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Late-Stage C-H Alkylation of Heterocycles and 1,4-Quinones via Oxidative Homolysis of 1,4-Dihydropyridines

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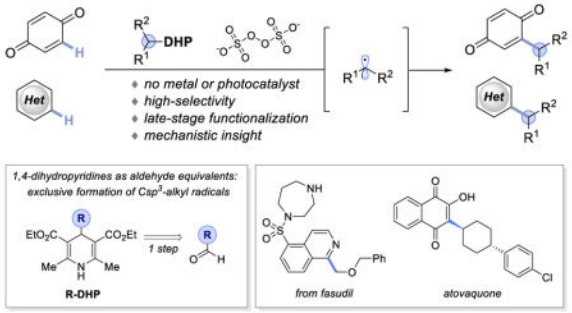
Abstract

Under oxidative conditions, 1,4-dihydropyridines (DHPs) undergo a homolytic cleavage, forming exclusively a Csp^3-centered radical that can engage in the C-H alkylation of heterocyclic bases and 1,4-quinones. DHPs are readily prepared from aldehydes, and, considering that aldehydes normally require harsh reaction conditions to take part in such transformations, with mixtures of alkylated and acylated products often being obtained, this net decarbonylative alkylation approach becomes particularly useful. The present method takes place under mild reaction conditions and requires only persulfate as a stoichiometric oxidant, making the procedure suitable for the late-stage C-H alkylation of complex molecules. Notably, structurally complex pharmaceutical agents could be functionalized or prepared with this protocol, such as the anti-malarial Atovaquone and anti-theilerial Parvaquone, thus evidencing its applicability. Mechanistic studies revealed a likely radical chain process via the formation of a dearomatized intermediate and provided a deeper understanding of the factors governing the reactivity of these radical forebears.

Graphical Abstract



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Notes

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Keywords

dihydropyridine; Hantzsch ester; radical alkylation; quinone; Minisci

INTRODUCTION

Nitrogen-containing heterocycles and quinones are ubiquitous chemical motifs present in pharmaceuticals, natural products, and ligand scaffolds among other examples, thus highlighting the importance of such structures.[1] Late-stage modification of these entities within the context of complex molecules is not trivial, and, often, a simple modification of such compounds requires a lengthy synthetic strategy where the new substituent must be installed in early stages. In an ideal scenario, numerous derivatives should be accessible from a common and complex molecule at any stage in a synthesis. Consequently, rapid, late-stage, selective alkylation processes of complex molecules under mild reaction conditions are of great value and significance.[2]

Polar approaches to such transformations are limited because of their typically lower functional group tolerance. By contrast, radical processes have the advantage of tolerating a wider array of functional handles. Yet, the reaction conditions required to generate radical intermediates are themselves often harsh, thus limiting their applicability.[3] Indeed, radical alkylation of complex heterocycles has been well developed in the Minisci reaction,[4] where a radical is coupled with a heterocycle under acidic, oxidizing conditions, delivering the functionalized product. Interestingly, the regioselectivity is orthogonal to that observed for the Friedel-Crafts reaction, thus increasing the appeal of such transformations. Traditionally, carboxylic acids[5] and halides[6] have been employed as radical precursors, but more recently the toolbox has been expanded to include alcohols,[7] boronic acids,[8] sulfinate salts,[9] alkenes,[10] and alkyltrifluoroborates.[11] However, in most of the previous contributions, high temperatures, (sub)stoichiometric amounts of expensive metal salts, an excess of the radical precursor, and strong oxidants or expensive photocatalysts[7,11a,12] are required to achieve good yields.

Aldehydes, which are readily available, have been employed as acyl radical precursors to access acylated products.[13] and, to a lesser extent and with limited applicability, as a source of alkyl radicals as well,[14] generated through decarbonylation of an acyl radical (**I**) (Scheme 1).[15] Unfortunately, this acyl radical can react with the heterocycle or undergo further oxidation, resulting in non-productive pathways. It is known that the acyl/alkyl radical equilibrium can be shifted by increasing the reaction temperature, resulting in a more efficient CO extrusion event.[16] Consequently, such transformations usually employ temperatures above 100 °C to improve the selectivity toward the alkylation, while an excess of the aldehyde motif is required to achieve competitive yields, thus highlighting the narrow applicability of such a strategy.[13–14]

Recently, 1,4-dihydropyridines (DHPs), which are readily prepared from aldehydes in one step,[17] have been demonstrated to undergo homolysis under photoredox conditions to form Csp^3-centered alkyl radicals that can be engaged in different processes with prefunctionalized substrates.[18] Notably, DHPs can be regarded as masked aldehydes that

exclusively deliver alkyl radicals by circumnavigating acyl radical intermediates, thus avoiding the formation of acylated byproducts or the requirement for high temperatures, strong oxidants, and excess of the aldehydic partner given the efficiency of oxidative fragmentation from DHPs. Based on this, we envisioned exploration of the reactivity of DHPs in a transformation beyond prefunctionalized substrates, targeting, therefore, a much more appealing, yet challenging, C-H bond. In this regard, we considered the C-H alkylation of nitrogen-containing heterocycles and 1,4-quinones, so that the traditional drawbacks of Minisci chemistry with aldehydes could be overcome, thus allowing a re-introduction of this attractive feedstock into radical C-H alkylation processes.

RESULTS AND DISCUSSION

For the optimization of the reaction conditions,[19] we chose **1a** as a model substrate in combination with *i*-Pr-DHP (**2a**) and found that the reaction proceeded in almost quantitative yields using a small excess of **2a**, sodium persulfate as oxidant, and trifluoroacetic acid (TFA) to activate the heterocycle. Cation exchange of the persulfate oxidant had little effect on the reaction outcome (entries 4–5) whereas stronger oxidants (entry 6) typically employed for aldehydes had a deleterious effect on the reactivity. Interestingly, the addition of TFA was not an absolute requirement for the reaction to proceed (entry 3), albeit a diminished yield was obtained without this additive. Trichloroacetic acid (TCA) showed no effect (entry 3 vs entry 7), whereas BF_3•OEt_2 (entry 9) showed activity similar to that of TFA.[19] Not surprisingly, the solvent system played a crucial role, as in this type of process diffusion between the aqueous phase hosting the oxidant and the organic phase accommodating the organic partners is critical.[21] Therefore, immiscible solvents gave poor yields (entry 10), whereas pure acetonitrile (entry 11) failed because of the poor persulfate solubility. Notably, more solubilizing DMSO rendered modest yields (entry 12). It should be noted that the use of DHPs allowed a metal-free, room temperature set of reaction conditions with an almost equimolar mixture of reaction partners in the presence of a mild oxidant, in striking contrast with previous reports using aldehydes as radical precursors that generally employed 3–20 equivalents of the aldehyde partner at 115–140 °C.[14]

Next, we tested this new set of reaction conditions with DHPs featuring different alkyl units at the C4-position (Table 2). Both acyclic (**3b–f**, **3l**) and cyclic radicals (**3g–k**) could be coupled with the heterocyclic backbone in moderate to good yields. Notably, alkene functional groups were well tolerated as demonstrated by the melonal-derived and cyclohexenyl DHPs (**3f** and **3h**, respectively). Sterically demanding systems were well accommodated as demonstrated with the norbornyl system (**3i**). Oxygen-containing heterocyclic motifs did not hamper the reaction (**3j–k**). Importantly, primary radicals could be engaged with **1a** in the presence of a stabilizing α-oxygen atom. Unfortunately, non-stabilized, primary alkyl radicals did not deliver the expected product because the corresponding DHP does not undergo homolytic C-C cleavage but rather C-H homolysis, resulting in the formation of a 4-alkylated-pyridine byproduct.[22]

Combinations of different heteroarenes with distinct DHPs were then explored in an effort to access unprecedented structural motifs (Table 3). For example, C2-alkylated lepidine

derivatives have shown antituberculosis activity,[23] and thus several different lepidine derivatives (**3m–o**) were prepared. Whereas simple alkyl motifs rendered high yields of the corresponding product (**3m**), more complex motifs led to lower yields (**3n–3o**). Interestingly, primary α-amidomethyl radicals could be employed, although with poor yields. Substituted quinolines were explored and satisfactorily yielded the expected products in moderate to good yields (**3p**, **3r–3s**). Likewise, isoquinolines were well accommodated (**3t–3u**) as well as pyridine (**3v**), pyrimidine (**3w**), and benzothiazole cores (**3x**). To test the regioselectivity of the protocol, heterocycles with differentially reactive C-H bonds were tested. Unfortunately, mixtures of mono- and dialkylation were observed (**3q**, **3v**). However, in the presence of other leaving groups under radical conditions (e.g., $MeSO_2$-, and Cl-, **3w**), exclusive addition at the C-H bond was observed.[24]

To highlight the applicability of the protocol, we attempted the late-stage C-H alkylation of different natural products and pharmaceuticals (Table 4). Notably, we observed a wide functional group tolerance (e.g., amines, alkenes, hydroxyls, sulphonamides) in alkylating natural products such as nicotine (**3y**) and caffeine (**3z**). Cinchonine, a common ligand scaffold for numerous organocatalytic processes,[25] could be quickly modified (**3aa**), allowing the formation of a new generation of cinchonine-based ligands under mild reaction conditions. Likewise, structurally related quinine, an antimalarial drug, could be diversified in high yields (**3bb, 3cc**). Antivasospatic fasudil hydrochloride[26] and apoptosis inducer camptothecin were effectively elaborated under the reaction conditions, delivering the C-H alkylated product in good to high yields and excellent regioselectivity (**3dd–3ff**). Notably, alkylated camptothecin-derivatives have shown even higher activities than the base molecule itself.[27]

Spurred on by the possibility of introducing the decarbonylated aldehyde feedstock while overcoming its inherent drawbacks in radical processes, we envisioned the introduction of quinones as radical acceptors. Quinones are of extreme importance because of their ability to partake in electron transport processes in primary metabolic routes. Furthermore, they display important pharmacological activities and are very versatile intermediates for organic synthesis.[28] Because functionalization of quinones usually relies on the use of transition metal catalysis,[29] we sought to carry out the metal-free C-H alkylation of quinones from DHPs under mild conditions. Previously, these interesting scaffolds have been functionalized using radicals generated with metal-based catalysts to afford mostly arylated quinones from organoboron compounds[30] and carboxylic acids,[31] among others.[32] However, aldehydes have never been employed before as alkyl radical precursors with this class of substrates,[33] thus ignoring an important feedstock that could help increase the chemical space.

To demonstrate the versatility of our protocol, different 1,4-quinones were tested.[34] Interestingly, in the presence of two identical reactive sites, monoalkylation was observed in good levels (**5a**). Apoptosis inducer Coenzyme Q_0, with only one reactive site and two methoxy groups, was effectively coupled with different DHPs in moderate to good yields (**5b–5c**). Notably, π-extended naphthoquinones such as vitamin K_3 (**5d**) smoothly reacted, as well as 2-hydroxynaphthoquinone (Lawsone reagent) (**5e–5f**), which, when combined with Cy-DHP, yielded Parvaquone (marketed as Clexon®, **7e**) in 54% yield. The latter is employed for the treatment of theileriosis, a cattle disease that represents an important threat

to livestock production in Africa, generating losses above $200 million annually.[35] Alternatively, Atovaquone (an anti-malarial drug that acts by inhibiting the mitochondrial electron transport system and marketed as Malarone® when combined with proguanil hydrochloride),[36] could be synthesized in a 54% yield as a kinetic mixture of diastereomers that could be easily converted to the more active *trans*-Atovaquone under acidic conditions.[31a] Importantly, previous syntheses of Atovaquone based on a radical alkylation approach relied on the use of silver salts, significantly increasing the total cost of such a synthetic route.[31a]

Encouraged by the robust reactivity of DHPs, we tested the possibility of achieving a one-pot procedure where the crude reaction mixture from the DHP synthesis was used in the C-H alkylative event without further manipulation (Scheme 2). Indeed, formation of product **3a** was observed in moderate yields when the reaction was run in diethylene glycol, whereas improved yields were observed when acetonitrile/water was added to the crude mixture. Although yields were slightly lower than those in the step-wise protocol, these results suggest particularly unstable DHP intermediates could be used directly as latent radicals without sequential purifications.[37]

Mechanistic studies

Once the versatility of DHPs as alkylating agents was demonstrated in radical C-H alkylating processes, we moved on to study the influence of the 1,4-dihydropyridine backbone in the reaction outcome. Because of their dual role as H-atom donors and C_{sp^3}-alkyl radical precursors, DHPs are becoming more prominent in organic synthesis.[18] Consequently, it was of interest to gain a deeper understanding of the factors controlling their reactivity. To this end, six different 1,4-dihydropyridine cores were tested under the developed reaction conditions (Scheme 3). Interestingly, cyano-substitution at C3 and C5(**2a-CN**) led to only traces of product, whereas acridine derivative **2a-Acr** led to no conversion at all, and only 6-isopropylacridine could be observed.[38] Not surprisingly, no relationship between the oxidation potential and the reactivity was observed because persulfate [E^{ox} ($S_2O_8^{2-}/SO_4^{2-}$) = 2.01 V vs SCE] and [E^{ox} ($SO_4^{\bullet 2-}/SO_4^{2-}$) = 2.6 V vs SCE] is strong enough to oxidize the different DHP backbones rapidly.[39] However, a trend between the steric bulk of the R^1 group at C3 and C5[40] and the reactivity was detected. It appears that greater steric hindrance at the C4-position of the pyridine byproduct formed upon oxidation decreases the tendency of the isopropyl radical to undergo competitive rebound with it, thus favoring the alkylation of lepidine and providing higher yields of the desired product **3m**. Notably, modification of the ester residue led to comparable yields for isopropyl substitution (**2a-*i*-Pr**) whereas the *tert*-butyl analog **2a-*t*-Bu** behaved poorly because of its low solubility in the solvent system.

Once the influence of the DHP backbone was studied, we then explored the subtleties of this transformation. Upon monitoring the reaction progress, an intermediate was observed via HPLC that was later consumed to form product (Figure 1). Later, we determined this observed intermediate to be the dearomatized compound **6a**.

To confirm its role as an intermediate, a reaction with **6a** under the developed reaction conditions was conducted, showing quantitative conversion to **3a**, thus demonstrating its competency as an intermediate (Scheme 4).

To gain further insight into the reaction mechanism, we performed two different deuterium-labelling experiments. First (Scheme 5A), an equimolar mixture of C2-deuterated and non-deuterated heterocycle **1a** was treated under reaction conditions. NMR analysis of the isolated compounds during various time points showed proton-enrichment of **1a**, indicating a secondary inverse KIE (0.69 and 0.79 at 20 and 70 min, respectively), which can be rationalized on the basis of a Csp^2–Csp^3 rehybridization upon addition of isopropyl radical **II** to the C2-position of the heterocycle.[41] Next, two similar reactions were performed, with the only modification being the use of a deuterated solvent-system and TFA-*d* for one of them (Scheme 5B). Notably, a solvent KIE of 8.5 was measured based on pyridine **7** formation, which probably arises from a fast scrambling of the DHP N-H proton with the deuterated protic solvent. Afterward, such a scrambling was confirmed to occur in less than 3 min by NMR analysis in 1:1 mixtures of CD_3CN/D_2O.[42]

The observed solvent isotope effect would be indicative of a slower homolysis for the *N*-deuterated DHP. Cyclic voltammetric studies demonstrated the oxidation of **2a-*d*** (E^{ox} = +1.23 V vs SCE) to be more demanding than for **2a** (E^{ox} = +1.05 V vs SCE), which could be the reason for a slower homolysis of the former. It should be noted that regardless of the deuteration of the solvent, similar yields were obtained upon reacting overnight. To study further the role of the N-H bond during the oxidative cleavage, a test reaction with the *N*-methylated DHP **2g-*N*-Me** was conducted (Scheme 6). Whereas no product was formed, **2g-*N*-Me** partially decomposed to several byproducts as judged by GC-MS. Based on precedented literature,[43] we believe that this result might be indicative of a deprotonation of the $DHP^{+\cdot}$ prior to the homolytic cleavage. The fact that no TFA was required for the reaction to proceed (Table 1, entry 3) serves as additional, indirect evidence supporting the generation of a proton upon oxidative cleavage of the DHP. The in situ generated proton would be responsible for selectively activating the heterocyclic substrate, which is more basic than the formed pyridine **7**, allowing the C-H alkylation event to occur even in the absence of an external proton source (**2a**, **3m** and **3cc**), a scenario not observed in previously reported protocols.

On the basis of the previous observations, we envision a mechanistic scenario[44] that is initiated by SET oxidation of the DHP **2a** by $Na_2S_2O_8$, resulting in the formation of pyridine **7** and alkyl radical **II** (Scheme 7). The nature of such a homolysis has been discussed above. Subsequently, the Csp^3-radical adds to the protonated heterocycle (**1aH**$^+$), resulting in the rehybridization of the C2-carbon to form radical cation intermediate **IIIa**, which is made evident by the observed inverse KIE. Next, based on the oxidation potential of **6a** (E^{ox} = +1.19 V vs SCE), we believe that **IIIa** is reduced by the DHP [E^{ox} (**2a**) = +1.05 V vs SCE] via SET, thus resulting in formation of **6a** and alkyl radical **II**. Such a succession of events would be indicative of a chain-radical mechanism. To confirm this hypothesis, a test reaction with 20 mol % of $Na_2S_2O_8$ was performed (Table 1, entry 13) resulting in the isolation of product **3a** in 47% yield and intermediate **6a** in 25% yield, indicating that at least 3.6 equivalents of DHP are generated per equivalent of oxidant, and supporting the initial

hypothesis of a radical chain propagation mechanism.[45,46] Eventually, **6a** will be oxidized by persulfate to deliver the final product **3a** (Scheme 4). Notably, the nature of this step remains unknown, with several available options such as SET oxidation to form **IIIa**, which will then undergo H-atom abstraction by $SO4^{\bullet-}$[47] or further oxidation and deprotonation.[21]

CONCLUSION

In summary, we have been able to demonstrate the ability of DHPs to deliver Csp^3-centered alkyl radicals, which can then be engaged in C-H alkylation of non-prefunctionalized heterocycles and quinones. Importantly, DHPs, which are easily accessible from aldehydes, eliminate the drawbacks associated with the latter for this kind of transformation, i.e., formation of acylated byproducts, harsh reaction conditions (strong oxidants at temperatures >100 °C), and use of an excess of the aldehyde motif. The mild reaction conditions developed allow late-stage C-H alkylation of natural products and drugs. More importantly, relevant marketed pharmaceuticals were prepared from readily available compounds. Finally, mechanistic studies revealed that the reaction proceeds under a radical-chain mechanism via a dearomatized intermediate (**6**). Key insights into the underlying nature of the DHP oxidation have been examined and elucidated. First, deuterium-labelling studies showed an inverse isotope effect arising from a rehybridization upon radical addition, whereas a solvent isotope effect pointed toward a slower homolytic cleavage of the DHP scaffold upon deuteration of the N-H bond. Reactivity studies showed a relationship between the steric bulk of the DHP substituents and the reaction outcome. These studies help inform the design and synthesis of improved DHP scaffolds and provide greater understanding of fragmentation and structural reorganization in DHP-like systems.

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37. The reviewers are acknowledged for their suggestions.
38. Further experiments suggest a C-C homolysis delivering isorpopyl radical and acridinium which will then react forming 9-isopropylacridine. See Supporting Information for further details.
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42. We observed that deuteration of the N-H bond of 2a in a 1:1 CD_3CN/D_2O occurred in less than 3 minutes (the time necessary to run an NMR). Furthermore, in a 10% of D_2O in CD_3CN, the observed rate constant was $k_{obs} = 2.10^{-3}\ s^{-1}$.
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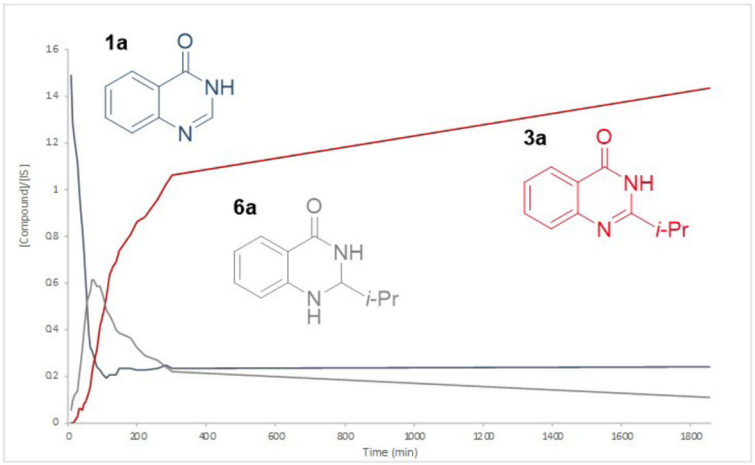
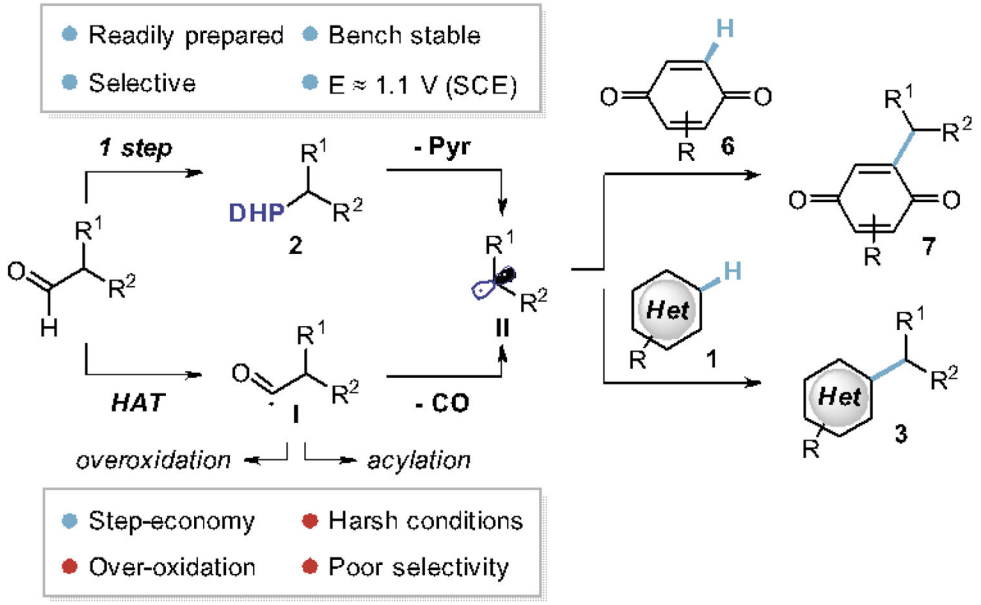
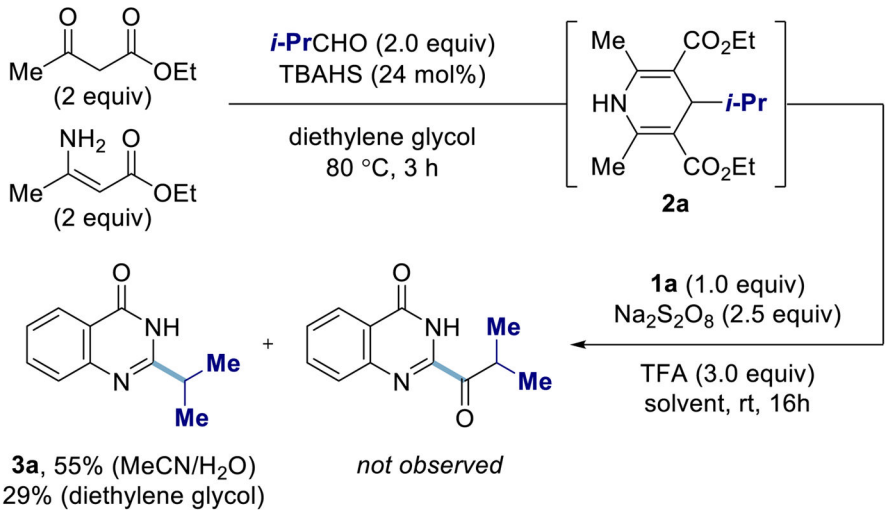


Figure 1.
Monitoring the reaction between **1a** and **2a**.



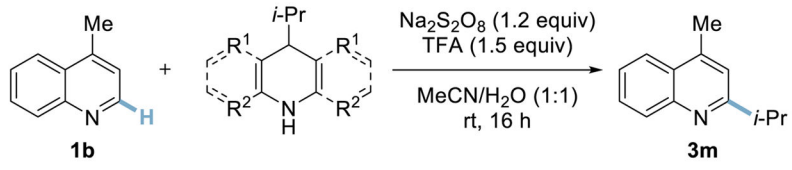
Scheme 1.

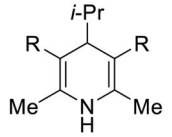
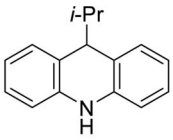
Circumnavigating acyl radicals from aldehydes via homolysis of DHPs.



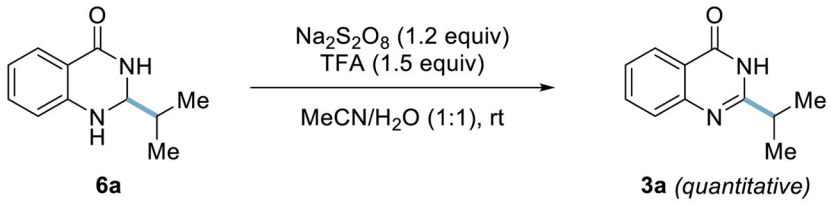
Scheme 2.

One-Pot C-H Alkylation of Heterocycles with in situ Generated DHP



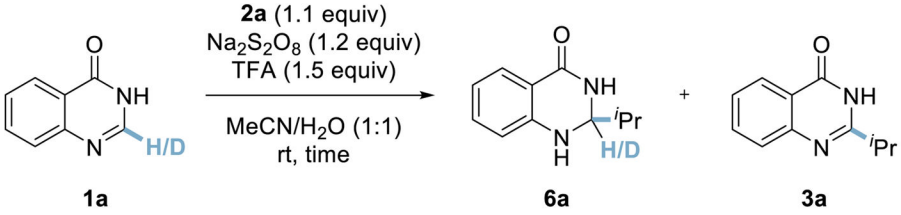
		3m (%)	A-value (R)[a]	E^{ox} (V)[b]
	R = CO_2Et; **2a**	78	1.20	1.05
	R = CO_2*i*-Pr; **2a-*i*Pr**	85	0.96	1.26
	R = CO_2*t*-Bu; **2a-*t*Bu**	5	--	1.21
	R = COMe; **2a-Ac**	50	1.17	0.99
	R = CN; **2a-CN**	5	0.17	1.34
	**2a-Acr**	*n.d.*	--	0.92

Scheme 3.
Influence of the DHP Backbone



Scheme 4.
Testing the Intermediacy of Dearomatized Intermediate 6a

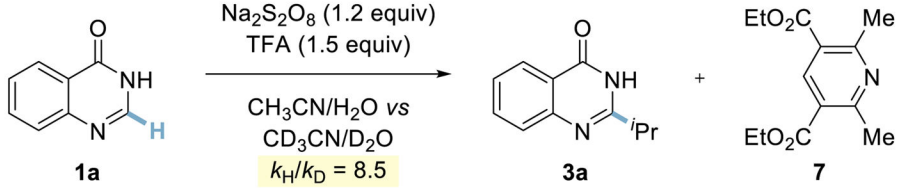
A. KIE (Intermolecular competition)



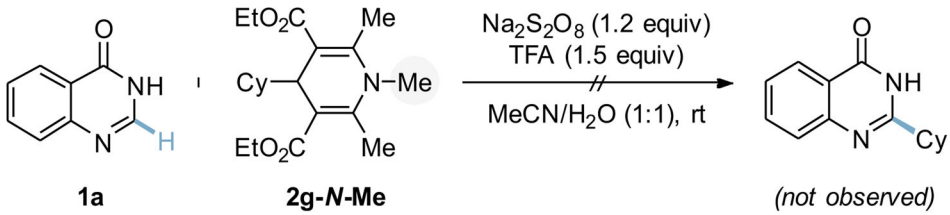
k_H/k_D (**1a** **6a**) = 0.69 (25 min)
k_H/k_D (**1a** **6a**) = 0.79 (70 min)

time (min)	1a	6a	3a
0	100% (50:50 *H/D*)	0%	0%
25	47% (59:41 *H/D*)	45% (60:40 *H/D*)	8%
70	18% (56:44 *H/D*)	47% (50:50 *H/D*)	21%

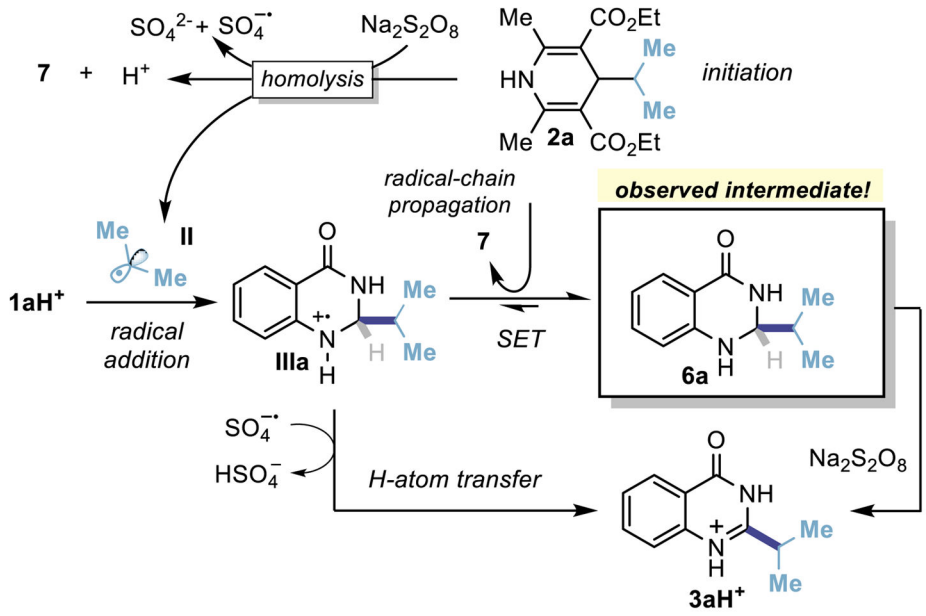
B. Solvent KIE



Scheme 5.
Kinetic Isotope Effect Studies



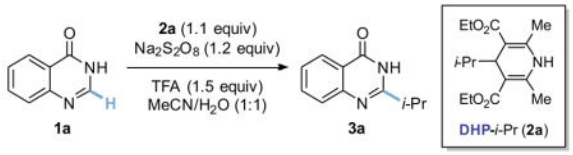
Scheme 6.
Influence of *N*-Substitution on the DHP Backbone



Scheme 7.
Putative reaction mechanism

Table 1

Optimization of the Reaction Conditions[a]



Entry	deviation from standard conditions	3 (%)[b]
1	none	98 (97)[c]
2	no $Na_2S_2O_8$ added	4
3	no TFA added	71
4	$K_2S_2O_8$ instead of $Na_2S_2O_8$	91
5	$(NH_4)_2S_2O_8$ instead of $Na_2S_2O_8$	88
6	*t*-BuOOH instead of $Na_2S_2O_8$	6
7	TCA instead of TFA	72
8	CSA instead of TFA	83
9	BF_3•OEt_2 instead of TFA	95
10	CH_2Cl_2/H_2O as solvent	13
11	CH_3CN as solvent	0
12	DMSO as solvent	59
13	$Na_2S_2O_8$ (20 mol %)	47[c] (25)[c,d]

[a]Conditions: **1a** (0.10 mmol, 1.0 equiv), **2a** (0.11 mmol, 1.1 equiv), oxidant (0.12 mmol, 1.2 equiv), additive (0.15 mmol, 1.5 equiv), solvent (1.0 mL, 0.1 M), 18 h, rt.

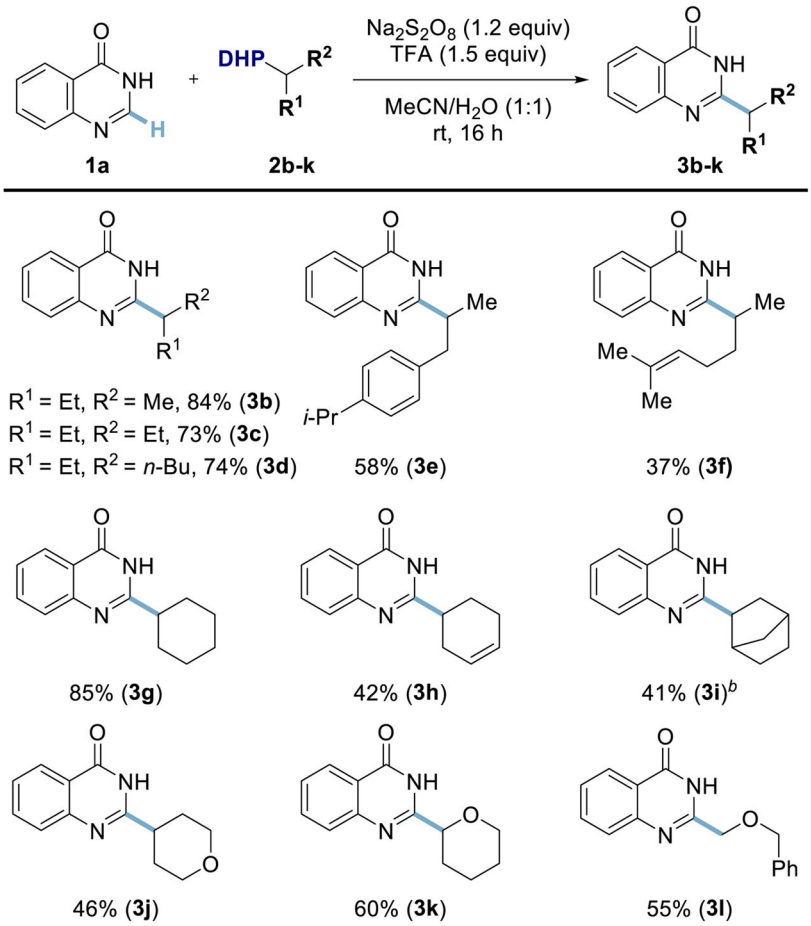
[b]HPLC yield using 4,4′-di-*tert*-butylbiphenyl as internal standard.

[c]Isolated yield.

[d]Yield of **6a**. TFA = trifluoroacetic acid. TCA = trichloroacetic acid. CSA = camphorsulfonic acid.

Table 2

Scope of 1,4-Dihydropyridines[a]

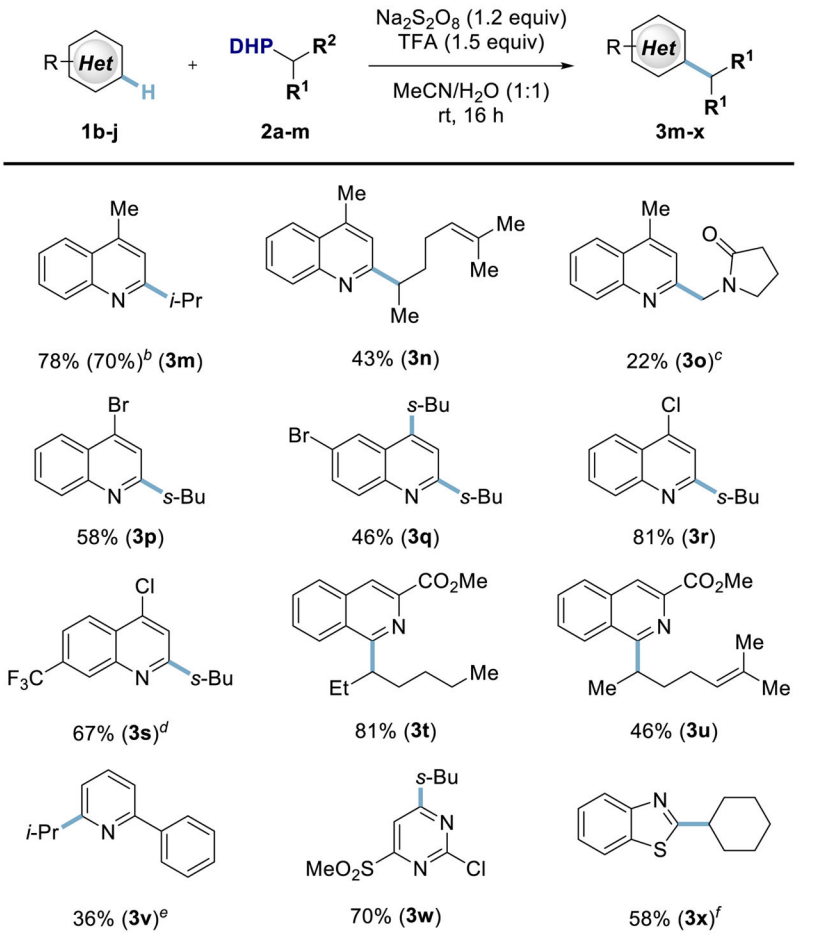


[a]As in Table 1 (entry 1), 0.50 mmol scale.

[b]>20:1 dr.

Table 3

Scope of Heteroarenes and Dihydropyiridines[a]



[a] As in Table 1 (entry 1), 0.50 mmol scale.

[b] No TFA added.

[c] **2n** (2.0 equiv), $Na_2S_2O_8$ (3.0 equiv).

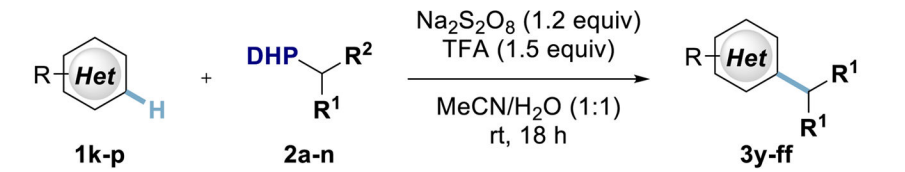
[d] **2b** (1.5 equiv), $Na_2S_2O_8$ (1.5 equiv).

[e] 36% yield of dialkylated product was obtained.

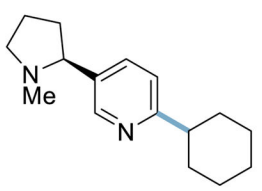
[f] $Na_2S_2O_8$ (2.2 equiv).

Table 4

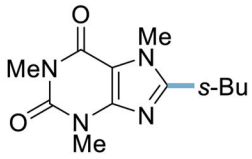
Late-Stage Alkylation of Natural Products and Drugs[a]



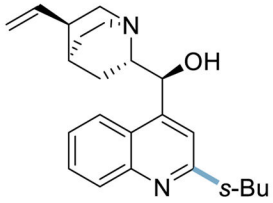
1k-p **2a-n** **3y-ff**



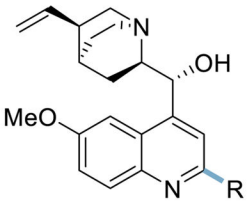
49% (**3y**)
from (–)-nicotine

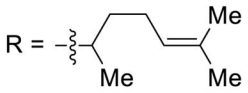


38% (**3z**)
from caffeine

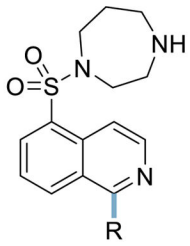


57% (**3aa**)[b]
from Cinchonine

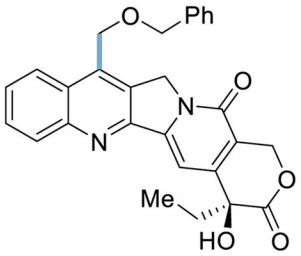




71% (**3bb**)[c]
R = Cy; 77% (**3cc**)
from Quinine



R = Cy; 84% (66%)[e] (**3dd**)[d]
R = CH_2OBn; 51% (**3ee**)[d]
from Fasudil·HCl



64% (**3ff**)[f]
from (+)-Camptothecin

[a] As in Table 1 (entry 1), 0.50 mmol scale.

[b] 1:1 dr.

[c] >20:1 dr.

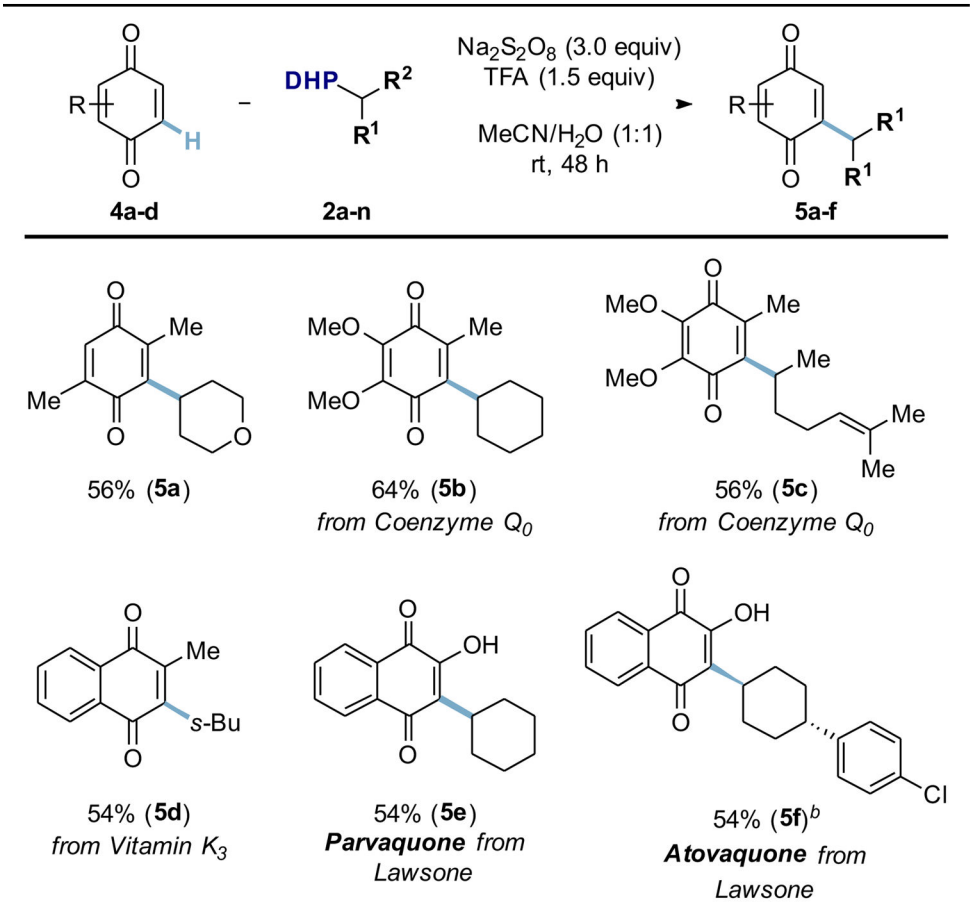
[d] **2g** or **2l** (1.5 equiv), $Na_2S_2O_8$ (1.5 equiv).

[e] No TFA added.

[f] **2l** (2.0 equiv), $Na_2S_2O_8$ (2.0 equiv), TFA (2.0 equiv).

Table 5

C-H Alkylation of *p*-Quinones[a]



56% (**5a**)

64% (**5b**) *from Coenzyme* Q_0

56% (**5c**) *from Coenzyme* Q_0

54% (**5d**) *from Vitamin* K_3

54% (**5e**) ***Parvaquone*** *from Lawsone*

54% (**5f**)[b] ***Atovaquone*** *from Lawsone*

[a] **4-** (0.50 mmol, 1.0 equiv), **2-** (1.00 mmol, 2.0 equiv), $Na_2S_2O_8$ (1.5 mmol, 3.0 equiv), TFA (0.75 mmol, 1.5 equiv), CH_3CN/H_2O (1:1 v/v) (5.0 mL, 0.1 M), 48 h, rt.

[b] 62:38 *cis/trans* ratio. >1:20 *cis/trans* ratio after acidic treatment.