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Iridium Catalyzed Aerobic α,β -Dehydrogenation of γ,δ -Unsaturated Amides and Acids: Activation of Both α - and β -C-H bonds through an Allyl-Iridium Intermediate

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Supporting Information Placeholder

ABSTRACT: Direct aerobic α,β -dehydrogenation of γ,δ -unsaturated amides and acids using a simple iridium/copper relay catalysis system is described. We developed a new strategy that overcomes the challenging issue associated with the low α -acidity of amides and acids. Instead of α -C-H metalation, this reaction proceeds by β -C-H activation, which results in enhanced α -acidity. Conjugated dienamides and dienoic acids were synthesized in excellent yield with this reaction, which uses a simple reaction protocol. Mechanistic experiments suggest a catalyst resting state mechanism in which both α -C-H and β -C-H cleavage is accelerated.

INTRODUCTION

 α,β -Unsaturated carbonyl compounds are arguably the most diverse synthetic building blocks with remarkable chemical versatility. Direct α,β -dehydrogenation takes advantage of the ubiquity of alkyl aldehydes, ketones, esters, acids or amides, and is the most straightforward strategy with which to access this important class of α,β -unsaturated carbonyl compounds. Common strategies used to affect direct dehydrogenation of carbonyl compounds are centered on enolate chemistry.¹ Earlier studies used stoichiometric strong oxidants such as SeO2^{1a-1d} or 1,4-benzoquinone derivatives^{1e-1g} for direct oxidization of ketones and aldehydes. The reaction conditions involved are harsh and the reactions themselves have limited substrate scopes. In 2000, Nicolaou developed a general and mild method using o-iodoxybenzoic acid (IBX) as a stoichiometric oxidant.² More recently, environmental pressures have prompted chemists to upgrade these methods with more atom-economical and byproduct-free processes.³ As a result, investigations have been focused on development of mild catalytic conditions using air or molecular oxygen as the terminal oxidant.⁴

Recent reports by Stahl,^{4b-4h} Wang,^{4i,j} Kang^{4k} and us⁴¹ provide a general solution to aerobic dehydrogenation of alkyl aldehydes and ketones, using palladium catalysis. This reaction generates the important α,β -unsaturated aldehyde and ketone products with high efficiency under mild conditions. Aerobic dehydrogenation of amides and acids is however, far more challenging,⁵ notwithstanding the prevalence of such compounds in biomass and industrial feedstocks. The mechanism of aerobic dehydrogenation of aldehydes and ketones shares a common intermediate: the palladium enolate. Due to the weak acidity of the α -C-H of amides and acids, it is difficult to identify catalytic conditions that can promote metal enolate formation, the subsequent β -hydride elimination and catalyst re-oxidation, all at the same time. Recently, Newhouse reported palladium-catalyzed, direct α,β -dehydrogenation of amides, esters and nitriles via a zinc enolate intermediate.^{5c,d} The palladium turnover was accomplished using allyl acetate as the terminal oxidant. Despite the use of stoichiometric lithium amide base and allyl acetate, this strategy represents a major advance in

the direct dehydrogenation of challenging amide, nitrile and ester substrates. Very recently, Dong reported Lewis-acid assisted dehydrogenation of imides^{5e} but primary amides or acids are generally not tolerated in these reactions due to the presence of an acidic residue that interferes with enolate formation (**Figure 1A**). In this paper, we report our findings in direct, aerobic, dehydrogenation of γ , δ -unsaturated amides and acids under conditions of Ir/Cu relay catalysis.



Figure 1. Direct dehydrogenation of carbonyl compounds

Our group has long sought catalytic conditions for aerobic dehydrogenation of amides, esters and acids. Due to the limited α acidity of these compounds, use of various Lewis acid activators to form a sufficient concentration of the metal enolates was largely unsuccessful. Accordingly, we examined alternative strategies whose rate-limiting step does not require formation of metal enolates. Amides and acids have been well documented as excellent directing groups for selective β -C-H insertion by various transition metals⁶ but, in spite of significant advances in C-H functionalization reactions in recent years, β -C-H activation has not been applied to dehydrogenation reactions.⁷ The use of a directing group locks the transition metal into a cyclic metal complex (Figure 1B), in a conformation that disfavors hydride elimination, both sterically and electronically. In order to solve this problem, we proposed a means of releasing transition metals from the directing group by forming metal-allyl complexes. Metal-allyl complexes are classical electron-deficient species that react readily with various nucleophiles under mild conditions.⁸ Despite a pioneering report by White on dehydrogenation of terminal olefins, direct dehydrogenation of olefinic amides and acids remains elusive.⁹ We hypothesized that the electron-withdrawing property of metal-allyl complexes can be harnessed by enhancing the α acidity of amides and acids to forge a new protocol for aerobic α,β -dehydrogenation of γ,δ -unsaturated amides and acids. The enhanced α -acidity of the metal-allyl intermediate resembles that of 1,3-dicarbonyl compounds, whose enolates are stabilized by an additional π^* orbital from the second carbonyl (Figure 1C). The resulting conjugated dienyl carbonyl products are versatile synthetic intermediates and often exist as key fragments in various natural products and their metabolites.

RESULTS AND DISCUSSION

To test this proposal, we began our investigation by exploring the use of transition metals for the α,β -dehydrogenation of N-(4methoxybenzyl)pent-4-enamide (1) in 1,2-dichloroethylene (DCE). Initially, 2.2 equivalents of Cu(OAc)₂ hydrate were used as the terminal oxidant. Most palladium catalysts were found to be ineffective in promoting the dehydrogenation. The intramolecular Wacker oxidation was the major side reaction that resulted in a cyclization product (Table 1, entry 1).¹⁰ No dehydrogenation occurs with nickel, cobalt and rhodium (entries 2-4) but use of 10 mol% ([Cp*IrCl₂]₂) and 25 mol% AgBF₄ produced the desired dienamide (2) in 54% yield at 60 °C (entry 5).^{11,12} Solvent screening led to the identification of dioxane as the optimum medium for this reaction. Product 2 was formed in 80% NMR yield (entry 5-11). Considering the undesirable use of super stoichiometric copper acetate as the terminal oxidant, we examined co-catalysts to turnover the previous Ir using molecular oxygen or air. Copper acetate hydrate was found to be a unique co-catalyst that turns over the iridium under air (entry 5, 12-15). The loading of both $[Cp^*IrCl_2]_2$ and $Cu(OAc)_2 \cdot H_2O$ can be lowered to 2 mol% and 4 mol%, respectively without compromising the yield (entry 16, see SI for detailed optimization of conditions). Although the loading of Cu can be further lower to 1 mol%, for the convenience of weighing, 4 mol% was used for the substrate scope study. Control experiments showed that Ir, Ag and Cu are essential for the aerobic dehydrogenation (entry 17-18). The reaction is remarkably clean, the only byproduct being water. Simple filtration through a short plug of silica gel affords the product in high purity as judged by NMR. No column chromatography is necessary.

Table 1. Screening of conditions of the dehydrogenation reaction^{*a,b*}

		⇔ ∩ H	cat., additive oxidant, solvent,		
	MeO		60 °C, 12h Me€		
entry	catalyst	additive	solvent	oxidant	yield(%) ^b
1 ^c	Pd(OAc) ₂	DAF	DCE	Cu(OAc) ₂ •H ₂ O	0
2	$Ni(acac)_2$	/	DCE	Cu(OAc) ₂ •H ₂ O	0
3	[Cp*Co(CO)I ₂]	$AgBF_4$	DCE	Cu(OAc) ₂ •H ₂ O	0
4	[Cp*RhCl ₂] ₂	$AgBF_4$	DCE	Cu(OAc) ₂ •H ₂ O	0
5	[Cp*IrCl ₂] ₂	$AgBF_4$	DCE	Cu(OAc) ₂ •H ₂ O	54
6	[Cp*IrCl ₂] ₂	$AgBF_4$	DMF	Cu(OAc) ₂ •H ₂ O	76
7	[Cp*IrCl ₂] ₂	$AgBF_4$	DMSO	Cu(OAc) ₂ •H ₂ O	0
8	[Cp*IrCl ₂] ₂	$AgBF_4$	MeCN	Cu(OAc) ₂ •H ₂ O	17
9	[Cp*IrCl ₂] ₂	$AgBF_4$	toluene	$Cu(OAc)_2 \cdot H_2O$	54
10	[Cp*IrCl ₂] ₂	$AgBF_4$	MTBE	Cu(OAc) ₂ •H ₂ O	32
11	[Cp*IrCl ₂] ₂	$AgBF_4$	dioxane	Cu(OAc) ₂ •H ₂ O	80
12	[Cp*IrCl ₂] ₂	$AgBF_4$	DCE	BQ	0
13	[Cp*IrCl ₂] ₂	$AgBF_4$	DCE	PhI(OAc) ₂	24
14	[Cp*IrCl ₂] ₂	$AgBF_4$	DCE	Ag ₂ O	10
15	[Cp*IrCl ₂] ₂	$AgBF_4$	DCE	O_2	<5
16 ^d	[Cp*IrCl ₂] ₂	AgBF ₄	dioxane	Cu(OAc) ₂ •H ₂ O /air	>99 ^e
17	/	$AgBF_4$	dioxane	Cu(OAc) ₂ •H ₂ O /air	0
18	[Cp*IrCl ₂] ₂	/	dioxane	Cu(OAc) ₂ •H ₂ O /air	8%

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^{*a*}Unless specified, reactions were performed using 0.1 mmol of substituted amides, 2 mol% of $[Cp*IrCl_2]_2$, 5 mol% of AgBF₄, 4 mol% Cu(OAc)₂•H₂O in 1 mL dioxane under air atmosphere at 60 °C for 12 h. ^{*b*}Isolated yield. Numbers in parentheses are NMR yield. ^{*c*} Run for 20 h. ^{*d*} Run for 36 h. ^{*e*} Run for 14 h. ^{*f*} Run for 24 h. ^{*g*} Run at 90 °C. ^{*h*} 4 mol% of $[Cp*IrCl_2]_2$, 10 mol% of AgBF₄, 4 mol% Cu(OAc)₂•H₂O were used. ^{*i*} Run at 50 °C. ^{*j*} 4 mol% of $[Cp*IrCl_2]_2$, 7.5 mol% of AgBF₄, 4 mol% Cu(OAc)₂•H₂O was used.

With the optimized dehydrogenation conditions in hand, we next surveyed the substrate scope and the functional group compatibility associated with this transformation (**Table 2**). Various *N*-alkyl amides and *N*-aryl amides were examined. *N*-Benzyl and *N*-aryl amides bearing either electron-donating or electronwithdrawing groups are well tolerated. Notably, the bromide (6) and compounds with free hydroxyl groups (7) are unaffected. The primary (9), secondary (10) and tertiary (11) *N*-alkyl amides afford excellent yields. *N*,*N*-Dialkyl amides react more slowly, requiring 90°C and 4 mol% [Cp^{*}IrCl₂]₂. The increased steric crowding of the carbonyl might weaken its coordination to the Ir catalyst in this case. Interestingly, the carbamate derivative (14) can also be dehydrogenated in high yield.

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Variations in the acyl chain were also investigated. Substitution at the γ -, and δ -atoms and beyond does not affect the dehydrogenation (15, 16) and the olefin geometry of the starting material is preserved. Excellent yields are obtained of the Z-olefinic amide (17). Low conversion is observed for α - substituted substrates (46). β-Substituted olefin amides undergo smooth dehydrogenation. The corresponding dienamides are prone to isomerization and a mixture of olefin isomers were obtained (45a and 45b). Functional groups including alkyl halides (18, 19), alkenes (20), silyl ethers (21), ethers (22), esters (23) and amides (24, 31) are all tolerated and high to quantitative yields are obtained for these substrates. Substrates with a styrene functionality react smoothly at 90°C (25-29). Exclusive regioselectivity is observed for substrates containing two carbonyl groups. Side chains with an additional carbonyl group for example, amide (31), aldehyde (32) and nitrile (30), are unaffected. The dehydrogenation occurs exclusively between the α - and β -carbons of the *N*-alkyl amides. The γ,δ - olefin is essential for this reaction. No conversion to 43 and 44 was observed using saturated alkyl amide substrates. The starting materials were recovered quantitatively. Most of the products listed in Table 2 can be isolated by simple filtration as mentioned above. The NMR spectroscopic data shown in the Supporting Information were collected without additional purification. The reactions performed at 90 °C generate small amounts of oligomeric side products, which can be removed by column chromatography.

In addition to amide groups, carboxylic acid has also been demonstrated to be an effective directing group promoting the β-C-H insertion reaction.¹³ After minor modifications of the reaction conditions, we found the reaction using (E)-oct-4-enoic acid performs well with 4 mol% [Cp*IrCl₂]₂, 7.5 mol% silver and 4 mol% copper. The dienoic acid (33) was obtained in 64% yield. A number of olefinic acids react under the dehydrogenation reaction conditions. Silvl ethers (34), alkenes (35), alkyl halides (36), aryl groups (37 to 39) and aryl halides (37, 39) are all tolerated and return moderate to good yields of the product. Interestingly, γ , δ enones also undergo the desired α , β -dehydrogenation with similar efficiency as acids (41, 42). Previous conditions of ketone dehydrogenation reported by Stahl^{4c} and us^{4l} are restricted to β -aryl ketones and cyclic ketones. In these cases, long chain ketones suffer from double and multiple dehydrogenation, outcomes that cannot be controlled. In this case, the dienone is obtained without these complications. Reactions involving ester (47, 48) and nitrile (49) are sluggish, suggesting that the metal binding affinity of the directing group is important for the β -C-H metalation step. Simple

terminal olefins fail to undergo the dehydrogenation under the standard conditions. $^{\rm 5b,9}$



Figure 2. Dehydrogenation profile. Blue dot: [9], red dot: [50]. Data were fit ($\mathbb{R}^2 = 0.99$) to linear relationship.

Preliminary kinetics studies were carried out. The correlation of [50] and [9] vs time was measured. From 0 to 12 hours, the change of substrate and product concentration maintains a linear relationship to time. The reaction rate remains constant regardless of [50]. This data support pseudo zero-order with respect to the amide substrate (resting state approximation, Figure 2). We speculate a substrate-bound catalyst resting state might be responsible for this observation.

Scheme 1. Control Experiments and KIE Studies

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The Ir turnover is believed to be catalyzed by copper. In the absence of copper, only a trace amount of the product was formed. The loading of Cu was examined, and the reaction showed a saturation kinetics at 1 mol% copper. Under the standard reaction conditions (4 mol% Cu), the turnover of the Ir catalyst is not the rate-limiting step. This step becomes slow only at very low copper loading (Scheme 1a). The optimum Ir/Ag ratio was found to be 1/1. Changing Ir/Ag to 1/2 resulted a significantly more sluggish reaction, suggesting $[Cp^*IrCI]^+$ might be the most active species (Scheme 1b). Reactions using air and oxygen were compared. Noticeably, higher yield was obtained using 1 atm oxygen is a result of over oxidation of the product, not substrate decomposition.

Isotope labelling experiments were carried out as well. No isotope effect was observed when β -deuterated substrate (**50-\beta-D**) was used (KIE = 1.04). Small KIE values were obtained when α deuterated amides (**50-\alpha-D** and **50-\alpha,\beta-D**) was tested (KIE = 1.23 and 1.18, respectively, **Scheme 1a**). These data indicate the β -C-H insertion is fast and not rate-limiting. HRMS showed rapid formation of a substrate-Ir complex. Although the exact structure of this resting state is currently ambiguous, we speculate it being the corresponding Ir-allyl species. The KIE effect observed for α deuterated amides suggests the rate-limiting step might be the α -C-H cleavage.¹⁴ In-depth studies are currently underway to fully elucidate the mechanistic details.

CONCLUSION

In summary, we have developed a new strategy for transitionmetal-catalyzed aerobic dehydrogenation of γ , δ -olefinic amides and acids under mild conditions. The reaction does not proceed by the previously reported mechanism of α -deprotonation and β elimination. Instead, an iridium catalyst undergoes β -C-H insertion to form an allyl-Ir species. Direct hydride elimination or ketone tautomerization, followed by 1,5-hydrogen shift, leads to the desired dehydrogenation products. This method is particularly effective for substrates containing acidic functional groups that are challenging when using previous protocols involving palladium enolates. Conjugated dienamides and dienoic acids were synthesized in excellent yield using this practical procedure.

Supporting Information

Experimental procedures, analytical and spectroscopic data for new compounds, copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interests.

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