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Efficient C(sp^3)–H Bond Functionalization of Isochroman by AZADOL Catalysis

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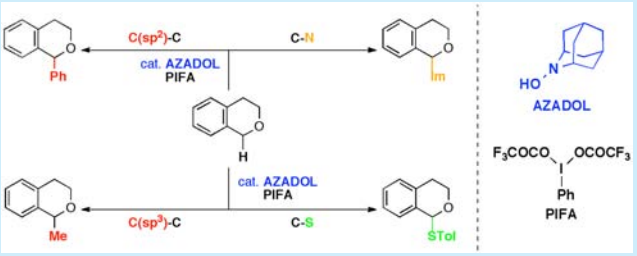
Supporting Information

ABSTRACT: A novel organocatalytic C(sp^3)–H bond functionalization of isochroman under practical conditions has been developed. In the presence of 5.0 mol % of AZADOL, the catalysis proceeded successfully with a broad range of substrates and nucleophiles in excellent yields.



Compounds bearing aryl groups at the benzylic position in benzyl ethers such as isochroman have attracted the attention of many synthetic chemists and biologists owing to their potential biological importance. For example, penidicitrinin B, which has been isolated from *Penicillium citrinum* strains, possesses antioxidant properties (Figure 1).[1] RS1478 is a new

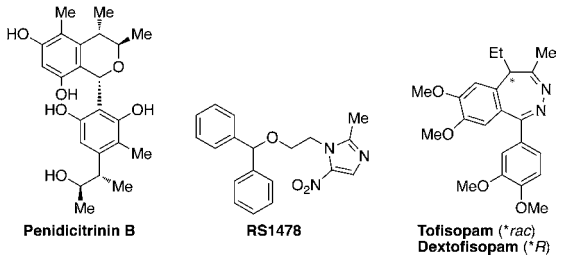
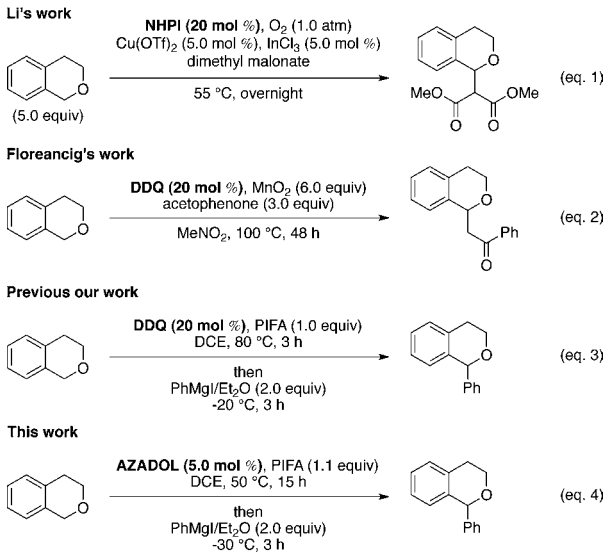


Figure 1. Biologically active compounds.

anti-human immunodeficiency virus (HIV) agent in 1-[2-(diarylmethoxy)ethyl]-2-methyl-5-nitroimidazole (DAMNI) analogues,[2] which is a novel class of HIV-1 non-nucleoside reverse transcriptase inhibitors. Further, isochroman derivatives are key intermediates in the synthesis of tofisopam and dextofisopam,[3] which are commonly prescribed for dysautonomia and irritable bowel syndrome, respectively; both medicines are marketed worldwide.[4] These bioactive compounds are typically synthesized by multistep syntheses, which may require protection–deprotection sequences. On the other hand, it may be possible to eliminate some of the synthetic steps if a method for the regioselective cleavage of inert C–H bonds and the introduction of functional groups, to form novel C–C bonds in a single step, is developed.

Over the last few decades, significant efforts have been put forth toward C–H bond functionalization by transition-metal catalysis and organocatalysis. Specifically, cross-dehydrogenative coupling (CDC) reactions are one of the most commonly used and atom-economic methods.[5,6] However, most CDC reactions have required the use of rare and expensive metals, stoichiometric amounts of peroxides, and harsh reaction conditions. Additionally, in spite of the recent innovative progress in synthetic chemistry, catalytic methods for C(sp^3)–H bond arylation at the C(1) position of isochroman are still limited.[6] Moreover, organocatalytic methods for the oxidative activation of C(sp^3)–H bonds in isochroman have not been reported other than by catalysis with *N*-hydroxyphthalimide (NHPI)[5b] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[5d] (eqs 1 and 2 of Scheme 1). Recently, we reported that [bis(trifluoroacetoxy)iodo]benzene (PIFA) promotes the

Scheme 1. AZADOL-Catalyzed C(sp^3)–H Bond Arylation of Isochroman



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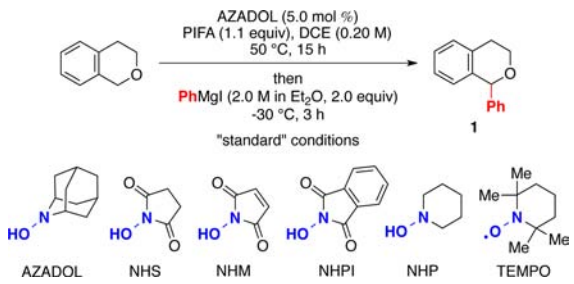
efficient regeneration of DDQ in the C(sp^3)−H bond arylation of isochroman (eq 3 of Scheme 1).[6f] The method could also be used to introduce various functional groups (aryl, alkyl, amide groups, etc.) into the C(1)-position of isochroman in a single step. In addition, rare and expensive metals were not required. However, owing to the toxicity concerns associated with DDQ, it is desirable to limit its use as much as possible.[7] Herein, we report a novel organocatalytic method employing a combination of *N*-hydroxy-2-azaadamantane (AZADOL) and PIFA to introduce aryl and various functional groups into the inert C(sp^3)−H bond of isochroman (eq 4 of Scheme 1).

We began the investigation by testing isochroman with commercially available *N*-hydroxyamines and hypervalent iodine(III) reagents.[8] The results are shown in Table 1. The oxidation of isochroman initiated by AZADOL (5.0 mol %) and PIFA (1.1 equiv) as a co-oxidant in 1,2-dichloroethane (DCE), followed by nucleophilic addition using PhMgI/Et_2O (2.0 equiv), afforded the desired coupling product **1** in 90% isolated yield (entry 1). AZADOL was developed by Iwabuchi[9] as an environmentally friendly oxidant as an alternative to 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO);[10] both oxidants are widely used to safely and efficiently transform alcohols into the corresponding aldehydes or ketones. Furthermore, AZADOL is more active than TEMPO[9] and has a longer shelf life than typical free-radical oxidants such as TEMPO and 2-azaadamantane *N*-oxyl (AZADO).[11] In the absence of either PIFA or AZADOL, the product yields significantly decreased (entries 2 and 3, 0% and 15% yields, respectively). Furthermore, the use of a smaller amount of AZADOL also resulted in an unsatisfactory yield (entry 4, 33% yield). A gram-scale reaction of isochroman under the same conditions as that in entry 1 afforded **1** in an isolated yield of 87%, and 7% isochroman was recovered (entry 5). The use of *N*-hydroxysuccinimide (NHS) instead of AZADOL resulted in good yield of **1** (entry 6, 69% yield). We tested several combinations of *N*-hydroxyamines and hypervalent iodine(III) reagents instead of the combination of AZADOL and PIFA, but no improvements in the yields were obtained (entries 7−14, 0−53% yields). The use of PhMgBr/Et_2O and PhMgCl/Et_2O resulted in excellent yields (entries 15 and 16, 89% and 85% yields, respectively), similar to PhMgI/Et_2O (entry 1). In contrast, the coupling reactions that employed THF solutions of the corresponding Grignard reagents afforded lower yields of **1** (entries 17, 18, and 19, 80%, 79%, and 45% yields, respectively). Other organometallic nucleophiles did not afford remarkable results (entries 20−22, 0−19% yields). Solvent screening was also carried out (entries 23−29). In PhCl, the catalysis proceeded smoothly to afford **1** (entry 23, 84% yield), as did the catalysis under the standard conditions that employed DCE. On the other hand, a smaller (<10%) conversion of isochroman was observed in ether-based solvents (entries 25−27), probably because the ethers deactivated the genuine oxidant, oxoammonium cation **A** (Scheme 2), generated from AZADOL and PIFA. Although DMF as a typical polar solvent resulted in a high conversion of isochroman, only 5% yield of **1** was obtained (entry 29). When hydroquinone monomethyl ether (HQME) was added as a radical scavenger in the oxidation step to help reaction mechanism, it completely halted the catalysis to produce **1**, and most isochroman was recovered (entry 30).[12]

With the proof of concept in hand, we next examined a variety of Grignard reagents and isochroman derivatives under the optimized conditions (Scheme 3). The catalytic C(sp^3)−H bond arylation of isochroman with aryl-Grignard reagents bearing electron-donating or electron-withdrawing substituents at the *ortho*-, *meta*-, or *para*-positions proceeded successfully to afford the corresponding coupling products **2**−**10** in high yields. Bulky

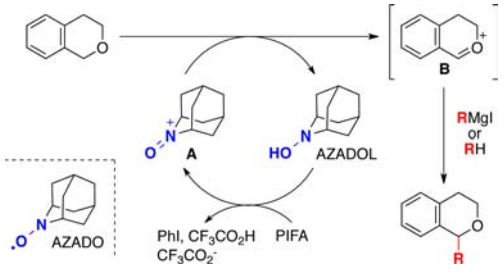
Table 1. AZADOL-Catalyzed C(sp^3)−C Bond Formation of Isochroman and Its Derivatives with Grignard Reagents



entry	variation from the "standard" conditions	yield of **1**[a] (%)
1	none	92 (90)[b]
2	no PIFA	0
3	no AZADOL	15
4	AZADOL (1.0 mol %)	33
5	1 g scale of isochroman	87[c] (87)[b,c]
6	NHS (5.0 mol %)	69
7	NHM (5.0 mol %)	27
8	NHPI (5.0 mol %)	10
9	NHP (5.0 mol %)	3
10	TEMPO (5.0 mol %)	53
11	PIDA (1.1 equiv)	7
12	PFPIFA (1.1 equiv)	22
13	C_3F_7(Ph)IOTf (1.1 equiv)	6
14	HO(Ph)IOTs (1.1 equiv)	0
15	PhMgBr/Et_2O (2.0 equiv)	90 (89)[b]
16	PhMgCl/Et_2O (2.0 equiv)	85
17	PhMgI/THF (2.0 equiv)	80
18	PhMgBr/THF (2.0 equiv)	79
19	PhMgCl/THF (2.0 equiv)	45
20	PhZnI/Et_2O (2.0 equiv)	0
21	PhZnBr/Et_2O (2.0 equiv)	0
22	PhLi/Bu_2O (2.0 equiv)	19
23	PhCl	84
24	PhMe	19
25	THF	0
26	Et_2O	3
27	CPME	6
28	MeCN	35
29	DMF	5
30	addition of HQME (1.1 equiv)	0

[a]The yields were calculated by ^{1}H NMR analysis using 1,4-bis(trifluoromethyl)benzene as the internal standard. [b]Isolated yields. [c]The oxidation of isochroman using AZADOL and PIFA proceeded for 24 h. PIDA = [bis(acetoxy)iodo]benzene. PFPIFA = [bis-(trifluoroacetoxy)iodo]perfluorobenzene.

Scheme 2. Possible Catalytic Cycle



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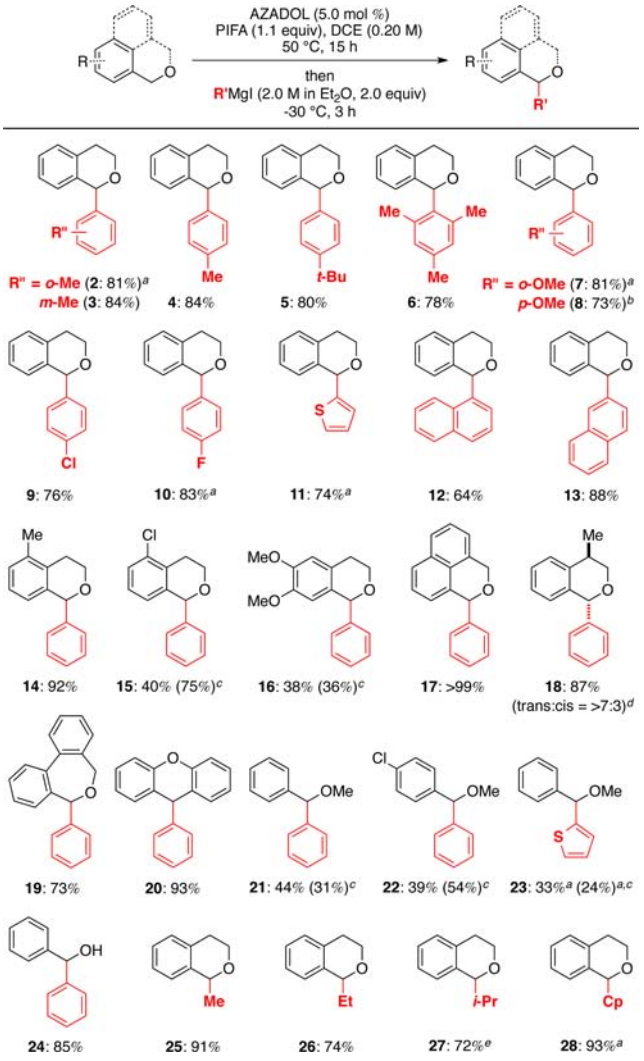
Scheme 3. AZADOL-Catalyzed C(sp^3)−C Bond Formation of Isochroman and Its Derivatives with Grignard Reagents

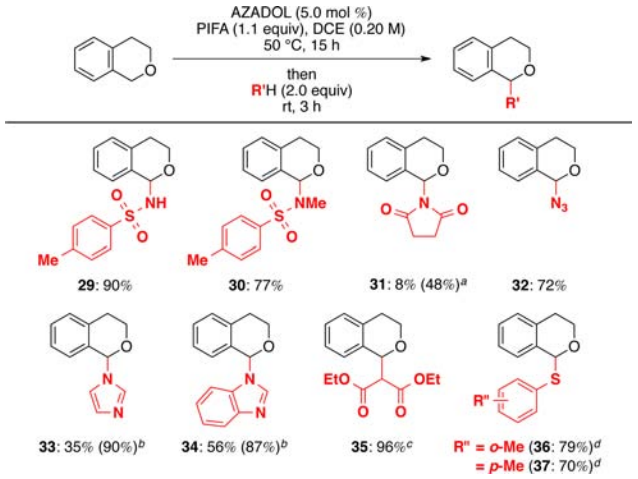


[a]R′MgBr/Et_2O was used. [b]R′MgBr/THF was used. [c]AZADOL (20 mol %) was used. [d]The ratio was calculated by ^{1}H NMR analysis. [e]R′MgBr/2-MeTHF was used.

or heterocyclic Grignard reagents also reacted with isochroman to produce **11**−**13** in 74%, 64%, and 88% yields, respectively. Furthermore, the catalytic conditions were applied in the C(sp^3)−H bond arylation of isochroman derivatives, xanthene, and acyclic benzyl ethers, as well as in the C(sp^3)−H bond alkylation of isochroman (**14**−**28**, 33−>99% yields). Specifically, **21** contains a partial fragment of RS1478. Additionally, it is known that DAMNI analogues such as **11** and **23** that contain a thiophene moiety show better anti-HIV-1 activity than RS1478;[2c] thus, our method can serve as a novel model technique in the synthesis of drug candidates. In some cases, moderate yields were observed (**15**, **16**, and **21**−**23**). The yields of **15** and **22** were easily improved by further addition of AZADOL, since the oxidation of the corresponding starting materials was most likely suppressed owing to the electronic effects of their Cl moieties. On the other hand, the yields of **16**, **21**, and **23** could not be improved because of the formation of side products.

The extension of this catalytic protocol to form novel C(sp^3)−C, C(sp^3)−N, and C(sp^3)−S bonds at the C(1)-position of isochroman is shown in Scheme 4. Tosylamides, sodium azide, and imidazoles acted as suitable nucleophiles under the catalytic

Scheme 4. AZADOL-Catalyzed C(sp^3)−X (X = C, N, S) Bond Formation of Isochroman



[a]The yield was calculated by ^{1}H NMR analysis using 1,4-bis(trifluoromethyl)benzene as the internal standard. [b]Nucleophilic addition of imidazoles (3.0 equiv) was carried out at 50 °C. [c]Al$(OTf)_3$ (5.0 mol %) was added. [d]See ref 13.

conditions to form C(sp^3)−N bonds in **29**, **30**, and **32**−**34** (72−90% yields). Additionally, succinimide also reacted with isochroman giving a moderate yield of the product **31**. Unfortunately, **31** was unstable on the SiO_2, resulting in a much lower isolated yield than that determined by ^{1}H NMR analysis. In contrast, structurally similar nucleophiles such as phthalimide and indole did not couple with isochroman at all. Finally, the enolate generated by the coordination of Al$(OTf)_3$ to diethyl malonate smoothly coupled with isochroman to provide **35**, as well as **36** and **37** via C(sp^3)−S bond formation with thiophenols.

A possible catalytic mechanism for the present AZADOL catalysis is illustrated in Scheme 2. Initially, PIFA radically oxidizes AZADOL to form oxoammonium cation **A** via AZADO.[14] Subsequently, the oxidation of isochroman by oxoammonium cation **A** provides oxocarbenium cation **B** and AZADOL.[15] Finally, the nucleophilic addition of various nucleophiles (RMgI and RH) to oxocarbenium cation **B** affords the corresponding C(1)-functionalized isochromans.

In conclusion, we have developed a novel catalytic strategy for the C(sp^3)−H bond functionalization of isochroman. This catalytic reaction proceeds smoothly in the presence of safe and environmentally friendly oxidants, AZADOL and PIFA, under practical conditions. In addition, the reaction conditions can be applied not only with various substrates (isochroman, its derivatives, and acyclic benzyl ethers) but also to introduce various functional groups (aryl, alkyl, amide, amino, and sulfanyl groups). The development of the asymmetric C(sp^3)−H bond functionalization of isochroman is now under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of spectra for all 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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DEDICATION

This work is dedicated to Professor Takeo Kawabata, Kyoto University, on the occasion of his 60th birthday.

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(7) Rat LD_{50} oral values of DDQ (82 mg/kg) are indicated on Acros Organics MSDS sheets. Additionally, DDQ poses a risk in that it reacts with water to liberate HCN.

(8) Several hypervalent iodine(III) reagents including PIFA are used as safe and environmentally friendly alternatives to toxic metallic and organic oxidants. 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) Yusubov, M. S.; Zhadankin, V. V. *Curr. Org. Synth.* **2012**, *9*, 247−272.

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(12) Additional experiments are described in the Supporting Information.

(13) The yields were calculated by ^{1}H NMR analysis after a mixture of **36** (or **37**) and the corresponding disulfide as a side product was isolated.

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