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Oxidative C–N Bond Formation of Isochromans Using an Electronically Tuned Nitroxyl Radical as Catalyst

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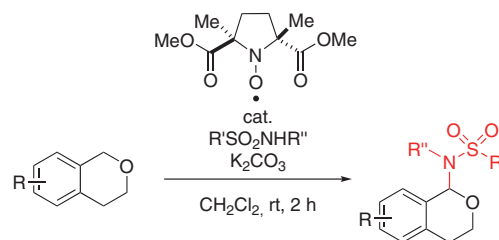
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Abstract The cross-dehydrogenative coupling between isochromans and nucleophiles using an electronically tuned nitroxyl radical catalyst, which effectively promotes the oxidation of benzylic ethers, has been investigated. Using sulfonamides as a nucleophile, modification of isochromans via oxidative C–N bond formation has been achieved at ambient temperature.

Keywords isochroman, cross-dehydrogenative coupling, nitroxyl radical, C–N bond formation, organocatalyst, oxidation

Owing to their attractive properties, isochromans, which are cyclic benzyl ethers that are frequently found in natural and synthesized bioactive compounds, have attracted considerable research attention (Figure 1).[1] To date, numerous synthetic methods have been reported for the modification of isochromans. The oxidative transformation of the benzylic carbon of isochromans has been widely reported as one of the most effective ways to synthesize isochromans functionalized at the α-position with respect to the oxygen atom. Indeed, a variety of transition-metal-catalyzed[2,3] and organocatalytic[4,5] methods have already been reported to achieve this transformation. Nitroxyl-type catalysts such as 2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO),[6] 2-azaadamantane N-oxyl (AZADO),[7] and their derivatives have frequently been employed as organocatalysts for the oxidation of alcohols. Due to their high level of safety and environmentally benign nature, these catalysts are even used in process chemistry.[8] Although examples of the use of nitroxyl-type catalysts for the oxidation of other functional groups are still scarce,[9] the oxidation of isochromans under acidic conditions using TEMPO sulfonate derivative **1** has recently been reported.[4a] In addition, Foss and co-workers have reported the oxidation of cyclic ethers with TEMPO in the presence of flavin and nitromethane,[4c] while Muramatsu and co-workers have developed oxidative C–C, C–N, and C–S bond-formation reactions using AZADOL, which is a reduced form of AZADO (Scheme 1a).[5b] Unfortunately, these catalytic transformations using TEMPO and AZADO require elevated temperatures,[4c,5b] and further improvement is required to realize practical applications.
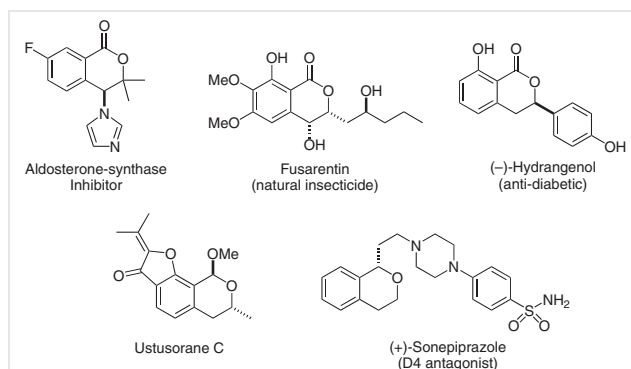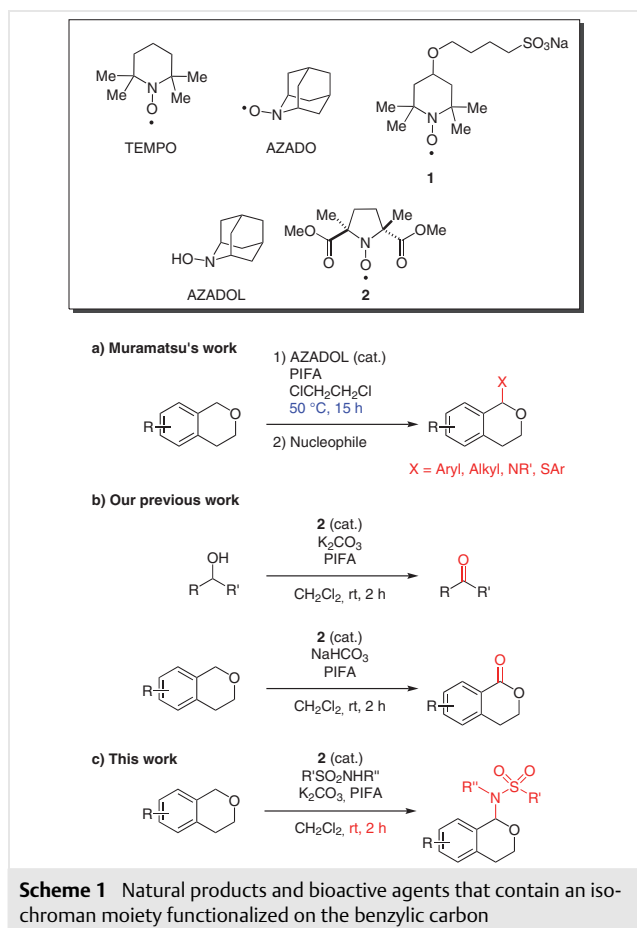

Figure 1 Natural products and bioactive agents that contain an isochroman moiety functionalized on the benzylic carbon

We have previously developed a highly reactive nitroxyl-radical catalyst **2** (Scheme 1), whose reactivity can be electronically tuned by introducing electron-withdrawing ester groups adjacent to the nitroxyl group.[10,11] This catalyst oxidizes acyclic benzylic ethers such as p-methoxybenzyl and benzyl ethers at room temperature, thus achieving the deprotection of benzyl-type protecting groups for alcohols.[12] We also applied the electronically tuned catalyst **2** to the oxidation of isochromans to synthesize isochroma-

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nones (Scheme 1b).[4d] The oxidative transformations of these benzylic ethers proceed rapidly at room temperature. In this paper, we report the modification of isochromans via oxidative C–N bond formation using nitroxyl-radical catalyst **2** at ambient temperature (Scheme 1c).

Scheme 1 Natural products and bioactive agents that contain an isochroman moiety functionalized on the benzylic carbon

As part of our efforts to develop a catalytic cross-dehydrogenative coupling using isochromans as substrates, we first investigated the optimal reaction conditions in terms of base and solvent (Table 1). Treatment of isochroman with 1.2 equivalents of phenyliodine bis(trifluoroacetate) (PIFA), 4 equivalents of potassium carbonate, and 2 equivalents of *p*-toluenesulfonamide in the presence of 10 mol% of racemic **2** in CH_2Cl_2 at room temperature resulted in the rapid formation of **3**, which contains a C–N bond, in 85% yield (entry 1).[13,14] While the yield was slightly reduced when no base was used (entry 2), the use of sodium bicarbonate had a similar effect on the improvement of yield as the use of potassium carbonate (entry 3). Pyridine was also tested as an organic base, which is soluble in dichloromethane, but the reaction did not proceed (entry 4).[15] Next, we tried to identify the optimal co-oxidant. Although [hydroxy(tosyloxy)iodo]benzene (HTIB) furnished **3** in 72% yield (entry 5), iodobenzenediacetate (PIDA) and trichloroisocyanuric

acid (TCCA), which have been used for the oxidation of nitroxyl radicals,[16] produced hardly any of the coupling product **3** (entries 6 and 7) due to their relatively low reactivity. A screening of solvents revealed that 1,2-dichloroethane afforded results similar to those obtained using dichloromethane (entry 8), whereas more polar solvents such as THF and MeCN resulted in lower yields and recovery of starting material (entries 9 and 10). Meanwhile, attempts to use diethyl malonate, TMSCN, and 2-methylbenzenethiol as nucleophiles for the oxidative coupling to achieve C–C or C–S bond formation did not afford the desired products.

Table 1 Optimization of the Reaction Conditions

Entry	Variation from the 'standard' conditions	Yield (%)[a]
1	none	85
2	no K_2CO_3	73
3	$NaHCO_3$ instead of K_2CO_3	79
4	pyridine instead of K_2CO_3	<5
5	HTIB instead of PIFA	72
6	PIDA instead of PIFA	<5
7	TCCA instead of PIFA	<5
8	$ClCH_2CH_2Cl$ instead of CH_2Cl_2	85
9	THF instead of CH_2Cl_2	<5
10	MeCN instead of CH_2Cl_2	<5

[a] Yield determined by ^1H NMR analysis of the crude reaction residue using methyl 3,5-dinitrobenzoate as an internal standard.

As compound **3** was obtained via the oxidative coupling of isochroman and *p*-toluenesulfonamide, we subsequently investigated the substrate scope of this reaction (Table 2). First, the effect of the substituent on the benzene ring was studied. An electron-donating methyl group at the *ortho*-, *meta*-, or *para*-position and a methoxy group at the *para*-position successfully afforded the corresponding coupling products **3–6** in good to high yield (63–87%). Although benzenesulfonamides without substituents and with a chloro group at the *para*-position gave **7** and **8** in moderate yield (49% and 46%, respectively). A sulfonamide with a nitro group at the *meta*-position, that was less nucleophilic than above, afforded **9** in low yield (35%). Then, alkylsulfonamides were investigated as nucleophiles, which revealed that methyl sulfonamide afforded **10** in 53% yield, whereas trifluoromethyl sulfonamide did not furnish the corresponding product **11**, probably due to the instability of **11** in the presence of the highly electron-withdrawing trifluoromethanesulfonyl group. Next, several *N*-methylsulfonamides **12–14** were synthesized, although the yields of the

products **12** and **13** were lower than the corresponding protonated sulfonamides **3** and **10**, possibly due to the steric hindrance of the nucleophiles. We also tested dibenzenesulfonimide as a nucleophile; unfortunately, the desired product **15** was not obtained, probably due to the high leaving-group properties of the sulfonimide. The effect of the presence of substituents on the phenyl ring of the isochromans was then investigated. An electron-rich arene bearing a methyl substituent yielded the corresponding product **16** in low yield, possibly because **16** is unstable due to the good stability of the oxocarbenium cation produced from 7-methylisochroman. In contrast, the electron-deficient fluorine-containing derivative afforded **17** in good yield (62%). We also tested a substrate with a naphthalene ring; however, the corresponding coupling product **19** was obtained only in low yield (26%).

A plausible mechanism for the oxidation of isochromans induced by **2** is shown in Scheme 2. First, oxoammonium **A** is formed via the oxidation of nitroxyl radical **2** by PIFA. The rate-determining hydride transfer from the benzylic C–H bond of the isochromans to the oxygen of oxoammonium **A** affords hydroxyamine **B** and oxocarbenium cation **C**.[4d,17] Subsequent addition of the sulfonamide to **C** then leads to hemiaminal ether **D**.

In conclusion, we have investigated the efficacy of the **2**/PIFA system for the cross-dehydrogenative coupling of isochromans.[18,19] Although it is generally not effective for several C–C bond formations, this system enables the fast formation of C–N bonds using sulfonamides as a nucleophile at room temperature. Further studies on the derivatization of the coupling products by taking advantage of the reactivity of sulfonamides are in progress in our laboratories.
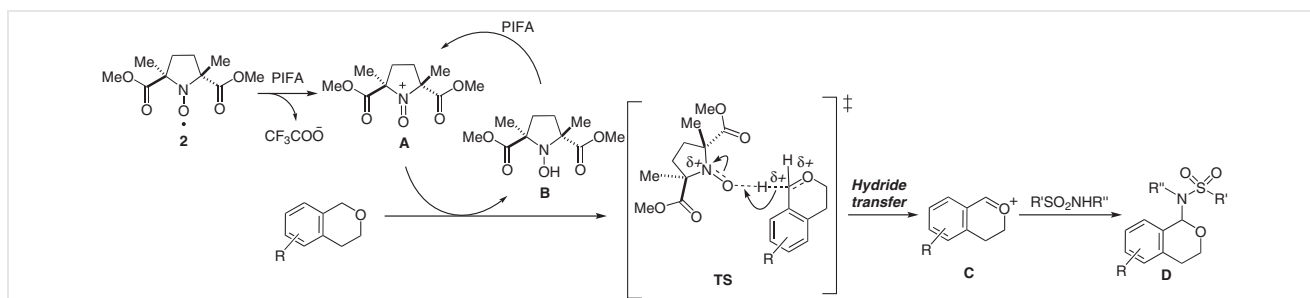
Conflict of Interest

The authors declare no conflict of interest.

Table 2 Substrate Scope
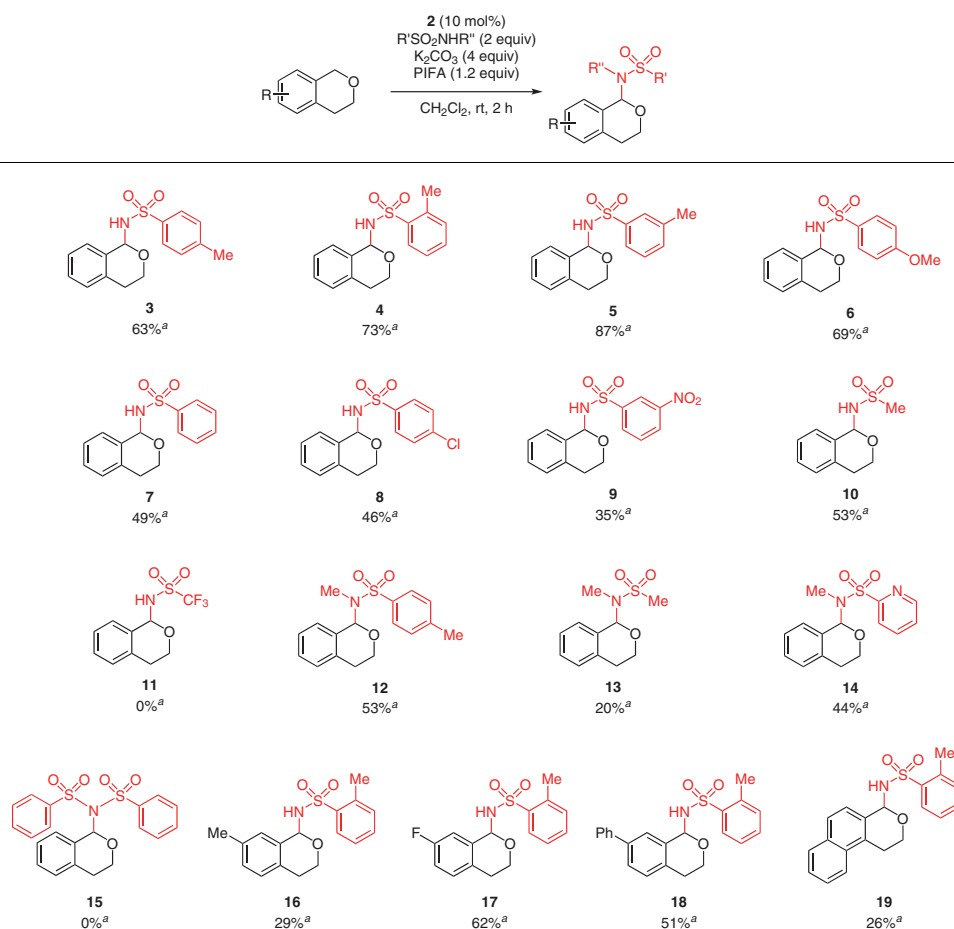
Scheme 2 Plausible mechanism for the oxidation of isochromans promoted by nitroxyl radical **2**

Funding Information

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1720118.

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(11) Catalyst **2** can be used in the oxidation of isochroman on a gram scale; for details, see ref. 4d

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(13) A small amount of 1-isochromanone was also produced as a byproduct.

(14) In the absence of **1**, no product was obtained.

(15) Weak inorganic bases probably neutralize trifluoroacetic acid derived from PIFA slowly in dichloromethane, whereas organic bases are much faster. The differences in solution acidity may affect the reactivity and selectivity of the oxidation catalyzed by **2**. For examples of the acidity affecting the reactivity of the oxidation mediated by nitroxyl-radical catalysts or oxoammonium salts, see: (a) Bailey, W. F.; Bobbitt, J. M.; Wiberg, K. B. *J. Org. Chem.* **2007**, *72*, 4504. (b) Hamada, S.; Sakamoto, K.; Miyazaki, E.; Elboray, E. E.; Kobayashi, Y.; Furuta, T. *ACS Catal.* **2023**, *13*, 8031.

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(17) The hydride-transfer step has already been proposed as the rate-determining step in the oxidation of isochromans to the corresponding oxocarbenium cations; for details, see ref. 4d.

(18) **General Procedure**
PIFA (103 mg, 0.240 mmol) was added to a mixture of isochroman (26.8 mg, 200 mmol), **2** (4.6 mg, 20 µmol), K_2CO_3 (111 mg, 0.800 mmol), and sulfonamide (0.400 mmol) in DCM (2.0 mL). The resulting mixture was stirred under N_2 atmosphere for 2 h

at room temperature. Then, the reaction was quenched with saturated aq. $Na_2S_2O_3$ and extracted with $CHCl_3$. Subsequently, the organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

(19) **Representative Spectral Data *N*-(Isochroman-1-yl)-4-methylbenzenesulfonamide (3)**[1]
The title compound **3** (38.0 mg, 63%) was synthesized from isochroman (26.8 mg, 0.200 mmol) and 4-methylbenzenesulfonamide (68.5 mg, 0.400 mmol).

Colorless solid; mp 178–181 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.5 Hz, 2 H), 7.31 (d, *J* = 7.9 Hz, 2 H), 7.26–7.18 (m, 3 H), 7.08 (d, *J* = 7.2 Hz, 1 H), 6.10 (d, *J* = 8.6 Hz, 1 H), 5.40 (d, *J* = 8.6 Hz, 1 H), 3.73–3.57 (m, 2 H), 2.85 (ddd, *J* = 15.9, 9.7, 6.0 Hz, 1 H), 2.61 (dt, *J* = 16.7, 4.0 Hz, 1 H), 2.44 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.40, 138.79, 134.54, 132.82, 129.52, 128.87, 128.47, 127.25, 126.84, 126.76, 79.91, 58.76, 27.58, 21.63. IR (ATR) 3202, 1328, 1157, 748 cm^{-1}. HRMS (ESI): *m/z* [M + Na]+ calcd for $C_{16}H_{17}NNaO_3S$: 326.0827; found: 326.0829.