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α,β-Dehydrogenation of esters with free O–H and N–H functionalities via allyl-palladium catalysis

Suzanne M. Szewczyk [a], Yizhou Zhao [a], Holt A. Sakai [a], Pascal Dube [b], Timothy R. Newhouse [a], *

[a] Department of Chemistry, Yale University, 225 Prospect Street, New Haven, CT 06520-8107, United States
[b] Nalas Engineering, 85 Westbrook Road, Centerbrook, CT 06409, United States

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ABSTRACT

A direct and selective method for the α,β-dehydrogenation of esters using palladium catalysis in the presence of free O–H and N–H functionalities is reported herein. Allyl-palladium catalysis allows for preservation of readily oxidizable functionalities such as amines and alcohols. Furthermore, an economical protocol using LDA was developed for the dehydrogenation of β-amino esters.

1. Introduction

Methodologies with defined chemoselectivity profiles are important for the practical synthesis of complex organic materials. In particular, the ability to oxidize a specific functional group in the presence of another allows for strategic orchestration of sequential synthetic transformations leading to efficient multistep syntheses. The functional group compatibility of methods to dehydrogenate carbonyl compounds has historically been limited to substrates that do not have other oxidation-prone functionalities owing to the strong, electrophilic oxidants employed in such methods.[1]

Our group has recently reported that a variety of carbonyl compounds, including esters,[2a] can be transformed to their unsaturated counterparts via conversion to the zinc enolates and treatment with catalytic Pd(II) and stoichiometric allyl oxidant (Fig. 1). Our initial report[2a] described the use of this approach for the dehydrogenation of nitriles and esters, and subsequently, we demonstrated the applicability of this mechanistic paradigm to amides,[2b] carboxylic acids,[2c] and ketones.[2d,2e] Interestingly, we found in the case of amide dehydrogenation our method could tolerate oxidation-prone functionality such as unprotected alcohols and N–H containing amide substrates, which could readily undergo oxidation to the corresponding C=X systems.[2b] The key to obtaining complete conversion and synthetically useful yields was forming the dianion with lithium cyclohexyl(2,6-diisopropylphenyl)amide (LiCyan) used as a hindered amide base.

In this report, we extend our earlier findings to the

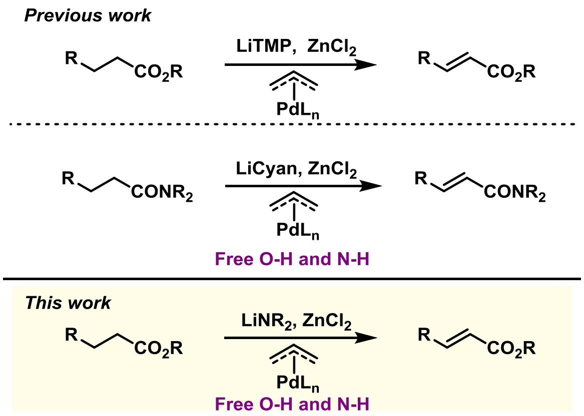

Fig. 1. Allyl-palladium catalysis for carbonyl α,β-dehydrogenation.

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* Corresponding author.
E-mail address: timothy.newhouse@yale.edu (T.R. Newhouse).

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dehydrogenation of O–H- and N–H-containing esters and additionally disclose a more cost-effective protocol using inexpensive LDA for the specific case of β-amino ester dehydrogenation. The success of allyl-palladium catalysis for these selective oxidation reactions is remarkable considering the known propensity for Pd(II) to coordinate to and even oxidize oxygen[3]- and nitrogen[4]-based nucleophiles.

2. Results and discussion

In our initial attempts to dehydrogenate ester **1a** in the presence of a free alcohol, reaction conditions previously reported by our group were examined (Table 1). The reaction proceeds via formation of a zinc enolate, transmetalation to Pd, and subsequent β-hydride elimination. To our delight, the conditions reported for dehydrogenation of amides (Entry 1) in the presence of free O–H and N–H functionalities were successful and provided slightly improved conversion as compared to our original conditions for ester and nitrile dehydrogenation (Entries 2–3). Zn(TMP)$_2$ (Entries 4–5), which was utilized for the dehydrogenation of carboxylic acids and ketones, proved to be minimally effective for this transformation.

2.1. *Optimization*

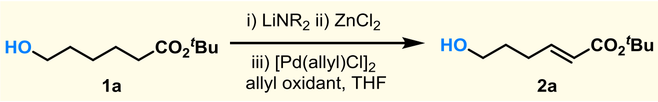
Table 2 shows a further examination of reaction conditions for the dehydrogenation of **1a**. The combination of allyl pivalate and LDA (Entry 1) led to slightly higher conversion than allyl acetate and LDA (Entry 2). Additionally, LDA outperformed other commercial bases such as LHMDS (Entry 3), and LiNCy$_2$ (Entry 4). Nonetheless, the optimal conditions for this transformation utilize LiCyan as the lithium anilide base (Entry 5). Examination of the equivalents of base and ZnCl$_2$ additive (Entries 6–7) demonstrated that formation of the dianion with an excess of ZnCl$_2$ was critical to achieving high conversion.

2.2. *Scope of tert-butyl ester dehydrogenation*

With these conditions in hand, we evaluated a variety of *tert*-butyl esters with free O–H and N–H functionalities (Fig. 2). A lactam (**2b**), indole (**2c**), and aniline (**2d**) were all tolerated and led to the generation of the dehydrogenated compound in high yields. Both secondary (**2e**) and primary alcohols (**2a**) remained intact as did a free phenol (**2f**).

More challenging methyl esters such as methyl 4-hydroxycyclohexane carboxylate proceeded with lower yields. This is partially due to lower solubility of the resultant dianion, as compared to the *tert*-butyl esters.

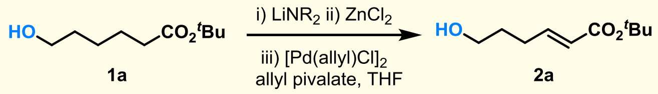
Table 1
Application of previously reported conditions.



Entry	Conditions	Base	Allyl Oxidant	Yield (%)[a]
1	amides[2b]	LiCyan	–OAc	90%
2	esters[2a]	LiTMP	–OPiv	87%
3	nitriles[2a]	LiTMP	–OAc	80%
4	ketones[2d]	Zn(TMP)$_2$	–OP(O)(OEt)$_2$	21%
5	acids[2c]	Zn(TMP)$_2$ • 2LiCl	–OAc	3%

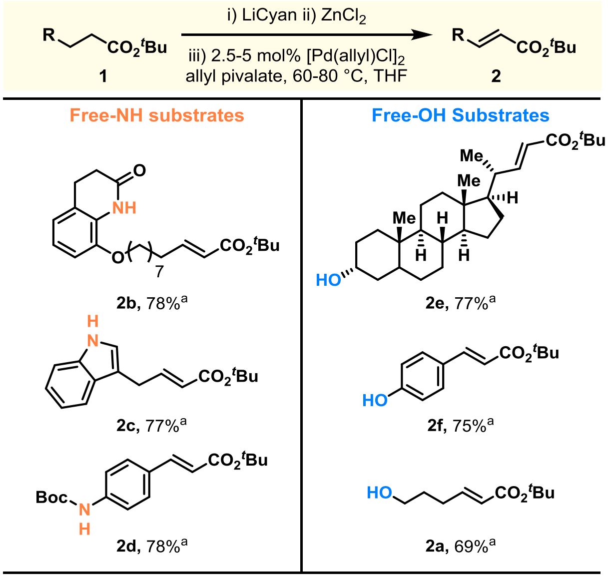
[a] Yields were determined by ^{1}H NMR analysis using dibromomethane as internal standard.

Table 2
Optimization of ester dehydrogenation.



Entry	Base	Equiv Base	Equiv ZnCl$_2$	Yield (%)[a]
1	LDA	2.5	4.0	79
2	LDA[b]	2.5	4.0	72
3	LHMDS	2.5	4.0	51
4	LiNCy$_2$	2.5	4.0	43
5	LiCyan	2.5	4.0	89
6	LiCyan	2.5	2.0	62
7	LiCyan	1.2	4.0	0 (21)

[a] Yields were determined by ^{1}H NMR analysis using dibromomethane as internal standard. Conversion is shown in parentheses.
[b] Allyl acetate was used instead of allyl pivalate.



[a]Isolated yields.

Fig. 2. Scope of *tert*-butyl ester dehydrogenation.

2.3. *Intermolecular experiments*

In order to further probe the scope of this reaction and demonstrate its robustness, a variety of commercial compounds with free O–H and N–H functionalities were introduced as additives to the standard reaction conditions for the dehydrogenation of ester **1g** with LiCyan (Fig. 3).[5] The change in yield of the dehydrogenated product (**2g**) relative to the control experiment without an additive was evaluated by ^{1}H NMR analysis. The yield of **2g** without additives is consistently around 99%. The additive was introduced directly after the starting material (**1g**), and an extra equivalent of the base presumably deprotonated the additive during the enolate formation stage. The reaction proceeded with good to excellent conversion in the presence of a variety of additives. Amines and anilines (Fig. 3A) are well tolerated, as are a variety of nitrogen-based heterocycles (Fig. 3B). Amides, carbamates, and lactams