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Versatile Cross-Dehydrogenative Coupling of Heteroaromatics and Hydrogen Donors via Decatungstate Photocatalysis

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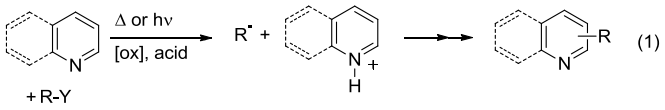
A facile sunlight-induced derivatization of heteroaromatics via photocatalyzed C-H functionalization in amides, ethers, alkanes and aldehydes is described. Tetrabutylammonium decatungstate (TBADT) was used as the photocatalyst and allowed to carry out the process under mild conditions.

The importance of functionalized heterocycles in medicinal chemistry is well known.[1] This calls for mild and efficient procedures for the introduction of substituents onto a preformed heterocycle. One dated example is the Minisci reaction, reported for the first time more than 40 years ago,[2,3] that is still an important tool for medicinal chemists.[3] The original protocol involved the thermal generation of radicals via decarboxylation of carboxylic acids mediated by an Ag^{I} salt as a catalyst in the presence of persulfate anion.[2] Radicals then attacked the protonated heterocycle and gave the desired alkylated derivatives via one-electron oxidation and deprotonation.[4]

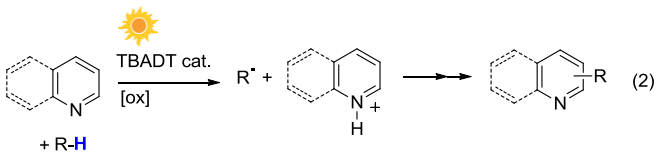
Several protocols have been later developed starting from a variety of radical sources which include alkyl halides,[5] aryl[6a] or alkyl boronic acids,[6b] alkyl or alkoxymethyl trifluoroborates,[6b,c] zinc sulfinate salts,[6d] aryl diazonium salts,[6e] *t*Bu esters[6f] and aminoacids[6g] as radical precursors (Scheme 1, eq 1; type a reaction). A more challenging approach, however, consists in the Minisci reaction via radicals formed by hydrogen abstraction from C-H bonds. Sparse examples were recently described, where radicals were obtained from ethers,[7] aldehydes,[8] amides,[9] toluenes[10] and even alkanes[2b,7a,11] by homolytic C-H cleavage (Scheme 1, eq 1; type b). Some drawbacks are apparent in the exploitation of the latter approaches. In fact, the proposed protocols are in most cases limited to the use of only a particular class of hydrogen donors (mostly ethers, due to the easy formation of α-oxy radicals).[7] The compulsory use of a high temperature[7c,8,11b,c] and/or hazardous organic peroxides,[2b,7c,8b,c,10,11b,c] and the fact that a

Minisci-type Reaction



type a: Y = halogen, $B(OH)_2$, BF_3K, $[SO_2]_2Zn$, N_2^+, COO*t*Bu, COOH
type b: Y = H in ethers, aldehydes, amides, toluenes, alkanes

This work



TBADT = $(Bu_4N)_4[W_{10}O_{32}]$

Scheme 1 Typical approaches for the functionalization of heteroaromatics via Minisci reaction by cleavage of a R-Y bond (type a) or a R-H bond (type b). Cross-dehydrogenative coupling between hydrogen donors (R-H) and heteroaromatics via TBADT photocatalyzed functionalization of C-H bonds (this work).

general method for the generation of alkyl radicals from R-H to be used in Minisci reaction is still lacking, calls for milder approaches. In this regard, seminal efforts have been made in the recent procedures based on visible light photoredox catalysis.[7b,d,9b]

In the last years, we (and others) had experience on the use of tetrabutylammonium decatungstate (TBADT; $(nBu_4N)_4[W_{10}O_{32}]$) as an efficient and robust photocatalyst able to promote photoredox reactions,[12] as well as hydrogen atom transfer processes, starting from different classes of organic substrates.[13,14] Another advantage of the use of TBADT is that it is active upon solar light irradiation, allowing to realize the so-called "window ledge chemistry".[15] TBADT, however, was used so far only for the functionalization of C=C (in electron-poor alkenes and fullerenes) and N=N bonds (in azodicarboxylates),[16] and for fluorination reactions,[14g] but not for the derivatization of aromatics. We envisaged that under appropriate conditions, TBADT could be used for the aromatic

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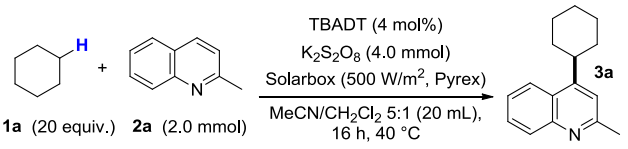
Electronic Supplementary Information (ESI) available: Typical experimental procedure and characterization for all products. See DOI: 10.1039/x0xx00000x

Table 1 Optimization of the reaction conditions.[a]



1a (20 equiv.) **2a** (2.0 mmol)

entry	Bu_4NBr (mol %)	conditions	GC yield (%)[b]	**2a** conversion (%)[b]
1	40	-	71	96
2	40	deaerated	51	77
3	40	without $K_2S_2O_8$	15	25
4	40	TFA 0.1 M	trace	78
5	**0**	**-**	**77**	**100**
6	0	without TBADT	0	8
7	0	without hν	0	0
8	0	without CH_2Cl_2	64	85

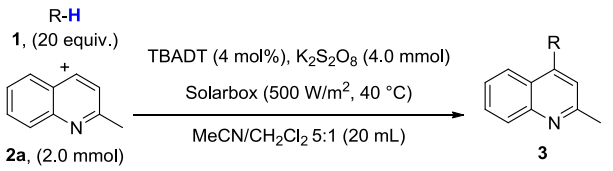
[a] Reaction conditions: **1a** (40 mmol), **2a** (2.0 mmol), TBADT (4 mol%), $K_2S_2O_8$ (4.0 mmol), MeCN/CH_2Cl_2 5:1 (20 mL). Irradiation carried out by using a Solarbox equipped with a 1.5 kW Xe lamp (500 W/m^2) under air equilibrated conditions. [b] Determined by GC analysis using dodecane as the internal standard.

homolytic substitution[17] of heterocycles via a cross-dehydrogenative coupling reaction with several hydrogen donors (R-H) as reaction partners (Scheme 1, eq 2).

As a model reaction we tested the alkylation of quinaldine (**2a**) with cyclohexane (**1a**) under different conditions (Table 1). The reaction was performed by using a solar simulator equipped with a Xe lamp in the presence of TBADT (4 mol%) and persulfate anion in the role of oxidant[6a,g,7a-b,7d-e,9b] and Bu_4NBr (40 mol%) as phase transfer agent.[7a,18] Gratifyingly, irradiation in MeCN/CH_2Cl_2 (5:1) for 16 h under aerated conditions gave alkylated quinaldine **3a** as the only product in 71% yield with an almost total consumption of **2a** (Table 1, entry 1). The absence of oxygen or the oxidant was detrimental for the process (entries 2-3), while the addition of a strong acid (TFA, 0.1 M) caused the precipitation of the decatungstate salt having the protonated heterocycle as counterion (entry 4). By contrast, omitting Bu_4NBr did not affect the overall yield (entry 5). Blank experiments (entries 6-7) clearly demonstrated that the presence of light and TBADT was mandatory. The adoption of CH_2Cl_2 as a co-solvent was likewise important to improve the conversion of **2a**. The functionalization of **2a** (2 mmol) in the presence of an equimolar mixture of cyclohexane and cyclohexane-d_{12} (20 mmol each) gave derivative **3a** and the corresponding deuterated analogue **3a**-d_{11} in a 70:30 ratio (see Figure S1 for further details).

We then investigated the functionalization of **2a** with several hydrogen donors by using the conditions described in Table 1, entry 5, and the results are collected in Table 2. The reaction with cyclopentane (**1b**) and cycloheptane (**1c**) gave similar results and likewise a clean alkylation in position 4 of quinaldine occurred (entries 2-3). Next, the reaction was extended to cyclic ethers, namely THF (**1d**) and 1,4-dioxane (**1e**), and adducts **3d** and **3e** were formed in a satisfactory yield (> 50%), although in the former case the presence of Bu_4NBr was helpful to increase the yield (entries 4-5). Even amides **1f** and **1g** were added photocatalytically to **2a** under the same reaction conditions to form acylated quinaldine **3f** and amidoalkylated quinaldine **3g** (entries 6-7).

Table 2 TBADT photocatalyzed addition of hydrogen donors (R-H) **1a-1i** onto quinaldine **2a**.[a]



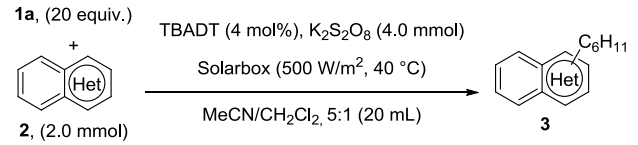
2a, (2.0 mmol) **3**

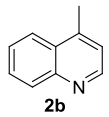
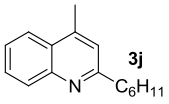
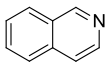
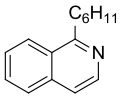
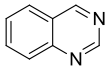
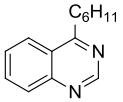
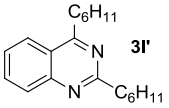
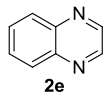
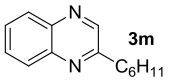
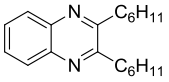
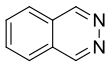
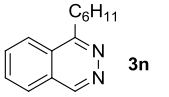
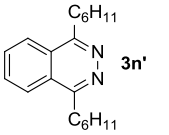
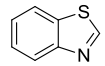
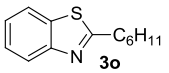
entry	**1**	time (h)	Product **3**	Yield (%)[b]
1	**1a**	16 h	**3a**	77
2	**1b**	20 h	**3b**	74
3	**1c**	16 h	**3c**	66
4[c]	**1d**	16 h	**3d**	53
5	**1e**	20 h	**3e**	73
6	**1f**	16 h	**3f**	47
7[c]	**1g**	20 h	**3g**	73
8[c]	**1h**	16 h	**3h**	67
9[c,d]	**1i**	24 h	**3i**	69

[a] Reaction conditions: **1** (40 mmol), **2** (2.0 mmol), TBADT (4 mol%), $K_2S_2O_8$ (4.0 mmol), MeCN/CH_2Cl_2 5:1 (20 mL). Irradiation carried out by using a Solarbox equipped with a 1.5 kW Xe lamp (500 W/m^2) under air equilibrated conditions. [b] Yields of product isolated after flash chromatography on SiO_2. [c] Bu_4NBr (40 mol%). [d] **1i** (50 equiv.), MeCN/H_2O 5:1 (20 mL).

Acylation of **2a** with heptaldehyde **1h** by a cross-dehydrogenative coupling proceeded well to afford **3h** in 67% yield (entry 8). Finally, the regioselective β-C-H fuctionalization in cyclopentanone **1i**[14h] was exploited for the synthesis of β-heteroaryl ketone **3i** in 69% yield (entry 9).

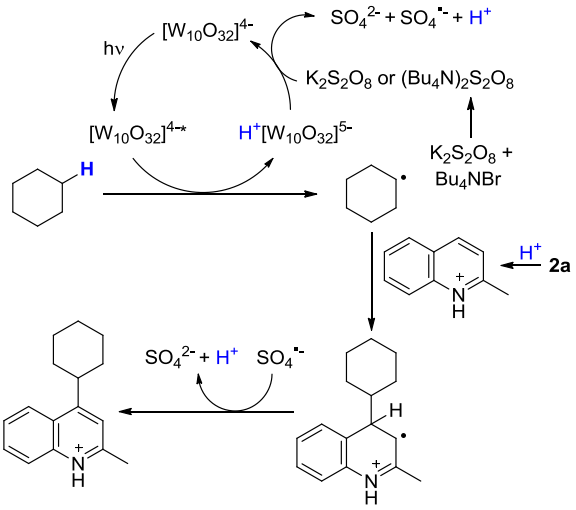
Table 3 TBADT photocatalyzed addition of cyclohexane onto heteroaromatics **2b-2g**.[a]



entry	2	time (h)	Product 3	Yield (%)[b]
1	 **2b**	48 h	 **3j**	81
2	 **2c**	20 h	 **3k**	40
3[c]	 **2d**	24 h	 **3l**	43
			 **3l'**	14
4[c]	 **2e**	48 h	 **3m**	60
			 **3m'**	24
5[c]	 **2f**	24 h	 **3n**	28
			 **3n'**	20
6[c]	 **2g**	24 h	 **3o**	60

[a] Reaction conditions: **1a** (40 mmol), **2** (2.0 mmol), TBADT (4 mol%), $K_2S_2O_8$ (4.0 mmol), $MeCN/CH_2Cl_2$ 5:1 (20 mL). Irradiation carried out by using a Solarbox equipped with a 1.5 kW Xe lamp (500 W/m^2) under air equilibrated conditions. [b] Yields of product isolated after flash chromatography on SiO_2. [c] Bu_4NBr (40 mol%).

We then focused our attention on the functionalization of other heteroaromatics (**2b-2g**, Table 3), while maintaining the same hydrogen donor (cyclohexane **1a**). The choice of **1a** was motivated by the fact that this is, among the R-H tested, the compound having the strongest C-H bond (99.5 kcal/mol).[19] Alkylation of lepidine **2b** took place in a regioselective way (at position 2) and in a high yield (81%, compound **3j**, Table 3, entry 1), albeit 48 h irradiation were required to convert all the starting **2b**. Interestingly, a similar clean reaction was found in the functionalization of isoquinoline **2c**, where compound **3k** was the sole derivative formed. The situation changed when heteroaromatics containing two nitrogens were tested. The addition of cyclohexane onto quinazoline **2d** gave a mixture of mono- (**3l**) and disubstituted (**3l'**) adducts (entry 3). Several attempts to modify the reaction conditions in order to have a clean mono- or disubstitution failed. The same holds for the experiments with quinoxaline **2e** and phtalazine **2f**, being the monoalkylated derivative (**3m** or **3n**, entries 4-5) the main product in each case (84% overall yield in the former case). Again, a clear cut process was found in the functionalization of benzothiazole **2g** to give **3o** (60% yield).



Scheme 2 Proposed reaction mechanism.

A tentative mechanism is depicted in Scheme 2 for the reaction between cyclohexane and **2a**. Excited TBADT is able to cleave homolytically the C-H bond in derivatives **1a-i**. The reduced form of the photocatalyst ($H^+[W_{10}O_{32}]^{5-}$) is oxidized by $K_2S_2O_8$,[20] liberating an equivalent of acid along with a strong oxidant ($SO_4^{\bullet-}$).[21] The thus formed cyclohexyl radical is trapped by the protonated heterocycle and the desired derivative is finally formed by oxidation of the adduct radical. Minor pathways could likewise operate, however. A minor amount of $SO_4^{\bullet-}$ could be formed directly from persulfate via thermal (40 °C) or photochemical cleavage. A role of $SO_4^{\bullet-}$ in the hydrogen abstraction of more labile C-H bonds (e.g. in ethers) could not be ruled out. Blank experiments demonstrate, however, that the presence of TBADT is mandatory for the success of the reaction. In some instances, the addition of Bu_4NBr as a phase transfer agent[7a,18] may help to accelerate the process, probably thanks to the formation of $(Bu_4N)_2S_2O_8$ via methathesis reaction of potassium persulfate and Bu_4NBr.[22] However, the isotopic effect of **3a**/**3a**-d_{11} = 2.3 is fairly in agreement to what previously observed in the TBADT photocatalyzed benzylation of fumaronitrile by using toluene and toluene-d_8.[23]

The method described here compares favorably with those previously reported involving C-H functionalization of the alkylating agent. First of all, this is a versatile approach since various substrates belonging to different classes of hydrogen donors (ethers, amides, aldehydes, cycloalkanones,

cycloalkanes) can be activated. As for the use of cycloalkanes and amides, these were used here in a 20 equiv. amount, contrary to other cases where the hydrogen donors were used as the solvent (or, at least, co-solvent).[9,11b,c] Different from other procedures, the presence of a strong acid (e.g. TFA or sulfuric acid) is not required since protonation of the heterocycle took place during the reaction (Scheme 2).

Acknowledgements

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