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Catalysis

Platinum-Catalyzed α,β-Desaturation of Cyclic Ketones through Direct Metal–Enolate Formation

*Ming Chen and Guangbin Dong**

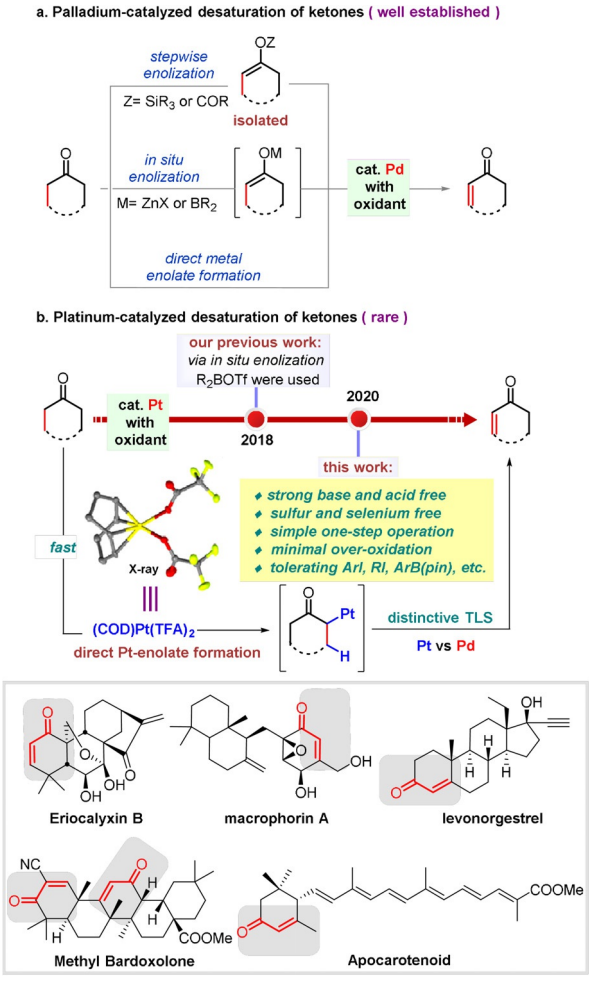
Dedicated to Professor Barry M. Trost on the occasion of his 80th birthday

Abstract: *The development of a platinum-catalyzed desaturation of cyclic ketones to their conjugated α,β-unsaturated counterparts is reported in this full article. A unique diene-platinum complex was identified to be an efficient catalyst, which enables direct metal-enolate formation. The reaction operates under mild conditions without using strong bases or acids. Good to excellent yields can be achieved for diverse and complex scaffolds. A wide range of functional groups, including those sensitive to acids, bases/nucleophiles, or palladium species, are tolerated, which represents a distinct feature from other known desaturation methods. Mechanistically, this platinum catalysis exhibits a fast and reversible α-deprotonation followed by a rate-determining β-hydrogen elimination process, which is different from the prior Pd-catalyzed desaturation method. Promising preliminary enantioselective desaturation using a chiral-diene-platinum complex has also been obtained.*

Introduction

As a fundamental organic transformation, α,β-desaturation of carbonyl compounds has found increasing importance in synthetic strategy planning and is frequently used in complex molecule synthesis.[1,2] Compared to conventional approaches, the transition metal-catalyzed desaturation generally operates under mild conditions and avoids strong oxidants, highly toxic reagents or multi-step operations. Among various transition metal-catalyzed carbonyl desaturation methods reported to date,[3] those catalyzed by palladium are most widely used. The reaction mechanism involves rate-determining Pd^{II}-enolate formation followed by rapid β-hydrogen elimination and regeneration of Pd^{II} via oxidation.[4,1d] According to how the Pd^{II} enolate is formed, three types of Pd-catalyzed desaturation have been developed (Scheme 1 a), including **(i)** stepwise enolization, for example, Saegusa–Ito oxidation,[5] **(ii)** in situ enolization, for example, forming zinc or boron enolates in one pot via hard or soft enolization,[6] and **(iii)** direct enolization by Pd^{II}, which does not require forming enolates prior to the catalysis.[7]

On the other hand, unlike palladium or nickel, oxidative addition of low valent platinum with electrophiles, such as polarizable C–X or C–O (X: halogen) bonds, is much less common.[8] Thus, a broader functional group tolerance could be anticipated with the Pt^0/Pt^{II} catalysis. However, compared to palladium, platinum-catalyzed carbonyl desaturation has been extremely rare. In 2018, we reported our preliminary study of a Pt^{II}-catalyzed carbonyl desaturation through an in situ soft-enolization approach.[9] A strong Lewis acid, Bu_2BOTf, was needed to generate the corresponding boron enolate prior to the catalytic desaturation. As such, acid-sensitive functional groups, for example, ketals and silyl ethers, were not compatible under these conditions. To the best of our knowledge, the Pt-catalyzed desaturation of carbonyl compounds through *direct enolization* remained an unknown transformation. Herein, we describe a full story of



Scheme 1. Pd and Pt-catalyzed desaturation of carbonyl compounds.

[*] M. Chen, G. Dong
Department of Chemistry, University of Chicago
Chicago, IL 60637 (USA)
E-mail: gbdong@uchicago.edu

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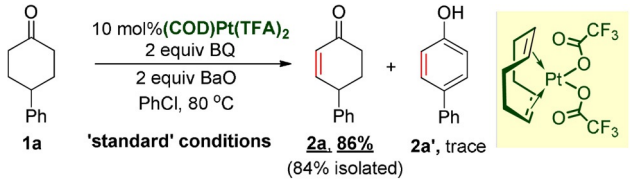
the development of a Pt-catalyzed direct desaturation of cyclic ketones without using strong bases or acids, which provides an efficient method to access α,β-unsaturated enones commonly found in bioactive compounds (Scheme 1b).[10] Complementary to other desaturation methods, a wide range of sensitive functional groups are tolerated. A well-defined diene-Pt^{II} complex has been identified as the optimal catalyst, and detailed mechanistic studies reveal a different mechanistic feature from the analogous Pd-catalyzed desaturation.

Results and Discussion

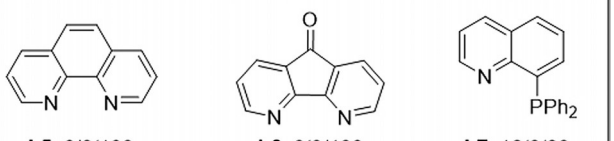
Our study began with employing cyclohexanone **1a** as the model substrate. After extensive optimization, a well-defined $(COD)Pt(TFA)_2$ complex was found to be the optimal catalyst, whose structure was unambiguously confirmed by X-ray crystallography (Table 1).[11] With BQ (1,4-benzoquinone) and insoluble BaO as the oxidant/base combination, the desired α,β-unsaturated ketone **2a** was obtained in 86% yield. The corresponding over-oxidation product, phenol **2a′**, was only generated in a trace amount.

Table 1: Selected optimization studies.



Entry	Variations from the "standard" conditions	Yield [%] of **2a**/**2a′**/**1a**[a]
1	Without $(COD)Pt(TFA)_2$ (**C1**)	0/0/100
2	Without BQ (**Ox1**)	10/0/85
3	Without BaO (**B1**)	32/2/54
4	**C2–5** instead of $(COD)Pt(TFA)_2$	Listed below
5	**L1–7** as the additional ligand	Listed below
6	carried out in air	78/12/4
7	5 mol% $(COD)Pt(TFA)_2$, 48 h	58/10/26
8	50 °C, 48 h	65/0/32
9	room temperature, 48 h	16/0/80
10	solvent = PhH	80/6/10
11	solvent = toluene	74/6/16

$Pt(COD)(OAc)_2$	$Pt(PPh_3)_4$	$Pt(COD)Cl_2$	$Pt(MeCN)_2Cl_2$
C2, 8/0/88	**C3**, 0/0/100	**C4**, 40/2/48[b]	**C5**, 12/0/80[b]
$(4\text{-}CF_3\text{-}C_6H_4)_3P$	dppe	dppp	bpy
L1, 0/0/100	**L2**, 10/0/86	**L3**, 4/0/92	**L4**, 0/0/100



L5, 0/0/100 **L6**, 0/0/100 **L7**, 16/0/80

[a] Each reaction was run on a 0.1 mmol scale in a sealed 4 mL vial under N_2 for 12 h; yields were determined by ^1H NMR using CH_2Br_2 as the internal standard. [b] 25 mol% of AgTFA was added. TFA = trifluoroacetate, COD = 1,5-cyclooctadiene, BQ = 1,4-benzoquinone.

To gain insights into the roles of each reactant, control experiments were carried out (for more details, see Supporting Information). Clearly, the platinum catalyst is critical to this transformation, as no product was observed in the absence of $(COD)Pt(TFA)_2$ (entry 1). A survey of different oxidants revealed that simple BQ is most effective. Interestingly, in the absence of oxidant, quantitative yield of the product based on Pt was obtained, suggesting that BQ may not play as a ligand in this reaction (entry 2). While base was not essential, the reaction was promoted by insoluble inorganic bases, such as BaO (entry 3). For comparison, soluble organic bases, such as Et_3N, DIPEA, DBU and KO^{t}Bu, shut down the reaction by poisoning the Pt catalyst. A range of other Pt complexes have been examined as catalysts (entry 4). First, $(COD)Pt(OAc)_2$ gave very poor yield (8%), suggesting the importance of the electron-deficient trifluoroacetate ligand. The Pt^0 catalyst, that is, $Pt(PPh_3)_4$, gave no conversion. The combination of $Pt(COD)Cl_2$ and AgTFA, which was intended to form $(COD)Pt(TFA)_2$ in situ, was less effective. The reactivity was even lower when using $Pt(MeCN)_2Cl_2$ instead, indicating the positive contribution of the COD ligand. For comparison, the use of other metals, such as Pd, Ir and Rh, gave much inferior results using COD as ligand. The addition of strongly coordinative ligands has also been examined (entry 5). While most ligands significantly inhibited the reaction, the use of bisphosphines (**L2** and **L3**) and P/N ligand (**L7**) yielded a small amount of product **2a**. It is worth to point out that the reaction can be carried out under air, albeit forming 12% yield of the phenol side-product (**2a′**), which indicates that the participation of oxygen may cause over oxidation (entry 6). When 5 mol% of the catalyst was used, 58% yield was still obtained (entry 7). While slower, the reaction can still take place at lower temperatures, such as 50 °C and even room temperature (entries 8 and 9). Finally, among different solvents tested, aromatic solvents are more effective (entries 10 and 11); by contrast, more polar solvents, such as 1,4-dioxane and THF, gave no desired product.

With the optimized conditions in hand, the substrate scope was next explored (Table 2). First, substitution at cyclohexanone α,β,γ-positions can all be tolerated (**2a**–**2ar**).[12] For α-substituted ketones, high site-selectivity was obtained with reaction taking place almost exclusively at the less substituted site (**2d** and **2e**). While lower selectivity was observed with β-substituted substrates, the major product was still formed via desaturation at the less bulky side (**2f**). Gratifyingly, steric bulkiness at either the α,β,γ-positions does not appear to significantly affect the reaction yields (**2g**–**2k**). As expected, this platinum catalysis condition can tolerate a wide range of functional groups, including acid-sensitive moieties, such as TBS ether (**2p**), acetal (**2q**), ketal (**2u** and **2v**) and aryl boronate (**2ar**), and nucleophile/base sensitive moieties, such as OTs (**2m**), ester (**2n**, **2y**, **2z**, **2bg**, **2bk** and **2bl**), alkyl halide (**2r** and **2w**) and aldehyde (**2an**). In particular, functional groups that can easily react with palladium, such as aryl iodide (**1s**, **1t** and **1ac**), aryl bromide (**2ad**), alkyl iodide (**1r**), alkyl bromide (**1w**) and pinacol boronate (**2ar**), were compatible. In addition, an acidic secondary sulfonamide (NHTs, **2x**) was tolerated. Moreover, common functional groups, such as trifluoromethyl (**2ak**),

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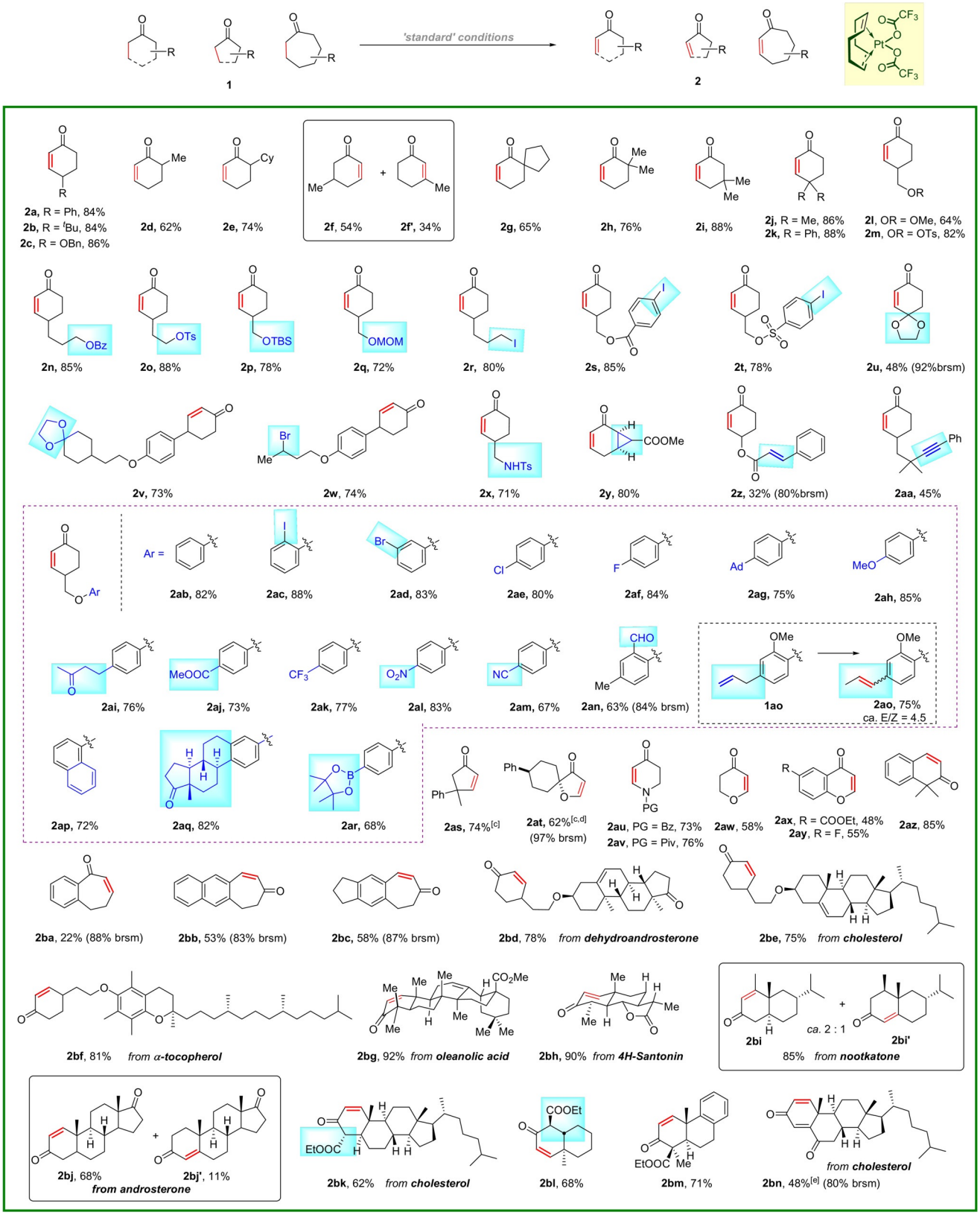
Table 2: Substrate scope.[a,b]



[a] Each reaction was run on a 0.1 mmol scale in a sealed 4 mL vial for 12 h. [b] Isolated yields. [c] The reaction was carried out without adding BaO as the base at 120 °C. [d] Product **2at** exists as a single diastereomer. The relative stereochemistry is tentatively assigned. [e] Reaction time was 48 h. brsm = based on recovered starting materials. Ts = *p*-toluenesulfonyl, TBS = *tert*-Butyldimethylsilyl, Bz = benzoyl, Piv = pivaloyl, Ad = 1-Adamantanyl.

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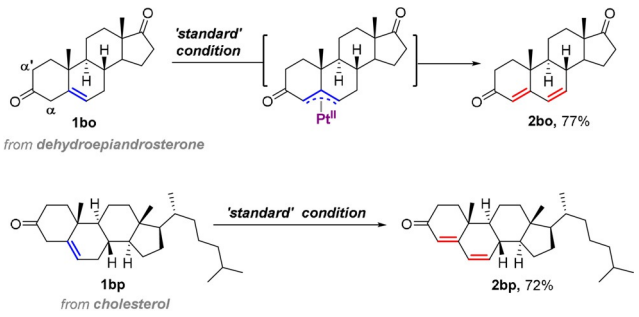
nitro (**2al**), nitrile (**2am**), cyclopropane (**2y**), alkene (**2z**) and alkyne (**2aa**), remained intact. It is interesting to note that terminal olefin **1ao** underwent complete migration to form the conjugated product, implying the involvement of metal-hydride species. It is of note that cyclohexanones containing sulfides, terminal alkynes, free alcohols, or carboxylic acids proved to be challenging substrates under the current conditions (see Supporting Information).

The reaction was highly selective for desaturation of six-membered ketones. Linear ketones (**2ai**) and cyclopentanones (**2aq** and **2bd**) were much less reactive under the standard conditions. This is likely not related to the pK_a of their α C–H bonds as cyclopentanone is known to be more acidic than cyclohexanone.[13] While the exact reason remains unclear at this stage and will be investigated thoroughly in the future, it is surprising that five-membered ketones **1as** and **1at** afforded the desired product in good yields in the absence of base at an elevated temperature. In addition, N and O-containing six-membered heterocyclic ketones generally gave satisfactory yields (**2au**–**2ay**), and 2,2-dimethyl β-tetralone reacted smoothly to deliever the unsaturated product (**2az**) in high yield. Moreover, moderate reactivity was observed with seven-membered cyclic ketones (**1ba**–**1bc**).

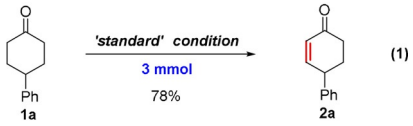
Notably, cyclohexanones derived from or tethered with bioactive natural products, such as dehydroandrosterone (**2bd**), cholesterol (**2be**, **2bk** and **2bn**), α-tocopherol (**2bf**), oleanolic acid (**2bg**), 4H-Santonin (**2bh**), nootkatone (**2bi**), and androsterone (**2bj**), all afforded the desired desaturation products in good to excellent yields. High site-selectivity was observed with α-substituted substrates (**2bh**, **2bk** and **2bl**). It is interesting that desaturation did not take place at the sides with more acidic C–H bonds (those with α-CO_2Et substituents, **2bk** and **2bl**); instead, the less bulky sides reacted exclusively, implying that α-deprotonation is *unlikely* to be the rate-determining step for the Pt-catalyzed desaturation (vide infra). Note that epimerization with **2bk** and **2bl** did not occur. Moderate selectivity was observed for the β-substituted substrates (**1bi** and **1bj**). When enone **1bn** was used as the substrate, the reaction proceeded at a much lower rate, giving the corresponding dienone in moderate yield.

Interestingly, β,γ-unsaturated ketones (**1bo** and **1bp**) selectively dehydrogenated at the alkene side to afford the conjugated 1,3-diene products (Scheme 2), which are in sharp contrast to the outcomes of the corresponding saturated substrates (**1bj** and **1bk**). We postulate that formation of a π-allyl-Pt intermediate is likely the driving force for such products.



Scheme 2. Desaturation of β,γ-unsaturated cyclic ketones.

To examine the practicality of this method, a large-scale reaction of **1a** was carried out [Eq. (1)]. On a 3.0 mmol scale, the desired cyclohexenone **2a** was still isolated in 78% yield.

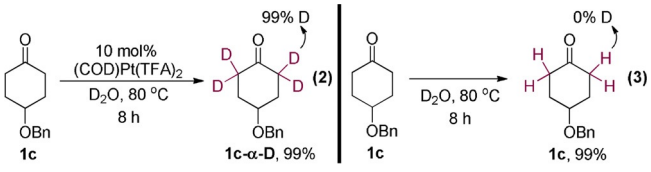


Efforts were then carried out to gain some mechanistic insights. To better understand the catalytic system, the kinetic profiles of the reaction with substrate **1a** were obtained (Figure S1). First, no induction period was observed. The reaction proceeded with a high initial reaction rate (0.5 mM min^{-1}) and became slower after 2 hours (at around 60% conversion). The product formation was plateaued after 6 hours. Notably, the mass balance was nearly perfect in this period, indicating that there was minimal decomposition of the substrate or product. Formation of phenol side-product (**2a′**) did not take place until the late stage of the reaction after the main reaction was nearly finished.

To understand the selectivity for the mono-desaturation and to investigate if product inhibition exists, the kinetic profiles of the reaction with cyclohexanone **1b** and the competition reaction between **1b** and cyclohexenone **2k** were measured (Figure S2). Substrate **1b** was used for easier analysis due to the distinguished ^{t}Bu peaks. The γ,γ-disubstituted **2k** was used as it would unlikely undergo aerobic oxidation to give a phenol. Based on the initial reaction rates and final product yields of these two reactions, it became clear that conjugated enones, despite with more acidic α-C–H bonds, are much less reactive towards further dehydrogenation under this platinum-catalyzed conditions (vide supra, **2bm**), which explains the high mono-desaturation selectivity. On the other hand, the results also suggest that enone products do not inhibit the reaction with saturated substrates.

To understand the reversibility of the platinum-enolate-forming step, two control experiments were conducted (Scheme 3). Treatment of substrate **1c** with 10 mol% (COD)Pt(TFA)$_2$ in D_2O for 8 h gave 99% D at the α position [Eq. (2)]. In contrast, no deuterium incorporation was found in the absence of the platinum catalyst [Eq. (3)]. These results suggest that the H/D exchange at ketone α position can be efficiently catalyzed by the Pt complex without aid of base, implying a fast and reversible formation of the platinum enolate intermediate in this reaction.

To gain insights into the turnover-limiting step (TLS), the kinetic isotope effect (KIE) of the reactions was studied (Scheme 4). The competitive experiment showed that no



Scheme 3. Studies of the deprotonation step with the platinum catalyst.

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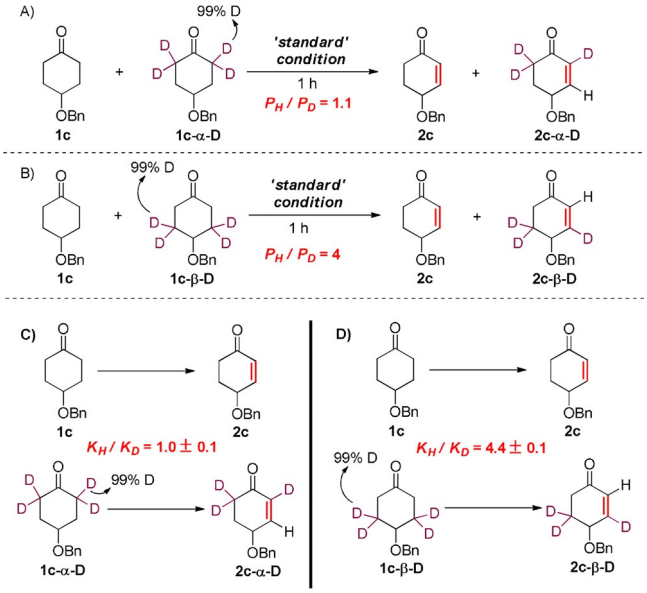


Scheme 4. Kinetic isotope effect studies.

primary KIE was observed at the ketone α-position; both competitive and parallel reactions showed large primary KIE values (4.0 and 4.4, respectively) when using the β-deuterated substrate, which correlates well with the prior Hartwig's mechanistic study of β-hydrogen elimination from organoplatinum(II) enolate complexes.[14] In addition, the kinetic orders of the substrate (**1c**), the Pt catalyst [(COD)Pt-$(TFA)_2$] and the oxidant (BQ) have been determined using the initial-rate method (Figure S18). The reaction exhibited first-order dependence on both the catalyst and the substrate, and zero-order on the oxidant. These results are consistent with elimination of the ketone β-hydrogen to be the TLS, as the TLS should not be deprotonation of the α-C–H bond due to the lack of primary KIE at that position and must involve the substrate based on the kinetic orders. This mechanistic feature is in sharp contrast to Stahl's Pd/O_2 system,[15] in which the α-C–H cleavage is the TLS. It is also different from Newhouse's base-mediated in situ enolization/dehydrogenation methods, which involve a rate-determining reductive elimination of the $Pd^{II}HX$ species.[6a]

While some mechanistic details remain unclear and are topics of ongoing investigations, the data based on the above studies allow us to propose a hypothesis for the catalytic cycle (Figure 1). The catalytic cycle starts with fast and reversible deprotonation of ketone α-C–H bonds by the Pt^{II} catalyst. The resulting Pt^{II}-enolate then undergoes a turnover-limiting β-hydrogen elimination to give the enone and a Pt^{II}-hydride species. The enone product subsequently dissociates from the Pt center via ligand exchange, and the Pt^{II} catalyst is regenerated through oxidation of the Pt^{II}-hydride species by BQ. A plausible role of the insoluble base is to neutralize the hydroquinone (HBQ) byproduct, though in the case of five-membered cyclic ketones the reaction worked much better without base.

To the best of our best knowledge, transition metal-catalyzed enantioselective direct desaturation of ketones has

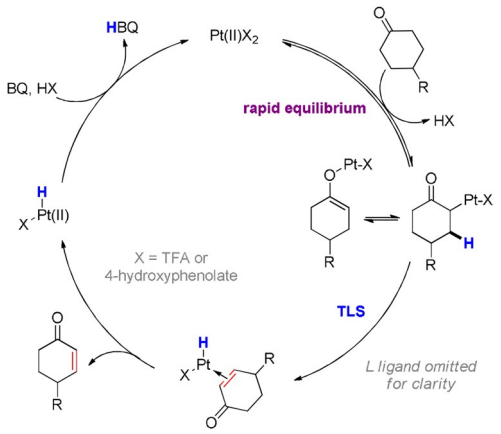
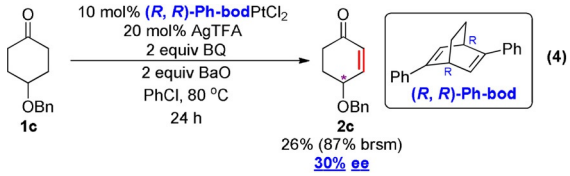


Figure 1. Proposed catalytic cycle.

not been reported.[16] As a promising preliminary result, when an optically pure bicyclo[2.2.2]octane-2,5-diene, namely (*R*,*R*)-Ph-bod, was employed as the ligand (instead of COD), 30% *ee* of the cyclohexenone product (**2c**) was obtained [Eq. (4)]. This indicates the feasibiltiy of developing enantioselective ketone desaturation using chiral diene ligands. Efforts on improving both the enantioselectivity and conversion are ongoing.



Conclusion

In summary, the platinum-catalyzed α,β-desaturation of cyclic ketones through direct metal enolate formation has been developed. The reaction operates under mild conditions without need of strong bases or acids. The tolerance of a large variety of sensitive functional groups and substitution patterns makes this method attractive for use in the synthesis of complex bioactive molecules. The key for the success of this transformation is the employment of a diene ligand. Additionally, the promising preliminary result obtained in this study will motivate the development of enantioselective dehydrogenation of cyclic ketones. Finally, mechanistic studies reveal a fast and reversible Pt-enolate formation, which is followed by a rate-determining β-hydrogen elimination process. This distinct mechanistic feature departs from the known palladium-catalyzed carbonyl dehydrogenation reactions, and thus could inspire the discovery of new platinum-catalyzed carbonyl functionalization methods.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: dehydrogenation · desaturation · enantioselectivity · ketones · platinum catalysis

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