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SHORT COMMUNICATION

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Benzoyl Peroxide Promoted Radical *ortho*-Alkylation of Nitrogen Heteroaromatics with Simple Alkanes and Alcohols

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Keywords: Ylides / Alkylation / Cross-coupling / Regioselectivity / Radicals

A catalytic amount of benzoyl peroxide (BPO)-initiated cross-dehydrogenative coupling reaction of *N*-iminopyridine ylides with simple alkanes and alcohols leads to the corresponding 2-alkylpyridines with high regioselectivity in moderate to good yields without an additional reduction step to remove the activated group.

Introduction

Pyridine moieties are key structural units and exist widely in a large number of natural products, functional materials, pharmaceuticals, and ligands.[1] As such, there has been significant interest in developing efficient methods for the synthesis of these molecular architectures. 2-Alkylpyridines are generally synthesized by C2 lithiation of pyridines, followed by alkylation.[2] Some other strategies involve the reaction of Grignard reagents with pyridine *N*-oxide.[3] Minisci and co-workers have made great efforts in the direct alkylation of pyridinium salts under acidic and oxidative conditions.[4] More recently, transition-metal-catalyzed selective C–H bond functionalization has attracted considerable attention for its outstanding advantages in atom efficiency and synthesis step efficiency. Bergman and Ellman recently reported a method[5] for *ortho*-alkylation of pyridines by using a Rh^{I}–phosphine complex catalyzed C–H bond addition to olefins. Then Guan and Hou have demonstrated that half-sandwich rare-earth dialkyl complexes in combination with $B(C_6F_5)_3$ can serve as an excellent catalyst for this similar transformation.[6] Moreover, Hiyama and co-workers developed a Ni/Lewis acid binary catalyst system for the selective C4 alkylation of pyridines.[7] In other cases, *ortho*-alkylation was achieved by activation of the pyridine as *N*-oxides or *N*-iminopyridinium ylides.[8–10] Although tremendous progress has been made in this area, some drawbacks still remain. First, in almost all previous reports, the use of expensive transition-metal catalyst systems limits their commercial use. Besides, most of them employed preactivated alkanes as the coupling partner.

On the other hand, a method to generate C–C bonds directly from two different C–H bonds in the presence of an oxidizing reagent through an overall cross-dehydrogenative coupling (CDC) has attracted significant interest.[11] Cui described the direct Pd-catalyzed C-2 alkylation of quinoline *N*-oxides (Scheme 1, a).[12] Li and co-workers also have established Pd-catalyzed coupling of *N*-heterocycles with simple alcohols, and even coupling with simple alkanes without transition metals (Scheme 1, b,c,e).[13] Antonchick and Burgmann have also developed an efficient method to afford alkylpyridines by using phenyliodine bis(trifluoroacetate) (PIFA) and NaN_3 as the initiator (Scheme 1, d).[14] However, the regioselectivity is still an intractable problem of the reaction. Inspired by the research mentioned above and as a continuation of our studies on C–H functionalization of *N*-iminopyridinium ylides,[15] we focused on the development of methods for CDC with simple alkanes.

Results and Discussion

On the basis of the reports by Li and co-workers,[13] we employed *N*-iminopyridinium ylide **1a** as the substrate and studied its reaction with cyclohexane **2a** (Table 1). To our surprise, the reaction was promoted by using *t*BuOO*t*Bu (DTBP; 2 equiv.) as the initiator to afford mono-alkylated and bis-alkylated products without the benzamide group, albeit in a total yield of 54% (Table 1, Entry 1). Meanwhile, benzamide as the N–N bond decomposition product was also detected. Increasing the amount of DTBP (2.0–5.0 equiv.) resulted in **3a′** becoming the major product (Table 1, Entry 2) whereas a decrease of DTBP (2.0–0.4 equiv.) could slightly improve the regioselectivity of the reaction (Table 1, Entries 3–4). Further decreasing the amount of DTBP (0.4–0.3 equiv.) resulted in a lower yield (Table 1, Entry 5). The selectivity was not affected when the coupling reaction occurred at 120 °C for 24 h (Table 1, Entry 6) and the reaction could not be initiated at 90 °C (Table 1, Entry 7). The reaction performed with more rea-

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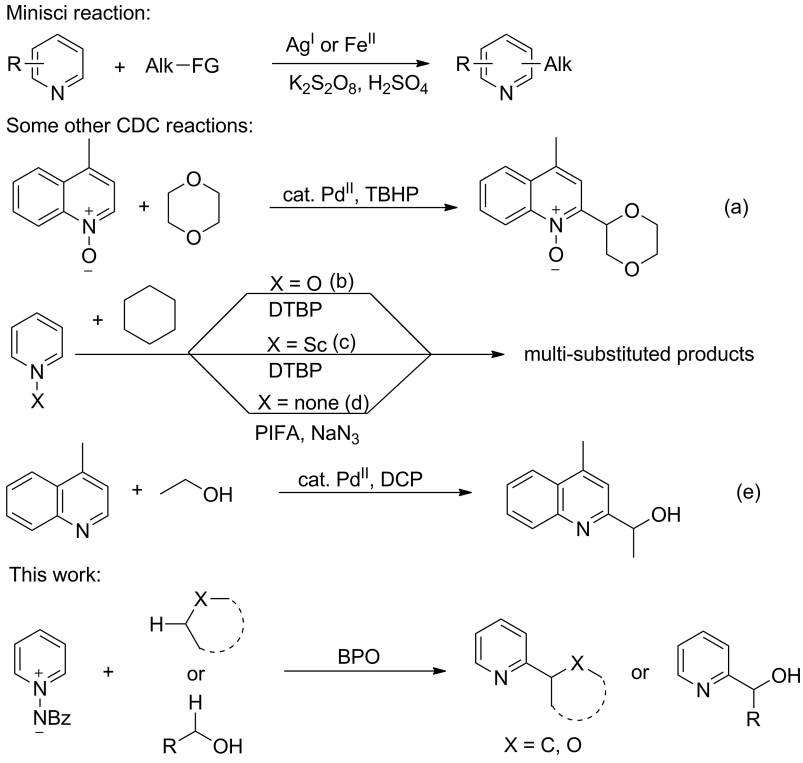
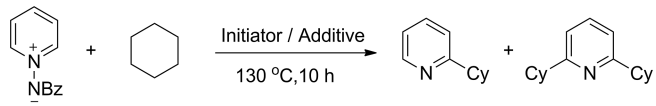


Scheme 1. Representative examples of alkylation.

sonable efficiency and selectivity when excessive cyclohexane was used (Table 1, Entries 8–11). Using 36.8 mmol (4 mL) cyclohexane increased the yield to 69% (Table 1, Entry 10) and further increasing the amount to 55.2 mmol (6 mL) (Table 1, Entry 11) provided only a marginal improvement, which did not justify the large excess. In light of recent advances in this area,[11] evaluation with other radical initiators identified benzoyl peroxide (BPO) as the most efficient initiator (Table 1, Entries 13–20). Moreover, the yield dramatically decreased when tetra-*n*-butylammonium bromide (TBAB) or H_2O were used as an additive.[12] The optimized reaction conditions were identified as 0.2 mmol **1a** in the presence of 0.3 equiv. BPO in 4 mL of cyclohexane at 130 °C for 10 h (Table 1, Entry 19). It is worth noting that this transformation was facile and practical as it required only a catalytic amount of radical initiator, but with a high selectivity.

With the optimized conditions in hand, various pyridinium ylides, alkanes and alcohols were investigated (Table 2). 3-Methyl and C4-substituted *N*-iminopyridinium could work smoothly to afford only monoalkylated product (**3e**–**3g**). However, with a substituent at the 2-position, C4-alkylated products were produced as byproducts unexpectedly (**3b**–**3d**). Interestingly, under standard conditions, only a trace amount of the alkylation product was observed when there was an electron-withdrawing group at the 4-position of pyridine. When an excess of BPO (2 equiv.) was added, the reaction could afford bisalkylated product (**3h**, **3i**) as the major product after stirring for 48 h. Moreover, *N*-iminoquinolinium ylide successfully formed the mono- (**3j**) and bisalkylated product (2,6-dicyclohexylquinoline),

Table 1. Optimization Studies for the cross-coupling reaction.[a]

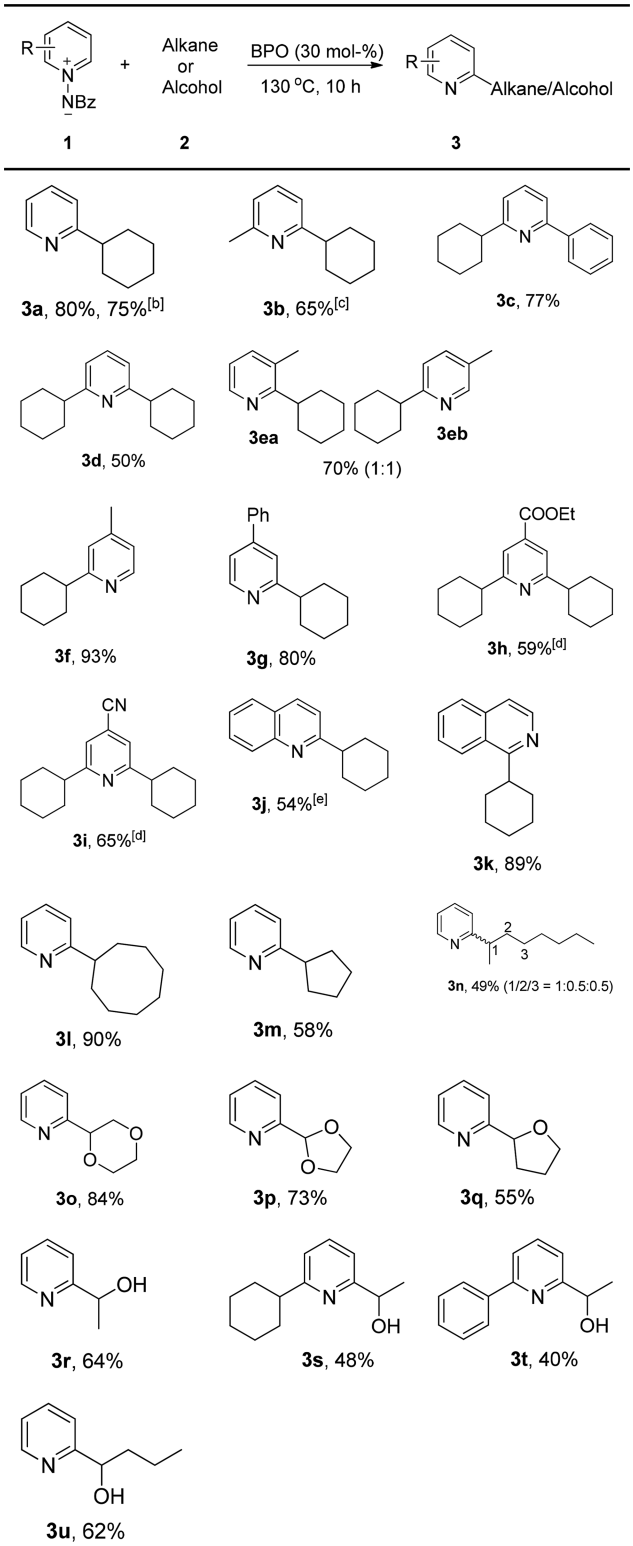


1a **2a** **3a** **3a'**

Entry	**2a** [mL]	Initiator [equiv.]	Yield [%][b] (**3a**/**3a′**)
1	1 (9.2 mmol)	DTBP (2.0)	34:20
2	1	DTBP (5.0)	25:30
3	1	DTBP (1.0)	38:18
4	1	DTBP (0.4)	45:9
5	1	DTBP (0.3)	37:N.D.
6[c]	1	DTBP (0.4)	38:17
7[d]	1	DTBP (0.4)	N.D.
8	2 (18.4 mmol)	DTBP (0.4)	50:10
9	3 (27.6 mmol)	DTBP (0.4)	65:trace
10	4 (36.8 mmol)	DTBP (0.4)	69:trace
11	6 (55.2 mmol)	DTBP (0.4)	70:trace
12	4	TBHP[e] (0.4)	41:trace
13	4	DCP (0.4)	43:trace
14	4	AIBN (0.4)	29:trace
15	4	I_2 (2)	N.D.
16	4	$K_2S_2O_8$ (2)	Trace
17	4	TBPB (0.4)	46:trace
18	4	BPO[f] (0.4)	70:5
19	4	BPO (0.3)	80:N.D.
20	4	DTBP (0.3)	43:N.D.
21	4	BPO (0.3)/H_2O (0.5 mL)	35:N.D.
22	4	BPO (0.3)/TBAB (1)	60:trace

[a] Conditions: *N*-iminopyridinium ylide **1a** (0.2 mmol), cyclohexane **2a** (1–6 mL), initiator (0.3–5 equiv.), 10 h, under air. [b] Isolated yield. [c] Reaction was carried out at 120 °C for 24 h. [d] Reaction was carried out at 90 °C for 24 h. [e] 70% TBHP in H_2O. [f] BPO was used after dehydration and recrystallization.

Table 2. Scope of *N*-iminopyrinium ylides and simple alkanes or alcohols as coupling partners.[a]

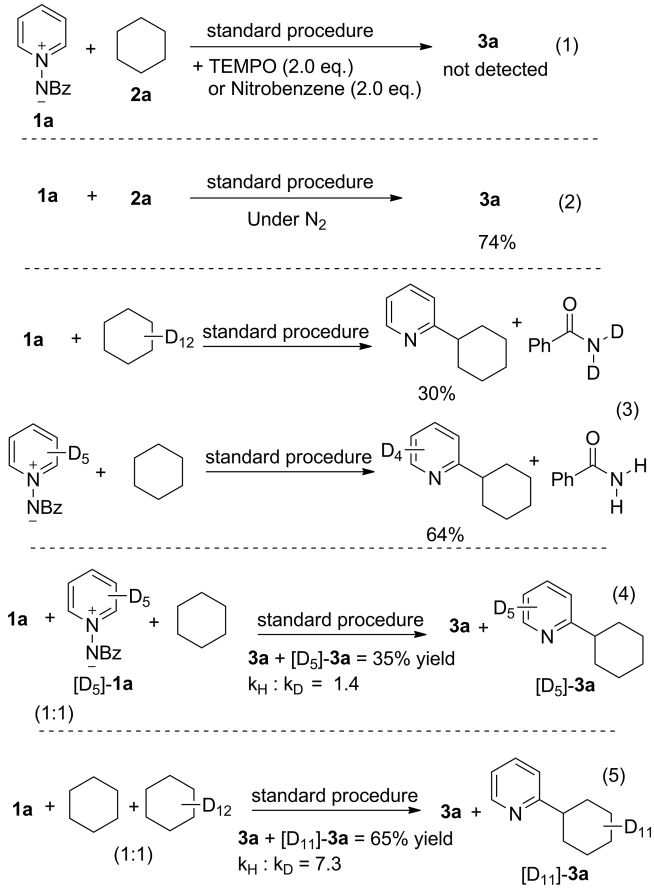


[a] Conditions: *N*-iminopyridinium ylide **1** (0.2 mmol), alkane **2a** (4 mL, 36.8 mmol), BPO (0.06 mmol, 30 mol-%), 10 h, under air. [b] 2.0 mmol scale. Isolated yield. [c] 15% C4-alkylated product was isolated additionally. [d] Reactions were performed by using 0.4 mmol (2.0 equiv.) BPO and stirring for 48 h. [e] Second addition of BPO (0.06 mmol) was added after stirring for 10 h. 16% bisalkylated product was isolated additionally.

presumably because of its high activity, in a moderate yield whereas *N*-iminoisoquinolinium ylide (**3k**) gave *ortho*-alkylated product with a high yield.

Subsequently, cyclooctane was also successfully employed for this reaction in 90% yield (**3l**) whereas cyclopentane (**3m**) showed a lower efficiency. Then, a linear substrate, heptane was examined and the reaction proceeded well and gave the desired products in a total yield of 49%, however, three isomers (**3na**–**3nc**) were obtained in a ratio of 1:0.5:0.5, and **3nb** and **3nc** could hardly be isolated. Notably, this reaction could also be applied to oxacycloalkanes (**3o**–**3q**) and even simple alcohols (**3r**–**3u**) could provide the corresponding *ortho*-alkylated product. In all cases except for **3h**, **3i** and **3j**, dialkylated products were not detected.

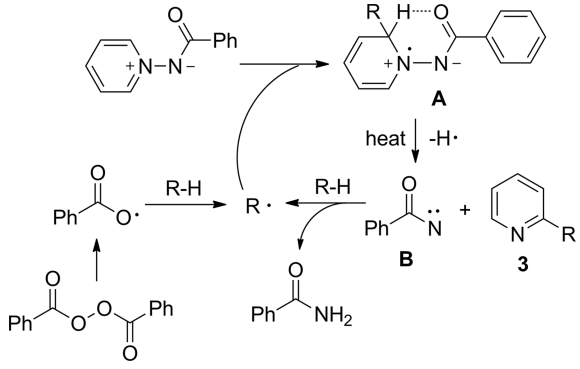
More experiments were conducted to gain some insight into this reaction. The addition of 2.0 equiv. TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxide) or 2.0 equiv. nitrobenzene inhibited the reaction [Scheme 2, Equation (1)]. A similar yield was obtained when the reaction was conducted under N_2, which indicated that O_2 did not participate [Equation (2)]. Additionally, isotopic labelling experiments employing *N*-iminopyridinium ylide and [D_{12}]-cyclohexane resulted in deuteration of the amino group in benzoic amide; with [D_5]*N*-iminopyridinium ylide alone, deuteration at this position was not observed [Equation (3)]. These results clearly pointed to cyclohexane as the source for



Scheme 2. Preliminary mechanism study.

amino protons in benzoic amide, which was generated after N–N bond fission. Furthermore, the intermolecular kinetic isotopic experiment confirmed the k_H/k_D for the arene C–H bond was 1.4 and k_H/k_D for alkane C–H was 7.3, indicating the cleavage of sp^3 C–H bond rather than the former sp^2 C–H bond was involved as the rate-determining step for this transformation [Equation (4), (5)].

On the basis of these experimental results, a proposed mechanism is illustrated in Scheme 3. First, benzoyl peroxide can be homolytically cleaved to form two effective initiating species, benzoxy radical PhCOO·, which can abstract a hydrogen atom from the alkane to form benzoic acid and an alkyl radical R· to initiate chain reactions. The alkyl radical R· is readily trapped by *N*-iminopyridinium ylide to form radical cation **A**, which releases a hydrogen atom to give an intermediate **B**. Subsequently, at elevated temperature, **A** is not stable and decomposes to give the desired product **3** and nitrene specie **B**,[16] which can abstract two hydrogen atoms from the alkane to form benzoic amide and alkyl radical R·.



Scheme 3. Proposed mechanism.

Conclusions

In summary we have developed a BPO-initiated cross-dehydrogenative coupling of *N*-iminopyridinium ylides and simple alkanes and alcohols. A catalytic amount of BPO is consumed in this metal-free and open-air system. Besides, this direct C–H bond alkylation transformation affords the corresponding C2-alkylated products with high regioselectivity in moderate to excellent yields without an additional reduction to remove the activated group. This finding offers a new, simple and mild method for synthesizing the alkylated pyridine derivatives.

Experimental Section

Starting Materials: *N*-iminopyridinium ylides were synthesized by a method according to literature procedures as follows.[17] Pyridine (0.1 mL, 1.24 mmol) and *O*-(2,4-dinitrophenyl)hydroxylamine (272 mg, 1.36 mmol) were added to H_2O/THF (1:1 mixture, 1.0 mL). The reaction flask was sealed with a septum, and the resulting suspension was stirred at 40 °C for 16 h. During this period, the reaction mixture turned dark red. The reaction was poured into aqueous NaOH (2.5 N, 6 mL) at room temperature and stirred for 5 min, and then benzoyl chloride (0.215 mL, 1.84 mmol) was added in one portion. After 5 h, the reaction was diluted with H_2O (5 mL), and extracted with $CHCl_3$ (3 × 10 mL). The combined organic phases were washed with NaOH (2.5 N, 5 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure affording the *N*-iminopyridinium ylide.

General Procedure for the Coupling: An oven-dried reaction vessel was charged with *N*-iminopyridinium ylide (**1**, 0.2 mmol), alkane or alcohol (**2**, 4 mL) and BPO (0.06 mmol, 30 mol-%). Then the reaction vessel was sealed and the resulting solution was stirred at 130 °C for 10 h. After cooling to room temperature, the volatiles were removed in vacuo and the residue was purified by column chromatography to give the pure product as a colorless oil.

Acknowledgments

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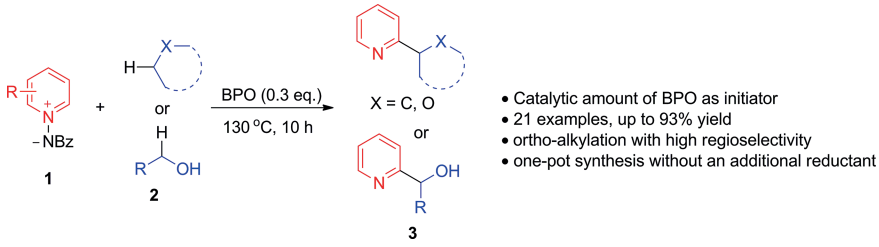
Radical Arylation



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