Expansion of Substrate Scope for Nitroxyl Radical/Copper-Catalyzed Aerobic Oxidation of Primary Alcohols: A Guideline for Catalyst Selection

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Four distinctive sets of optimum nitroxyl radical/copper salt/additive catalyst combinations have been identified for accommodating the aerobic oxidation of various types of primary alcohols to their corresponding aldehydes. Interestingly, less nucleophilic catalysts exhibited higher catalytic activities for the oxidation of particular primary allylic and propargylic alcohols to give α,β-unsaturated aldehydes that function as competent Michael acceptors. The optimum conditions identified herein were successful in the oxidation of various types of primary alcohols, including unprotected amino alcohols and divalent-sulfur-containing alcohols in good-to-high yields. Moreover, N-protected alaninol, an inefficient substrate in the nitroxyl radical/copper-catalyzed aerobic oxidation, was oxidized in good yield. On the basis of the optimization results, a guideline for catalyst selection has been established.

Key words oxidation; nitroxyl radical; copper; chemoselectivity; alcohol

Introduction

The oxidation of alcohols to their corresponding carbonyl compounds is a fundamental transformation in the synthesis of medicinally relevant compounds and various other industrially valuable materials.1–3 Numerous methods have been developed to realize this visually-simple transformation. However, methods that satisfy good functional group tolerance as well as environmental friendliness are limited. Oxidations that utilize molecular oxygen as the terminal oxidant are ideal reactions because of the availability of molecular oxygen and environmental friendliness of the byproduct, namely water. Therefore, aerobic oxidation of alcohols has been extensively investigated, and various catalytic systems have been reported.4–8 One of the most investigated catalytic systems is the combination of a nitroxyl radical (Fig. 1) and copper salt.9–12 Following the first report by Semmelhack et al. in 1984,13 entailing the use of 2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO) and CuCl as catalysts for the oxidation of benzylic and allylic alcohols, the efficiency and substrate scope of nitroxyl radical/copper-catalyzed aerobic alcohol oxidation has been improved with the discovery of suitable ligands and additives, such as 2,2′-bipyridine (bpy; Sheldon and colleagues),14,15 and N-methylimidazole (NMI; Kumpulainen and Koskinen).16 In 2011, Hoover and Stahl reported a catalytic system consisting of TEMPO/copper(I) trifluoromethanesulfonate (CuOTf)/bpy/NMI capable of oxidizing a wide range of unactivated aliphatic primary alcohols in high yields at room temperature in ambient air.17 In 2013, Steves and Stahl utilized 9-azabicyclo[3.3.1]nonane N-oxyl (ABNO), a less-hindered nitroxyl radical, instead of TEMPO, to efficiently oxidize secondary alcohols.18 We have disclosed an exceptionally chemoselective aerobic alcohol oxidation method wherein a combination of 2-azaadamantane N-oxyl (AZADO) and a copper salt are employed. The catalyst combination of AZADO/CuCl/bpy/4-dimethylaminopyridine (DMAP) selectively oxidized alcohols even in the presence of unprotected amines in good to high yields with molecular oxygen in ambient air at room temperature.19 Furthermore, the AZADO/copper-catalyzed aerobic alcohol oxidation protocol tolerated divalent sulfur functionalities.20 The usefulness of the reaction has been demonstrated by its successful application to the oxidation of multifunctional alcohols in the synthesis of natural products.21–26 While optimizing the reaction conditions for nitroxyl radical/copper-catalyzed aerobic oxidation of several alcohols, we established that the optimum combination of nitroxyl radical and copper salt is dependent on the nature of the substrate.27 During this optimization study, we discovered that less hindered nitroxyl radicals, such as ABNO and AZADO, were deactivated during the oxidation of simple linear aliphatic alcohols, most likely due to oxidative condensation of the aldehyde products with catalytic hydroxylamines generated from less hindered nitroxyl radicals. The use of TEMPO is an effective solution for preventing such deactivation and obtaining aldehydes in high yields, likely as a result of the steric bulkiness of TEMPO. However, this steric effect attenuates the catalytic efficiency of the desired reaction, especially in the oxidation of β-branchied alcohols, which necessitates elevated temperatures.17 These factors complicate the choice of catalysts for the nitroxyl radical/copper-catalyzed aerobic alcohol oxidation of primary alcohols. These considerations urged us to establish a guideline for catalyst selection. Herein, we report a careful optimization of reaction conditions for the oxidation of various types of primary alcohols. Through op-
timization, we were able to identify four distinctive optimum combinations of nitroxyl radicals, copper salts, and an additive for the oxidation of various primary alcohols in good to high yields. On the basis of the optimization results, a guideline for determining the optimum conditions for the nitroxyl radical/copper-catalyzed aerobic oxidation of primary alcohols has been established.

**Results and Discussion**

Careful optimization of reaction conditions was conducted using allylic alcohols $1a$–$1c$, linear aliphatic alcohols $1d$–$1h$, and $\beta$-branched alcohols $1i$–$1m$ as model substrates (Table 1).

| entry | substrate | GC conv. $^a$ | TEMPO | 1-Me-AZADO | AZADOL | 4-AcNHN-TEMPO |
|-------|-----------|--------------|-------|------------|--------|---------------|
| 1     | $1a$      | 100% $(x=2, 1\,\text{h})$ | 100% $(x=2, 1\,\text{h})$ | N. D. | 100% $(x=2, 2\,\text{h})$ |
| 2     | $1b$      | 100% $(x=2, 2\,\text{h})$ | 100% $(x=2, 2\,\text{h})$ | N. D. | 100% $(x=2, 3\,\text{h})$ |
| 3     | $1c$      | 61% $(x=3, 18\,\text{h})$ | 21% $(x=3, 0.5\,\text{h})$ | 25% $(x=3, 0.5\,\text{h})$ | 74% $(x=3, 12\,\text{h})$ |
| 4     | $1d$      | 88% $(x=2, 9\,\text{h})$ | 82% $(x=2, 3\,\text{h})$ | N. D. | 80% $(x=2, 9\,\text{h})$ |
| 5     | $1e$      | 97% $(x=2, 24\,\text{h})$ | 91% $(x=2, 6\,\text{h})$ | N. D. | N. D. |
| 6     | $1f$      | 93% $(x=3, 5\,\text{h})$ | 96% $(x=3, 5\,\text{h})$ | N. D. | N. D. |
| 7     | $1g$      | 94% $(x=3, 6\,\text{h})$ | 94% $(x=3, 2\,\text{h})$ | 56% $(x=3, 1\,\text{h})$ | N. D. |
| 8     | $1h$      | 71% $(x=3, 2\,\text{h})$ | 86% $(x=3, 1\,\text{h})$ | N. D. | N. D. |
| 9     | $1i$      | 20% $(x=2, 6\,\text{h})$ | 100% $(x=2, 2\,\text{h})$ | 100% $(x=2, 2\,\text{h})$ | N. D. |
| 10    | $1j$      | 0.54% $(x=2, 1\,\text{h})$ | 97% $(x=2, 6\,\text{h})$ | 95% $(x=2, 6\,\text{h})$ | N. D. |
| 11    | $1k$      | 1.4% $(x=3, 3\,\text{h})$ | 46% $(x=3, 3\,\text{h})$ | 46% $(x=3, 3\,\text{h})$ | N. D. |
| 12    | $1l$      | 0.95% $(x=5, 1\,\text{h})$ | 100% $(x=5, 1\,\text{h})$ | 96% $(x=5, 1\,\text{h})$ | N. D. |
| 13    | $1m$      | 9.5% $(x=3, 3\,\text{h})$ | 84% $(x=3, 3\,\text{h})$ | 50% $(x=3, 1\,\text{h})$ | N. D. |

*Table 1. Optimization of Nitroxyl Radicals*

*a* GC conv. was determined as the ratio of the peak areas [product/[product + substrate]].

N. D. = not determined.

b) Side product $3$ was observed.  c) The reaction was performed at $0\,\text{C}$. 
Alcohols 1f, 1g, and 1k contain a divalent sulfur functional group; 1h and 1l contain an unprotected amino group, while the amino moiety of 1m was protected. Catalytic efficiencies were evaluated by GC.

Catalytic activities of the nitroxyl radicals (x mol%; the values of x are indicated in Table 1) were evaluated using CuBr (2x mol%), bpy (x mol%), and DMAP (2x mol%) as co-catalysts, in acetonitrile at room temperature in ambient air. The steric effect of the nitroxyl radicals was evaluated by comparison of the results obtained with TEMPO (the most hindered), 1-Me-AZADO (moderately hindered), and AZADOL (commercially available hydroxylamine equivalent of AZADO and the least hindered). The electronic effect was evaluated by employing TEMPO and electron-withdrawing-group-bearing 4-acetamido-TEMPO (4-AcNH-TEMPO) in the oxidation, and employing TEMPO and electron-withdrawing-group-bearing 4-acetamido-TEMPO (4-AcNH-TEMPO) in the oxidation, and comparing the results thereof. Allylic alcohols 1a and 1b were quantitatively oxidized with all the tested reagents, namely TEMPO, 1-Me-AZADO, and 4-AcNH-TEMPO (entries 1 and 2). Interestingly, TEMPO afforded a significantly higher conversion (61%) in the oxidation of 3-bromoallyl alcohol (1c) than that attained with 1-Me-AZADO and AZADOL, whereby the reaction did not progress after 30 min and approximately 20% conversion (entry 3). 4-AcNH-TEMPO provided a higher conversion (74%) than obtained with TEMPO for this reaction. TEMPO afforded superior results to those of 1-Me-AZADO for the oxidation of linear aliphatic alcohols 1d and 1e, lacking amino and sulfur functional groups (entries 4 and 5). Small amounts of dimeric esters 3d and 3e were observed during the oxidation of 1d and 1e with 1-Me-AZADO, while these side products were not formed in the reaction with TEMPO. The conversion of 3-phenylpropanol (1d) was lower with the use of 4-AcNH-TEMPO than that with TEMPO. While 1-Me-AZADO and TEMPO provided comparable conversions in the oxidation of sulfur-containing alcohols 1f and 1g (entries 6 and 7), 1-Me-AZADO led to a higher conversion than obtained with TEMPO in the oxidation of unprotected amino alcohol 1h (entry 8). TEMPO was inefficient in the oxidation of β-branched alcohols 1i–1m, resulting in low conversion to products (entries 9–13). On the other hand, 1-Me-AZADO and AZADOL led to significantly higher conversions and 1-Me-AZADO exhibited superior activity to that of AZADOL, especially in the oxidation of tert-butoxycarbonyl (Boc)-protected amino alcohol 1m. Note that the oxidation of thiacycle-containing alcohol 1k at room temperature generated several side products (data not shown). Although lowering the reaction temperature to 0°C suppressed the generation of side products, it decelerated the desired reaction, resulting in moderate conversion (entry 11).

Using the optimal nitroxyl radical for each substrate, the copper salt and additive were optimized. On the basis of Stahl's previous results, the combinations of CuBr/NMI, CuBr/DMAP, CuOTf/NMI, and CuOTf/DMAP were examined (Table 2). CuBr/DMAP oxidized allylic alcohols 1a and 1b quantitatively within the shortest time (1 h), while the other combinations provided the same conversion (entries 1 and 2). However, the oxidation of 3-bromoallyl alcohol (1c) was not quantitative with the use of CuBr/DMAP, in contrast to conversions obtained with the other combinations (entry 3). Linear aliphatic alcohols 1d and 1e, lacking amino and sulfur functional groups, were oxidized with the highest conversion within the shortest time with CuOTf/DMAP (entries 4 and 5). For the oxidation of linear aliphatic alcohols 1f–1h, bearing an amino or sulfur functional group, DMAP gave comparable or superior results when compared to those of NMI, and the catalytic activities of CuBr/DMAP and CuOTf/DMAP were similar (entries 6–8). In the case of β-branched alcohols 1i–1m, DMAP afforded a shorter reaction time for 1i, and a higher conversion for 1m than the corresponding reactions with NMI (entries 9 and 13). For the remaining β-branched alcohols, all examined combinations led to equivalent conversions (entries 10–12). The moderate conversion obtained in the oxidation of 1k was not improved by the optimization of copper salts and additives when the reaction was performed at 0°C to suppress the generation of side products (entry 11). Conducting the reaction at room temperature with increasing amounts of catalysts achieved near-complete consumption of 1k.

Chemical yields of the aldehyde products were determined using individually optimized conditions. Aldehydes 2c, 2e, and 2l were converted to the corresponding α,β-unsaturated esters 4 to circumvent their instability, volatility, and racemization, respectively (Table 3). Allylic alcohols 1a–1e, aliphatic alcohols 1d, 1e, 1i, and 1j, lacking an amino or sulfur functional group, were successfully oxidized to the corresponding aldehydes in high yields (entries 1–5, 9, and 10). Although sulfide-containing linear aliphatic alcohol 1f was oxidized in high yield, dithiane- and unprotected-amine-containing alcohols 1g and 1h were converted to aldehydes 2g and 2h, respectively, in yields below 90% (entries 6–8). In the oxidation of 1f, 1g, and 1h with 1-Me-AZADO, dimeric esters in approximately 3% yield (see compound 3 in Table 1) were observed in the NMR spectra of the crude products. The use of TEMPO instead of 1-Me-AZADO improved the yield of sulfur-containing aldehydes 2f and 2g, but it provided a lower yield of unprotected amino aldehyde 2h due to a lower conversion (entries 6–8). Note that dimeric esters 3 were not observed in the NMR spectra of the crude products obtained from TEMPO-mediated oxidation of 1f, 1g, and 1h. These results indicate that TEMPO is suitable for the oxidation of linear aliphatic alcohols with divalent sulfur functionalities, and that 1-Me-AZADO is suitable for the oxidation of linear aliphatic alcohols bearing unprotected amines. More challenging substrates, specifically β-branched alcohols bearing sulfur or amino functional groups, were oxidized in 69–82% yields (entries 11–13). No racemization was observed for the oxidation of N-benzylprolinol (1l) (entry 12).

During the above-described optimization of reaction conditions, it was noted that 3-bromoallyl alcohol (1c) exhibited reactivity that was distinct from that of the other alcohols. That is, 4-AcNH-TEMPO and NMI provided higher conversions than those obtained with TEMPO and DMAP. Note that, in our previous study, we found that the combination of a nitroxyl radical lacking an electron-withdrawing group and DMAP consistently exhibited higher catalytic activity than that of a nitroxyl radical bearing an electron-withdrawing group and NMI. It was hypothesized that the specific optimum catalyst combination for 1c arose from the reactivity of the nitroxyl radicals and additives with the aldehyde product, 3-bromoaureinol (2e), which is a competent Michael acceptor. Highly nucleophilic hydroxylamines generated in situ from the nitroxyl radicals and additives would be deactivated via Michael addition to 2e, while those with lower nucleo-
philicity would stay intact during alcohol oxidation (Chart 1).

The electron-withdrawing nature of the acetamido group of 4-AcNH-TEMPO reduces the nucleophilicity of the resultant hydroxylamine. Mayr’s nucleophilicity parameter $N$ indicates the lower nucleophilicity of NMI ($N = 10.9$ in MeCN) compared to that of DMAP ($N = 15.8$ in MeCN).28)

To evaluate the reactivity of DMAP and NMI with 3-bromoacrolein (2c), which cannot be isolated because of its instability, we conducted reactions with in situ generated 2c and these two reagents. A stoichiometric amount of each nucleophilic reagent was added to the 1c oxidation reaction mixture after confirmation of full conversion (Chart 2). The amount of remaining 2c was quantified by GC analysis 30 min after the addition. In the case of DMAP, the majority of 2c was consumed within 30 min and a white precipitate was formed. On the other hand, 83% of 2c remained in the case of NMI.

Table 2. Optimization of Copper Salts and Additives

| entry | substrate | nitroxyl radical | CuBr, NMI | CuBr, DMAP | CuOTf, NMI | CuOTf, DMAP |
|-------|-----------|------------------|-----------|------------|------------|-------------|
| 1     | Ph - OH   | TEMPO            | 100% (x=2, 2 h) | 100% (x=2, 1 h) | 100% (x=2, 4 h) | 100% (x=2, 3 h) |
| 2     | Me - OH   | TEMPO            | 100% (x=2, 2 h) | 100% (x=2, 2 h) | 100% (x=2, 9 h) | 100% (x=2, 6 h) |
| 3     | Br - OH   | 4-AcNH-TEMPO     | 100% (x=3, 1 h) | 74% (x=3, 12 h) | 100% (x=3, 3 h) | 100% (x=3, 9 h) |
| 4     | Ph - OH   | TEMPO            | 91% (x=2, 9 h) | 98% (x=2, 9 h) | 98% (x=2, 9 h) | 94% (x=2, 4 h) |
| 5     | MeS - OH  | TEMPO            | 90% (x=2, 12 h) | 97% (x=2, 12 h) | 100% (x=2, 12 h) | 100% (x=2, 8 h) |
| 6     | 1-Me-AZADO | 1-Me-AZADO     | 89% (x=3, 9 h) | 95% (x=3, 5 h) | 95% (x=3, 6 h) | 92% (x=3, 6 h) |
| 7     | 1-Me-AZADO | 1-Me-AZADO     | 92% (x=3, 6 h) | 94% (x=3, 2 h) | 96% (x=3, 6 h) | 96% (x=3, 2 h) |
| 8     | 1-Me-AZADO | 1-Me-AZADO     | 88% (x=3, 1 h) | 66% (x=3, 1 h) | 66% (x=3, 1 h) | 78% (x=3, 2 h) |
| 9     | 1-Me-AZADO | 1-Me-AZADO     | 100% (x=2, 6 h) | 100% (x=2, 2 h) | 100% (x=2, 6 h) | 100% (x=2, 3 h) |
| 10    | 1-Me-AZADO | 1-Me-AZADO     | 96% (x=2, 6 h) | 97% (x=2, 6 h) | 99% (x=2, 24 h) | 100% (x=2, 24 h) |
| 11    | 1-Me-AZADO | 1-Me-AZADO     | 45%b (x=3, 3 h) | 48%b (x=3, 3 h) | 44%b (x=3, 3 h) | 49%b (x=3, 12 h) |
| 12    | 1-Me-AZADO | 1-Me-AZADO     | 100% (x=5, 1 h) | 100% (x=5, 1 h) | 100% (x=5, 2 h) | 100% (x=5, 1 h) |
| 13    | 1-Me-AZADO | 1-Me-AZADO     | 75% (x=3, 2 h) | 84% (x=3, 3 h) | 91% (x=3, 6 h) | 98% (x=3, 12 h) |

a) GC conv. was determined as the ratio of the peak areas [product/product + substrate].
b) The reaction was performed at 0 °C.
These results indicated that DMAP reacts with 2c at a higher rate than NMI.

Catalytic activities of DMAP and NMI were compared in the oxidation of 3-phenyl-2-propyn-1-ol (1n), the oxidation product of which is likewise a competent Michael acceptor (Chart 3). As expected from the aforementioned findings, DMAP-mediated oxidation furnished aldehyde 2n in 65% yield and a precipitate was generated while 16% 1n remained unreacted. On the other hand, conditions entailing NMI gave a high yield (89%) of aldehyde 2n with complete conversion. The oxidation of N-protected alaninol was examined. Hoover and Stahl reported that the oxidation of N-benzyl-
oxycarbonyl (Cbz)-alaninol proceeded incompletely (64\% of the substrate remained) under TEMPO/CuOTf/bpy/NMI-catalyzed conditions. Here, N-Boc-alaninol (1o) was used as the substrate, and the aldehyde product was converted to its corresponding $\alpha,\beta$-unsaturated ester 5o before isolation to prevent aldehyde racemization (Chart 4). During the optimization of reaction conditions (see Supplementary Materials) it was found that molecular sieves and an oxygen atmosphere at balloon pressure were necessary to achieve complete conversion. Eventually, optimal conditions were established, entailing a 1-Me-AZADO/CuBr/bpy/DMAP (3/6/3/6 mol\%) catalyst combination in acetonitrile in the presence of molecular sieves 3A under molecular oxygen at balloon pressure at room temperature, for the complete oxidation of 1o within 10 min, and the subsequent Wittig reaction afforded 5o in the highest yield (71\%). Although these conditions induced a slight loss of enantiopurity (91\% enantiomeric excess (ee)), Swern oxidation of the same substrate induced a more significant loss (24\% ee), and the loss observed with Dess–Martin oxidation conditions (92\% ee) was comparable to that of our protocol. Note that CuOTf, which gave the highest conversions for the $\beta$-branched alcohols in Table 2, also oxidized 1o completely, but gave a slightly lower yield (64\%) of 5o than obtained with CuBr (see Supplementary Materials).

On the basis of the aforementioned results, a guideline for the selection of optimum combinations of nitroxyl radical/copper salt/additive for the oxidation of primary alcohols is proposed as a flow chart in Fig. 2. Note that the presence of the bpy ligand is essential for the oxidation of all alcohol substrates. In cases where the oxidation products are competent Michael acceptors, less nucleophilic catalysts, namely, 4-AcNH-TEMPO and NMI, in combination with CuBr, are optimal for the oxidation of the corresponding alcohols. In cases where the substrates are allylic alcohols, the combination of TEMPO/CuBr/DMAP is optimal for their oxidation. Furthermore, according to our experience, benzylic alcohols were oxidized most efficiently under the latter conditions. $\beta$-Branched alcohols and those bearing unprotected amino groups are oxidized most effectively with 1-Me-AZADO/CuOTf/DMAP. Linear aliphatic alcohols without unprotected amino groups deliver the highest aldehyde yields when a combination of TEMPO/CuOTf/DMAP is applied. Note that if the alcohols to be oxidized contain amino or divalent sulfur groups, CuBr and/or NMI might give slightly better yields of the aldehydes than CuOTf and/or DMAP.

**Conclusion**

In conclusion, we have identified four distinct sets of optimum conditions for the aerobic chemoselective oxidation of primary alcohols under nitroxyl radical/copper catalysis. Careful optimization of the reaction conditions for various types of
primary alcohols revealed that the optimum catalyst combinations are dependent on the substrate type. Interestingly, less nucleophilic catalysts are suitable for the oxidation of allylic and propargylic alcohols into competent Michael acceptors. The sets of optimum catalyst combinations oxidized various types of primary alcohols in good to high yields, including N-Boc-alaninol, a problematic substrate for this approach. On literature procedure: (E)-3-bromoallyl alcohol (1c); distilled at 67–77 °C (25 hPa) prior to use;29) 6,8-bis(methylthio) octan-1-ol (1f), N-allyl-N-benzyl-6-amino-1-hexanol (1h), and N-benzyl-l-prolinol (1i).30)

Experimental

General Experimental Procedures All reactions were performed under an argon atmosphere with anhydrous solvents, unless otherwise noted. Anhydrous tetrahydrofuran (THF) and CH2Cl2 were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). Other solvents were dried and distilled according to standard protocols. Reagents were obtained from commercial suppliers and used without further purification, unless otherwise noted.

Reactions were monitored by TLC performed on 0.25 mm Merck silica gel plates (60F-254), or by GC performed on an Agilent 7890A GC system with an HP-5 column (0.32 mm × 30 m, 100 μm, Agilent Technologies, CA, U.S.A.) and a CBP1 column (0.22 mm × 50 m, 0.25 μm, Shimadzu, Kyoto, Japan). Column chromatography was performed using Silica Gel 60N (Kanto Chemical Co., Inc., spherical, neutral, particle size 63–210 μm) and flash column chromatography was performed using Silica Gel 60N (Kanto Chemical Co., Inc., spherical, neutral, particle size 40–50 μm), unless otherwise noted.

Melting points were recorded on a Yawaza BY-2 instrument and are uncorrected. IR were obtained on a JASCO FT/IR-4600 and are reported in wavenumbers. 1H-NMR spectra were recorded using JEOL JMN-AL400 (400 MHz) spectrometers. Chemical shift (δ) is reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS; 0.00 ppm). Coupling constants (J) are reported in Hz. 13C-NMR spectra were recorded using JEOL JMN-AL400 (100 MHz) spectrometers. Chemical shifts are reported in ppm relative to the center line of the 13C(CD3)3 triplet signal (77.0 ppm). Low resolution MS were recorded on JEOL JMS-700 or JMS-T100GC. High resolution (HR) MS were recorded on a JMS-T100GC instrument using electron impact (EI). Elemental analyses were performed using on a Yanaco CHN CORDER MT-6 instrument. Analytical chiral HPLC were performed with a Hitachi Chromaster 5000 HPLC system utilizing CHIRALPAK IC and IE (each is 4.6 mm × 25 cm) obtained from Daicel Chemical Industries, Ltd. (Osaka, Japan).

Preparation of Substrates The following alcohols were purchased from commercial suppliers: (E)-cinnamyl alcohol (1a), trans-2-tridecen-1-ol (1b), 3-phenyl-1-propanol (1d), 1-octanol (1e), 2-butyl-1-n-octanol (1i), 1-adamantanemethanol (1j), and 3-phenyl-2-propyn-1-ol (1n).

The following alcohols were prepared according to a literature procedure: (E)-3-bromoallyl alcohol (1c); distilled at 67–77 °C (25 hPa) prior to use;29) 6,8-bis(methylthio)octan-1-ol (1f), N-allyl-N-benzyl-6-amino-1-hexanol (1h), and N-benzyl-l-prolinol (1i).30)

Synthesis of 4-(2-Methyl-1,3-dithian-2-yl)butan-1-ol (1g)
(neat, cm$^{-1}$): 3472, 2940, 2872, 1716. MS $m/z$: 115 ([M$^+$]), 99 (100%). HRMS (EI): Caled for C$_3$H$_7$O$_2$ 115.0759, found: 115.0779.

**4-(2-Methyl-1,3-dithian-2-yl)butan-1-ol (1g)** A solution of 6-hydroxyhexan-2-one (S2) (1.40 g, 12.2 mmol), 1,3-propanedithiol (1.20 mL, 12.2 mmol), and BF$_3$·OEt$_2$ (660 µL, 5.25 mmol) in CH$_2$Cl$_2$ (60 mL) was stirred at rt for 4 h. Acetone was added (to remove excess thiol) and stirring was continued for 1 h. The mixture was then extracted with Et$_2$O. The organic layer was washed with aq. NaHCO$_3$, water, and brine, dried over Na$_2$SO$_4$, and evaporated. The residue was purified by column chromatography (AcOEt/hexane = 1/4) to afford 4-(2-methyl-1,3-dithian-2-yl)butan-1-ol (1g) (2.33 g, 11.3 mmol, 93%) as a colorless oil.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 3.68 (t, $J$ = 5.8 Hz, 2H), 2.87–2.84 (m, 4H), 1.99–1.92 (m, 4H), 1.65–1.55 (m, 4H), 1.63 (s, 3H), 1.39 (s, 1H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$: 62.4, 49.0, 41.3, 32.6, 27.6, 26.3, 25.2, 20.7. IR (neat, cm$^{-1}$): 3399, 2917, 2240, 1712, 1431. MS $m/z$: 99 (100%). HRMS (EI): Calcd for C$_6$H$_{11}$O$_2$ 115.0759, found: 115.0779.

**Synthesis of (Tetrahydro-2H-thiopyran-4-yl)methanol (1k)** A solution of tetrahydro-4H-thiopyran-4-one (S3) (3.00 g, 25.8 mmol) and toluenesulfonylmethyl isocyanide (TosMIC, 5.55 g, 29.39, 1421, 1069. MS $m/z$: 206 ([M$^+$]), 133 (100%). HRMS (EI): Caled for C$_9$H$_{18}$OS$_2$ 206.0799, found: 206.0811.

4-(2-Methyl-1,3-dithian-2-yl)butan-1-ol (1g) (3.00 g, 25.8 mmol) in dimethoxyethane (105 mL) was cooled to 0 °C and toluenesulfonylmethyl isocyanide (TosMIC, 5.55 g, 29.39, 1421, 1069. MS $m/z$: 206 ([M$^+$]), 133 (100%). HRMS (EI): Caled for C$_9$H$_{18}$OS$_2$ 206.0799, found: 206.0811.

**Synthesis of (Tetrahydro-2H-thiopyran-4-yl)carboxylate (1m)**

**Synthesis of tert-Butyl (5)-(1-Hydroxypropen-2-yl)carbamate (1o)** To a solution of 4-piperidinemethanol (S6) (500 mg, 4.34 mmol) in CH$_2$Cl$_2$ (5 mL) was added Boc$_2$O (1.01 mL, 4.77 mmol) in a dropwise manner at 0 °C. After stirring for 30 min at room temperature, the mixture was diluted with H$_2$O and extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and evaporated. The residue was purified by flash column chromatography (MeOH/CHCl$_3$ = 1/50) to afford tert-butyl (4-hydroxymethyl)piperidine-1-carboxylate (1m) (960 mg, quant.) as a colorless solid.

mp 73–75 °C (hexane). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 4.14 (brs, 2H), 3.50 (d, $J$ = 5.8 Hz, 2H), 2.71 (t, $J$ = 12.6 Hz, 2H), 1.73–1.61 (m, 3H), 1.46 (s, 9H), 1.15 (qd, $J$ = 12.2, 4.6 Hz, 2H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$: 154.8, 79.3, 67.3, 43.5, 38.7, 28.5, 28.3. IR (neat, cm$^{-1}$): 3435, 2925, 1694, 1170. MS $m/z$: 215 ([M$^+$]), 57 (100%). HRMS (EI): Caled for C$_{11}$H$_{14}$O$_3$ 215.1521, found: 215.1550.

To a solution of l-alanine (S7) (2.0 g, 22.4 mmol) in THF was slowly added LiAIH$_4$ (1.28 g, 33.6 mmol) in several portions at room temperature. The mixture was diluted with H$_2$O and extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated to afford a yellow crude product. To a solution of the crude product in THF were added NaHCO$_3$ (6.18 mL, 26.9 mmol) at room temperature and the mixture was stirred and heated under reflux for 18 h. After cooling to 0 °C, the reaction was quenched by 15% aq. NaOH (1 mL) and H$_2$O (4 mL). The resulting mixture was filtered through a pad of Celite and the filtrate was evaporated to afford a yellow crude product. To a solution of the crude product in THF were added NaHCO$_3$ (2.07 g, 24.6 mmol) and Boc$_2$O (6.18 mL, 26.9 mmol) at room temperature and the mixture was stirred for 3 h, after which time it was diluted with H$_2$O and THF was removed in vacuo. The residue was extracted with CHCl$_3$. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was purified by flash column chromatography (AcOEt/hexane = 1/2 to 1/10 to 1/4) to afford tert-butyl (5)-(1-hydroxypropen-2-yl)carbamate (1o) (2.27 g, 12.9 mmol, 58% (2 steps)) as a colorless solid.

mp 55–57 °C (hexane). $[\alpha]$_D$^{28}$ = +0.95 (c 0.24, CHCl$_3$). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 4.59 (brs, 1H), 3.81–3.73 (m, 1H), 3.65 (ddd, $J$ = 10.6, 6.5, 3.9 Hz, 1H), 3.54–3.48 (dt, $J$ = 11.1, 5.4, 1.6 Hz, 1H).
1H, 2.41 (brs, 1H), 1.45 (s, 9H), 1.15 (d, J = 6.8 Hz, 3H).

$^{13}$C-NMR (100 MHz, CDCl$_3$) δ: 156.3, 79.5, 67.0, 48.5, 28.3, 17.2. IR (neat, cm$^{-1}$): 3340, 2977, 1687, 1172. MS m/z: 176 ([M$^+$]), 57 (100%). HRMS (EI): Calcd for C$_{11}$H$_{16}$O$_3$: 175.1208, found: 175.1241.

**General Procedure for Alcohol Oxidation: 1-Adamantane-carbaldehyde (2j)** To a solution of 1-adamantane-methanol (Ij) (66.5 mg, 0.400 mmol), 1-Me-AZADO (3.32 mg, 20.0 µmol), 1-Me-AZADO (1.99 mg, 12.0 µmol), bpy (1.87 mg, 12.0 µmol), and DMAP (2.93 mg, 24.0 µmol) in MeCN (2.0 mL) was added CuOTf·1/2benzene (10.1 mg, 40.0 µmol), and the mixture was stirred under ambient air for 1 h. The reaction was quenched with sat. aq. NaHCO$_3$ and the mixture with Et$_2$O. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The crude product was purified by flash column chromatography (AcOEt/hexane = 1/0 to 1/100) to afford 1-adamantanecarbaldehyde (2j) (61.0 mg, 0.371 mmol, 92%) as a colorless solid.

**Wittig Reaction: (S)-Ethyl 3-(1-Benzoylpyrrolidin-2-yl)-acrylate (5l)** To a solution of 1-adamantane-carbaldehyde (2j) (26.9 mg, 0.154 mmol), ZP (3.12 mg, 20.0 µmol), bpy (1.87 mg, 12.0 µmol), and DMAP (2.93 mg, 24.0 µmol) in MeCN (2.0 mL) was added CuOTf·1/2benzene (10.1 mg, 40.0 µmol), and the mixture was stirred at the same temperature for 3 h. The reaction was quenched with sat. aq. NaHCO$_3$ and the mixture with Et$_2$O. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The crude product was purified by flash column chromatography (AcOEt/hexane = 1/0 to 1/100) to afford an inseparable mixture of (S,E)-ethyl 3-(1-benzyopyrrolidin-2-yl)acrylate (E-5l) and (S,Z)-ethyl 3-(1-benzyopyrrolidin-2-yl)acrylate (Z-5l) and their ratio were determined as 78% and E-5l:Z-5l = 8.0:1, respectively, by $^1$H-NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. The crude product containing the internal standard was purified by flash column chromatography (Et$_2$O/hexane = 1/3) to afford an inseparable mixture of E-5l and Z-5l (86.0 mg, 0.332 mmol, 83%, E-5l:Z-5l = 8.2:1, >99% ee) as a yellow oil.

**Acrylate (5o)** To a solution of 1-adamantanecarbaldehyde (2j) (86.0 mg, 0.332 mmol, 83%) in MeCN (2.0 mL) was added CuOTf·1/2benzene (10.1 mg, 40.0 µmol), and the mixture was stirred under ambient air for 1 h. The reaction was quenched with sat. aq. NaHCO$_3$ and the mixture with Et$_2$O. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The crude product was purified by flash column chromatography (AcOEt/hexane = 1/0 to 1/100) to afford an inseparable mixture of E-5o and Z-5o (99% ee) as a yellow oil.

**Ethyl (S)-4-((tert-Butyloxycarbonyl)amino)pent-2-enoate (5p)** To a solution of tert-butyl (S)-(1-hydroxypropan-2-yl)-carbamate (1o) (70.1 mg, 0.400 mmol), 1-Me-AZADO (1.99 mg, 12.0 µmol), bpy (1.87 mg, 12.0 µmol), DMAP (2.93 mg, 24.0 µmol), and MS3A (120 mg) in MeCN (2.0 mL) was added CuBr (3.44 mg, 24.0 µmol) at room temperature. The mixture was stirred at the same temperature under ambient air for 2 h. The reaction was quenched with sat. aq. NaHCO$_3$ and the mixture with Et$_2$O. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The crude product was purified by flash column chromatography (AcOEt/hexane = 1/0 to 1/100) to afford an inseparable mixture of (S,E)-4-((tert-butyloxycarbonyl)amino)pent-2-enoate (E-5p) and ethyl (S,Z)-4-((tert-butyloxycarbonyl)amino)pent-2-enoate (Z-5p) (70.0 mg, 0.288 mmol, 71%, E-5p:Z-5p = 26:1, 91% ee) as a yellow oil.

**Conflict of Interest** The authors declare no conflict of interest.

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interest.

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