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Direct sp^3 C–H bond arylation, alkylation, and amidation of tetrahydroisoquinolines mediated by hypervalent iodine(III) under mild conditions†

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We have developed a method for the sp^3 C–H bond functionalization of tetrahydroisoquinolines (THIQs) mediated by [bis(trifluoroacetoxy)iodo]benzene (PIFA). The treatment of the THIQs with various nucleophiles in the presence of PIFA in a green solvent alternative gave the coupled products, with a C–C, C–N, or quaternary carbon center in high yields.

Direct sp^3 C–H bond activation such as a cross-dehydrogenative-coupling (CDC) reaction[1] is a widely used and powerful method for functionalizing natural products and developing new drug candidates in current organic synthesis. In particular, the selective sp^3 C–H bond arylation of tetrahydroisoquinolines (THIQs) is one of the major current challenges due to their biological activities.[2] Over the recent decades, efficient one-step methods for C–C, C–N, C–O *etc*. bond formation have been reported. However, most of these methods are for the indolation of THIQs,[3] and methods for the arylations are limited to a few articles.[4] Furthermore, most of these methods use heavy metals, such as Fe, Cu, or Ir, and required high temperatures and long reaction times to proceed to completion. We previously reported a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-mediated sp^3 C–H bond arylation of THIQs with aryl-MgBr in chlorobenzene (PhCl) under mild conditions.[5] This reaction has numerous advantages, including the absence of heavy metals, short reaction times (3 hours), and mild reaction temperatures (0 to 20 °C). However, the toxicity of DDQ[6] and the potential for HCN liberation cannot be ignored. Furthermore, PhCl also has toxicity issues regarding human health and the environment. Hypervalent iodine(III) has been widely recognized as a useful alternative oxidant in place of toxic heavy-metal oxidants and toxic organic oxidants.[7] During our recent investigations, we found that [bis(trifluoroacetoxy)iodo]benzene (PIFA) was a suitable oxidant, to replace DDQ, for the sp^3 C–H bond arylation, alkylation, and amidation of THIQs. Herein, we report the direct sp^3 C–H bond functionalization (arylation, alkylation, and amidation) of THIQs, to form novel C–C bonds, C–N bonds, and quaternary carbon centers, mediated by hypervalent iodine(III), under mild conditions.

2-MeTHF was initially chosen as the solvent, due to its wide usage in industry as a green solvent.[8] As a result of the careful scrutiny of a number of reaction parameters and conditions, the treatment of *N*-*p*-methoxyphenyl (*N*-PMP)-THIQ[4d] with 2.0 equiv. of PhMgBr–THF in the presence of 1.0 equiv. of PIFA in 2-MeTHF gave the corresponding coupled product **1** with the optimum yield (entry 1 of Table 1; 99% yield). The *N*-PMP could be easily removed by using ammonium cerium(IV) nitrate (CAN).[9] Under the optimum conditions without PIFA, only the starting material, *N*-PMP-THIQ, was recovered in a quantitative yield (entry 2). From the economic and environmental viewpoints, the recycling and catalytic utilization of PIFA has made significant advances in various fields of chemistry. Additionally, the formation of PIFA from phenyl iodide (PhI) using peroxides is well known.[10] We attempted to carry out the reaction using catalytic PIFA in the presence of an external oxidant. Unfortunately, these attempts only resulted in a very low yield of the coupled product **1** (entries 3–6). The use of alternative hypervalent iodine(III) reagents also resulted in low to moderate yields of **1** (entries 7–9). High yields were obtained when PhMgCl, PhMgI, and Ph_2Zn were used instead of PhMgBr (entries 10–11 and 15). Furthermore, an Et_2O solution of PhMgBr could be employed in place of a THF solution, without a loss in the yield (entry 12).[11] On the other hand, PhZnBr and PhZnI gave only trace amounts of **1** under the same conditions (entries 13–14), whilst PhLi resulted in no product formation at all (entry 16). The sp^3 C–H bond arylation proceeded well in a variety of solvents (entries 17–23), with the exception of DMF, which gave only 3% of **1** (entry 24). From a the toxicity, safety and environmental

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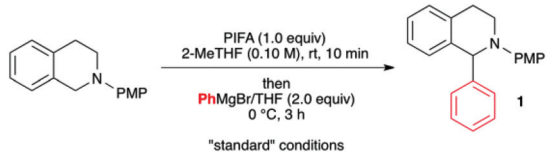
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data for all compounds, and copies of spectra. See DOI: 10.1039/c3ob42354a

Table 1 PIFA-mediated sp^3 C–H bond arylation of *N*-PMP-THIQ

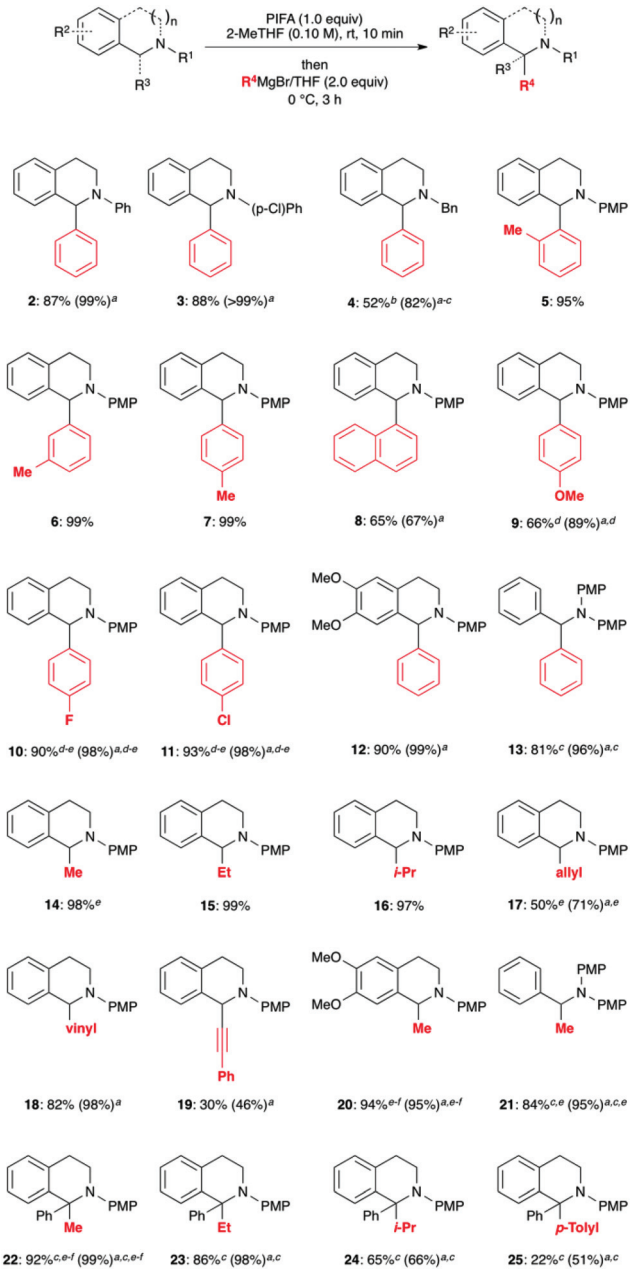


Entry	Variation from the "standard" conditions	Yield of **1**[a] (%)
1	None	>99 (99)[b]
2	No PIFA	0
3[c]	PIFA (20 mol%), Oxone (1.0 equiv.)	20
4[c]	PIFA (20 mol%), *m*CPBA (1.0 equiv.)	5
5[c]	PIFA (20 mol%), H_2O_2·urea (1.0 equiv.)	13
6[d]	PIFA (20 mol%), $K_2S_2O_8$ (1.0 equiv.)	31
7	PIDA,[e] instead of PIFA	12
8	PFPIFA,[f] instead of PIFA	61
9	C_3F_7(Ph)IOTf	11
10	PhMgCl–THF, instead of PhMgBr–THF	>99
11	PhMgI–THF, instead of PhMgBr–THF	>99
12	PhMgBr–Et_2O, instead of PhMgBr–THF	>99
13	PhZnBr–THF, instead of PhMgBr–THF	5
14	PhZnI–THF, instead of PhMgBr–THF	5
15	Ph_2Zn, instead of PhMgBr–THF	88
16	PhLi–Bu_2O, instead of PhMgBr–THF	0
17	PhCl, instead of 2-MeTHF	>99
18	PhMe, instead of 2-MeTHF	83
19	DCE, instead of 2-MeTHF	>99
20	THF, instead of 2-MeTHF	83
21	TBME, instead of 2-MeTHF	90
22	CPME, instead of 2-MeTHF	91
23	MeCN, instead of 2-MeTHF	>99
24	DMF, instead of 2-MeTHF	3

[a] The yield was determined by ^{1}H-NMR analysis *versus* a calibrated 1,4-bis(trifluoromethyl)benzene as an internal standard. [b] Isolated yield. [c] The oxidation using PIFA (20 mol%) was carried out at rt for 2 h. [d] The oxidation using PIFA (20 mol%) was carried out at rt for 24 h. [e] PIDA = [bis(acetoxy)iodo]benzene. [f] PFPIFA = [bis(trifluoroacetoxy)-iodo]pentafluorobenzene.

aspects, this method is especially valuable as the reactions proceeded well in common green solvent alternatives, such as 2-MeTHF[8] and CPME,[12] without the need for heavy metals.

On the basis of these findings, we next examined the direct sp^3 C–H bond arylation and alkylation of THIQ derivatives with various aryl- and alkyl-Grignard reagents, as representative C–C coupling partners (Scheme 1). An array of THIQs, bearing different aryl and benzyl groups, were found to undergo the desired transformation to give the corresponding coupled products **2–4** in good yields. Unfortunately, the coupling reaction between PhMgBr and THIQs bearing several protection groups, such as Ac-, Cbz-, and the Boc-group was not accomplished, which is because these THIQ derivatives are not oxidized by PIFA. Aryl-MgBr bearing *ortho*-, *meta*-, and *para*-substituents coupled successfully with *N*-PMP-THIQ, to give the corresponding coupled products **5–7** in excellent yields. When the sterically hindered 2-naphthyl-MgBr was used, the coupling reaction fortunately proceeded in a good yield. *N*-PMP-THIQ coupled smoothly with both electron-rich and electron-deficient aryl-MgBr species, giving the corresponding coupled products **9–11** in moderate to excellent yields. Finally,



Scheme 1 PIFA-mediated sp^3 C–H bond arylation and alkylation of THIQ derivatives. [a] In DCE instead of 2-MeTHF. [b] The oxidation using PIFA was carried out at 80 °C. [c] The oxidation using PIFA was carried out for 30 min. [d] The nucleophilic addition using R^4MgBr was carried out at 20 °C. [e] R^4MgBr–Et_2O was used. [f] R^4MgBr (3.0 equiv.) was used.

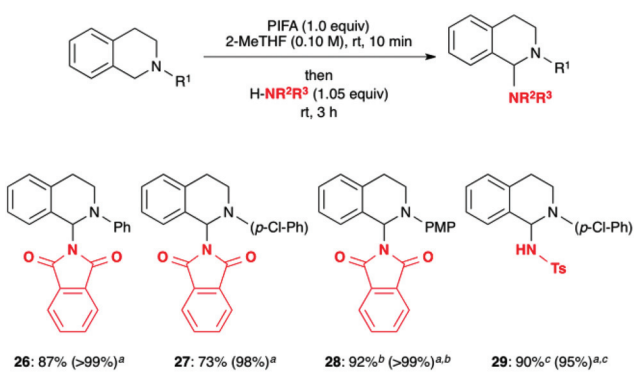
N-PMP-THIQ bearing methoxy substituents and the acyclic benzylamine were found to react successfully with PhMgBr and afforded the corresponding coupled products **12** and **13**, respectively, in high yields. The optimized system was then applied to the sp^3 C–H bond alkylation of *N*-PMP-THIQ derivatives and acyclic benzylamine, with a wide range of alkyl Grignard reagents. The alkylation of the amines using MeMgBr, EtMgBr, *i*-PrMgBr, and vinyl-MgBr afforded the corresponding coupled products **14–16**, **18**, and **20–21** in

75–99% yields. Attempts to use allyl-MgBr and phenylethynyl-MgBr as the nucleophile gave the corresponding coupled products **17** and **19**, respectively, in significantly lower yields.

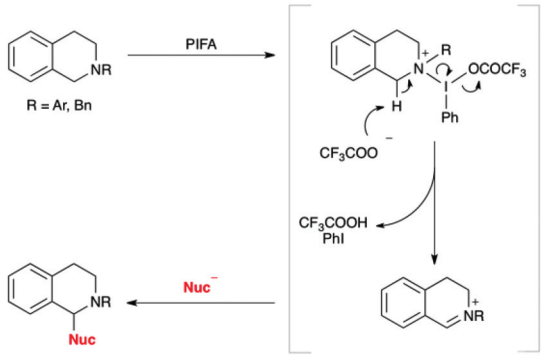
Furthermore, the use of a more bulky nucleophile, *t*-BuMgBr, resulted in a very low yield (9%) of the desired product. During these investigations, we successfully achieved the construction of an all-carbon quaternary center at the C-1 position of *N*-PMP-THIQ. When MeMgBr, EtMgBr, and *i*-PrMgBr were coupled with **1**, the corresponding coupled products **22–24** were afforded in excellent yields. Disappointingly, the use of *p*-TolMgBr as the nucleophile afforded the desired coupled product **25** in a low yield using 2-MeTHF. Fortunately, the yield of **25** could be increased by using DCE as the solvent (51% yield). These results are the first examples of forming a quaternary carbon center at the C-1 position of THIQ derivatives using a direct sp^3 C–H bond arylation and alkylation.

The synthesis of THIQ derivatives with a N–C–N moiety is quite difficult, due to the stability of the aminal unit. Only one method for the intermolecular sp^3 C–H bond amidation has been reported by Prabhu *et al.*[4h] Their approach is quite interesting and enabled the formation of C–C, C–N, C–O, C–P bonds formations at the C-1 position of THIQ, using catalytic iodine under aerobic conditions. However, the aminal products were not isolated in a high purity. Therefore, we attempted the direct sp^3 C–H bond amidation of THIQ derivatives using our method, to synthesize the corresponding aminals in high purity (Scheme 2).

N-Ph-THIQ was reacted with 1.05 equiv. of phthalimide in the presence of 1.0 equiv. of PIFA at room temperature. After completion, the reaction mixture was purified by flash chromatography using alumina and the corresponding coupled product **26** was isolated in an 87% yield with high purity. The method was also applied to the direct sp^3 C–H bond amidation of *N*-(*p*-Cl–Ph)-THIQ with phthalimide, affording product **27** in a high yield. Unfortunately, we could not purify the coupling products **28** (of *N*-PMP-THIQ with phthalimide) and **29** (of *N*-(*p*-Cl–Ph)-THIQ with *p*-toluenesulfonamide), due to their instability on the neutral silica gel and alumina.



Scheme 2 PIFA-mediated sp^3 C–H bond amidation of THIQ derivatives. [a] In DCE instead of 2-MeTHF. [b] The yield was determined by ^{1}H-NMR analysis *versus* a calibrated dimethyl sulfoxide as an internal standard. [c] The yield was determined by ^{1}H-NMR analysis *versus* a calibrated 1,4-bis(trifluoromethyl)benzene as an internal standard.



Scheme 3 Proposed mechanism of PIFA-mediated sp^3 C–H bond functionalization.

The proposed mechanism for the PIFA-mediated sp^3 C–H bond arylation, alkylation, and amidation is illustrated in Scheme 3. An ammonium cation is generated by a nucleophilic substitution reaction of THIQ to PIFA. The α-proton of the ammonium cation is deprotonated, forming an iminium cation, by the trifluoroacetate ion (CF_3COO^-). Finally, the iminium cation couples to Grignard reagent or amide, giving the desired C–C or C–N coupled product.

In conclusion, we have developed a PIFA-mediated, one-step method for sp^3 C–H bond arylation, alkylation, and amidation at the C-1 position of a wide range of THIQ derivatives mediated by PIFA under mild conditions. This current method has advantages over the previous methods as it avoids the use of heavy metals and toxic organic oxidants, and proceeds successfully in green solvent alternatives, under mild conditions. Further studies into the scope, mechanism, and applications of this novel reaction, as well as the development of a catalytic and asymmetric process, are currently under investigation.

Acknowledgements

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