C–H Functionalization

International Edition: DOI: 10.1002/anie.201500346
German Edition: DOI: 10.1002/ange.201500346

Regioselective Acceptorless Dehydrogenative Coupling of N-Heterocycles toward Functionalized Quinolines, Phenanthrolines, and Indoles**

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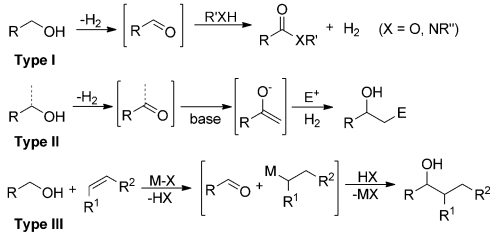
In memory of Wu Chi

Abstract: *A new strategy has been developed for the oxidant- and base-free dehydrogenative coupling of N-heterocycles at mild conditions. Under the action of an iridium catalyst, N-heterocycles undergo multiple sp^3 C–H activation steps, generating a nucleophilic enamine that reacts in situ with various electrophiles to give highly functionalized products. The dehydrogenative coupling can be cascaded with Friedel–Crafts addition, resulting in a double functionalization of the N-heterocycles.*

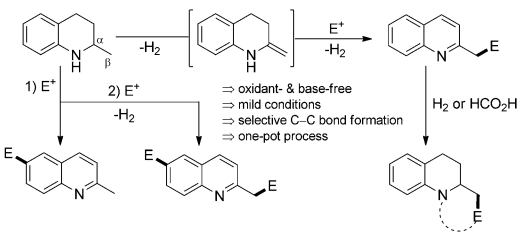
Circumventing the use of stoichiometric oxidants, acceptorless dehydrogenation reactions have recently become a rapidly growing area of research.[1] These reactions produce H_2 as the only byproduct, which is a valuable feedstock itself and energy carrier.[2] Not only can such reactions be applied to the synthesis of unsaturated compounds, they also allow for easy bond formation. Indeed, the last few years have witnessed the application of this novel acceptorless dehydrogenative coupling (ADC) strategy to the synthesis of many value-added compounds in a manner that is more straightforward and economic and greener than the conventional methods.[1,3,4] There are mainly three types of ADC reactions that have appeared (Scheme 1). Type I features the most reported cases, in which an alcohol is first dehydrogenated, generating an electrophilic carbonyl species that can react with a common nucleophile.[3,4] Dehydrogenative C–C bond formation that results in formal alcohol substitution is a type II ADC reaction. Thus, an alcohol is dehydrogenated to an electrophilic carbonyl, or a nucleophilic enolate, which subsequently reacts with a carbon nucleophile, or an electrophile, generating an unsaturated bond to be reduced in situ by the H_2 borrowed from the initial dehydrogenation.[5] Alcohol dehydrogenation that triggers hydrometalation of a π-unsaturated substrate is a type III ADC reaction, in which a nucleophile–electrophile pair is formed, which reacts to afford alcohol C–H functionalization (Scheme 1).[6]



Scheme 1. General modes of ADC reactions reported in the literature.

Acceptorless dehydrogenation of N-heterocycles is rare, however, and ADC of N-heterocycles is even rarer. To the best of our knowledge, there is only one report, in which an *N*-phenyl tetrahydroisoquinoline was alkylated with carbon nucleophiles at the 1-position,[7] whilst the activation of an amine to generate an enamine to allow for subsequent C–C coupling remains unknown in the context of ADC.[8] Although a number of excellent examples have been demonstrated in the cross dehydrogenative coupling of N-heterocycles with nucleophiles, these reactions generally necessitate the use of stoichiometric oxidants, rather than releasing the hydrogen as H_2.[9]

N-Heterocycles are abundant in natural products, fine chemicals, and pharmaceuticals, and have also been viewed as organic hydrides for potential hydrogen storage systems.[10,11] Their dehydrogenation is generally effected with non-chemoselective heterogeneous catalysts.[12] The groups of Fujita and Yamaguchi,[13] Jones,[14] and ours[15] have recently reported homogeneous acceptorless dehydrogenation of N-heterocycles with well-defined metal complexes.[16] During our investigation, we were intrigued by the mechanism of the



Scheme 2. ADC, Friedel–Crafts/ADC, and ADC/reduction reactions accomplished in this study.

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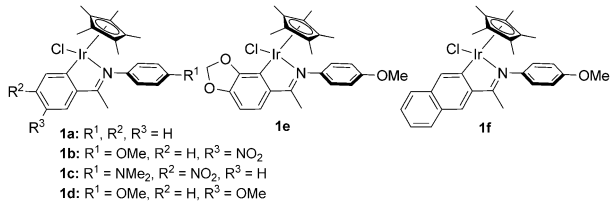
[**] We thank EPSRC and the University of Liverpool for a DTA studentship (D.T.) and EPSRC/TSB for a postdoctoral fellowship (H.Y.L.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201500346.

dehydrogenation of 2-methyl-1,2,3,4-tetrahydroquinoline with a cyclometalated iridium complex.[15] When performed in a deuterated solvent, the reaction led to extensive H–D exchange at the α- and β-positions, suggesting that the dehydrogenation leads to the generation of an imine, which isomerizes to an enamine at these positions (Scheme 2). We envisioned that this nucleophilic intermediate might be intercepted by a carbon-based electrophile, thus affording C–C bond formation at the α-methyl. This would lead to a new method for the functionalization of 2-methyl azaarenes, complementing those necessitating the use of 2-methyl azaarenes.[17] Herein, we show that not only does this ADC strategy enable the coupling of the sp^3 carbon with a range of electrophiles, but it can also be cascaded with Friedel–Crafts addition at sp^2 carbons and with reduction to generate novel saturated N-heterocycles (Scheme 2).

We initiated our study by testing various cyclometalated iridium complexes (iridacycles) **1** for the ADC of 2-methyl-1,2,3,4-tetrahydroquinoline (**2a**) with ethyl 3,3,3-trifluoropyruvate (TFP) as an electrophile (Scheme 3). After extensive



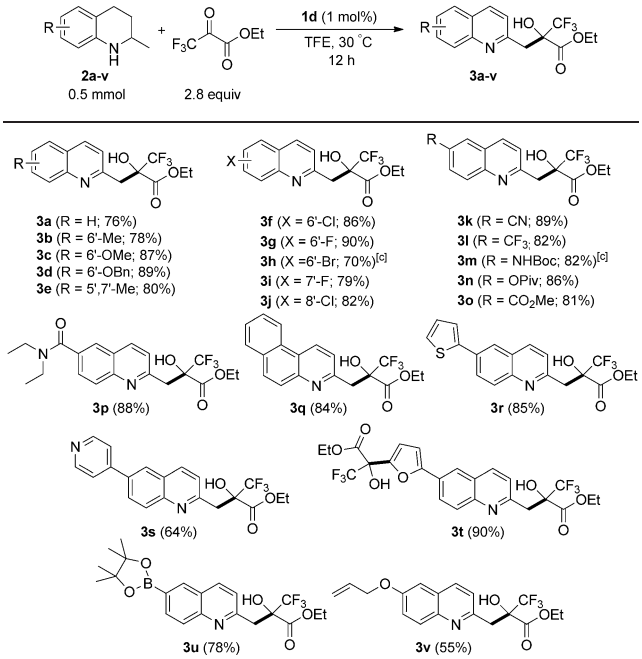
Scheme 3. Iridacycles used in this study.

screening, complex **1d** was identified as the precatalyst of choice, which was further shown to be most efficient in acidic trifluoroethanol (TFE) in terms of the yield of the desired ADC product (see the Supporting Information, SI).

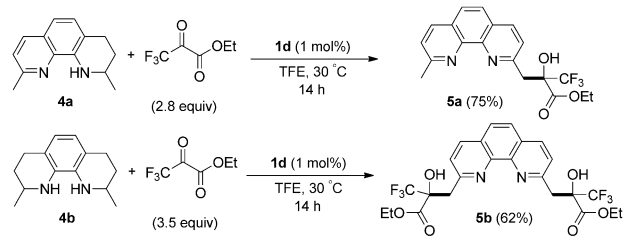
Using the optimal conditions established, the ADC of various tetrahydroquinolines **2a–v** with TFP was explored. In each case, the corresponding products **3a–v** were obtained in good to excellent isolated yields, with the C–C coupling taking place almost exclusively at the β-position (Table 1).[18] These quaternary trifluoromethyl hydroxy compounds are highly valuable in pharmaceuticals due to their biological activities.[17g,19]

A variety of functionalities was tolerated, demonstrating the utility of the protocol in practice. Thus, substrates bearing either electron-donating or -withdrawing groups all gave excellent yields regardless of their positions (**3b–e** and **3k–l**), and hydrogenation-labile aromatic halides afforded the coupling products **3f–j** in more than 70% yield. Whilst ester and amide moieties are typically employed in *ortho*-directed C–H functionalization, regioselective ADC took place when **2m–p** were coupled with TFP, furnishing excellent yields for the expected **3m–p**. Delightfully, thiophene- and pyridine-containing substrates (**2r–s**) underwent the ADC without poisoning the catalyst. However, when the furan derivative **2t** was subjected to the ADC, competitive Friedel–Crafts alkylation was observed at the furan ring, leading to a highly functionalized product **3t**. It is known that furan can undergo electrophilic aromatic substitution at the 2-position

Table 1: Regioselective dehydrogenative sp^3 C–H functionalization of 2-methyl tetrahydroquinolines.[a,b]



[a] See the SI for experimental details. [b] Yields of isolated product in parentheses. [c] Yields determined by ^{1}H NMR spectroscopy.

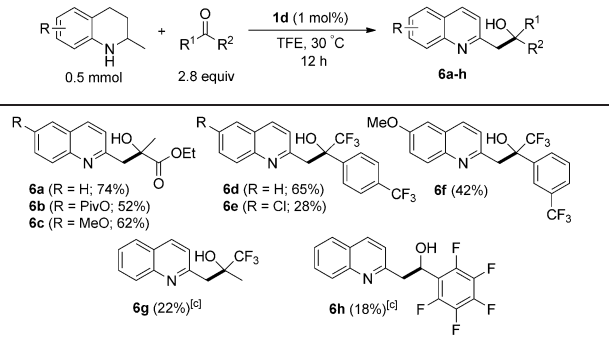


Scheme 4. Regioselective dehydrogenative functionalization of tetra- and octa-hydrophenanthroline.

in acidic media.[19,20] Further to our delight, substrates containing boronic acid pinacol ester and allyl ether groups were also well tolerated, furnishing the corresponding products in good yields (**3u–v**). These functional groups can easily induce other reactions, such as cross-coupling and aromatic Claisen rearrangement.[21,22]

Remarkably, the coordinating compounds **4a**,**b** could be selectively mono- or dialkylated, affording **5a**,**b** in good yield (Scheme 4). The exclusive monofunctionalization of **4a** shows that dehydrogenation at the saturated ring is much easier than C–H activation[17b–g] or deprotonation at the 9-Me position (cf. 2-methyl pyridine: pK_a 34),[17a] and the latter reactions, which would lead to alkylation at that methyl substituent, are difficult to achieve under the mild ADC conditions employed. These phenanthrolines are valuable and are often employed as donor ligands for transition metals.[23] However, selective dialkylation or monoalkylation of 2-methyl phenanthrolines has been challenging and is typically performed under harsh conditions.[24]

Table 2: Regioselective functionalization with other electrophiles.[a,b]



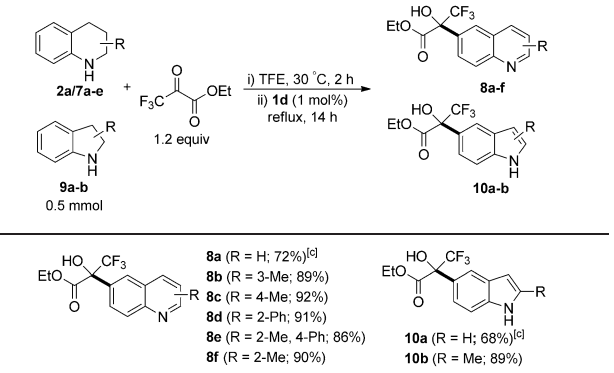
[a] See the SI for experimental details. [b] Yields of isolated product in parentheses. [c] Yields determined by ^{1}H NMR spectroscopy.

To further demonstrate the usefulness of the protocol, ADC using different electrophiles was investigated. As can be seen from Table 2, the reaction worked, although the product yield varied with both the electrophiles and nucleophiles. In particular, low yields were obtained with 1,1,1-trifluoroacetone and pentafluorobenzaldehyde (**6g–h**), presumably as a result of their lower electrophilicity. 1,1,1-Trifluoroacetone can interact with protic solvents, leading to addition products.[25]

It is known that tetrahydroquinolines can undergo Friedel–Crafts reactions at the 6-position.[26] Indeed, **2a** was alkylated with TFP at this position when they were mixed in TFE in the absence of **1d** (SI). Following the Friedel–Crafts reaction, introduction of **1d** should trigger dehydrogenation at the other ring, resulting in a one-pot synthesis of 6-alkylated quinolines. This would provide a simple way of generating these products, which are traditionally synthesized using stoichiometric organometallic reagents.[27] Satisfactorily, reacting **2a** and **7a–e** with TFP for 2 h followed by adding the catalyst **1d** afforded **8a–f** in excellent yields, regardless of the position of the substituents on the N-containing ring (Table 3).

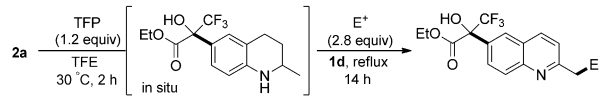
Furthermore, functionalized indoles could also be obtained in good yields (Table 3, **10a**,**b**). Friedel–Crafts addition at the 5-position of indoles is challenging, as the 3-position is more reactive.[26b] As maybe expected, the Friedel–Crafts reaction did not proceed when 2-methyl quinoline, instead of **7**, was used under the reaction conditions.

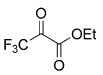
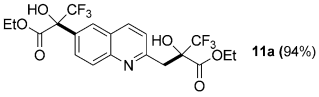
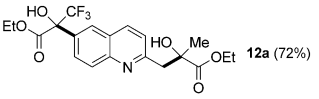
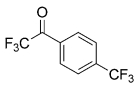
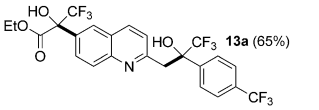
Table 3: Selective Friedel–Crafts addition followed by dehydrogenation of tetrahdroquinolines and indolines.[a,b]



[a] See the SI for experimental details. [b] Yields of isolated product in parentheses. [c] Yields determined by ^{1}H NMR spectroscopy.

Table 4: One-pot sequential Friedel–Crafts dehydrogenative sp^2 C–H and sp^3 C–H functionalization of **2a**.[a,b]

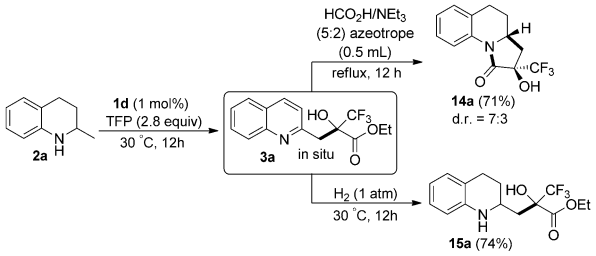


Electrophile (E^+)	Product
	 **11a** (94%)
	 **12a** (72%)
	 **13a** (65%)

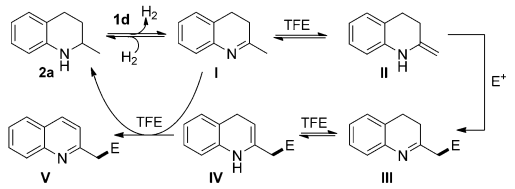
[a] See the SI for experimental details. [b] Yields of isolated product in parentheses.

More interestingly, double functionalization of tetrahydroquinolines becomes possible when the Friedel–Crafts reaction is cascaded with the ADC. Table 4 presents the unprecedented, one-pot sequential Friedel–Crafts addition and ADC reactions, which allow the functionalization of both the 6-position and α-methyl of **2a** to give **11a** in excellent yield. Two different electrophiles can also be introduced into the nucleophile in this one-pot strategy, as demonstrated by the synthesis of the highly functionalized **12a** and **13a**. Such double functionalization will be difficult, if not impossible, with Pd-catalyzed C–H activation or traditional deprotonation.[17]

We have previously reported that the iridacycles are capable of catalyzing both hydrogenation and transfer hydrogenation reactions.[28] Thus, saturated, functionalized N-heterocycles could also be obtained by reduction in a one-pot fashion. Indeed, hydrogenating **3a** with H_2, in situ generated from **2a** through ADC, afforded **15a** in 74% yield at 30 °C (Scheme 5). Surprisingly, a novel compound **14a** was isolated in 71% yield when the reductant was switched from H_2 to HCO_2H. Most likely, the high reaction temper-



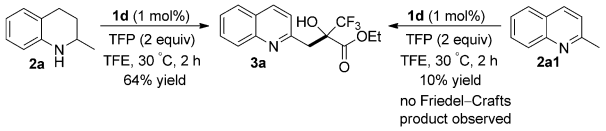
Scheme 5. In situ reduction of dehydrogenated product with the same catalyst.



Scheme 6. A plausible reaction pathway for the ADC.

ature together with the acidic reaction conditions employed in the transfer hydrogenation promoted the formation of the lactam product. These reactions further demonstrate the versatility of **1d** in both dehydrogenation and hydrogenation reactions.

On the basis of previous studies[15,29] and observations made here (SI), a plausible reaction pathway is proposed in Scheme 6. In the presence of **1d** in TFE (pK_a 12.5), **2a** is in rapid equilibrium with the imino intermediate **I** and the enamine **II**. The nucleophilic **II**, expected to be highly active, attacks an electrophile to give **III**, which can equilibrate with **IV** under the intervention of TFE and/or **1d**. As previously suggested, the final product together with **2a** could be formed upon **IV** reducing activated **I**.[15] Further support for the proposal comes from the reactions shown in Scheme 7, which indicates that the coupling with TFP precedes the aromatization.



Scheme 7. Control experiments supporting that nucleophilic attack by the imino intermediate precedes aromatization.

In conclusion, we have developed a new protocol for the oxidant- and base-free functionalization of N-heterocycles to afford novel quinoline, phenanthroline, and indole derivatives. The core strategy is the ADC chemistry, which enables acceptorless dehydrogenation of the N-heterocycles and site-selective C–C bond formation thereafter. The ADC catalyst also allows the dehydrogenated product to be saturated under either hydrogenation or transfer hydrogenation conditions, giving rise to structurally diverse products.

Keywords: C–C coupling · C–H functionalization · dehydrogenation · iridium complexes · N-heterocycles

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 5223–5227
Angew. Chem. **2015**, *127*, 5312–5316

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Received: January 14, 2015
Published online: March 10, 2015

