

Direct Selective Oxidative Cross-Coupling of Simple Alkanes with Heteroarenes**

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Dedicated to the Max Planck Institute of Molecular Physiology, Dortmund, on the occasion of its 100th anniversary

Aliphatic C–H bonds are ubiquitous in organic compounds and are among the least reactive bonds. Direct and selective methods of alkane functionalization are an important and longstanding goal in chemistry.^[1] Achieving selectivity by discriminating between C–H bonds remains a challenge. Over the past decades, enormous progress has been reported for oxidative functionalization of C_{sp}³–H bonds to form carbon–heteroatom bonds.^[2,3] The direct conversion of C–H bonds into C–C bonds by cross-coupling allows for the most efficient synthesis of products.^[4,5] Known direct methods of C_{sp}³–C bond generation from two different C–H bonds are based on the use of an oxidizing reagent and a metal catalyst.^[6] These methods typically require high temperature, an excess of reagents, and are limited to cycloalkanes. The development of efficient methods of C_{sp}³–H bond functionalization is highly desired. Herein, we report on the selective formation of C_{sp}³–C bonds by cross-dehydrogenative coupling (CDC) of simple alkanes with heteroaromatic compounds using mild reaction conditions. This method allows for the selective functionalization of stronger C_{sp}³–H bonds in the presence of weaker C–H bonds at ambient temperature.

As a continuation of our studies^[7] on C–H functionalization, we focused on the development of methods for CDC with simple alkanes. We began our studies by evaluating various conditions for the direct alkylation of 4,7-dichloroquinoline (**1a**) with cyclohexane (**2a**; Table 1).^[8,9] To our delight, we found that product **3a**, resulting from the direct alkylation of heteroarene **1a** with simple alkane **2a**, can be obtained under transition-metal-free and mild conditions at ambient temperature. Product **3a** was obtained with a yield of 46% in presence of [bis(trifluoroacetoxy)iodo]benzene (PIFA) and NaN₃ using benzene as the solvent (Table 1, entry 1). Both PIFA and NaN₃ were essential for the formation of product **3a**; in their absence, product **3a** was not detected. In additional experiments, various solvents were tested (Table 1, entries 1–7; see also the Supporting information).

Table 1: Optimization of the reaction conditions.^[a]

Entry	Oxidant	Additive	Solvent	t [h]	Yield [%]
1	PIFA	NaN ₃	PhH	16	46
2	PIFA	NaN ₃	DCE	3	67
3	PIFA	NaN ₃	MeCN	16	44
4	PIFA	NaN ₃	CH ₂ Cl ₂	3	72
5	PIFA	NaN ₃	CHCl ₃	16	37
6	PIFA	NaN ₃	EtOAc	16	19
7	PIFA	NaN ₃	C ₆ H ₁₂	16	30
8	PhI(OAc) ₂	NaN ₃	CH ₂ Cl ₂	24	n.d.
9	PhI(OH)OTs	NaN ₃	CH ₂ Cl ₂	24	28
10	F ₅ -PIFA	NaN ₃	CH ₂ Cl ₂	4	60
11	IBX	NaN ₃	CH ₂ Cl ₂	24	n.d.
12	tBuOOH	NaN ₃	CH ₂ Cl ₂	24	n.d.
13	Na ₂ S ₂ O ₈	NaN ₃	CH ₂ Cl ₂	24	n.d.
14	PIFA	TMSN ₃	CH ₂ Cl ₂	3	51
15	PIFA	(<i>n</i> Bu) ₄ NN ₃	CH ₂ Cl ₂	24	n.d.
16	PIFA	I ₂	CH ₂ Cl ₂	24	n.d.
17 ^[b]	PIFA	NaN ₃	CH ₂ Cl ₂	4	85

[a] Conditions: **1a** (0.2 mmol), **2a** (1.0 mmol), oxidant (0.4 mmol) additive (0.4 mmol) in solvent (1 mL) at ambient temperature. Yields given are for isolated **3a**. [b] Using 10 equiv of **2a**. DCE = 1,2-dichloroethane, PIFA = bis(trifluoroacetoxy)iodobenzene, F₅-PIFA = [bis(trifluoroacetoxy)iodo]pentafluorobenzene, IBX = 2-iodoxybenzoic acid, n.d. = not detected.

The use of polar solvents led to lower yields of **3a**. The best results, 72% and 67% of **3a**, were obtained using dichloromethane and 1,2-dichloroethane, respectively, as solvents. Afterwards, various oxidants were screened (Table 1, entries 8–13; see also the Supporting information). The use of [bis(trifluoroacetoxy)iodo]pentafluorobenzene or PhI(OH)OTs instead of PIFA provided access to product **3a**, but with lower yields.^[10] Subsequently, various additives were tested (Table 1, entries 14–16; see also the Supporting information). Whereas other additives were unsuccessful, the desired product **3a** was obtained when using a metal-free source of azide, such as trimethylsilyl azide (Table 1, entry 14). Finally, when using an increased loading of cyclohexane (10 equiv), **3a** was isolated with a yield of 85% (Table 1, entry 17; see also the Supporting information). Further increases in the amount of cyclohexane, and variations in the amounts of PIFA and NaN₃ did not lead to significant difference in the yield of **3a**. Therefore, for the

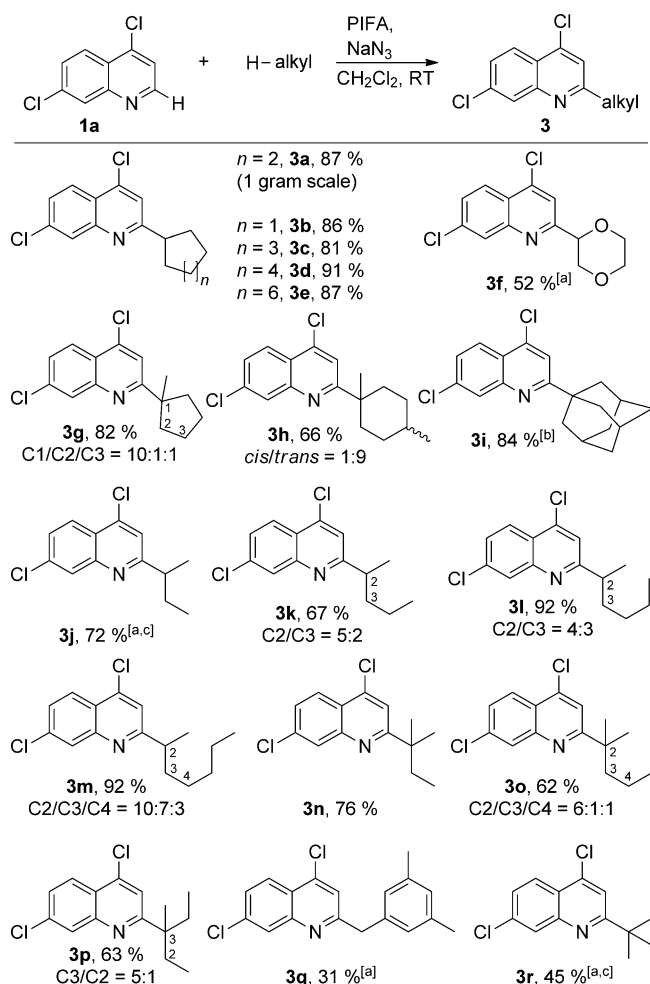
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following experiments we used PIFA (2 equiv) and NaN_3 (2 equiv) in dichloromethane at ambient temperature.

With these optimized reaction conditions in hand, we performed a scale-up experiment using **1a** (5 mmol). Product **3a** was smoothly formed in the scale-up experiment, which was performed in a flask open to the air, and resulted in a yield of 87 % (**3a**; Scheme 1). Afterwards, we focused on



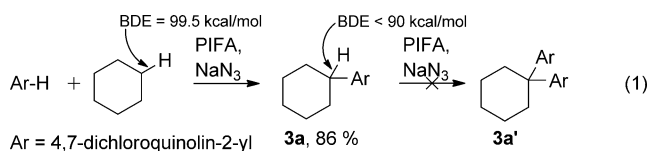
Scheme 1. Scope of alkanes in CDC. Conditions: **1a** (0.2 mmol), alkane (4.0 mmol), oxidant (0.4 mmol), additive (0.4 mmol) in CH_2Cl_2 (1 mL) at ambient temperature. Isomer ratio determined by ^1H NMR analysis; structure and yield given for the major isomer isolated.

[a] Using PIFA (0.8 mmol) and NaN_3 (0.8 mmol). [b] Using adamantane (0.4 mmol). [c] Using alkane (10.0 mmol).

determining the generality of the reaction with regards to the alkane substrates. Under optimized reaction conditions, various alkanes led to $\text{C}_{\text{sp}^3}\text{-H}$ bond arylation products in yields of 81–91 % (**3b–3e**; Scheme 1). When 1,4-dioxane was employed, it underwent cross-arylation in 52 % yield (**3f**). A high 3° site selectivity was observed for substituted cycloalkanes, (**3g–3i**; Scheme 1).

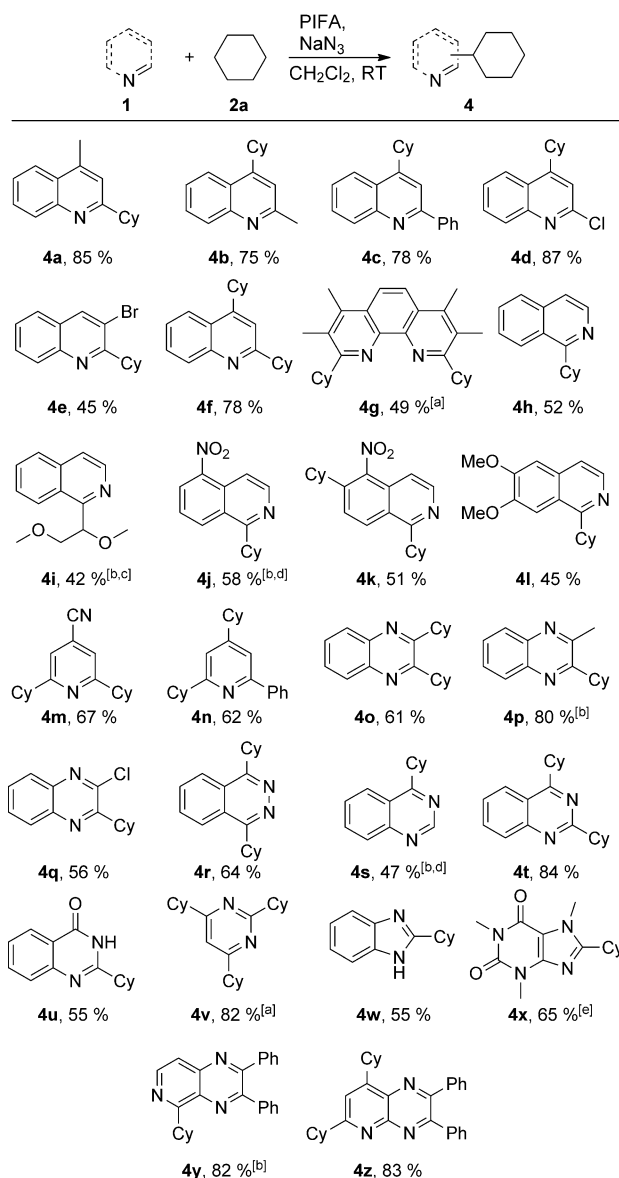
Acyclic alkanes afforded moderate to high yields of products (**3j–3p**; Scheme 1). Exclusive 2° site functionalization was observed. Reaction with *n*-butane led to **3j** in a yield

of 72 %. Although the difference in C–H bond dissociation energies (BDE) between the C1 position ($100.7 \text{ kcal mol}^{-1}$) and the C2 position ($98.3 \pm 0.5 \text{ kcal mol}^{-1}$) is below 3 % for *n*-butane, highly selective functionalization at the C2 position was observed.^[11] This extraordinary selectivity for the 2° site was also observed for the higher acyclic homologs (**3k–3m**; Scheme 1). This is notable because the difference in BDE for these compounds is even smaller. For example, the BDE of *n*-hexane is $99.0 \text{ kcal mol}^{-1}$ at the 1° site and $98.0 \text{ kcal mol}^{-1}$ at the C2 position. Nevertheless, higher homologs of acyclic alkanes gave a mixture of regioisomers at 2° site, although the BDEs are almost equal. The ratio of isomers was correlated with the abundance of C–H bonds at the given position (**3k–3m**). For example, when using *n*-pentane, **3k** was formed with a ratio of C2/C3 = 5:2, whereas the ratio based on the abundance of C–H bonds is C2/C3 = 4:2. For the branched acyclic alkanes, a clear preference for arylation at the 3° site over the 2° site was observed with yields of 62–76 % (**3n–3p**). Arylation of the secondary positions of alkanes leads to the formation of a new, weaker C–H bond ($\text{BDE} < 90 \text{ kcal mol}^{-1}$). However, **3a'**, which is the product of over-oxidation, was not observed [Eq. (1)]. This method allows preferential



activation of stronger C–H bonds in the presence of weaker C–H bonds. A selective CDC of **1a** with mesitylene resulted in lower yield (**3q**; Scheme 1). Finally, we applied a mixture of propane and butanes (Campingaz) for coupling with **1a**. The product of the selective coupling with the most reactive alkane (*iso*-butane) was isolated with a yield of 45 % (**3r**); an inseparable mixture of isomers was also recovered in 20 % yield. A variety of simple alkanes were selectively arylated with moderate to excellent yields using the developed method. Aside from the formation of product **3q**, where the homodimer of mesitylene was formed as by-product, dimers were not observed during oxidative coupling.

We next explored the scope of heteroarenes in the oxidative cross-coupling with cyclohexane. Various derivatives of quinoline reacted selectively at the most electron-poor positions (Scheme 2, products **4a–4g**). In the case of 4-methylquinoline and 2-methylquinoline, weak C–H bonds are found in the benzylic positions, with $\text{BDE} = 86.1$ and $87.6 \text{ kcal mol}^{-1}$, respectively. Of particular note, cyclohexane, with a BDE of $99.5 \text{ kcal mol}^{-1}$, is nevertheless highly selective in this reaction, forming $\text{C}_{\text{sp}^3}\text{-C}_{\text{sp}^2}$ bonds with yields of 75–85 % (**4a** and **4b**). Phenyl or halogen groups at the 2 position of quinoline are well tolerated (**4c** and **4d**). Reaction with quinoline leads to a mixture of 2- and 4-substituted products. The substrate 3-bromoquinoline, which has two possible sites for alkylation, can be selectively mono-functionalized, and affords the kinetic product **4e**. Products of the dialkylation of quinoline and phenanthroline were obtained in 49–78 % yield (**4f** and **4g**). Isoquinoline,

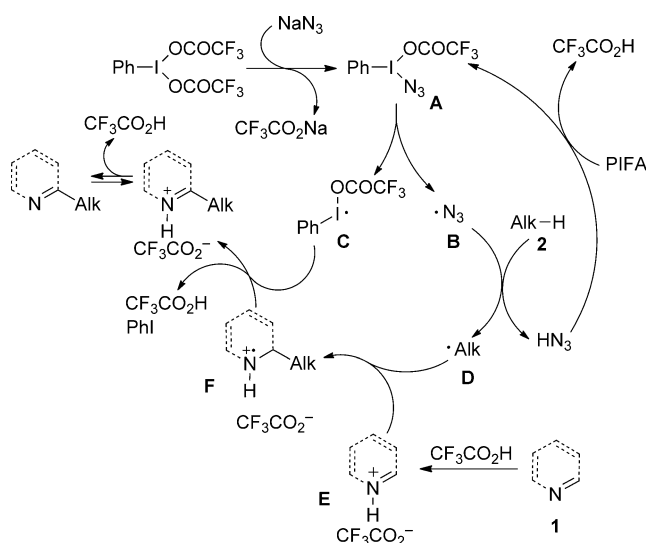


Scheme 2. Scope of heterocycles in CDC. Conditions: heterocycle (0.2 mmol), alkane (4.0 mmol), oxidant (0.8 mmol), additive (0.8 mmol) in solvent (1 mL) at ambient temperature. [a] Using PIFA (1.2 mmol) and NaN_3 (1.2 mmol). [b] Using PIFA (0.4 mmol) and NaN_3 (0.4 mmol). [c] Using 1,2-dimethoxyethane instead of cyclohexane [d] Some amount of dialkylated product was formed; see the Supporting Information for details [e] Using PIFA (2.0 mmol) and NaN_3 (2.0 mmol). Cy = cyclohexyl.

along with its electron-rich and electron-poor derivatives, selectively reacts with **2a** and dimethoxyethane to give monoalkylated products in moderate yields (products **4h–4l**). Using an excess of reagents, the dialkylation of 5-nitroisoquinoline is possible at the 1 and 6 positions (product **4k**). The second nucleophilic functionalization occurs on the non-heteroaromatic ring. Furthermore, numerous heteroaromatics, including pyridine, quinoxaline, phthalazine, quinazoline, pyrimidine, benzimidazole, purine, and pyridopyrazines, undergo CDC to provide the desired products with a similar trend in selectivity (**4m–4z**; Scheme 2).

Product **4v**, from the trialkylation of pyrimidine, was isolated in good yield. Fine tuning of reaction conditions allows selective mono-functionalization of quinazoline (**4s**).

Having established the scope of the method, we performed a study on the reaction mechanism. The formation of product **3a** was suppressed in the presence of radical scavengers. Based on this finding, we concluded that radical processes are involved in the oxidative cross-coupling.^[12] Furthermore, we observed a strong kinetic isotopic effect (KIE = 7.6) when using $[\text{H}_{12}]$ cyclohexane and **1a** (see the Supporting information for details). Therefore, the abstraction of hydrogen from cyclohexane is the rate-limiting step in the oxidative cross-coupling. A proposed mechanism for the cross-coupling is shown in Scheme 3. Initially, PIFA reacts



Scheme 3. Proposed reaction mechanism.

with NaN_3 to form intermediate **A**, which undergoes thermolysis to give an azide radical (**B**) and an iodine-centered radical **C**. A double exchange of the trifluoroacetyl group by azide ions in PIFA could also occur to give $\text{PhI}(\text{N}_3)_2$, which would show similar properties to **A**. Radical **B** selectively reacts with the alkane to form an alkyl radical (**D**) and hydrazoic acid. Released hydrazoic acid may react with PIFA to form **A**. Based on the observed trend of reactivity with heteroaromatic compounds, radical **D** possesses a nucleophilic character. The heteroaromatic base is protonated by trifluoroacetic acid and forms the corresponding salt (**E**). Radical **D** reacts with salt **E** by attack at the most electron-deficient position to form radical cation **F**, which is oxidized by radical **C** to give the product of cross-coupling after deprotonation.

In conclusion, we have developed an efficient and scalable method for the oxidative cross-coupling of heteroarenes with simple unfunctionalized alkanes. The desired products were smoothly formed under mild reaction conditions, with short reaction times, at ambient temperature. The formation of new $\text{C}_{\text{sp}^3}\text{--C}_{\text{sp}^2}$ bonds selectively occurred at the electron-poor position of arenes. This method allows the preferential

transformation of stronger $C_{sp^3}-H$ bonds in the presence of weaker $C_{sp^3}-H$ bonds.

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