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Simple and Direct sp^3 C−H Bond Arylation of Tetrahydroisoquinolines and Isochromans via 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone Oxidation under Mild Conditions

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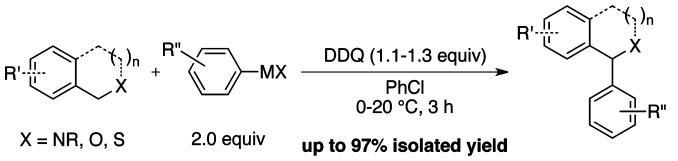
ABSTRACT



The 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-mediated sp^3 C−H bond arylation of tetrahydroisoquinolines and isochromans is described. The corresponding products were facilely synthesized via a simple nucleophilic addition reaction between readily available aryl Grignard reagents and iminium (or oxonium) cations generated in situ by DDQ oxidation of tetrahydroisoquinolines (or isochromans) under mild conditions.

Owing to their wide variety of biological activities, selective functionalization of tetrahydroisoquinoline (THIQ) and isochroman has attracted considerable attention from the synthetic community.[1] For instance, Solifenacin (VesiCare), a urinary antispasmodic of the antimuscarinic class, is commonly used in the treatment of an overactive bladder with or without urge incontinence.[2] As another example, Penidicitrinin B is a compound that has been isolated from *Penicillium citrinum* strains and is well-known for its potent antioxidant activity.[3]

Increasing environmental awareness has given rise to a great deal of interest in the direct arylation of selected C−H bonds.[4] Recent efforts have focused on cross-dehydrogenative-coupling (CDC) reactions for forming new C−C bonds,[5] and an excellent method for sp^3 C−H bond arylation of THIQs with indoles has been reported in a number of articles.[6] In 2008, we reported Cu-catalyzed sp^3 C−H bond arylation of THIQs with a variety of arylboronic acids.[7] This catalytic method has numerous

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(1) For examples, see: (a) Taylor, E. C., Weissberger, A., Eds. *The Chemistry of Heterocyclic Compounds*; John Wiley & Sons: New York, 1981, 1990, 1995, Vol. 38, Parts 1−3. (b) Charifson, P. S. *Drugs Future* **1989**, *14*, 1179–1185. (c) Hoffman, B.; Cho, S. J.; Zheng, W.; Wyrick, S.; Nichols, D. E.; Mailman, R. B.; Tropsha, A. *J. Med. Chem.* **1999**, *42*, 3217–3226.

(2) (a) Ohtaka, A.; Ukai, M.; Hatanaka, T.; Kpbayashi, S.; Ikeda, K.; Sato, S.; Miyata, K.; Sasamata, M. *Eur. J. Pharmacol.* **2004**, *492*, 243–250. (b) Cardozo, L.; Lisec, M.; Millard, R.; Trip, O. V.; Kuzmin, I.; Drogendijk, T. E.; Huang, M.; Ridder, A. M. *J. Urology* **2004**, *172*, 1919–1924. (c) Smulders, R. A.; Krauwinkel, W. J.; Swart, P. J.; Huang, M. *J. Clin. Pharmacol.* **2004**, *44*, 1023–1033.

(3) (a) Clark, B. R.; Capon, R. J.; Lacey, E.; Tennant, S.; Gill, J. H. *Org. Biomol. Chem.* **2006**, *4*, 1520–1528. (b) Lu, Z.-Y.; Lin, Z.-J.; Wang, W.-L.; Du, L.; Zhu, T.-J.; Fang, Y.-C.; Gu, Q.-Q.; Zhu, W.-M. *J. Nat. Prod.* **2008**, *71*, 543–546. (c) Liu, H.-C.; Du, L.; Zhu, T.-J.; Li, D.-H.; Geng, M. Y.; Gu, Q.-Q. *Helv. Chim. Acta* **2010**, *93*, 2224–2230.

(4) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.

(5) (a) Li, C,-J. *Acc. Chem. Res.* **2009**, *42*, 335–344. (b) Liu, L.; Floreancig, P. E. *Org. Lett.* **2010**, *12*, 4686–4689. (c) Tsang, A. S.-K.; Jensen, P.; Hook, J. M.; Hashmi, A. S, K; Todd, M. H. *Pure Appl. Chem.* **2011**, *83*, 655–665.

(6) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968–6969. (b) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317–5325. (c) Dhineshlumar, J.; Lamani, M.; Alahiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092–1095. (d) Zhong, J.-J.; Meng, Q.-Y.; Wang, G.-X.; Liu, Q.; Chen, B.; Feng, K.; Tung, C.-H.; Wu, L.-Z. *Chem.—Eur. J.* **2013**, *19*, 6443–6450.

(7) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661–3663.

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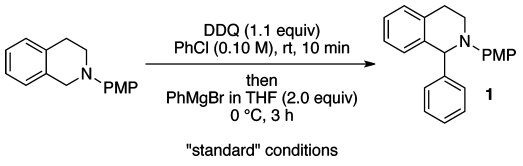
advantages, including the use of a minimally toxic and relatively cheap Cu salt as the catalyst. However, the reaction required a high temperature and long reaction time to proceed to completion. These factors are generally disadvantageous for achieving asymmetric C−H bond functionalization at the benzyl position, owing to the high probability of racemization. Subsequently, Schnürch et al. reported the Ru-catalyzed sp^3 C−H bond arylation of THIQs with various aryl halides. However, this method also required a high temperature (140 °C) and long reaction time (24 h).[8] Yet, suitable methods for sp^3 C−H bond arylation of isochroman have been rarely reported,[9] even though the pharmacological and physiological effects of the compounds are likely to be as beneficial as those of THIQ. To resolve these issues, we have investigated the direct sp^3 C−H bond arylation of THIQ and isochroman under mild conditions. Herein, we report a heavy-metal-free sp^3 C−H bond arylation with readily available aryl Grignard reagents via 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation.

Table 1. DDQ-Mediated C−H Bond Arylation of THIQ[a]



entry	variation from the "standard" conditions	yield of **1** (%)[b]
1	none	>99 (95)[c]
2	no DDQ	0
3	DDQ (10 mol %), Mn_2O (1.1 equiv)	8
4	CuBr (10 mol %), TBHP (1.1 equiv)	0
5	CPh_3BF_4, instead of DDQ	43
6	chloranil, instead of DDQ	56
7	*o*-chloranil, instead of DDQ	90
8	O_2 (1 atm), instead of DDQ	10
9	CAN, instead of DDQ	11
10	NHPI, instead of DDQ	0
11	*m*CPBA, instead of DDQ	0
12	PhMgBr,[d] instead of PhMgBr	44
13	PhMgCl,[e] instead of PhMgBr	81
14	PhZnI or PhZnBr,[e] instead of PhMgBr	0
15	PhH, instead of PhCl	75
16	PhMe, instead of PhCl	71
17	$CHCl_3$, instead of PhCl	42
18	THF, instead of PhCl	69
19	DMF, instead of PhCl	19
20	addition of HQME (1.1 equiv)	51

[a] All data are the average of two experiments. [b] The yield was determined by ^1H NMR analysis versus a calibrated 1,4-bis(trifluoromethyl)-benzene as an internal standard. [c] Isolated yield. [d] Et_2O solution was used. [e] THF solution was used.

After a series of optimization studies, we found that the sp^3 C−H bond arylation at C(1) in *N*-*p*-methoxyphenyl (PMP)-protected THIQ[7] proceeded efficiently in the presence of 1.1 equiv of DDQ and 2.0 equiv of PhMgBr (THF solution) in chlorobenzene at 0 °C under an Ar atmosphere (entry 1 of Table 1; 95% yield). The *N*-PMP can be easily removed to give the α-arylated N−H-free THIQ.[10] In the absence of DDQ, essentially no reaction was observed (entry 2). The use of a catalytic amount of DDQ with MnO_2 as a co-oxidant gave **1** in an unsatisfactory yield of 8% (entry 3).[11] When the previously reported CuBr/*tert*-butyl hydroperoxide (TBHP) system[7] was tested in chlorobenzene at 0 °C, the reaction did not proceed (entry 4). The use of CPh_3BF_4[12] or chloranil instead of DDQ gave **1** in moderate yields of 43% and 56%, respectively (entries 5 and 6). When *o*-chloranil was employed as the oxidant in place of DDQ under the optimum conditions, a high yield of 90% was achieved (entry 7). However, other common oxidants, including oxygen, cerium ammonium nitrate (CAN), *N*-hydroxyphthalimide (NHPI), and *m*-chloroperoxybenzoic acid (*m*CPBA), did not oxidize THIQ effectively (entries 8−11). Furthermore, we examined the scope of DDQ-mediated sp^3 C−H bond arylation with respect to the effects of both organometallic nucleophiles and solvents. When an Et_2O solution of PhMgBr was used instead of a THF solution, the yield was reduced to 44% (entry 12). The solvent effect of PhMgBr (entry 1 vs 12) is still unclear. However, it seems that the coordination of their solvents with THIQ affects the reactivity. PhMgCl (THF solution) could be employed in place of PhMgBr (THF solution) as a nucleophile (entry 13; 81% yield); however, PhZnI and PhZnBr showed very little reactivity under the same conditions (entry 14). The sp^3 C−H bond arylation with DDQ and PhMgBr proceeded smoothly in less polar solvents such as benzene and toluene, as well as chlorobenzene (entries 15−19). When hydroquinone monomethyl ether (HQME) was added as a radical scavenger to help clarify the reaction mechanism, the yield of **1** was decreased to 51% with 52% conversion of THIQ (entry 20).

We next examined the scope of the oxidative arylation reaction of THIQ with a variety of substituted ArMgBr (Scheme 1). *N*-Ph- and *N*-Bn-protected THIQs were found to be effective and regioselective for this transformation. Unfortunately, *N*-Ac-, *N*-Cbz, and *N*-Boc-protected THIQs did not couple under the optimum conditions. Regardless of the position of the substituents, both electron-donating and -withdrawing substituted ArMgBr (THF solution) successfully coupled to THIQ, giving excellent yields. Interestingly, the sp^3 C−H bond arylation of THIQ with the very sterically hindered 2-naphthylMgBr afforded **7** in good yield.

(8) Dastbaravardeh, N.; Schnürch, M.; Mihovilovic, M. D. *Eur. J. Org. Chem.* **2013**, 2878–2890.

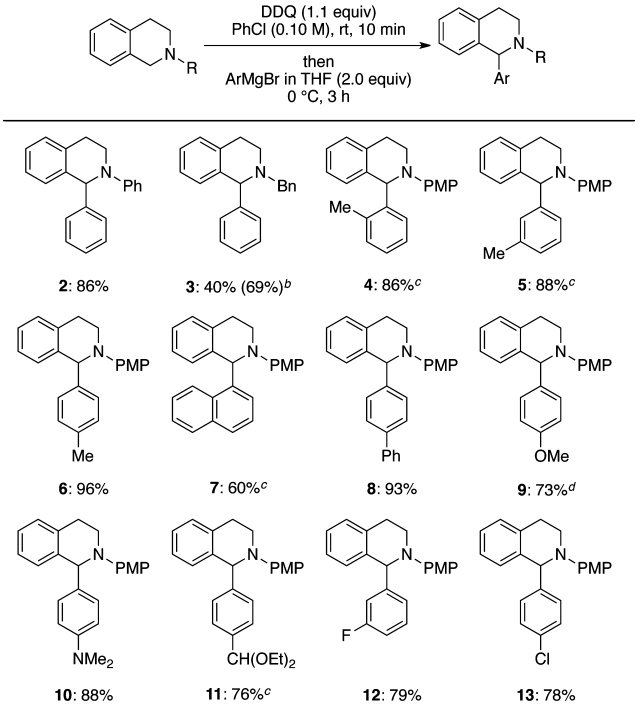
(9) (a) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnürch, M. *Chem. Commun.* **2010**, *46*, 8836–8838. (b) Ghobrial, M.; Schnürch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2011**, *76*, 8781–8793. (c) Park, S. J.; Price, J. R.; Todd, M. H. *J. Org. Chem.* **2012**, *77*, 949–955.

(10) Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1999**, *10*, 221–223.

(11) Yi, H.; Liu, Q.; Liu, J.; Zeng, Z.; Yang, Y.; Lei, A. *ChemSusChem* **2012**, *5*, 2143–2146.

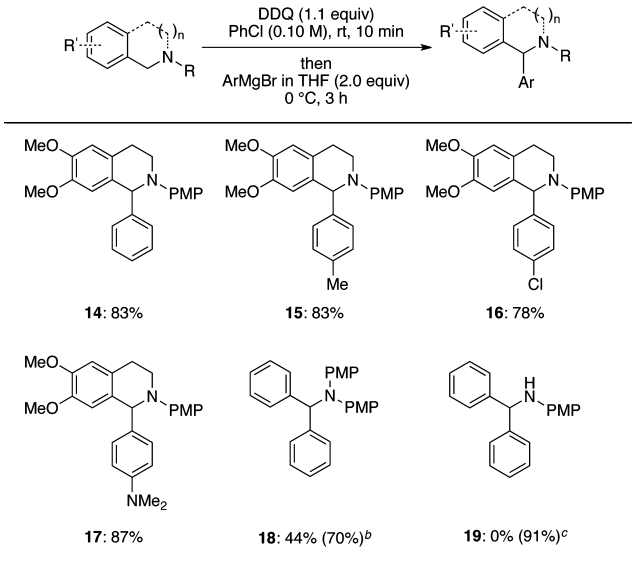
(12) (a) de Costa, B. R.; Radesca, L. *Synthesis* **1992**, 887–890. (b) Ludwig, M.; Hoesl, C. E.; Höfner, G.; Wanner, K. T. *Eur. J. Med. Chem.* **2006**, *41*, 1003–1010.

Scheme 1. Scope of THIQ and Its Derivatives in the C−H Bond Arylation[a]



[a] All data are the average of two experiments. [b] The oxidation using DDQ was carried out at 80 °C instead of rt. [c] The nucleophilic addition using ArMgBr was carried out at 20 °C instead of 0 °C. [d] DDQ (1.0 equiv) was used.

Scheme 2. Scope of THIQ Derivatives and Acyclic Benzylamines in the C−H Bond Arylation[a]



[a] All data are the average of two experiments. [b] The oxidation using DDQ was carried out at 80 °C instead of rt. [c] PhLi in Bu_2O was used as a nucleophile.

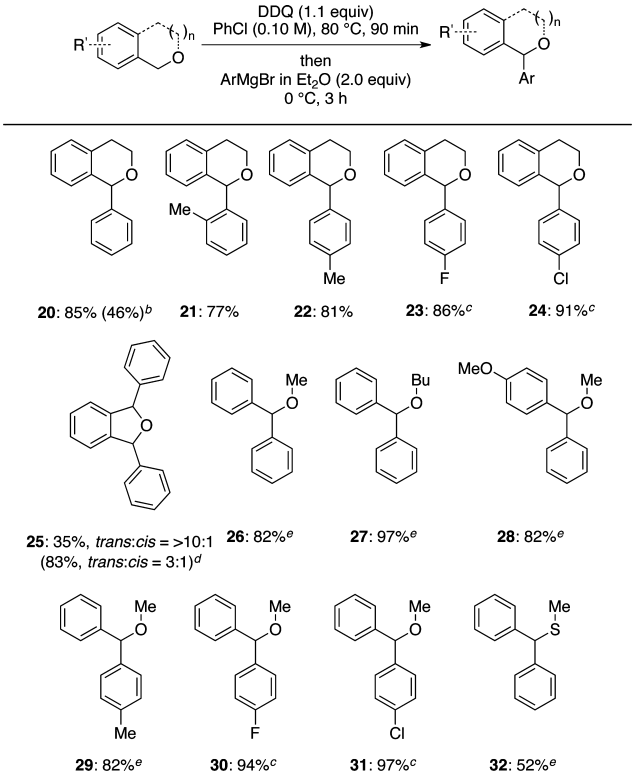
The optimized system was then taken forward to evaluate the sp^3 C−H bond arylation of a wide range of THIQ derivatives and acyclic benzylamines (Scheme 2). The arylation of a THIQ derivative with ArMgBr (in THF solution) bearing electron-donating or -withdrawing groups afforded the corresponding products **14**−**17** in 78−87% yields. On the other hand, attempts to use *N*-PMP-protected isoindoline[13] as a starting material did not give the corresponding coupling product. The reaction with *N*-$(PMP)_2$-protected acyclic benzylamine[14] gave **18** in moderate yield. On the other hand, the use of *NH*-PMP-protected acyclic benzylamine as starting materials did not afford desired coupling product **19**, but the corresponding imine in quantitative yield. Fortunately, this problem could be resolved by using PhLi instead of PhMgBr (**19**, 91% yield).

The protocol was also shown to be applicable to the direct sp^3 C−H bond arylation of isochroman,[9] phthalan,[15] and acyclic benzyl ethers (Scheme 3). When PhMgBr (THF solution) was used, the coupling with isochroman proceeded to give the product **20** in 46% yield. Interestingly, the use of PhMgBr (Et_2O solution) successfully afforded **20** in a much higher yield (85% yield). Based on these results, we subsequently examined the coupling reaction of isochroman using an Et_2O solution of ArMgBr. Both electron-donating and -withdrawing substituted ArMgBr (Et_2O solution) coupled with isochroman to give **21**−**24** in excellent yields. When phthalan was used as the starting material under the same conditions, only disubstituted compound **25** was produced in 35% yield with good selectivity (*trans*/*cis* = >10:1)[16] with no formation of the desired monosubstituted coupling product. When the nucleophilic addition using PhMgBr (Et_2O solution; 3.0 equiv) in the presence of DDQ (2.1 equiv) was carried out at 80 °C, the yield of **25** was improved (83% yield). We additionally tried to form a quaternary carbon center using this method with 1-methyl-isochroman; however, this was unsuccessful.

Finally, we attempted the sp^3 C−H bond arylation of acyclic benzyl ethers and a sulfide under mild conditions. Their coupling products were normally synthesized by benzylation of alcohols (or thiols) in the presence of a strong base such as NaH,[17] or by dehydration of alcohols.[18] To the best our knowledge, therefore, a simple and widely applicable method for such a reaction has not been reported thus far. When the readily available benzyl alkyl (Me and Bu) ethers were treated with ArMgBr (Et_2O solution) bearing electron-donating or -withdrawing groups under the same conditions, **26**−**31** were successfully produced in 82−97% yield. Contrary to our expectations, the coupling of benzyl phenyl ether results in the recovery of the starting materials with no formation of side products. The C−H

(13) Mourad, A.-F. E.; Nour-el-din, A. M.; Hassan, A. A. *Bull. Soc. Chim. Belg.* **1986**, *95*, 1045–1051.
(14) Ohta, K.; Chiba, Y.; Ogawa, T.; Endo, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5050–5053.
(15) Guo, X.; Pan, S.; Liu, J.; Li, Z. *J. Org. Chem.* **2009**, *74*, 8848–8851.
(16) Smith, J. G.; McCall, R. B. *J. Org. Chem.* **1980**, *45*, 3982–3986.
(17) For examples, see: (a) Strazzolini, P.; Runcio, A. *Eur. J. Org. Chem.* **2003**, 526–536. (b) Onishi, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Chem. Lett.* **2011**, *40*, 1223–1225.
(18) For examples, see: (a) Welch, C. M.; Smith, H. A. *J. Am. Chem. Soc.* **1950**, *72*, 4748–4750. (b) Salehi, P.; Iranpoor, N.; Behbahani, F. K. *Tetrahedron* **1998**, *54*, 943–948.

Scheme 3. Scope of Isochroman and Its Derivatives in C−H Bond Arylation[a]



[a] All data are the average of two experiments. [b] PhMgBr in THF solution was used instead of its Et_2O solution. [c] The reaction was carried out in PhCl (0.20 M). [d] DDQ (2.1 equiv) was used, and then the nucleophilic addition using PhMgBr in Et_2O solution (3.0 equiv) was carried out at 80 °C instead of 0 °C. [e] DDQ (1.3 equiv) was used.

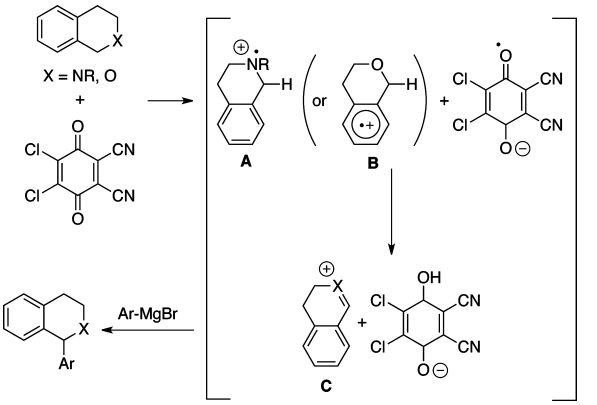
bond arylation of benzyl methyl sulfide afforded **32** in 52% yield and recovered 20% of starting material.

The mechanism for the DDQ-mediated sp^3 C−H bond arylation can be explained in Scheme 4. In the case of using THIQ, a radical cation **A** is generated by a single electron transfer from THIQ to DDQ.[5c] The DDQ radical oxygen then abstracts a H-atom from **A** to generate an iminium cation **C**. Finally, the nucleophilic addition of an aryl Grignard reagent generates the desired coupling product. In the case of using isochroman, on the other hand, three possible mechanisms for the generation of the oxonium cation have been suggested.[19,20] Most recently, the mechanistic study

(19) Trost, B. M. *J. Am. Chem. Soc.* **1967**, *89*, 1847–1851.

(20) (a) Zhang, X.-M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 904–908. (b) Baciocchi, E.; Del Giacco, T.; Elisei, F.; Lanzalunga, O. *J. Am. Chem. Soc.* **1998**, *120*, 11180–11181.

Scheme 4. Plausible Mechanism for DDQ-Mediated C−H Bond Arylation



based on kinetic isotope effects by Floreancig indicated that the most plausible among their mechanisms is the pathway where a radical cation **B** generated by a single electron transfer from isochroman to DDQ is accessed through H-atom abstraction to form oxonium cation **C**.[21]

In conclusion, a simple and direct process for sp^3 C−H bond arylation with DDQ in high yield under mild conditions was developed. The method was found to be applicable to a wide range of THIQs, isochromans, and their derivatives, providing the ability to synthesize many potentially biologically active compounds. The optimized protocol has numerous advantages: it is heavy-metal-free and has high regioselectivity, a short reaction time, and mild reaction temperature. The scope, applications, mechanism, and asymmetric synthesis of this reaction are currently under investigation.

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Supporting Information Available. Experimental procedures, characterization data, and copies of spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Jung, H. H.; Floreancig, P. E. *Tetrahedron* **2009**, *65*, 10830–10836.

The authors declare no competing financial interest.