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Organocatalytic Approach for C(sp^3)−H Bond Arylation, Alkylation, and Amidation of Isochromans under Facile Conditions

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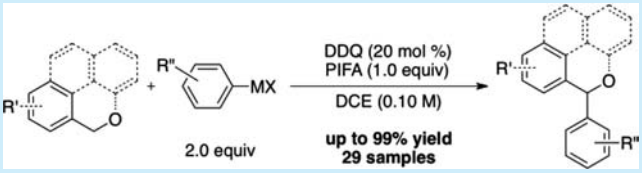
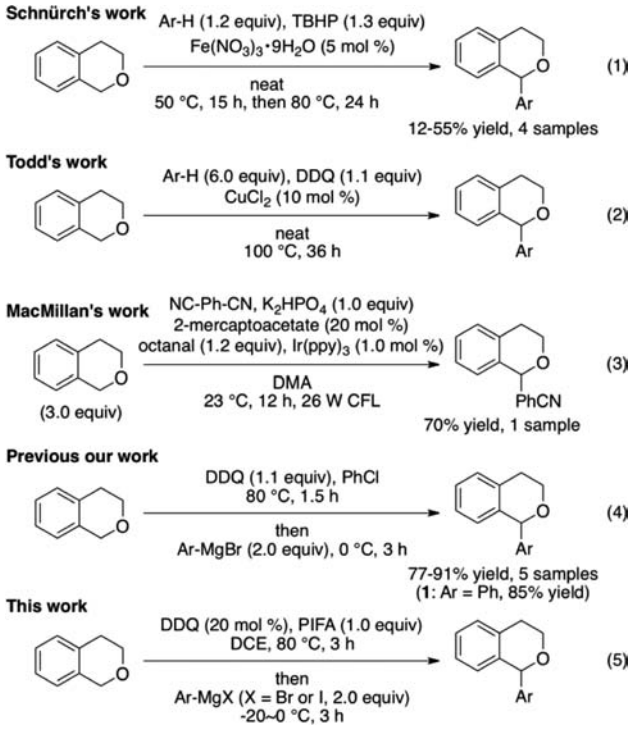
Supporting Information

ABSTRACT: A new catalytic approach for the synthesis of isochroman derivatives via direct C(sp^3)−H bond arylation is described. The oxidation reaction with [bis(trifluoroacetoxy)-iodo]benzene facilitates the regeneration of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in the C(sp^3)−H bond arylation of isochroman. The reaction conditions can also be used for alkyl Grignard reagents and amides to afford the corresponding isochroman derivatives.



With the rapid development of synthetic organic chemistry over the past few decades, significant progress has been made in carrying out very difficult chemical reactions, in particular, C−H bond activation reactions such as cross-dehydrogenative-coupling (CDC) reactions.[1] We are primarily interested in investigating the activation of the inert C(sp^3)−H bond of benzyl ethers such as isochroman. Because isochroman derivatives exhibit various potential bioactivities[2] and may serve as important building blocks in drug development in the future, the C−H bond activation reaction has attracted attention as one of the most efficient synthetic methods. Studies on the direct C(sp^3)−C(sp^3) and C(sp^3)−C(sp) bond formations at the C(1) position of isochroman via C(sp^3)−H bond activation have been widely reported.[3] Additionally, in recent years, Liu and co-workers have also reported a one-pot enantioselective C(sp^3)−C(sp^3) bond formation with a chiral organocatalyst.[4] On the other hand, only a few methods for the catalytic and noncatalytic C(sp^3)−H bond arylation at the C(1) position of isochroman have been reported by four research groups.[5] Schnürch and co-workers first developed the catalytic system by employing 5.0 mol % of $Fe(NO_3)_3{\cdot}9H_2O$ and 1.3 equiv of TBHP as the oxidant in 2010 (eq 1 of Scheme 1).[5a,b] Todd and co-workers utilized 10 mol % of $CuCl_2$ and 1.1 equiv of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant in 2012 (eq 2 of Scheme 1).[5c] MacMillan and co-workers succeeded in the C(sp^3)−H bond arylation of isochroman via photoredox catalysis in 2014 (eq 3 of Scheme 1).[5e] Recently, we reported that the desired coupled products with an aryl group at the C(1) position of isochroman could be obtained in 77−91% yields when isochroman was oxidized with 1.1 equiv of DDQ, followed by treatment with ArMgBr/Et_2O (eq 4 of Scheme 1).[5d] Our method can be considered as an inexpensive, effective, and highly versatile reaction because it not only affords the desired coupling products in a short period under mild reaction conditions but also does not require expensive heavy-metal catalysts. However, because a stoichiometric amount of DDQ is needed, its toxicity should be considered.[6] Herein we report the first organocatalytic method with high efficiency and functional compatibility for the direct C(sp^3)−H bond arylation of isochroman (eq 5 of Scheme 1), and application of the method to C(sp^3)−H bond alkylation and amidation.

Scheme 1. General Methods for C(sp^3)−H Bond Arylation of Isochromans



Listed in Table 1 is some information about variations from "standard" conditions for the catalytic C(sp^3)−H bond

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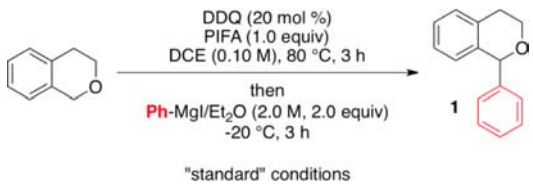
Table 1. DDQ-Catalyzed C(sp^3)−H Bond Arylation of Isochroman



entry	variation from the "standard" conditions	yield of **1** (%)[a]
1	none	86 (84)[b]
2	no DDQ	<1
3	no PIFA	18
4	MnO_2, instead of PIFA	9
5	$Mn(OAc)_3$, instead of PIFA	13
6	HCl/EtOH, PbO_2, instead of PIFA	5
7	HNO_3, instead of PIFA	<1
8	N_2O_4/DCE instead of PIFA	<1
9[c]	addition of $NaHCO_3$ (2.0 equiv)	81
10[c]	addition of Na_2CO_3 (2.0 equiv)	64
11[c]	addition of K_2CO_3 (2.0 equiv)	80
12[c]	addition of pyridine (2.0 equiv)	17
13[c]	addition of 2,4,6-collidine (2.0 equiv)	66
14	chloranil, instead of DDQ	6
15	*o*-chloronil, instead of DDQ	22
16	PIDA, instead of PIFA	54
17	PFPIFA, instead of PIFA	55
18	C_3F_7(Ph)IOTf, instead of PIFA	<1
19	PhMgI/Et_2O (1.0 M), instead of 2.0 M	76
20	PhMgCl/Et_2O, instead of PhMgBr/Et_2O	77
21	PhMgBr/Et_2O, instead of PhMgI/Et_2O	81
22	PhMgI/THF, instead of PhMgI/Et_2O	85
23	PhMgBr/THF, instead of PhMgI/Et_2O	81
24	PhZnBr/Et_2O, instead of PhMgI/Et_2O	5
25	PhZnI/Et_2O, instead of PhMgI/Et_2O	4
26	Ph_2Zn, instead of PhMgI/Et_2O	66
27	PhLi/Bu_2O, instead of PhMgI/Et_2O	21
28	PhCl, instead of DCE	69
29	PhMe, instead of DCE	38
30[d]	1,1-DCE, instead of DCE	50
31[e]	DBE, instead of DCE	57
32[d]	THF, instead of DCE	5
33[d]	Et_2O, instead of DCE	<1
34	CPME, instead of DCE	8
35	MeCN, instead of DCE	59
36	DMF, instead of DCE	9

[a]The yield was determined by ^{1}H NMR analysis using a calibrated 1,4-bis(trifluoromethyl)benzene as the internal standard. [b]Isolated yield. [c]The base was added after the oxidation with cat. DDQ and PIFA was carried out. [d]The oxidation with cat. DDQ and PIFA was carried out under reflux. [e]The nucleophilic addition by using PhMgI/Et_2O was carried out at 20 °C.

arylation of isochroman. When 1.0 equiv of a hypervalent iodine(III) reagent, [bis(trifluoroacetoxy)iodo]benzene (PIFA), was used as the co-oxidant in combination with 20 mol % of DDQ, the desired coupling product **1** was formed in a similar yield, as reported earlier by using a stoichiometric amount of DDQ (entry 1 of Table 1, 84% yield vs eq 4 of Scheme 1, 85% yield). In recent years, several hypervalent iodine(III) reagents have been used as an alternative to toxic metals and organic oxidants and have attracted attention as user- and eco-friendly oxidants.[7] In addition, PIFA can be easily synthesized from inexpensive and readily available chemicals such as iodobenzene, trifluoroacetic acid (TFA), and Oxone.[8] As expected, PIFA alone was not effective in promoting the oxidation of isochroman (entry 2). Moreover, in the absence of PIFA, the catalytic reaction hardly progressed because DDQ could not be regenerated (entry 3, 18% yield). To the best of our knowledge, as of today, seven oxidants[9] including PIFA[9c] have been reported in the oxidation of 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ) to DDQ. We then tested the DDQ-catalyzed C(sp^3)−H bond arylation of isochroman using these oxidants.

However, when these oxidants except for electrolysis[9d] were used instead of PIFA, poor yields of the coupling products **1** were obtained (entries 4−8 of Table 1). Although isochroman was consumed completely, the yield (86% NMR yield) given in entry 1 was lower than the expected result. This is probably because of the decomposition of **1** or the neutralization of PhMgI by TFA generated by the reduction of PIFA. To overcome this limitation, several bases were added; however, the yields did not improve (entries 9−13). The few organic oxidants and hypervalent iodine(III) reagents investigated did not lead to improvement in yields (entries 14−18). When a 1.0 M Et_2O solution of PhMgI was used instead of a 2.0 M solution, the yield decreased slightly (entry 19, 76% yield). When PhMgCl/Et_2O and PhMgBr/Et_2O were used instead of PhMgI/Et_2O, **1** was obtained in a desirable yield (entries 20 and 21, 77% and 81% yields, respectively). In our previous studies, we reported that the use of a THF solution of a Grignard reagent with a stoichiometric amount of DDQ gave a significantly lower yield than the use of a Et_2O solution of a Grignard reagent.[5d] In the case of this catalysis, surprisingly, the THF solution of Grignard reagents could be used in place of the Et_2O solution (entries 22 and 23, 85% and 81% yields, respectively). On the other hand, when PhZnBr/Et_2O, PhZnI/Et_2O, Ph_2Zn, and PhLi/Bu_2O were used, low yields of **1** were obtained (entries 24−27). The effect of solvent on the catalytic reaction was remarkable. Although the reactions in PhCl, 1,1-DCE, DBE, and MeCN proceeded well, polar and ether solvents did not give satisfactory results (entries 28−36).

Under the best suitable conditions, a variety of aryl-Grignard reagents reacted with isochroman, isochroman derivatives, and acyclic benzyl ethers (Scheme 2). A high yield was observed for aryl-Grignard reagents with both electron-donating and -withdrawing groups (79−90% yields of **2**−**5** and **7**−**9**). Increased steric bulk was well tolerated (80%, 72%, and 66% yields of **6**, **10**, and **11**, respectively). 4-Me-isochroman[10] coupled smoothly in 76% yield of **12** with good selectivity (*trans*/*cis* = >7: 3). Isochroman bearing Me- and Cl-groups at the C(5) position were found to react successfully with PhMgI/Et_2O and afforded the corresponding coupled products **13** and **14**, respectively, in high yields.[10] Isochroman bearing the MeO-group at the C(6) position was one of the less reactive coupling partners.[5c] Under our reaction conditions, gratifyingly, the isochroman derivative[10] gave the desired coupling product **15** in 25% yield. When six- and seven-membered cyclic benzyl ethers were used,[11] single addition of the Ph-group proceeded selectively to form **16** and **17**. On the other hand, the DDQ-catalyzed C(sp^3)−H bond arylation of phthalan afforded only a double additional compound **18** in 54% yield with excellent selectivity (*trans*/*cis* = >9: 1). Acyclic benzyl ethers were also compatible with the coupling system, though only moderate yields were obtained (54%, 70%, and 53% yields of **19**, **20**, and **21**, respectively). Applications for our catalytic system were

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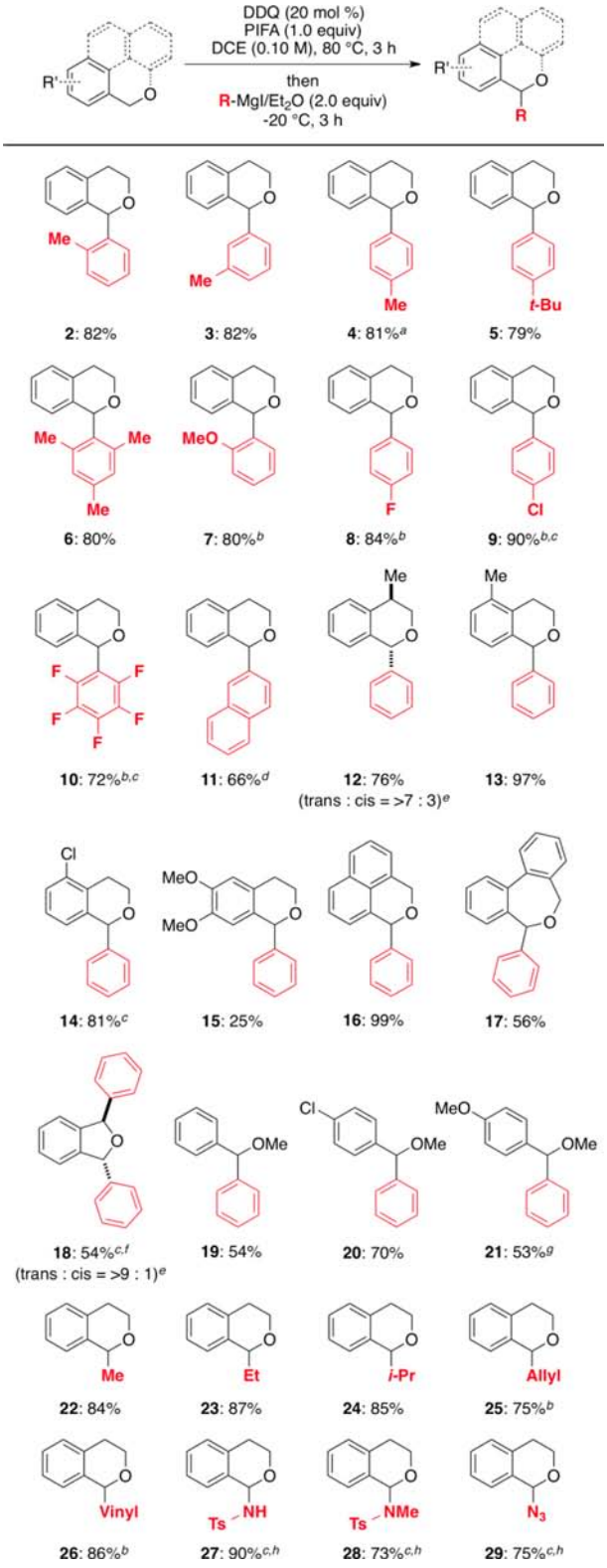
Scheme 2. DDQ-Catalyzed C(sp^3)−H Bond Arylation, Alkylation, and Amidation of Isochroman and Its Derivatives



[a]The nucleophilic addition by using RMgI/Et_2O was carried out at 0 °C. [b] RMgBr/Et_2O was used. [c] In DCE (0.20 M). [d] RMgBr/THF was used. [e] The ratio was determined by ^{1}H NMR analysis. [f] PIFA (2.0 equiv) and RMgBr/Et_2O (4.0 equiv) were used. [g] The oxidation with cat. DDQ and PIFA was carried out at 40 °C. [h] The nucleophilic additions by using H_2NTs, HNMeTs, and NaN_3, respectively, were carried out at room temperature.

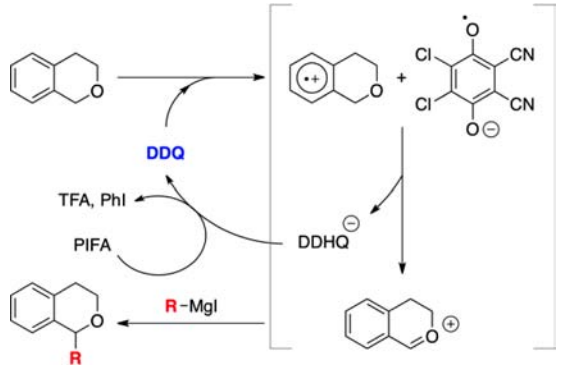
next investigated. The coupling reaction of isochroman with alkyl-, allyl-, and vinyl-Grignard reagents proceeded successfully with 75−87% yields of **22**−**26** in a single step.

Unfortunately, neither **1** nor **22** led to the desired coupling products with a quaternary carbon center, although **1** and **22** were consumed sufficiently by formation of the corresponding oxocarbenium cations.

Further examples for C(sp^3)−N bond formation of isochroman were also demonstrated. Sulfonamides, H_2NTs and HNMeTs, underwent the C(sp^3)−H bond amidation with isochroman in satisfactory yields (90% and 73% yields of **27** and **28**, respectively). Azide was also a good coupling partner and furnished the C(sp^3)−N bonded product **29** in 75% yield.

The plausible reaction mechanism for this organocatalytic reaction is shown in Scheme 3. First, the one-electron oxidation

Scheme 3. Plausible Mechanism for DDQ-Catalyzed sp^3 C−H Bond Functionalization



of isochroman with DDQ affords a radical cation. Second, the abstraction of the H-radical by the DDHQ radical anion affords the oxocarbenium cation and the DDHQ anion.[12] Finally, we presume that the nucleophilic addition of the Grignard reagent to the oxocarbenium cation affords the desired coupling product. The DDHQ anion is oxidized by PIFA to regenerate DDQ, thus completing the catalytic cycle.[9c]

In summary, a new organocatalytic approach for C(sp^3)−H bond arylation of isochroman has been developed. The coupling reaction can now proceed with a catalytic amount of DDQ in high yield under simple and facile conditions. Additionally, the catalytic method was applicable to a C(sp^3)−H bond arylation, alkylation, and amidation of a wide range of isochroman derivatives and benzyl ethers. A method for enantioselective C(sp^3)−H bond functionalizations of isochroman as well as cyclic and acyclic benzyl ethers is currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

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.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949−1952. (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335−344. (c) Tsang, A. S.-K.; Jensen, P.; Hook, J. M.; Hashmi, A. S. K.; Todd, M. H. *Pure Appl. Chem.* **2011**, *83*, 655−665.

(2) (a) Dalterio, S.; Bartke, A.; Burstein, S. *Science* **1977**, *196*, 1472−1473. (b) Martin, P.; Consroe, P. *Science* **1976**, *194*, 965−967. (c) Zhi, L.; Tegley, C. M.; Kallel, E. A.; Marschke, K. B.; Mais, D. E.; Gottardis, M.; Jones, T. K. *J. Med. Chem.* **1998**, *41*, 291−302. (d) de Groot, M. J.; Alex, A. A.; Jones, B. C. *J. Med. Chem.* **2002**, *45*, 1983−1993. (e) Yamaori, S.; Kushihara, M.; Yamamoto, I.; Watanabe, K. *Biochem. Pharmacol.* **2010**, *79*, 1691−1698.

(3) For examples, see: (a) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497−7500. (b) Song, C.-X.; Cai, G.-X.; Farrell, T. R.; Jiang, Z.-P.; Li, H.; Gan, L.-B.; Shi, Z.-J. *Chem. Commun.* **2009**, 6002−6004. (c) Correia, C. A.; Li, C.-J. *Heterocycles* **2010**, *82*, 555−562. (d) Richter, H.; Rohlmann, R.; Mancheño, O. G. *Chem.—Eur. J.* **2011**, *17*, 11622−11627. (e) Pinter, A.; Klussmann, M. *Adv. Synth. Catal.* **2012**, *354*, 701−711. (f) Liu, X.; Sun, B.; Xie, Z.; Qin, X.; Liu, L.; Lou, H. *J. Org. Chem.* **2013**, *78*, 3104−3112.

(4) Meng, Z.; Sun, S.; Yuan, H.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 543−547.

(5) (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. (d) Muramatsu, W.; Nakano, K.; Li, C.-J. *Org. Lett.* **2013**, *15*, 3650−3653. (e) Qvortrup, K.; Rankic, D. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 626−629.

(6) Rat LD_{50} oral values of DDQ, 82 mg/kg, can be found on Acros Organics MSDS sheets.

(7) Rat LD_{50} oral values of PIFA cannot be found on MSDS sheets. For examples, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299−5358. (b) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052−9070. (c) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185−1197. (d) Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1524−1552. (e) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517−538. (f) Kita, Y.; Dohi, T.; Morimoto, K. *J. Synth. Org. Chem., Jpn.* **2011**, *69*, 1241−1250. (g) Fernandez Gonzalez, D.; Benfatti, F.; Waser, J. *ChemCatChem* **2012**, *4*, 955−958. (h) Yusubov, M. S.; Zhdankin, V. V. *Curr. Org. Synth.* **2012**, *9*, 247−272.

(8) Zagulyaeva, A. A.; Yusubov, M. S.; Zhdankin, V. V. *J. Org. Chem.* **2010**, *75*, 2119−2122. Commercial costs in the 2012−2014 Aldrich catalog (all price quotes are based on 50−100 g or 100 mL bottles of the reagent) and rat LD_{50} oral values on Acros Organics MSDS sheets for each reagent are shown as follows: DDQ ($666/mol, rat LD_{50} oral values 82 mg/kg) vs PhI ($102/mol, rat LD_{50} oral values 1749 mg/kg), TFA ($54/mol, rat LD_{50} oral values 200−400 mg/kg), Oxone ($134/mol, rat LD_{50} oral values of $KHSO_4$, 2340 mg/kg; rat LD_{50} oral values of K_2SO_4, 6600 mg/kg).

(9) (a) Brook, A. G. *J. Chem. Soc.* **1952**, 5040−5041. (b) Mitchell, P. W. D. *Can. J. Chem.* **1963**, *41*, 550−553. (c) Spyroudis, S.; Varvoglis, A. *Synthesis* **1975**, 445−447. (d) Brinker, U. H.; Tyner, M., III; Jones, W. M. *Synthesis* **1975**, 671. (e) Kim, K. H.; Grunewald, G. L. *Org. Prep. Proced. Int.* **1976**, 141−143. (f) Scott, J. W.; Parrish, D. R.; Bizzarro, F. T. *Org. Prep. Proced. Int.* **1977**, *9*, 91−94. (g) Newman, M. S.; Khanna, V. K. *Org. Prep. Proced. Int.* **1985**, *17*, 422−423. (h) Liu, L.; Floreancig, P. E. *Org. Lett.* **2010**, *12*, 4686−4689.

(10) These isochroman derivatives were provided from the corresponding phenethyl alcohol and paraformaldehyde. See: Isobe, K.; Takeda, N.; Mohri, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1989**, *37*, 3390−3392.

(11) These cyclic benzyl ethers are provided in the following references. See: (a) Azzena, U.; Demartis, S.; Pilo, L.; Piras, E. *Tetrahedron* **2000**, *56*, 8375−8382. (b) Mihara, M.; Ishino, Y.; Minakata, S.; Komatsu, M. *Synlett* **2002**, 1526−1528.

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