C–H Functionalization

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Metal-Free Cross-Dehydrogenative Coupling of Heterocycles with Aldehydes**

*Kiran Matcha and Andrey P. Antonchick**

Dedicated to Professor Dieter Seebach on the occasion of his 75th birthday

The direct transformation of nonfunctionalized C–H bonds into C–C bonds is a fundamental challenge in organic chemistry and offers substantial benefits. The synthetic method to generate C–C bonds directly from two different C–H bonds under oxidative conditions, termed cross-dehydrogenative coupling (CDC), represents the state-of-art in C–C bond-forming reactions.[1,2] Such a coupling allows the use of simple nonfunctionalized substrates, thus making syntheses shorter and more efficient. Two issues with CDC methods are low reactivity and selectivity, owing to the high-energy of dissociation and the ubiquity of C–H bonds in organic molecules, respectively. The development of new and efficient CDC reactions is a fundamental and important challenge in organic synthesis.

Nitrogen-containing heterocycles are abundant in nature and have extensive applications in chemistry and biology.[3] Numerous methods for the de novo synthesis of electron-deficient heterocycles have been described, but their functionalization by cross-dehydrogenative coupling is far less studied. In contrast to the acylation of electron-rich aromatic compounds (Friedel–Crafts reaction), very few methods are available for the acylation of electron-deficient heterocycles. Among these methods, the addition of nucleophilic acyl radicals to electron-deficient heterocyclic aromatic bases, that is, the Minisci reaction, is a commonly used approach.[4–7] But, this reaction has been underutilized because of harsh reaction conditions, such as heating in the presence of peroxy compounds and metals. Additional reported issues include low site selectivity, incomplete conversion of starting materials, limited substrate scope, and the use of metals in up to stoichiometric amounts.[4a] Direct acylation of heterocycles with aldehydes is difficult owing to the electron-deficient nature of both partners, and because the products of radical acylation can be more susceptible to radical attack than the starting material. Based on previous reported acylations, we hypothesized that the generation of nucleophilic acyl radicals under mild reaction conditions could be key to eliminating the difficulties in direct acylations.[4,5] Herein, we describe an unprecedented metal-free, cross-dehydrogenative coupling of heterocycles with aldehydes at ambient temperature. Furthermore, this method was used for the synthesis of natural products in one step.

In connection to our continued interest in developing efficient metal-free C–H functionalization strategies,[8] we decided to investigate the use of hypervalent iodine reagents for the direct acylation of N-heterocycles with aldehydes.[9] Initially, we evaluated numerous reaction conditions for the direct coupling of isoquinoline (**1a**) and benzaldehyde (**2a**). To our delight, the cross-coupling occurred in presence of (bis(trifluoroacetoxy)iodo)benzene ($PhI(OCOCF_3)_2$) and sodium azide at ambient temperature in ethylacetate to form product **3a** in 47% yield (Table 1, entry 1).[10] Notably, functionalization of isoquinoline (**1a**) occurred selectively at the C1-position to give only one regioisomer of **3a**. Product **3a** was not formed in the absence of either $PhI(OCOCF_3)_2$ or NaN_3. A variety of polar and nonpolar solvents were successfully employed (Table 1, entries 1-4 and the Supporting Information). The best yield (52% of **3a**) was achieved for the reaction with benzene as the solvent.

Next, we examined the influence of various oxidants in the cross-dehydrogenative coupling (Table 1, entries 4–11). A number of other hypervalent iodine based oxidants were screened, and only the use of Koser's reagent and (bis(trifluoroacetoxy)iodo)pentafluorobenzene (Table 1, entries 7 and 8) provided product **3a**, although in lower yield than with $PhI(OCOCF_3)_2$. Other oxidizing agents, such as *t*BuOOH and *m*CPBA, did not promote the desired transformation (Table 1, entries 9–11, and Supporting Information). With $PhI(OCOCF_3)_2$ as the obvious choice of oxidant, we tested different additives. Changing the additive from NaN_3 to $TMSN_3$ resulted in a dramatic rise of the yield to 90% (Table 1, entry 12). The use of other sources of azide and iodine did not lead to formation of the product (Table 1, entries 13–15). With the optimized oxidant and additive established, we looked into the relative ratio of reactants (Table 1, entries 16–21 and Supporting Information). Decreasing the amount of aldehyde from 4 equivalents to 3 and 1.5 equivalents led to a drop in yield to 70% and 26%, respectively, and lowering the amount of oxidant and/or additive to 1 equivalent did not prove beneficial.

Equipped with a set of optimized conditions (Table 1, entry 16), we explored the scope of this cross-coupling reaction by investigating the reaction between isoquinoline (**1a**) and various aldehydes (Scheme 1). The scope turned out to be very broad, and various aliphatic, aromatic and heteroaromatic aldehydes, including those with electron-

[*] Dr. K. Matcha, Dr. A. P. Antonchick
Max-Planck-Institut für Molekulare Physiologie
Abteilung Chemische Biologie
Otto-Hahn-Strasse 11, 44227 Dortmund (Germany)
E-mail: andrey.antonchick@mpi-dortmund.mpg.de

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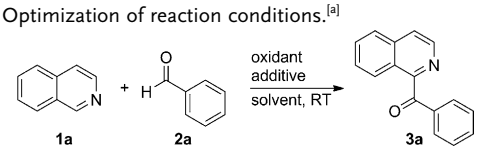
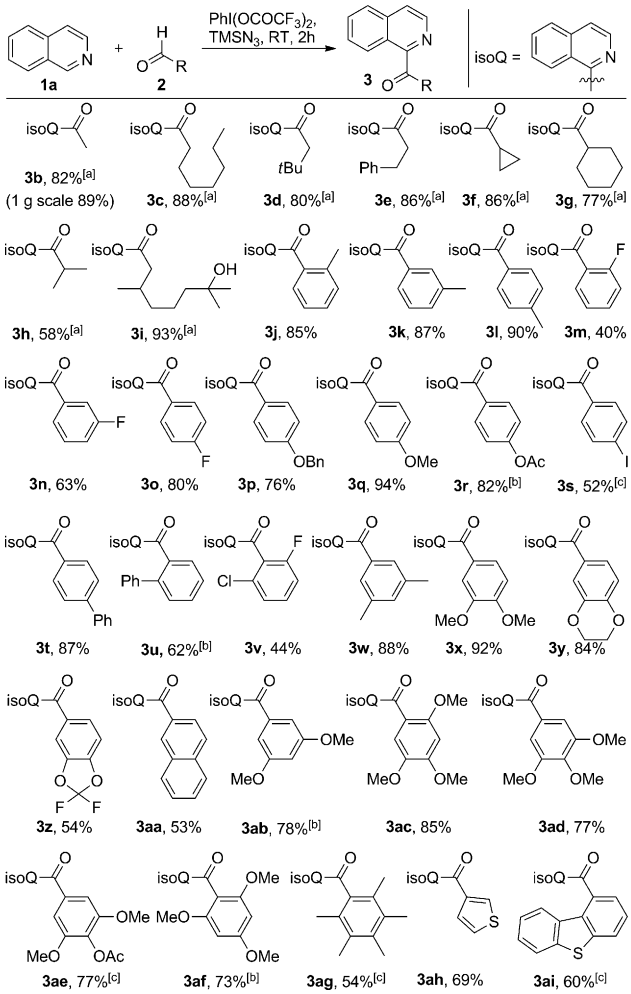
Table 1: Optimization of reaction conditions.[a]



1a 2a 3a

Entry	Solvent	Oxidant	Additive	*t* [h]	Yield [%][b]
1	EtOAc	$PhI(OCOCF_3)_2$	NaN_3	2	47
2	CH_3CN	$PhI(OCOCF_3)_2$	NaN_3	2	43
3	toluene	$PhI(OCOCF_3)_2$	NaN_3	2	30
4	benzene	$PhI(OCOCF_3)_2$	NaN_3	2	52
5	benzene	$PhI(OAc)_2$	NaN_3	24	n.d.
6	benzene	$PhI(OCOtBu)_2$	NaN_3	24	n.d.
7	benzene	PhI(OH)OTs	NaN_3	6	22
8	benzene	$C_6F_5I(OCOCF_3)_2$	NaN_3	4	34
9	benzene	DMP	NaN_3	24	n.d.
10	benzene	*t*BuOOH	NaN_3	24	n.d.
11	benzene	*m*CPBA	NaN_3	24	n.d.
12	benzene	$PhI(OCOCF_3)_2$	$TMSN_3$	2	90
13	benzene	$PhI(OCOCF_3)_2$	$(nBu)_4NN_3$	24	n.d.
14	benzene	$PhI(OCOCF_3)_2$	$(PhO)_2PON_3$	24	n.d.
15	benzene	$PhI(OCOCF_3)_2$	I_2	24	n.d.
16[c]	benzene	$PhI(OCOCF_3)_2$	$TMSN_3$	2	86
17[d]	benzene	$PhI(OCOCF_3)_2$	$TMSN_3$	2	70
18[e]	benzene	$PhI(OCOCF_3)_2$	$TMSN_3$	2	26
19[f]	benzene	$PhI(OCOCF_3)_2$	$TMSN_3$	2	60
20[g]	benzene	$PhI(OCOCF_3)_2$	$TMSN_3$	2	68
21[h]	benzene	$PhI(OCOCF_3)_2$	$TMSN_3$	2	49

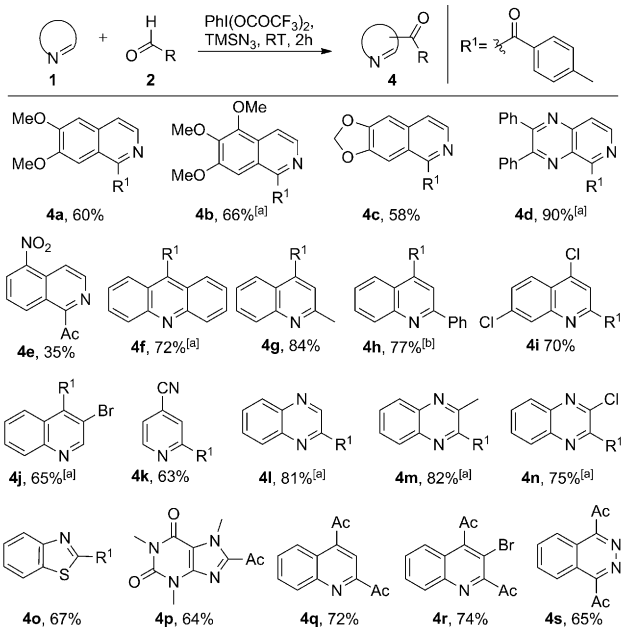
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mmol), oxidant (0.4 mmol), additive (0.4 mmol) in solvent (1.5 mL). [b] Yield of isolated product after chromatography on silica gel. [c] **2a** (0.8 mmol). [d] **2a** (0.6 mmol). [e] **2a** (0.3 mmol). [f] $PhI(OCOCF_3)_2$ (0.2 mmol) and $TMSN_3$ (0.2 mmol). [g] $PhI(OCOCF_3)_2$ (0.4 mmol) and $TMSN_3$ (0.2 mmol). [h] $PhI(OCOCF_3)_2$ (0.2 mmol) and $TMSN_3$ (0.4 mmol). DMP = Dess–Martin periodinane, *m*CPBA = *meta*-chloroperbenzoic acid, n.d. = not detected, TMS = trimethylsilyl, Ts = *para*-toluenesulfonyl.



Scheme 1. Scope of aldehydes in CDC. Reaction conditions: isoquinoline **1a** (0.2 mmol), aldehyde **2** (0.8 mmol), $TMSN_3$ (0.4 mmol), and $PhI(OCOCF_3)_2$ (0.4 mmol) in benzene (1.5 mL) at room temperature for 2 h. Yields are given for isolated products after column chromatography. [a] Using $PhI(OCOCF_3)_2$ (0.22 mmol), $TMSN_3$ (0.22 mmol). [b] Using $PhI(OCOCF_3)_2$ (0.6 mmol), $TMSN_3$ (0.6 mmol). [c] Using $PhI(OCOCF_3)_2$ (0.8 mmol), $TMSN_3$ (0.8 mmol).

donating and electron-withdrawing substituents in various positions, and polysubstituted benzaldehydes, were efficiently and selectively coupled to isoquinoline in 2 h under metal-free conditions at ambient temperature. General trends observed were: 1) aliphatic aldehydes can be efficiently coupled with isoquinoline by using smaller amounts (1.1 equivalent) of iodine(III) and $TMSN_3$ (Scheme 1, compounds **3b**–**3i**); 2) products from aromatic aldehydes with electron-donating groups at *ortho, meta*, and *para* positions were obtained in comparable yields (Scheme 1, products **3j**–**3l**), whereas the products from aldehydes with electron-withdrawing groups at *para* position were obtained in better yields than their *ortho*- and *meta*-substituted isomers (products **3m**–**3o**); 3) polysubstituted aromatic aldehydes were well-tolerated, thus indicating the minor role of the steric effect (Scheme 1, products **3v**–**3ag**). Aldehydes containing sensitive groups, such as cyclopropyl, next to the reaction center can be employed (Scheme 1, product **3f**). Moreover, polymethoxy-substituted benzaldehydes, which represent a common scaffold for natural products, were well-tolerated (Scheme 1, products **3ab**–**3af**). Reactions of sulfur-containing heterocyclic aldehydes (Scheme 1, products **3ah** and **3ai**) also provided cross-coupled products in good yields without overoxidation to sulfoxides or sulfones. Finally, compound **3b** was obtained in 89% yield from a large scale reaction (one gram of **1a**) carried out in an open flask. These observations clearly demonstrate the efficiency of this newly developed mild direct cross-coupling method.

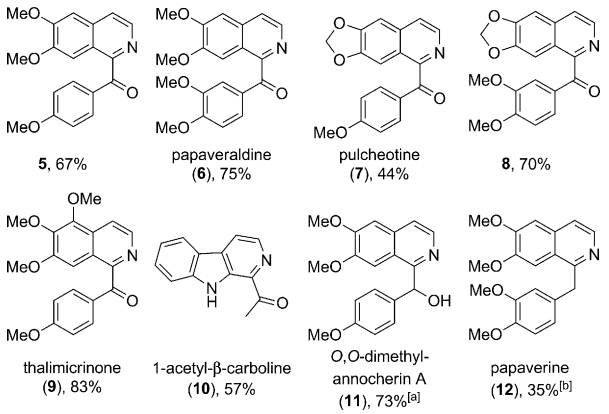
After investigating the scope of the aldehydes in the cross-dehydrogenative coupling, we next focused our attention to the scope of the heterocycles (Scheme 2). Pleasingly, a variety of heterocycles reacted smoothly with aldehydes. Reactions of electron-rich isoquinolines, which we expected to be less reactive than isoquinoline, also provided products in good yields (Scheme 2, products **4a**–**4s**), and an acceptable yield was achieved with 5-nitroisoquinoline (Scheme 2, product **4e**). Although when quinoline was used a mixture of mono- and disubstituted products was provided, the use of quinolines with either electron-rich or electron-poor groups at the 2-, 3-, or 4- positions provided products in very good yields (Scheme 2, products **4g**–**4j**). Interestingly, highly selective functionalization at the 4-position was observed in case of 3-bromoquinoline (see product **4j**). Furthermore, quinaxaline



Scheme 2. Scope of N-heterocycles in CDC. Reaction conditions: heterocycle **1** (0.2 mmol), aldehyde **2** (0.8 mmol), $TMSN_3$ (0.8 mmol), and $PhI(OCOCF_3)_2$ (0.8 mmol) in benzene (1.5 mL) at room temperature for 2 h. Yields are given for isolated products after column chromatography. [a] Using $PhI(OCOCF_3)_2$ (0.4 mmol), $TMSN_3$ (0.4 mmol). [b] Using $PhI(OCOCF_3)_2$ (0.6 mmol), $TMSN_3$ (0.6 mmol). Ac = acetyl.

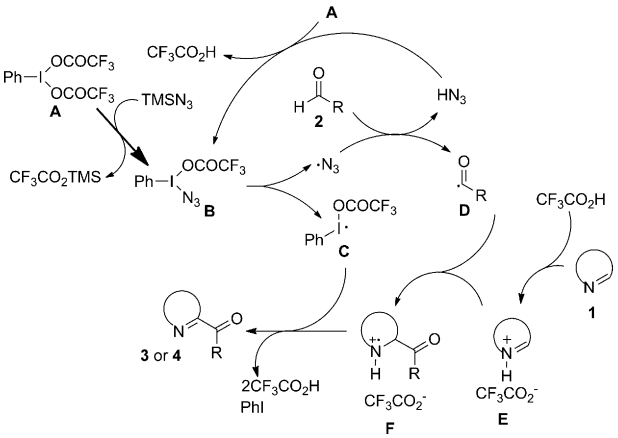
and 2-substituted quinaxalines were selectively monofunctionalized in good yield (Scheme 2, products **4l**, **4m**, and **4n**). Other heterocycles, such as acridine (see product **4f**), benzothiazole (see product **4o**), and caffeine (see product **4p**), were also functionalized smoothly. Finally, by using an excess of reagents, selective double functionalization was possible in good yield (Scheme 2, products **4q**–**4s**).

Isoquinoline alkaloids are widely distributed in nature and exhibit important biological and medicinal properties.[3] Moreover, acylated heterocycles are present in numerous drugs and pharmacologically significant biological probes. In this context, we envisaged that the developed method for C–H bond functionalization would provide rapid access to natural alkaloids from simple, widely available chemicals, thus representing an improvement on traditional multistep approaches. To execute such an idea and to show the application of the developed method, we synthesized several natural alkaloids by one step cross-coupling between isoquinolines and aldehydes (Scheme 3, products **5**–**9**).[11,12] The obtained products represent natural alkaloids and could be used as starting materials for the preparation of related alkaloids including simple derivatives of isoquinoline, aporphines, protoberberines, and pavines. For example, a reduction of the carbonyl group of **5** and **6** to give the corresponding alcohol and alkane provided an additional set of natural products (Scheme 3, products **11** and **12**).[13] Moreover, a natural alkaloid based on the β-carboline scaffold was obtained in one step from commercially available chemicals by using the developed method (Scheme 3, product **10**).[14]



Scheme 3. Selected examples of alkaloid synthesis. Reaction conditions: N-Heterocycle (0.6 mmol), aldehyde (2.4 mmol), $PhI(OCOCF_3)_2$ (2.4 mmol), $TMSN_3$ (2.4 mmol) in benzene (5 mL). Yields are given for isolated products after column chromatography. [a] Prepared from **5** by reduction with $NaBH_4$. [b] Prepared from **6** by Wolff–Kishner reduction.

Next the mechanism of the direct acylation was studied. The formation of product **3l** was suppressed in the presence of radical traps (see the Supporting Information for the details). An adduct of the 2,2,6,6-tetramethylpiperidine-1-oxyl free radical and the aldehyde was isolated under our reaction conditions, thus providing evidence of an acyl radical formation. The kinetic isotopic effect is 5.7 and was measured by using $[D_6]$benzaldehyde in a competition experiment (see the Supporting Information for the details). This result could indicate that the formation of the acyl radical is the rate-limiting step of the developed direct acylation. Based on these observations, a plausible mechanism is proposed (Scheme 4).



Scheme 4. Proposed mechanism for the direct metal-free acylation.

Initial ligand exchange between $PhI(OCOCF_3)_2$ (**A**) and $TMSN_3$ would provide intermediate **B**. A double exchange of the trifluoracetyl groups in **A** by azide ions could also occur to give $PhI(N_3)_2$, which would have similar properties to **B**. Intermediate **B** undergoes thermal homolytic cleavage owing to a weak I–N bond to generate an azide radical and radical **C**.[10r,t] The azide radical reacts with aldehyde **2** to generate nucleophilic acyl radical **D**, and then subsequent attack of the

acyl radical onto the protonated heterocycle **E** would provide intermediate **F**.[10h,l] The released hydrazoic acid could react with **A** to provide the reactive intermediate **B**. The selectivity of the acylation could be explained by the nucleophilic character of the acyl radical **D**, which attacks at the electrophilic position of the protonated heterocycle under thermodynamic control (see Scheme 2, product **4j**). Rearomatization of **F** provides the desired product **4**.

In conclusion we have developed an efficient, mild and scalable method for the direct functionalization of heterocycles with aldehydes under metal-free conditions that was not sensitive to moisture. Desired compounds were obtained at room temperature in short time. The generality of the method was illustrated by the broad aldehyde and heterocycle scope. Moreover, this one-step cross-coupling reaction was utilized in the synthesis of a collection of natural products.

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