal after dissociation of multimeric precursors. [c]Yield determined by reverse phase HPLC analysis versus durene as an internal standard; values in parentheses indicate the yield of isolated product. [d]Norbornene (2 equiv) was added. [e]Reaction carried out with acetophenone (1 equiv) instead of pentamethylacetophenone **1**.

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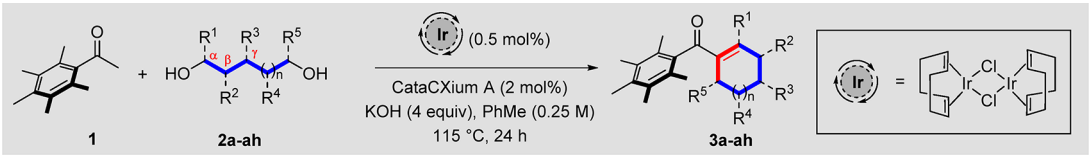
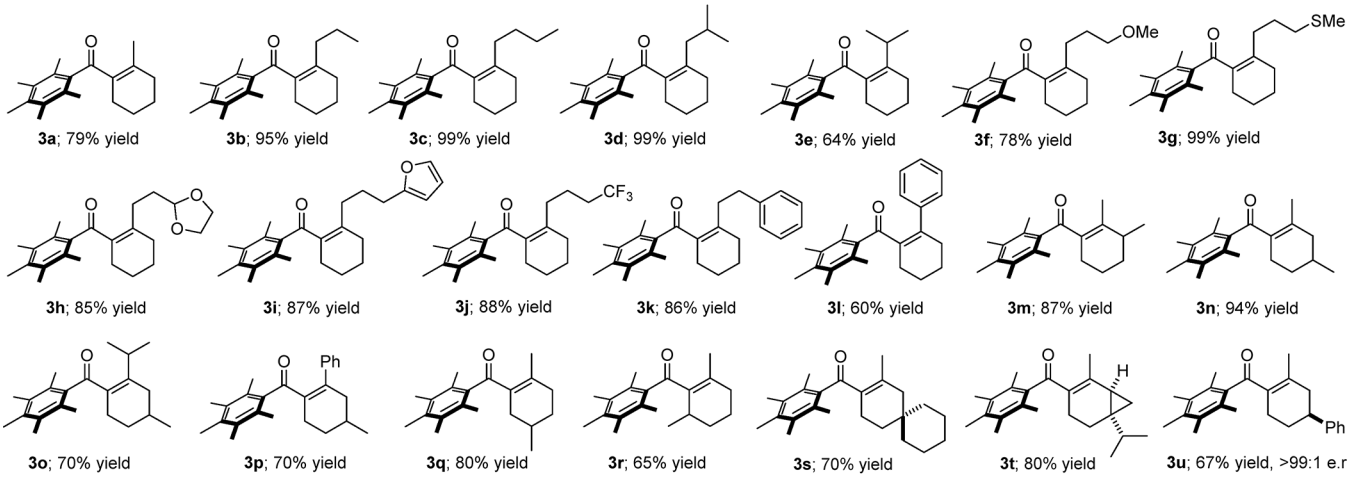
J. Am. Chem. Soc. 2020, 142, 2514–2523

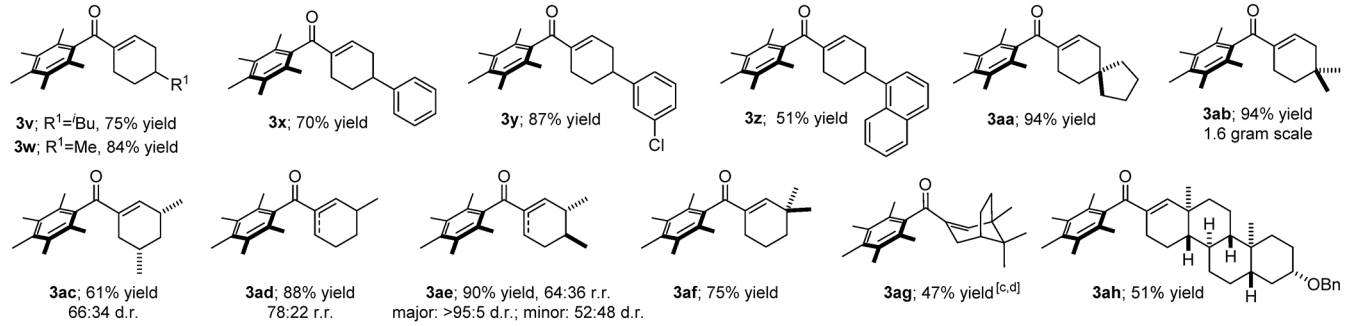
Table 2. Substrate Scope for the Synthesis of Acyl-Cyclohexenes from Diols[ab]



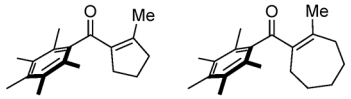
Tetrasubstituted Cyclohexenes



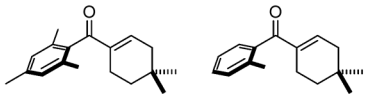
Trisubstituted Cyclohexenes



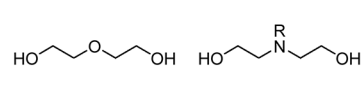
Other Ring Sizes



Other Ketones



Unsuccesful Diols



[a]Reaction conditions: pentamethylacetophenone **1** (1 equiv), diol (2 equiv), KOH (4 equiv), $[Ir(cod)Cl]_2$ (0.5 mol %), CataCXium A (2 mol %), PhMe (0.25 M), 115 °C, 24 h. [b]Yields refer to isolated material after column chromatography. [c]Reaction time of 48 h. [d]Isolated as an inseparable mixture with Ph*COMe. [e]Uncyclized compounds $Ph*CO(CH_2)_6COCH_3$ and $Ph*CO(CH_2)_6CH(OH)CH_3$ were isolated in yields of 19% and 33% respectively. [f]Significant amounts of over reduced products were obtained (see the Supporting Information for details).

with acetophenone, we observed a complex mixture of polar products by HPLC, with significant formation of 1,3-diphenyl-1-butanone (Table 1, entry 13). This result highlights the key role played by the bulky Ph* group in preventing undesired homodimerization reactions.

With optimal conditions in hand for the synthesis of acyl-cyclohexenes, we set out to investigate the generality of the process (Table 2).[15] All diols used were either commercially available or readily prepared in 1−2 steps (details of diol synthesis are provided in the Supporting Information). We first investigated the effect of sterics on the reaction and found that increasing the size of the α-substituent from methyl to *n*-propyl or *n*-butyl had no detrimental effect on reactivity and the corresponding products **3b** and **3c** were isolated in yields of 95% and 99% respectively. The reaction also proceeded efficiently with branched substituents, affording isobutyl and isopropyl substituted products **3d** and **3e** in high yields. We then investigated the functional group tolerance of the reaction and found that cyclohexenes containing ether (**3f**), thioether (**3g**), acetal (**3h**), furan (**3i**), trifluoromethyl (**3j**), and benzyl (**3k**) groups were all obtained in excellent yields with no evidence of any competing side reactions. A diol substituted with a phenyl group also underwent the desired reaction to generate cyclic chalcone **3l** in 60% yield. We next investigated extending the methodology to multisubstituted diols aiming to introduce substituents at each position around the newly formed cyclohexene ring. We were pleased to find that an α,β-dimethyl substituted diol reacted cleanly to afford 1,2,3-

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J. Am. Chem. Soc. 2020, 142, 2514−2523

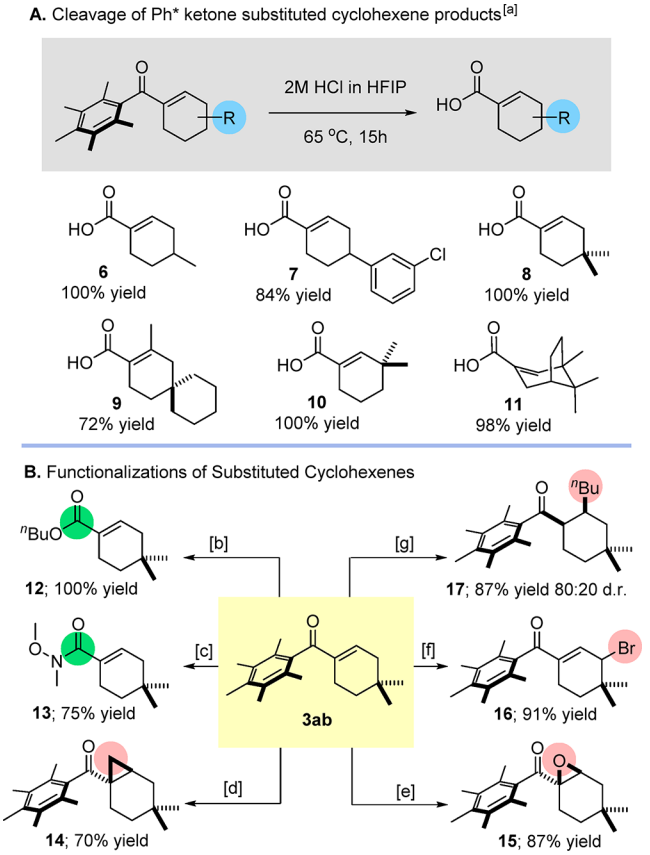
trisubstituted cyclohexane **3m** in 87% yield. α,γ-disubstituted diols also underwent the desired transformations leading 1,2,4-trisubstituted cyclohexenes **3n**−**3p** in excellent yields. Cyclohexenes **3q** and **3r** featuring 1,2,5- and 1,2,6-substitution patterns respectively were also isolated in high yields. We found that we could also employ geminally disubstituted diols in this chemistry enabling the synthesis of spirocyclic acyl-cyclohexene **3s** in 70% yield. Annulation with a multi-substituted diol derived from Thujone afforded 1,2,3,4-tetrasubstituted cyclohexene **3t** in 80% yield as a single regio- and diastereoisomer. Finally, we employed an enantiopure α,γ-disubstituted diol and found that acyl-cyclohexene product **3u** was formed in 67% yield with no loss of stereochemical integrity.

We next applied the optimized conditions for cyclohexene formation to double primary diols. Our expectation was that we would observe a significant amount of over reduction in these reactions as the trisubstituted enone products would be considerably easier to reduce than tetrasubstituted enones.[11] We were therefore surprised and pleased to find the reaction remained highly selective and 1,4-disubstituted cyclohexenes **3v** and **3w** were isolated in yields of 75% and 84%, respectively, with only traces of the corresponding over-reduced cyclohexanes. Other diols substituted at the γ-position were also well tolerated, leading to arylated cyclohexenes **3x**−**3z** and spirocycle **3aa**. The annulation could also be performed on gram scale enabling access to geminally substituted product **3ab** in 94% yield. A symmetrical β,β'-disubstituted diol reacted cleanly to afford cyclohexene **3ac** in 61% yield as a mixture of diastereoisomers. When we investigated nonsymmetrical diols bearing a β-substituent we observed some regioselectivity in favor of the C3-substituted products (for example **3ad** and **3ae**). These results imply that the initial oxidation and aldol condensation occurs more rapidly at the least hindered alcohol and is in good agreement with our previous studies in this area.[8b] To probe this hypothesis further, we investigated a reaction of a more sterically encumbered diol substituted with a geminal dimethyl group at the β-position. In this case, we were delighted to find that the corresponding cyclohexene **3af** was isolated in 75% yield as a single regioisomer. We were also able to apply this method to natural product derived diols to access more complex cyclohexenes **3ag** and **3ah**. In both cases, these products were obtained with complete regiocontrol in favor of initial C−C bond formation at the least hindered end of the diol.

The annulation reaction appears to be most efficient for the construction of cyclohexenes and we found that a 1,4-diol reacted to afford cyclopentene **3ai** in reduced yield. Interestingly, an analogous reaction with heptane-1,6-diol did not afford any of the desired cycloheptene product **3aj** and instead a mixture of monoalkylated intermediates was isolated (see the Supporting Information for details). This result implies that increasing the ring size makes the final aldol condensation significantly less favorable. We next set out to probe the role of the Ph* group in more detail by systematically removing methyl substituents from the aryl ring. Pleasingly, a mesityl ketone reacted cleanly to afford **3ak** in 86% yield. In contrast, an aryl ketone bearing a single *ortho*-methyl group underwent annulation to afford **3al** in significantly reduced yield (9%) accompanied by significant reduction of the carbonyl group (see the Supporting Information for details). This effect was even more pronounced with unhindered ketones such as acetophenone and acetone, and the corresponding enones **3am** and **3an** were not observed. Taken in conjunction, these results imply that a key role of the Ph* group is to sterically shield the carbonyl against reduction. Not all of the diols we investigated underwent the desired annulation reaction. For example, attempts at heterocycle formation with diethylene glycol (**2ao**) and *N*-protected diethanolamines (**2ap**−**ar**) returned only unreacted pentamethylacetophenone.

With a general method for cyclohexene synthesis in hand, we set out to demonstrate the utility of the Ph* containing products by carrying out a series of derivatization reactions (Scheme 2). We were pleased to find that moderately acidic

Scheme 2. Derivatizations of Cyclohexene Products[a]



[a](a) Enone (1 equiv, 0.1 mmol), 2 M HCl in HFIP (1 mL), 65 °C. (b) **3ab** (1 equiv, 0.175 mmol), H_2SO_4 (0.3 mL), 65 °C, then ^{n}BuOH (1 mL), 65 °C. (c) **3ab** (1 equiv), 2 M HCl in HFIP 65 °C, then EDCI (1.5 equiv), DIPEA (5 equiv), HOBT (1.5 equiv), MeNH(OMe).HCl (1.5 equiv), DMF, RT. (d) **3ab** (1 equiv), Me_3SOI (1.5 equiv), NaH (1.6 equiv), DMSO, 50 °C. (e) **3ab** (1 equiv), ^{t}BuOOH (5 equiv), NaOH (5 equiv), ^{t}BuOH, 85 °C. (f) **3ab** (1 equiv), Br_2 (1.2 equiv), $CHCl_3$, −17 °C to RT. (g) **3ab** (1 equiv), *n*-BuLi (2 equiv), pentane, RT then 2,6-di-*tert*-butylphenol (4 equiv), −78 °C to RT.

2 M HCl in hexafluoroisopropanol (HFIP) was sufficient to cleave the Ph* group to the corresponding carboxylic acid via a retro-Friedel−Crafts acylation (details of the optimization of this process are provided in the Supporting Information). We applied these conditions to cleave a representative series of Ph* containing acyl-cyclohexenes to the corresponding cyclohexenecarboxylic acid derivatives **6**-**11** which were formed in uniformly excellent yields (Scheme 2A).[16] In

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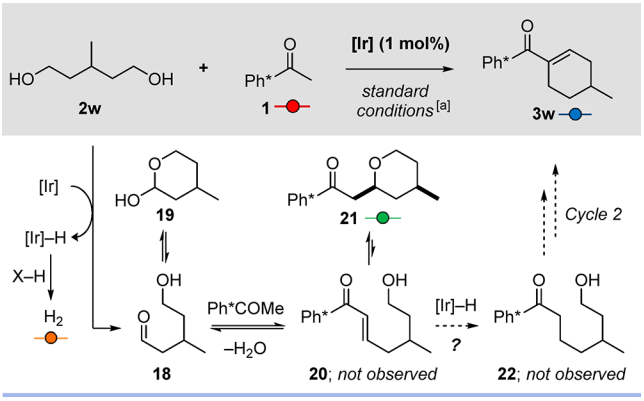
J. Am. Chem. Soc. 2020, 142, 2514−2523

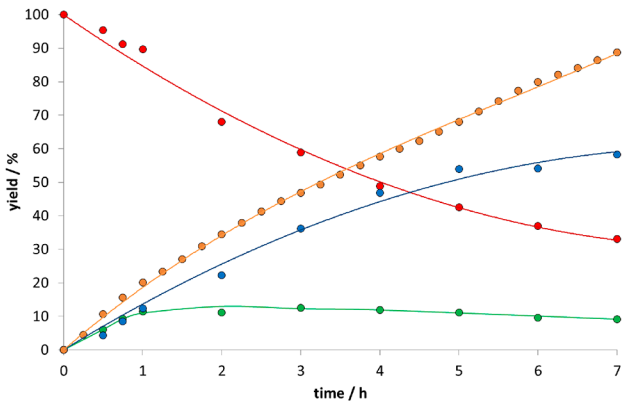
addition to carboxylic acid synthesis, we were able to cleave enone **3ab** to ester **12** by Fisher esterification (Scheme 2B). Weinreb amide **13** was synthesized in 75% yield by a pseudo one-pot procedure involving Ph* hydrolysis followed by amide coupling. In addition to the versatile Ph* group, all of the products **3a**-**3al** contain an enone motif which leads to many opportunities for further functionalization. For example, we found that **3ab** could undergo Corey−Chaykovsky cyclopropanation to afford bicyclic ketone **14** in 70% yield or Weitz−Scheffer epoxidation to generate epoxy ketone **15** in 87% yield. Treatment of **3ab** with bromine resulted in an unexpected allylic bromination reaction to form **16** in 91% yield.[17] Finally, we investigated conjugate addition of carbon nucleophiles to the enone. Typically, this would necessitate preparation of organocuprate reagents to avoid competing 1,2-addition, but remarkably we found that when the Ph* containing enones were treated with *n*-BuLi we observed completely regioselective 1,4-addition. This is presumably a consequence of the bulky (and twisted) Ph* group which shields the enone carbonyl group from direct addition. By quenching the resulting lithium enolate with a bulky proton source (2,6-di-*tert*-butylphenol) we isolated the contra-thermodynamic *cis*-diastereoisomer **17** in 87% yield and 80:20 d.r. This method is complementary to our previously reported synthesis of cyclohexanes which selectively produces the thermodynamic *trans*-diastereoisomer.[8]

Having developed an efficient method to access substituted acyl-cyclohexenes, we set out to study the mechanism of the process. We began by monitoring the course of the iridium-catalyzed annulation of **2w** over the first 7 h by analyzing a series of aliquots by reverse phase HPLC (Scheme 3). As expected, we observed steady consumption of Ph*COMe (**1**) along with buildup of the acyl-cyclohexene product **3w**. We also observed another species, which we identified as pyran **21** which formed in approximately 10% yield over the first hour and then was gradually consumed. We also measured the volume of hydrogen gas that was released from the reaction and found that H_2 was steadily released throughout the first seven hours. Overall, this picture is consistent with a mechanistic scenario in which the iridium catalyst dehydrogenates **2w**, slowly releasing the corresponding hydroxyaldehyde **18** which likely exists in equilibrium with the corresponding lactol **19** (vide infra). Condensation with Ph*COMe would then generate acyclic enone **20** which is not observed as it is reversibly converted to pyran **21**, which is an off-cycle intermediate. According to our originally conceived mechanism, the next step would involve reduction of acyclic enone **20** by iridium hydride to from ketone **22**. However, despite several attempts, we were unable to observe or isolate intermediate **22**, which was surprising. As discussed previously, this mechanism also does not fully account for the fact that acyclic enone **20** would have to be fully reduced by iridium hydride, whereas the cyclic enone product **3w** is barely reduced at all. Taken in conjunction, these results led us to consider an alternative mechanistic pathway in which acyclic enone **20** is directly converted to the corresponding cyclohexene product *in the absence of iridium catalyst*.

To test this hypothesis, we independently synthesized lactol **19** by DIBAL-H reduction of the corresponding lactone and treated it with pentamethylacetophenone **1** and KOH in the absence of iridium catalyst (Scheme 4A). We were excited to find that under these conditions cyclohexene **3w** was isolated in 84% yield confirming that an alternative iridium-free

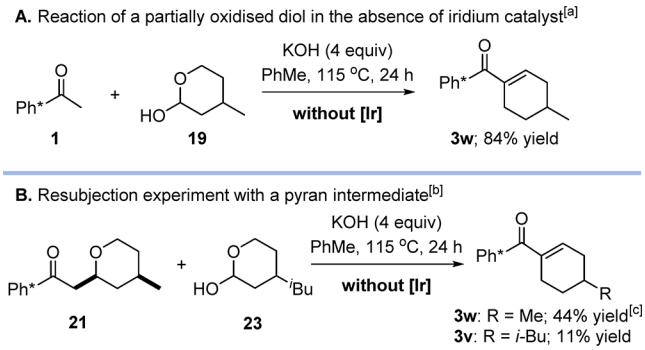
Scheme 3. Reaction Profile for Cyclohexene Synthesis[a]





[a](a) Reaction conditions: **1** (1 equiv), **2w** (2 equiv), KOH (4 equiv), $[Ir(cod)Cl]_2$ (0.5 mol %), CataCXium A (2 mol %), PhMe (0.25 M), 115 °C, 24 h. Yields of **1**, **21**, and **3w** were determined by analyzing aliquots by reverse phase HPLC vs hexamethylbenzene. H_2 evolution was measured volumetrically and converted to absolute concentration using the ideal gas law assuming a temperature of 298 K.

Scheme 4. Resubjection Experiments in the Absence of Iridium Catalyst[a]



[a](a) Reaction conditions: **1** (1 equiv), **19** (2 equiv), KOH (4 equiv), PhMe (0.25 M), 115 °C, 24 h. (b) **1** (1 equiv), **23** (1 equiv), KOH (4 equiv), PhMe (0.25 M), 115 °C, 24 h. (c) Products were isolated as an inseparable mixture, and ratios were determined by ^{1}H NMR spectroscopy (see the Supporting Information).

pathway is indeed operative. We also carried out a related experiment in which methyl substituted pyran **21** was treated with KOH along with an isobutyl substituted lactol **23**, which resulted in formation of a mixture of methyl and isobutyl substituted cyclohexenes **3w** and **3v** in yields of 44% and 11%

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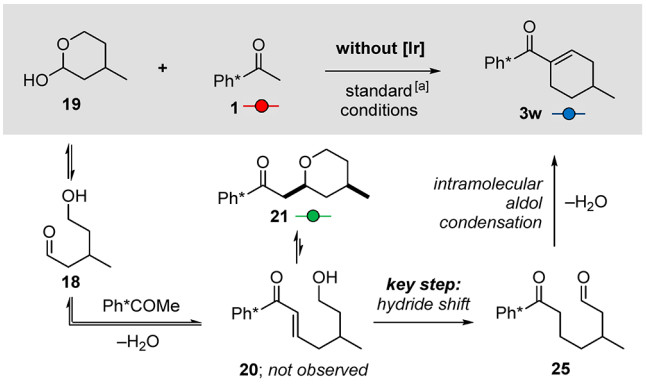
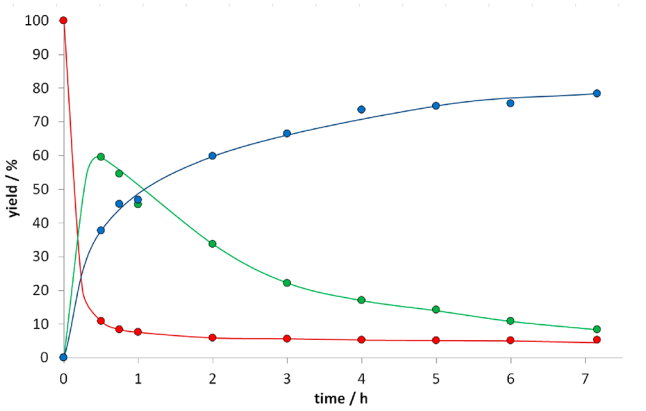
J. Am. Chem. Soc. 2020, 142, 2514−2523

respectively (Scheme 4B). From this experiment we drew two conclusions: (i) pyran **21** is a competent precursor for the metal-free annulation process, most likely via equilibration with acyclic enone **20** under the basic reaction conditions; (ii) the formation of crossover product **3v** suggests that the initial aldol condensation is partially reversible.

In an attempt to study this metal-free annulation process in more detail, we repeated the iridium-free reaction of pentamethylacetophenone with lactol **19** and followed the course of the reaction by reverse phase HPLC (Scheme 5). We

Scheme 5. Reaction Profile for Cyclohexene Synthesis[a]



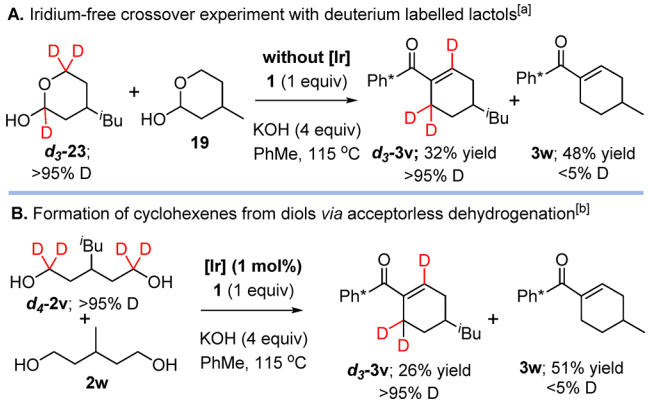


[a](a) Reaction conditions: **1** (1 equiv), **19** (2 equiv), KOH (4 equiv), PhMe (0.25 M), 115 °C, 24 h. Yields of **1**, **21**, and **3w** were determined by analyzing aliquots by reverse phase HPLC *vs* hexamethylbenzene.

discovered that, within the first 30 min of the reaction, pentamethylacetophenone **1** is rapidly consumed and converted to pyran **21**. This intermediate is then itself gradually consumed along with concomitant formation of the corresponding cyclic enone product **3w**. In this case, we observed no evolution of H_2 gas which suggests that the process is overall redox-neutral and confirms the key role played by the iridium catalyst in promoting acceptorless dehydrogenation of the diol. Overall, this data led us to propose a mechanism in which lactol **19** opens to form hydroxyaldehyde **18** and then undergoes rapid (and reversible) aldol condensation to form acyclic enone **20**. This species is then reversibly captured via oxa-Michael addition to form pyran **21** which is observed as an isolable intermediate. The key step would be a hydride transfer to form intermediate **25**, which would undergo facile intramolecular aldol condensation to afford the acyl-cyclohexene product **3w**. The concept of forming a reactive nucleophile−electrophile pair by hydrogen transfer from an alcohol to alkene bears some similarity to elegant chemistry developed by Krische and co-workers.[18]

These experiments strongly implicated a mechanism involving transition-metal-free hydride transfer, but we were uncertain if this process occurred via an intramolecular or intermolecular pathway. In order to probe this experimentally, we set out to perform a double label crossover experiment. To this end, lactol d_3-**23** was synthesized and subjected to iridium-free annulation conditions with an equimolar amount of nondeuterated lactol **19** (Scheme 6A). This experiment

Scheme 6. Double Label Crossover Experiments[a]



[a]The extent of deuterium labelling was determined by separating enone products d_3-**3v** and **3w** by preparative TLC followed by analysis employing a combination of ^{1}H, ^{2}H, and ^{13}C NMR spectroscopy (see the Supporting Information for details). For all compounds, the percentage of D incorporation indicated refers to the amount of D present at each site. (a) Reaction conditions: **1** (1 equiv), d_3-**23** (1 equiv), **19** (1 equiv), KOH (4 equiv), PhMe (0.25 M), 115 °C, 24 h. (b) Reaction conditions: **1** (1 equiv), d_4-**2v** (1 equiv), **2w** (1 equiv), KOH (4 equiv), $[Ir(cod)Cl]_2$ (0.5 mol %), CataCXium A (2 mol %), PhMe (0.25 M), 115 °C, 24 h.

produced isobutyl and methyl substituted cyclohexene products d_3-**3v** and **3w** in yields of 32% and 48%, respectively. These cyclohexenes were then separated by preparative TLC, and the degree of deuteration was analyzed by a combination of ^{1}H, ^{2}H, and ^{13}C NMR spectroscopy (see the Supporting Information for details). This revealed >95% deuterium incorporation at both the C2 and C6 positions of cyclohexene d_3-**3v** and <5% deuterium incorporation at the analogous positions in **3w**. The absence of any crossover of the deuterium label between these products led us to the unambiguous conclusion that the key step proceeds via an intramolecular hydride shift.

In order to confirm our hypothesis that the same process occurs in the iridium catalyzed formation of cyclohexenes from diols, we synthesized tetra-deuterated diol d_4-**2v** and carried out an analogous crossover experiment with a stoichiometric quantity of unlabeled diol **2w** (Scheme 6B). Under our standard conditions for iridium catalyzed annulation, we isolated a mixture of cyclohexenes d_3-**3v** and **3w** in yields of 26% and 51%, respectively. Separation and analysis of these products again revealed that d_3-**3v** was fully deuterated at the C2 and C6 positions (>95%) and **3w** contained no deuterium. This result strongly suggests that the intramolecular hydride shift is also a key step of the iridium mediated annulation

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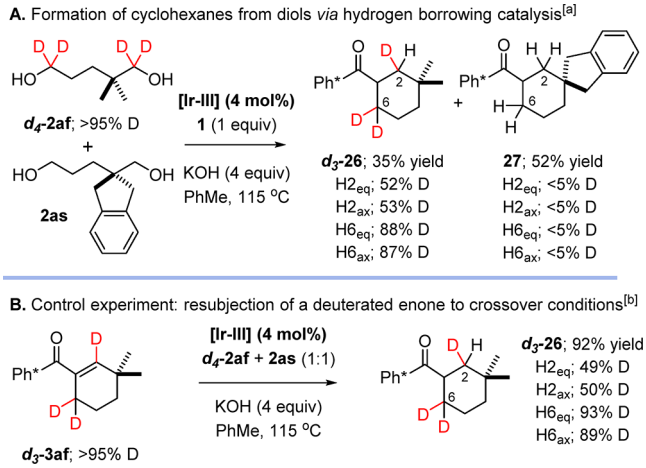
J. Am. Chem. Soc. 2020, 142, 2514−2523

process. The lack of crossover of the deuterium label also implies that under these conditions oxidation of the diol to the hydroxyaldehyde is an irreversible process.

These results led us to question whether this newly identified intramolecular hydride shift-aldol cascade mechanism could also be operative in related hydrogen borrowing annulations reported by our group[8a−c] and others[8d] for the synthesis of cyclohexanes. To test this theory, we carried out a related double label crossover experiment with unsymmetrical diols d_4-**2af** and **2as**, but this time at higher concentration and in the presence of 2 mol % $[Cp^*IrCl_2]_2$(conditions from Table 1, entry 1). As anticipated, under these originally published and more reducing conditions, no cyclohexene products were observed and the only products isolated were cyclohexanes d_3-**26** and **27** in yields of 35% and 52%, respectively (Scheme 7A). To understand the mechanism of the process, we studied

Scheme 7. Double Label Crossover Experiment to Investigate Cyclohexane Formation with $[Cp^*IrCl_2]_2$[a]



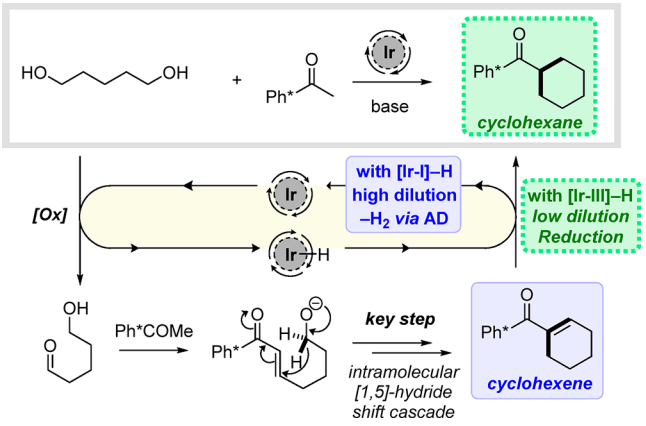
[a]The extent of deuterium labelling was determined by separating cyclohexane products d_3-**26** and **27** by column chromatography followed by analysis employing a combination of ^1H, ^2H, and ^{13}C NMR spectroscopy (see the Supporting Information for details). For starting materials d_4-**2af** and d_3-**3af**, the percentage of D incorporation indicated refers to the amount of D present at each site; for the products each site is listed individually. (a) Reaction conditions: **1** (1 equiv), d_4-**2af** (1 equiv), **2as** (1 equiv), KOH (4 equiv), $[Cp^*IrCl_2]_2$ (2 mol %), PhMe (4 M), 115 °C, 24 h. (b) Reaction conditions: d_3-**3af** (1 equiv), d_4-**2af** (1 equiv), **2as** (1 equiv), KOH (4 equiv), $[Cp^*IrCl_2]_2$ (2 mol %), PhMe (4 M), 115 °C, 24 h.

the deuterium incorporation pattern in these reduced products. We have previously established that, under identical reaction conditions, deuterium is extensively "washed out" by exchange of Ir−D with protic species in the reaction mixture, such that the amount of deuterium introduced at the β-position during iridium catalyzed reduction is typically very small.[8b] Consequently, a mechanism involving two separate cycles of hydrogen borrowing would be expected to introduce one hydrogen at the C6 position and one hydrogen at the C2 position. Conversely, if the hydride shift cascade pathway is operative, only one final reduction by Ir−H would be involved and we would therefore anticipate no H incorporation at the C6 position and incorporation of one H at the C2 position.

When we analyzed the distribution of deuterium in the cyclohexane products, we found that, as expected, substituted cyclohexane **27** contained essentially no deuterium label. Dimethyl substituted cyclohexane d_3-**26** was isolated with 1.75:0.25 D/H at the C6-position whereas the C2 position contained much more deuterium (1.05:0.95 D/H). On the basis of these results, we concluded that the hydride-shift cascade process is the predominant mechanism in the reductive annulation reaction.[19] To support this result, we independently synthesized triply deuterated enone d_3-**3af**, which is the proposed intermediate following the hydride shift and resubjected it to identical conditions with a mixture of d_4-**2af** and **2as** (Scheme 7B). Under these conditions, clean transfer hydrogenation was observed to form cyclohexane d_3-**26** in 92% yield. The pattern of deuterium incorporation was very similar to that observed in the hydrogen borrowing reaction, which supports the hypothesis that acyl-cyclohexene d_3-**3af** is the key intermediate involved in the hydrogen borrowing crossover experiment.

Overall, these mechanistic experiments have led us to a unified mechanistic picture for both cyclohexene and cyclohexane forming annulation processes, which is summarized in Scheme 8. Both reactions are initiated by iridium mediated

Scheme 8. Revised Unified Mechanism for Iridium Mediated Synthesis of Cyclohexenes and Cyclohexanes[a]



[a]AD = acceptorless dehydrogenation.

oxidation of the diol starting material to the corresponding hydroxyaldehyde which then undergoes aldol condensation with Ph*COMe to form an alkoxy enone. This intermediate then undergoes a novel cascade involving an intramolecular [1,5]-hydride shift followed by aldol condensation to form the corresponding cyclohexene. Although [1,5]-hydride shifts involving alkoxide C−H donors are rare,[20] analogous shifts from the corresponding ethers and amines to enones have been reported by several groups.[21] In the presence of an Ir(III) catalyst, the cyclohexene can be reduced to the corresponding cyclohexane product regenerating the active iridium catalyst (Scheme 8, green). Alternatively, with an Ir(I) catalyst along with a bulky CataCXium ligand, iridium hydride is recycled by protonation, releasing H_2 and enabling the isolation of the valuable acyl cyclohexene products (Scheme 8, blue).

3. CONCLUSIONS

Synthesis of the cyclohexyl motif is of paramount importance in the preparation of naturally occurring and biologically relevant molecules. We have developed a new intermolecular (5 + 1) strategy for cyclohexene synthesis utilizing readily accessible and commercially available 1,5-diols along with

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J. Am. Chem. Soc. 2020, 142, 2514−2523

pentamethylacetophenone. This method provides straightforward access to a wide range of highly functionalized cyclohexenes with high levels of regiocontrol. It was also demonstrated that enantiopure γ-substituted diols can undergo annulation to afford C4-substituted cyclohexenes with no loss of stereochemical integrity. The Ph* containing acyl-cyclohexene products can be diversified into a wide range of carbonyl derivatives under mildly acidic conditions. Based on a series of mechanistic experiments, it was found that the reaction proceeded via catalyst controlled acceptorless dehydrogenation followed by an intramolecular cascade involving a sequential [1,5]-hydride shift followed by aldol condensation. Moreover, we have discovered that a similar intramolecular [1,5]-hydride shift is embedded within our previously reported cyclohexane synthesis, leading us to revise our originally proposed mechanistic hypothesis. We anticipate that this chemistry will find widespread application in the synthesis of valuable acyl-cyclohexenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b12296.

Detailed experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(15) The operational simplicity of this procedure is particularly noteworthy: the reactions did not require anhydrous solvent and were set up with no attempt to exclude air.

(16) The cleavage of enone **3ag** proceeded smoothly in the presence of unreacted Ph*COMe, which allowed for the isolation of carboxylic acid **11**.

(17) This process could occur by formation of an extended enol followed by bromination or via a radical pathway. For a related example, see: Lansbury, P. T.; Erwin, R. W.; Jeffrey, D. A. Gamma-Alkylation of Alpha, Beta-Unsaturated Ketones. Gamma-Arylsulfonyl Groups as Regioselective Control Elements. *J. Am. Chem. Soc.* **1980**, *102* (5), 1602−1608.

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(19) Based on this result, ≤25% of the cyclohexane product is formed by a double hydrogen borrowing cycle. However, given that the deuterium incorporation in the diol starting material d_4-**2af** is ∼96% at each position (see the Supporting Information for details), the contribution from a double hydrogen borrowing mechanism is likely even smaller. Moreover, we cannot rule out a small amount of deuterium "wash-out" at the α-position of the diol arising from reversible oxidation/reduction under these more reducing conditions.

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