C-H Functionalization

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

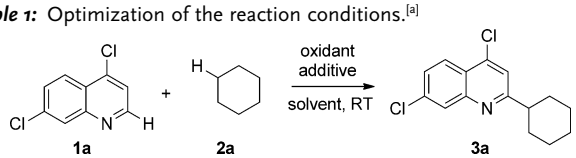
*Andrey P. Antonchick* and Lars Burgmann*

*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 $NaN_3$ using benzene as the solvent (Table 1, entry 1). Both PIFA and $NaN_3$ 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). 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 $NaN_3$ did not lead to significant difference in the yield of **3a**. Therefore, for the

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




**1a** **2a** **3a**

| 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 | $NaN_3$ | $CH_2Cl_2$ | 3 | 72 |
| 5 | PIFA | $NaN_3$ | $CHCl_3$ | 16 | 37 |
| 6 | PIFA | $NaN_3$ | EtOAc | 16 | 19 |
| 7 | PIFA | $NaN_3$ | $C_6H_{12}$ | 16 | 30 |
| 8 | $PhI(OAc)_2$ | $NaN_3$ | $CH_2Cl_2$ | 24 | n.d. |
| 9 | PhI(OH)OTs | $NaN_3$ | $CH_2Cl_2$ | 24 | 28 |
| 10 | $F_5$-PIFA | $NaN_3$ | $CH_2Cl_2$ | 4 | 60 |
| 11 | IBX | $NaN_3$ | $CH_2Cl_2$ | 24 | n.d. |
| 12 | *t*BuOOH | $NaN_3$ | $CH_2Cl_2$ | 24 | n.d. |
| 13 | $Na_2S_2O_8$ | $NaN_3$ | $CH_2Cl_2$ | 24 | n.d. |
| 14 | PIFA | $TMSN_3$ | $CH_2Cl_2$ | 3 | 51 |
| 15 | PIFA | $(nBu)_4NN_3$ | $CH_2Cl_2$ | 24 | n.d. |
| 16 | PIFA | $I_2$ | $CH_2Cl_2$ | 24 | n.d. |
| 17[b] | PIFA | $NaN_3$ | $CH_2Cl_2$ | 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)iodo]benzene, $F_5$-PIFA = [bis(trifluoroacetoxy)iodo]pentafluorobenzene, IBX = 2-iodoxybenzoic acid, n.d. = not detected.

[*] Dr. A. P. Antonchick, L. Burgmann
Max-Planck-Institut für Molekulare Physiologie, Abteilung Chemische Biologie, Otto-Hahn-Strasse 11, 44227 Dortmund (Germany)
E-mail: andrey.antonchick@mpi-dortmund.mpg.de
L. Burgmann
Technische Universität Dortmund, Fakultät Chemie
Otto-Hahn-Strasse 6, 44227 Dortmund (Germany)

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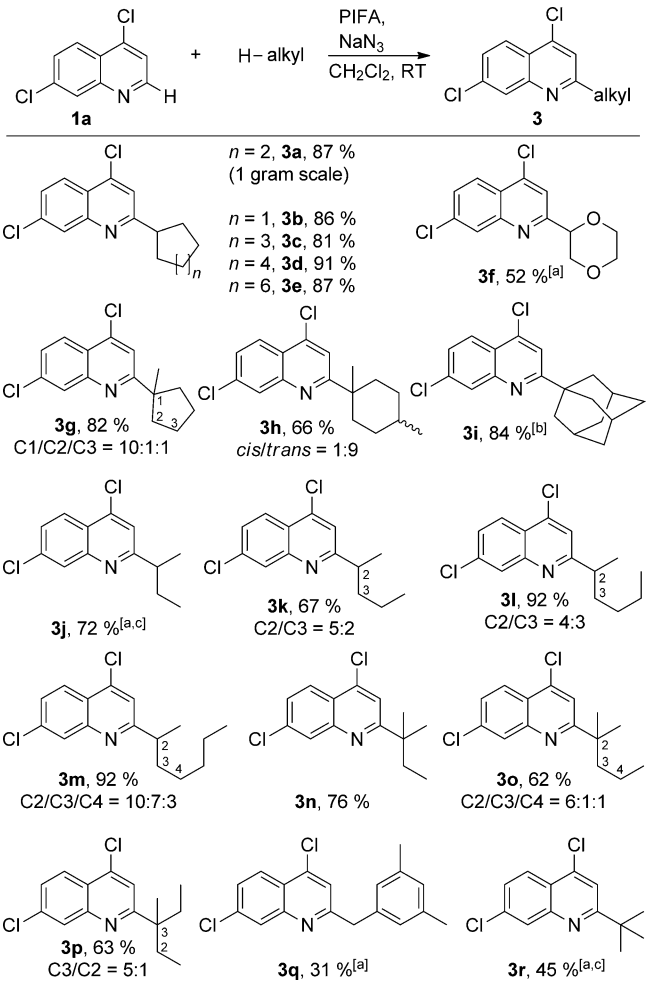
following experiments we used PIFA (2 equiv) and $NaN_3$ (2 equiv) in dichloromethane at ambient temperature.

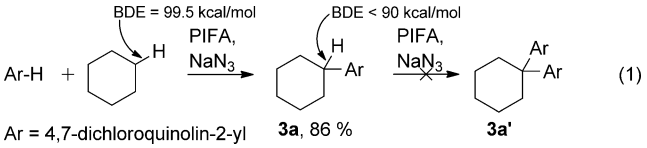
With these optimized reaction conditions in hand, we performed a scale-up experiment using **1a** (5 mmol). Product **3a** was smoothly formed in the scale-up experiment, which was performed in a flask open to the air, and resulted in a yield of 87% (**3a**; Scheme 1). Afterwards, we focused on




***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 adamantine (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 $C_{sp^3}$–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 kcal mol$^{-1}$) and the C2 position (98.3 ± 0.5 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 kcal mol$^{-1}$ at the 1° site and 98.0 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 (BDE < 90 kcal mol$^{-1}$). However, **3a′**, which is the product of over-oxidation, was not observed [Eq. (1)]. This method allows preferential

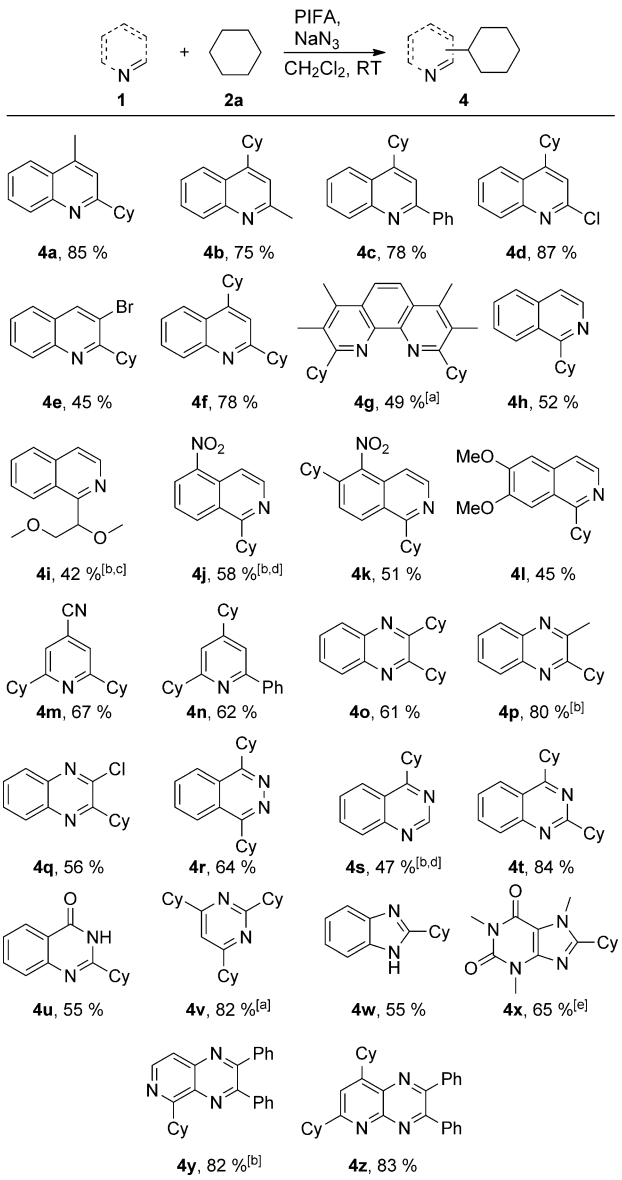



(1)

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 BDE = 86.1 and 87.6 kcal mol$^{-1}$, respectively. Of particular note, cyclohexane, with a BDE of 99.5 kcal mol$^{-1}$, is nevertheless highly selective in this reaction, forming $C_{sp^3}$–$C_{sp^2}$ 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,

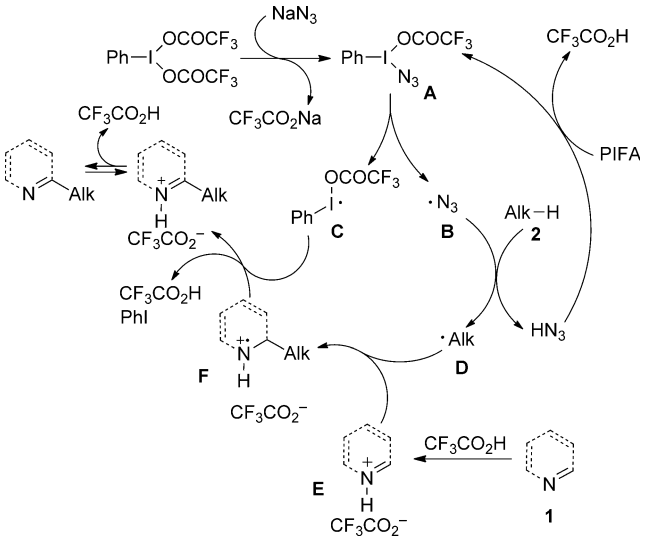
  




***Scheme 2.*** Scope of heterocycles in CDC. Conditions: heterocycle (0.2 mmol), alkane (4.0 mmol), oxidant (0.8 mmol), additive (0.8 mmol) in solvent (1 mL) at ambient temperature. [a] Using PIFA (1.2 mmol) and $NaN_3$ (1.2 mmol). [b] Using PIFA (0.4 mmol) and $NaN_3$ (0.4 mmol). [c] Using 1,2-dimethoxyethane 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 [$^2H_{12}$]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 trifluoracetyl group by azide ions in PIFA could also occur to give $PhI(N_3)_2$, 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 $C_{sp^3}$–$C_{sp^2}$ 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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