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Synthesis of benzyl esters from the commercially available alcohols catalyzed by TBAI via C(sp³)-H bond functionalization†

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A direct esterification of alcohols catalyzed by TBAI via C(sp³)-H bond functionalization was achieved under mild and clean conditions. A series of benzyl esters were obtained in good to excellent yields via the C(sp³)-H bond functionalization of alkyl-substituted azaarenes.

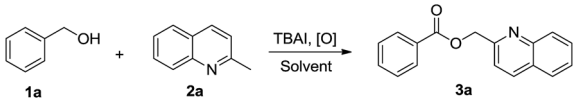
Alkyl-substituted azaarenes, as key structural skeletal frameworks of many natural products and pharmaceuticals, have attracted considerable interest because of their important biologically active properties.¹ One of the most efficient methods for preparing alkyl-substituted azaarenes is direct C(sp³)-H functionalization of the alkyl-substituted azaarenes. For example, the direct addition of C(sp³)-H bond of the alkyl-substituted azaarenes to the unsaturated chemical bonds was first independently realized in 2010 by Huang and co-workers.^{2f} At present, esterification catalyzed by transition metals,² Bronsted acids,³ and microwave⁴ has been explored. Even in some cases, these reactions can also be realized without any catalyst.^{4d,e} However, versatile and practical methods for the synthesis of alkyl-substituted azaarenes are still desirable.

On the other hand, Bu₄Ni has received extensive attention in organic synthesis because it can overcome the drawbacks of the expensive, poisonous, and air-sensitive properties of metals or organometallics.⁵ In the presence of an oxidant (H₂O₂, tBuOOH, etc.), Bu₄Ni has been explored as an efficient catalyst for the formation of C-O,⁶ C-N,⁷ and C-C⁸ bonds. For example, the synthesis of α-ketoamides promoted by TBHP/I₂ was described by the Wang group.⁹ In 2014, Wan and his co-workers reported the synthesis of substituted pyrazoles using TBAI as a catalyst and TBHP as an oxidant.¹⁰ Tetrabutylammonium iodide-catalyzed phosphorylation of benzyl C-H bonds via a cross-dehydrogenative coupling (CDC) reaction was also realized by the Tang group.¹¹ In line with our interest in green chemistry,¹² herein, we report a TBAI/TBHP-promoted synthesis of benzyl esters from the commercially available alcohols via C(sp³)-H bond functionalization under mild reaction conditions.

At the beginning of our investigation, optimization of the reaction conditions was focused on a variety of reaction parameters using the model reaction of phenylmethanol (**1a**)

with 2-methylquinoline (**2a**). As shown in Table 1, when H₂O₂ was chosen as the oxidant for the model reaction, only a 20% yield of the desired product was achieved (Table 1, entry 1). Although O₂ was also used as the oxidant for this reaction, the yield of the product was very low (Table 1, entry 2). However, the model reaction smoothly proceeded in the presence of *tert*-butyl hydroperoxide (TBHP) and the corresponding product was isolated in 86% yield (Table 1, entry 3). With respect to the catalyst, a very low yield of ester **3a** was formed when TBAI was replaced by KI, I₂O₅, or I₂ (Table 1, entry 4–6). The effect of the solvent on the model reaction was also investigated and it was found that water was the most effective solvent. Moreover, a lower yield was observed when the reaction was conducted in methanol (Table 1, entry 7) or acetonitrile (Table 1, entry 8). The optimized reaction conditions for the model reaction were TBAI (20 mol%) and TBHP (5.0 equiv.) in water at 90 °C for 12 h.

Table 1 Acyloxylation of 2-methylquinoline with phenylmethanol^a

			
Entry	Catalyst	Oxidant	Yield (%)
1	TBAI	H ₂ O ₂	20
2	TBAI	O ₂	Trace
3	TBAI	TBHP	86
4	KI	TBHP	16
5	I ₂	TBHP	Trace
6	I ₂ O ₅	TBHP	Trace
7 ^b	TBAI	TBHP	30
8 ^c	TBAI	TBHP	7

^a Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), catalyst (0.2 mmol), oxidant (4.0 mmol), water (2 mL), 90 °C and 12 h; isolated yield. ^b CH₃CN was used as the solvent. ^c CH₃OH was used as the solvent.

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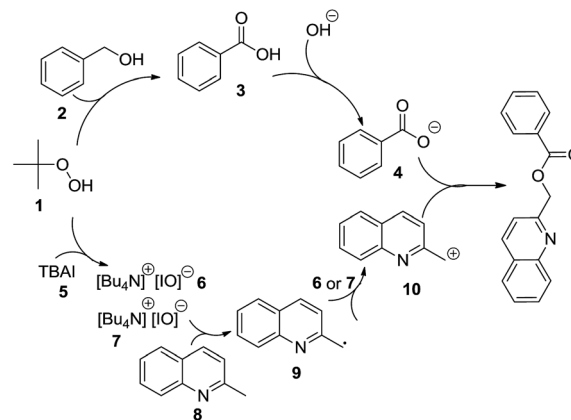


With the optimized reaction conditions in hand, the scope of the substituted alkyl azaarenes and alcohols was investigated. The results are shown in Table 2. A variety of benzyl alcohols bearing substituents on the benzene ring were examined for the synthesis of benzyl esters *via* the C(sp³)–H bond functionalization of 2-alkyl-substituted azaarenes.

The results indicated that a variety of functional groups, including electron-donating (Table 2, **3g**, **3e**, **3t**, and **3v**) and electron-withdrawing (Table 2, **3b**, **3c**, **3h**, **3i**, **3j**, **3k**, and **3l**) groups were tolerated and the reactions produced the corresponding products in good to excellent yields (Table 2, **3a–w**). Note that 2-naphthalene methanol, 1-naphthalene methanol, and 2-thiophenemethanol also smoothly reacted to generate their corresponding products in 70–95% yield (Table 2, **3m**, **3n**, **3o**, and **3s**). The present reaction conditions were also suitable for the reaction of benzyl alcohols with other alkyl-substituted azaarenes. Various functional groups, such as fluoro, chloro, bromo, and methyl (Table 2, **3d**, **3g**, **3r**, and **3u**) were well tolerated under the reaction conditions. Finally, the reaction of 2-methylquinoxaline with phenylmethanol generated the desired product in 68% yield (Table 2, **3w**).

Table 2 Esterification of 2-methyl azaarenes with various alcohols^a

^a Reaction conditions: alcohol (1.0 mmol), 2-alkyl azaarene (0.5 mmol), catalyst (0.2 mmol), oxidant (4.0 mmol), water (2 mL), 90 °C and 12 h; isolated yield.



Scheme 1 Proposed mechanism.

According to a report,⁵ a plausible mechanism was proposed for this reaction (Scheme 1). The first step involves the reaction between TBHP and TBAI to generate the intermediate ammonium hypoiodite **6** or iodite **7**. Then, hypoiodite **6** or iodite **7** induces the production of benzyl radical **9** *via* the homolysis of a benzyl C–H bond. The benzyl radical could be further oxidized to the benzyl cation **10**. Moreover, the oxidation of phenylmethanol **2** by TBHP occurred to form benzoic acid **3**; after deprotonation, the benzoate anion **4** reacts with the benzyl cation **10** to provide the final product.

In summary, a direct synthetic method for the preparation of benzyl esters *via* TBAI-catalyzed C(sp³)–H bond functionalization has been reported. The reactions generate the corresponding products in good yields in most of the cases under simple and mild reaction conditions. This organic TBAI-catalyzed one-step reaction provides a new synthetic protocol for the synthesis of 2-alkyl azaarene derivatives. Further investigations on the detailed reaction mechanism and application of this methodology are in progress.

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