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Switchable Palladium-Catalyst Reaction of Bromomethyl Sulfoxides, CO, and N-Nucleophiles: Aminocarbonylation at Csp^3 versus Oxidative Carbonylation of Amines

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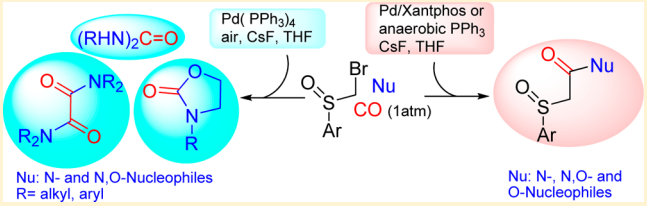
Supporting Information

ABSTRACT: The palladium-catalyzed reaction of α-bromomethyl sulfoxides, carbon monoxide, and N-nucleophiles follows different reaction pathways according to the catalytic system and the reaction conditions. The Pd-xantphos catalyst affords high yields of α-sulfinyl amides by an aminocarbonylation process and is the first example of this type of transformation for a nonbenzylic sp^3-hybridized carbon. On the other hand, the oxidative carbonylation of amines occurs with α-bromomethyl sulfoxides, carbon monoxide, and catalytic $Pd(PPh_3)_4$ under aerobic conditions, yielding ureas and oxalamides from either primary or secondary amines. The reaction with ambident nucleophiles such as amino alcohols was highly selective and took place exclusively at the amino group despite the presence of the alcohol functionality. In parallel to the reaction paths for simple amines, amino alcohols were converted into hydroxy sulfinyl amides when the reaction was catalyzed by Pd-xantphos, while $Pd(PPh_3)_4$ catalyst afforded cyclic carbamates. The alkoxycarbonylation reaction of bromomethyl sulfoxides with simple alcohols and CO leading to the corresponding sulfinyl esters is also described.



INTRODUCTION

Palladium-catalyzed cross-coupling reactions are now a mainstay of fine chemical synthesis. The good compatibility of palladium-catalyzed synthetic procedures with a wide range of subsidiary functional groups on the reactive partners justifies the continuous efforts being made to extend the scope of the organic transformations promoted by this metal.[1] In this area, carbonylation reactions[2] occupy a prominent place because they provide direct, convenient access to the omnipresent carbonyl building blocks. In general, the three-component reaction is carried out with carbon, oxygen or nitrogen nucleophiles, carbon monoxide, and aryl or alkyl halides as electrophiles. The alkoxycarbonylation reaction is perhaps the most robust among palladium-catalyzed carbonylation processes since alternative side reactions are limited and poorly favored.[3] The opposite can be said of the carbonylative reaction of aryl halides with aryl metal reagents[4] or amines.[5] Nevertheless, the use of the carbonylation reaction has been progressively extended by challenging contributions. In this way, the development of new and effective palladium ligands has overcome the drawbacks derived from competing side reactions; moreover, the array of suitable substrates has been extended to include reluctant electrophiles such as aryl chlorides or aryl bromides in the case of carbonylative Sonogashira reactions or nucleophiles, such as ammonia, phenols, or anilines.[6] In general, alkyl halides prove to be worse substrates than aryl halides, and only a few examples of the carbo-[7] and alkoxycarbonylation[8] of alkyl derivatives have been described to date. In addition, the intermolecular aminocarbonylation reaction with alkyl halides, benzyl halides,[9] or α-halomethyl ketones is a difficult transformation because direct nucleophilic substitution is highly favored. In sharp contrast, α-bromomethyl sulfoxides do not react with amines at the electrophilic α carbon,[10] and, for this reason, they are singular substrates for the aminocarbonylation at sp^3-hybridized carbon atoms, as shown in this paper. This transformation is also interesting from a synthetic point of view because α-sulfinyl carbonyl derivatives are reliable synthetic intermediates[11] and metal ligands.[12] These compounds are readily available in the homochiral pure form following the procedure reported herein. Furthermore, interesting singular structural properties of these compounds, such as the S···O interaction between sulfur and the carbonyl oxygen atom, have been described.[13] This intramolecular interaction seems to play a critical role in, for instance, the stereochemical control of the Pummerer rearrangement. Previously, we showed that bromomethyl sulfoxides give keto sulfoxides with moderate to good yields in carbonylative Suzuki reactions with boronic acids and CO at atmospheric pressure at 60 °C. The high chemoselectivity of the three-component reaction versus direct coupling is observed under these conditions.[14] The new carbon−carbon bond formation, which occurs at the α position of a sulfinyl group from a halo sulfoxide, overcomes the limitation of uncatalyzed reactions where nucleophiles such as Grignard reagents react at the sulfur atom with displacement of the halomethyl group.[15] Alternatively, other α-functionalizations of sulfoxides described to date usually occur through the

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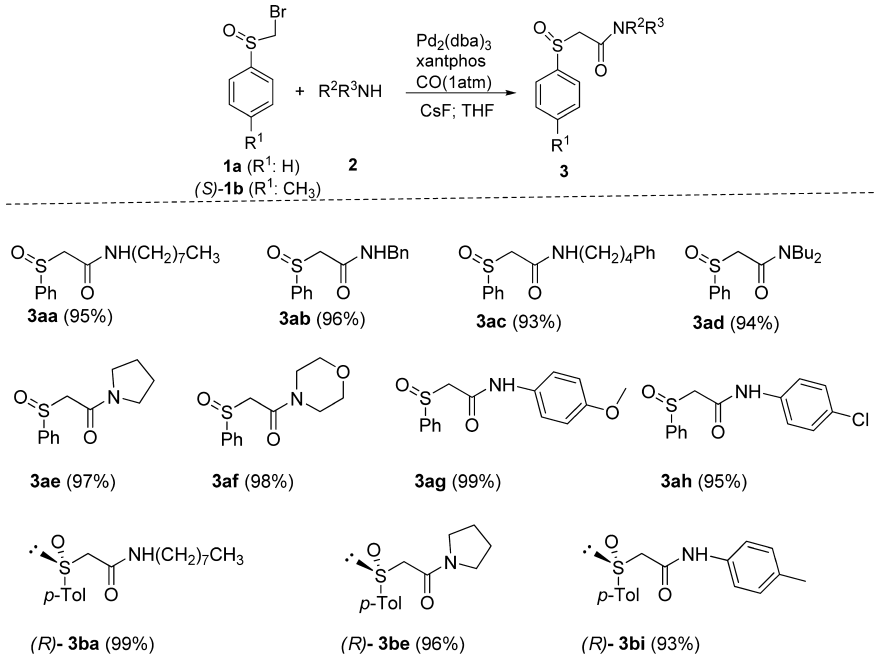
Table 1. Palladium-Catalyzed Synthesis of Chiral and Racemic Sulfinyl Amides



corresponding anions[11] and require strong bases that often favor secondary competing reactions.[16] This scenario prompted us to further explore the palladium-catalyzed carbonylation of halo sulfoxides by testing their reaction with amines, alcohols, and amino alcohols.

RESULTS AND DISCUSSION

The palladium-catalyzed aminocarbonylation reaction in primary alkyl halides is a difficult transformation because oxidative addition in this kind of substrate is slow,[17] while the competitive direct nucleophilic substitution with amines proves favorable. This trend is observed even with benzyl halides,[9] which are activated toward the palladium oxidative addition. In contrast, bromomethyl sulfoxides are good substrates in palladium-catalyzed cross-coupling reactions[18] but are poor substrates in S_N2 reactions with usual nucleophiles.[10,15] By bearing this background in mind, we first explored the possibility of carrying out the aminocarbonylation of the sp^3-hybridized carbon of bromomethyl sulfoxides. The aminocarbonylation of sulfoxides **1a** or (*S*)-**1b** took place adequately with aliphatic **2a**−**f** and aromatic amines **2g**−**i** with CO at atmospheric pressure and catalytic $Pd_2(dba)_3$-xantphos, affording the corresponding racemic (**3aa**−**3ah**) or chiral sulfinyl amides (**3ba**, **3be**, and **3bi**) with high yields (93−99%) (Table 1). Palladium-catalyzed aminocarbonylation requires the presence of the base in stoichiometric amount or an excess of base to neutralize the acid formed during the reaction. Common organic trialkylamines and inorganic salts (K_3PO_4, K_2CO_3, CsF) were tested to promote the reaction. CsF was found to be the most effective, which is in agreement with previous results in several carbonylative Suzuki reactions.[14]

Sulfinyl amides prove to be attractive substrates as potential chiral ligands. The scarce references available on the synthesis of this class of compounds involve the use of dicylohexylcarbodiimide to activate the corresponding acid[13] or the use of amide anions previously generated under strongly basic conditions. Therefore, the aminocarbonylation described herein is a competitive alternative for these compounds in simplicity and atom economy terms. The absolute configuration of the starting chiral sulfoxides is retained in the formation of the corresponding sulfinyl amides. The palladium-catalyzed cross-coupling reactions of chiral bromomethyl sulfoxide (*S*)-**1b** and boronic acids, previously described by us,[18] also takes place with retention of the configuration. As expected, the chiral HPLC analysis of sulfinyl amides **3ba**, **3be**, and **3bi** proved that chiral purity is preserved during transformation. The absolute configuration of sulfinyl amides **3be** and **3bi** has been established by single-crystal X-ray diffraction (for ORTEP diagrams, see Supporting Information). The crystal structure of sulfinyl amide (*R*)-**3bi** is shown in Figure 1.

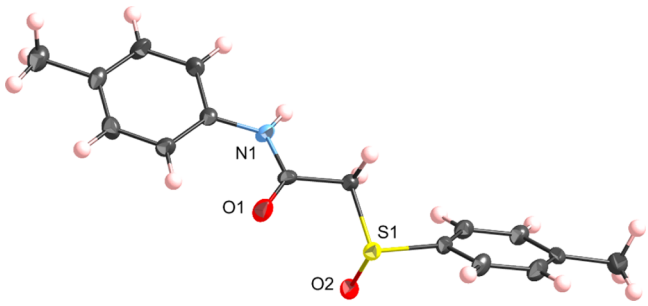


Figure 1. X-ray thermal ellipsoid plot of compound (*R*)-**3bi** (50% probability level).

The palladium-catalyzed reaction of amines, carbon monoxide, and bromethyl sulfoxides depends on the ligand and also on the presence or absence of oxygen. Sulfinyl amides **3** were prepared in high yields with $Pd_2(dba)_3$-xantphos as the catalyst under aerobic or anaerobic conditions. Conversely, the preparation of compounds **3** using $Pd(PPh_3)_4$ requires the rigorous exclusion of oxygen. Under aerobic conditions (see Experimental Section[19]), oxidative carbonylation of the amine[20] occurs, while ureas **4** or oxalamides **5** were the main products from the primary or secondary amines (Table 2). Ureas **4a**−**c**, slightly contaminated by sulfinyl amides **3aa**−**ac**, were obtained

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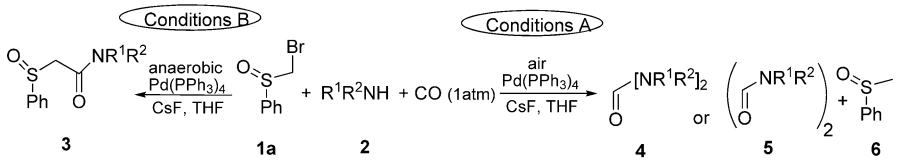
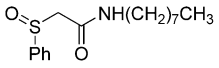
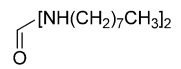
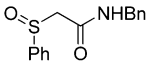
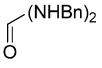
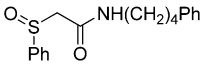
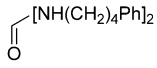
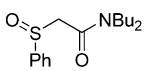
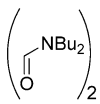
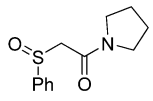
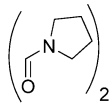
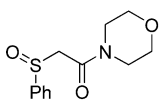
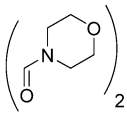
Table 2. Palladium-Catalyzed Oxidative Carbonylation of Amines Mediated by α-Bromomethyl Sulfoxide 1a



Conditions	Products		
			
A	**3aa** (5%)	**4a** (95%)	-
B	**3aa** (52%)	**4a** (24%)	**6** (18%)
			
A	**3ab** (3%)	**4b** (93%)	-
B	**3ab** (53%)	**4b** (20%)	**6** (19%)
			
A	**3ac** (5%)	**4c**(93%)	-
B	**3ac**(51%)	**4c** (20%)	**6** (19%)
			
A	**3ad** (9%)	**5a** (60%)	**6** (9%)
B	**3ad** (89%)	**5a** (5%)	**6** (3%)
			
A	**3ae** (5%)	**5b** (48%)	**6** (8%)
B	**3ae** (90%)	**5b** (4%)	**6** (4%)
			
A	**3af** (5%)	**5c** (55%)	**6** (8%)
B	**3af** (89%)	**5c** (5%)	**6** (6%)

with very high yields from amines **2a**–**c**. Oxalamides **5**, the common byproducts in the carbonylation of amines, were not detected from amines **2a**–**c** under our reaction conditions. In contrast, oxalamides **5a**–**c** were the major products of secondary aliphatic amines **2d**–**2f**, which were contaminated only by sulfinyl amides **3ad**–**af**, the three-component cross-coupling products (Table 2). Primary amines gave symmetrical ureas **4**, most probably through an isocyanate intermediate (vide infra), which is an unfeasible reaction pathway in the case of secondary amines. Detection of isocyanates in the oxidative carbonylation of amines has been previously reported.[20]

The formation of ureas and oxalamides described herein occurred under very mild conditions if compared with the precedents in this area. In this sense, it is noteworthy that (i) carbonylation takes place with CO at atmospheric pressure (previous procedures require up to 50 atm of CO), and that (ii) ureas are the only product from primary amines that are free of contamination by oxalamides, the usual byproducts in these amine carbonylations.

Next, we turned our attention to explore selective amino-carbonylation reactions using dinucleophiles, such as amino alcohols, where amino- and/or alkoxycarbonylation could take place alternatively. The alkoxycarbonylation of bromomethyl sulfoxides has not yet been described; hence, the reaction of 1-bromomethyl sulfoxides, CO, and simple alcohols was first evaluated (Table 3). To optimize the reaction conditions, sulfoxide **1a**, ethanol, and $Pd(PPh_3)$ were selected. The initial screening was conducted in alcohol with an excess or stoichiometric hydroxylic base, which is usual in palladium-catalyzed alkoxycarbonylation reactions.[2b] Reactions took place in aprotic-coordinating solvents, such as THF, containing 2 equiv of alcohol but did not proceed in ethanol. A moderate

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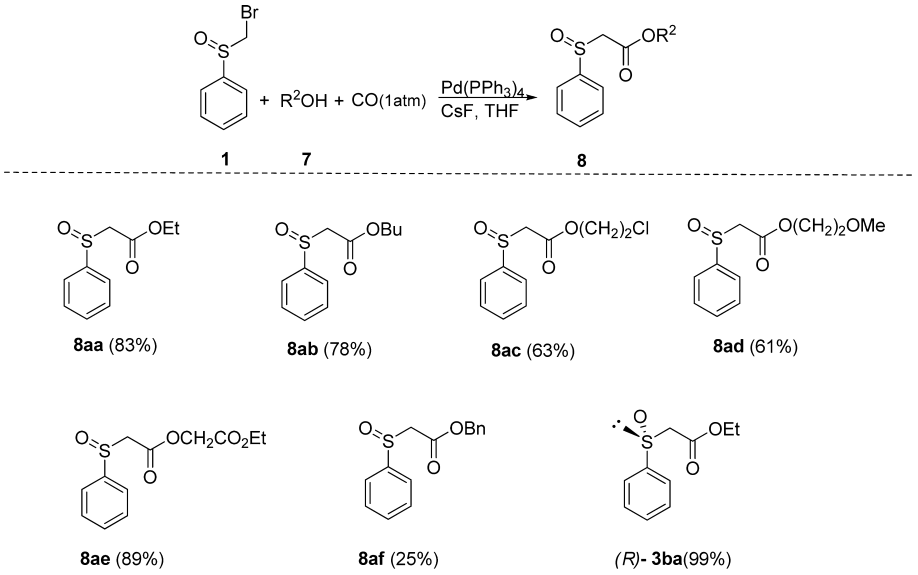
Table 3. Palladium-Catalyzed Alkoxycarbonylation of α-Bromomethyl Sulfoxides 1



base such as CsF proved more effective than other usual bases employed to promote the reaction. The yields obtained using $Pd_2(dba)_3$-xantphos or $Pd(PPh_3)_4$ in the alkoxycarbonylation of bromomethylsulfoxide were similar.

The carbonylation of bromomethyl sulfoxide with aliphatic low-boiling point primary alcohols and catalytic $Pd(PPh_3)_4$ gave the corresponding sulfinyl esters with excellent yields (Table 3). Reactions were conducted below the alcohol boiling temperature and did not require special equipment. On the other hand, benzyl alcohol, which is easily oxidized under palladium catalysis, gave only a moderate yield (Table 3). Substituted alcohols containing additional functional coordinating groups also reacted efficiently in the three-component process (Table 3).

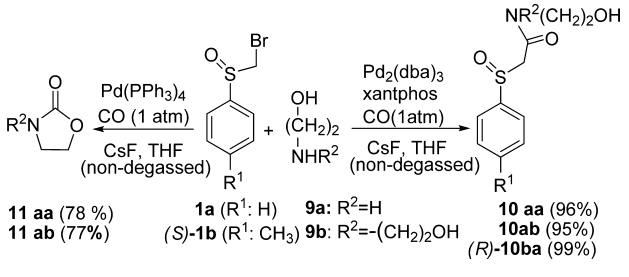
Bromomethyl sulfoxide behaves better than halomethyl ketones[8b−d] in the alkoxycarbonylation reaction because the competitive dehalogenation reaction is more difficult in the former case.

A three-component reaction between bromomethyl sulfoxide **1**, CO, and amino alcohols occurred and exclusively gave aminoacarbonylation products **10** when $Pd(dba)_2$-xantphos was used as the catalyst. However, selectivity dramatically changed when $Pd(PPh_3)_4$ was used to catalyze the reaction; cyclic carbamates **11** were obtained in the latter case (Scheme 1). The different coordination possibilities of compounds **10** endow them with interesting features for the facultative use as ligands.

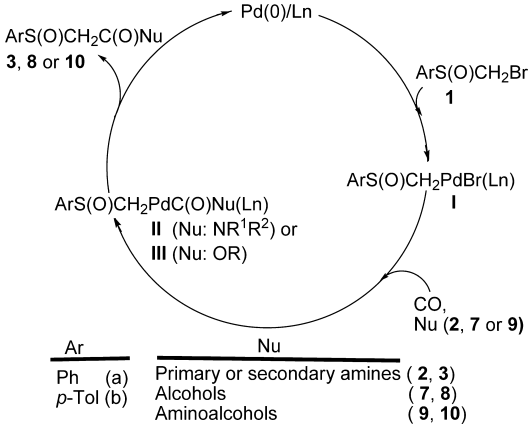
Mechanisms. The most frequently postulated catalytic cycle[2a,b] to account for amino- and alkoxycarbonylation involves the following steps: oxidative addition of the electrophile to Pd(0) (step 1), migratory insertion of carbon monoxide (step 2), and attack of the nucleophile (alcohol or amine) on the acyl complex (step 3). Nevertheless, based on our previous findings in the palladium-catalyzed carbonylative Suzuki reaction with these compounds,[14] the above proposal hardly explains the results obtained in the case of bromomethyl sulfoxides. In fact, the experimental data from this work suggest an atypical sequence in the catalytic cycle, with the insertion of carbon monoxide taking place after the transmetalation step instead of the usual CO insertion into the oxidative addition complex. Moreover, we proved the reluctance of the oxidative addition complex **I** to insert CO by monitoring this process by NMR.

Therefore, the amino- and alkoxycarbonylation of bromomethyl sulfoxides could be explained better as follows:[21] first, oxidative addition of sulfoxide **1** to palladium(0), followed by the attack of the nucleophile (amine or alcohol) on the coordinated CO leading to complexes **II** or **III**, and then the reductive elimination step (Scheme 2). Formation of intermediate $ArS(O)CH_2PdOR$ via metathesis from the

Scheme 1. Palladium-Catalyzed Carbonylation of α-Bromomethyl Sulfoxides 1 and Amino Alcohols 9



Scheme 2. Cycle 1: Proposed Catalytic Cycle for the Palladium-Catalyzed Alkoxy- and Aminocarbonylation of Sulfoxides 1



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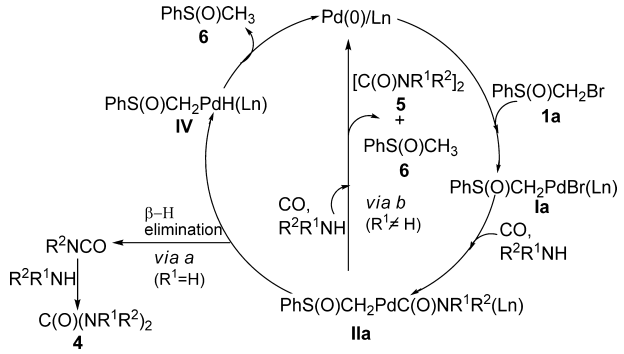
oxidative addition complex, followed by insertion of carbon monoxide into the Pd−OR bond, and finally reductive elimination cannot be ruled out to explain the alkoxycarbonylation reaction. In fact, this alternative involving Pd−OR species could account for the competitive oxidation of alcohols observed in some cases. A similar catalytic cycle based on kinetic studies to account for the alkoxycarbonylation of aryl iodides in the presence of sodium alkoxides has been previously postulated; however, this sequence is less likely in absence of strong bases.[22]

The $Pd_2(dba)_3$-xantphos catalyzed aminocarbonylation reaction of α-bromomethyl sulfoxides **1** occurs in the absence of competitive side reactions (Scheme 2). Conversely, dehalogenation of the sulfoxide and oxidative carbonylations of the amine[20] leading to ureas or oxalamides resulted in detectable side pathways with $Pd(PPh_3)_4$ under anaerobic conditions. In this case, bromomethyl sulfoxide behaves as an oxidant[23] (Scheme 3). A schematic catalytic cycle 2 (Scheme 3) to account for the oxidative carbonylation of amines is proposed to involve a complex **Ia** formed in the oxidative addition of bromomethyl sulfoxide to Pd(0). Accordingly, **Ia** would react with CO and amine to give **IIa**, a carbamoyl dioorganopalladium complex. In the case of primary amines, the subsequent hydrogen transfer to the metal leads to palladium hydride complex **IV** and an isocyanate (via a). Ureas **4** are formed by the reaction of the isocyanate with a second equivalent of amine, while methyl phenyl sulfoxide **6** results by reductive elimination from complex **IV**. Alternatively, oxalamides **5** and methyl phenyl sulfoxide **6** would be produced from the reaction of complex **IIa** and a second equivalent of the corresponding secondary amine and carbon monoxide (via b).

Scheme 3. Cycle 2: Proposed Catalytic Cycles for the Palladium-Catalyzed Oxidative Carbonylation of Amines with Sulfoxide 1a as Oxidant

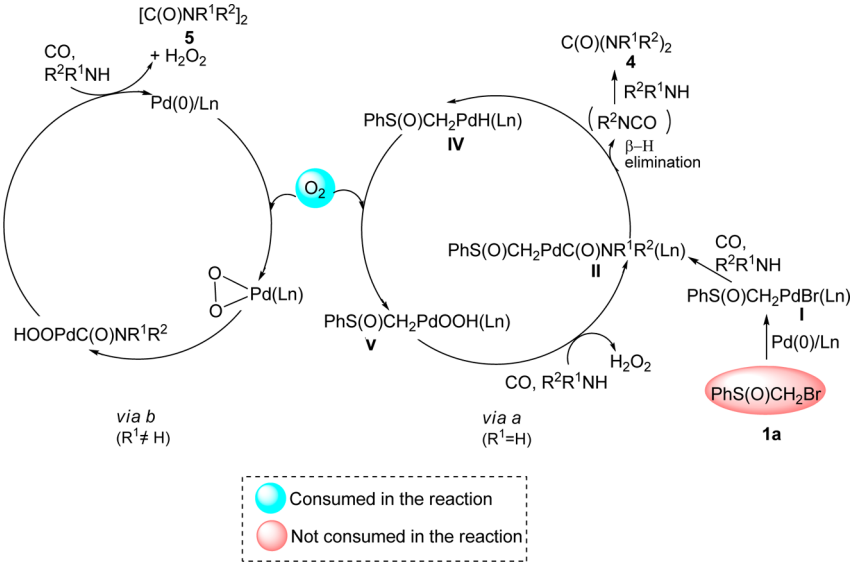


Conversely under aerobic conditions, the oxidative carbonylation of amines became the main process in the reaction of bromomethyl sulfoxide **1a** with amines and $Pd(PPh_3)_4$. Ureas **4** or oxalamides **5** were formed by a catalytic cycle in which molecular oxygen acted as the oxidant (Scheme 4). Oxidative carbonylation could be explained by an alternative catalytic cycle involving a peroxo complex[24] of palladium without the participation of bromomethyl sulfoxide. However, the catalyst displays longer activity and proves highly efficient in the presence of **1**, which is not consumed during the process but is recovered (about 80%) after completing the reaction. Thus, a catalytic cycle 3 is proposed to account for the oxidative carbonylation of amines (Scheme 4). Intermediate complex **IV** participates in cycles 2 and 3 (Schemes 3 and 4), but its evolution differs in the presence or absence of O_2. Insertion of molecular oxygen into the palladium−hydrogen bond in complex **IV** and loss of hydrogen peroxide by ligand exchange with CO and amine under aerobic conditions close the catalytic cycle, with the regeneration of complex **IIa**. The generated hydrogen peroxide could play the role of a further oxidant, but palladium has been reported to accelerate its decomposition in O_2 and water.[25] Hydrogen peroxide is a stronger oxidant than molecular oxygen. Nevertheless, the data from other palladium-catalyzed oxidation reactions suggest that it is not a kinetically competent oxidant.[25]

The formation of cyclic carbamates **11** from amino alcohols **9** is explained by following an equivalent reaction pathway.

Formation of oxalamides **5** from secondary amines cannot be explained in the same way as ureas **4** given the lack of a β-hydrogen to be transferred from the corresponding carbamoyl

Scheme 4. Cycle 3: Proposed Catalytic Cycles for the Palladium-Catalyzed Oxidative Carbonylation of Amines with O_2 as Oxidant



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intermediate **IIa**. The oxidative carbonylation of secondary amines could be explained by an alternative catalytic cycle, where molecular oxygen (via a peroxo complex of palladium)[24] acts as the oxidant. In addition, the formation of dehalogenated sulfoxide **6** under aerobic conditions suggests that bromomethyl sulfoxide acts concomitantly with O_2 as oxidant. In contrast for primary amines, bromomethyl sulfoxide seems to act as an oxidant but only under anaerobic conditions because dehalogenated sulfoxide is only detected in this way.

The ligand effect encountered in the palladium-catalyzed carbonylation reaction of sulfoxides **1** with amines could be attributed to differences in the ligand-dependent trans−cis isomerization in complex **II**, the common intermediate in both cycles. The trans−cis isomerization process in complex **II** with monophosphine ligands opens temporary coordination sites in palladium, which allows either the transfer of hydrogen in the case of a primary amine or the coordination of CO followed by amine attack in the case of secondary amines, thus favoring the occurrence of the oxidative carbonylation of amines instead of the aminocarbonylation reaction. These events may be minimized in the case of the diphosphine xantphos which promotes a faster isomerization.[26] Besides, the wide bite angle of xantphos favors the reductive elimination process, and consequently the formation of α-sulfinyl amides results in the prevailing pathway. The slower reductive elimination promoted by monophosphines enhances the competitive oxidative carbonylation of amines as an alternative reaction pathway.

CONCLUSION

We describe palladium-catalyzed carbonylation involving a sp^3-hybridized carbon and N- and N,O-nucleophiles for the first time. The reaction takes advantage of the reluctance of the electrophilic partner, that is, α-bromomethyl sulfoxides, to participate in nucleophilic substitution reactions. Consequently, the aminocarbonylation reaction can be carried out with high selectivity for a wide range of amines and amino alcohols. The developed method requires neither overpressure of carbon monoxide nor sophisticated palladium ligands. The mild reaction conditions allow us to obtain chiral and racemic α-sulfinyl amides with very high efficiency. The effect of the ligand and reaction conditions driving the outcome of the process for the aminocarbonylation reaction or the oxidative carbonylation of amines in almost a completely selective manner shows the high potential of the three-component reactions presented herein, which allows access to a wide range of products with minimal changes in simple and easily available starting materials and catalyst systems.

EXPERIMENTAL SECTION

General Methods. Solvents were degassed by the freeze−pump−thaw method (five cycles) to ensure the absolute strict absence of oxygen. Proton magnetic resonance and carbon magnetic resonance were recorded at 300 MHz and 75 Hz, respectively. Chemical shifts are reported in δ ppm in relation to the $CHCl_3$ peak at 7.20 ppm (^{1}H) or 77.0 ppm (^{13}C). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The ee values of the products were determined by HPLC (Chiralcel IA). Optical rotation measurements were determined at room temperature. All the melting points were uncorrected. Reactions were monitored by analytical thin layer chromatography using commercial aluminum sheets precoated (0.2-mm layer thickness) with silica gel 60 F_{254}. Product purification was performed by flash chromatography with silica gel (230−400 mesh).

Starting Materials. Bromomethyl phenyl sulfoxide (**1a**),[27] (*S*)-1-(bromomethylsulfinyl)-4-methylbenzene (**1b**),[18a] and *trans*-[Pd(CH$_2$SOPh)Br(PPh$_3$)$_2$][18a] were prepared according to the previously described procedures.

General Procedure for the Carbonylation of Amines, Amino Alcohols, and Alcohols. *Aerobic Conditions.* A mixture of α-bromomethyl sulfoxide **1** (0.3 mmol), N- or O-nucleophile (0.6 mmol), CsF (1.2 mmol), and the appropriate catalyst (0.03 mmol) was added to a flask fitted with a reflux condenser and a septum inlet. The flask was fluxed with carbon monoxide and then charged with THF (10 mL). The mixture was stirred at 65 °C under atmospheric pressure of carbon monoxide (balloon).[19] After the appropriate time, the mixture was cooled to room temperature, quenched with water (10 mL), and extracted with diethyl ether (2 × 15 mL) and dichloromethane (3 × 15 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure.

Anaerobic Conditions. A mixture of α-bromomethyl sulfoxide **1** (0.3 mmol), N-nucleophile (0.6 mmol), CsF (1.2 mmol), and Pd(PPh$_3$)$_4$ (0.03 mmol) was added to a flask fitted with a reflux condenser and a septum inlet. The flask was fluxed several times with carbon monoxide and then charged with degassed THF (10 mL). The mixture was stirred at 65 °C under atmospheric pressure of carbon monoxide (the balloon was immediately inflated before starting the reaction to minimize air diffusion).[19] After the appropriate time, the mixture was cooled to room temperature, quenched with water (10 mL), and extracted with diethyl ether (2 × 15 mL) and dichloromethane (3 × 15 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated under reduced pressure.

*N-Octyl-2-(phenylsulfinyl)acetamide (**3aa**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 84 mg, 95% yield; mp 40−44 °C; ^{1}H NMR ($CDCl_3$) δ 7.70−7.67 (m, 2H), 7.46−7.44 (m, 3H), 3.62 (d, J = 14.1 Hz, 1H), 3.41 (d, J = 14.1 Hz, 1H), 3.18−3.05 (m, 2H), 1.19 (m, 12H), 0.81 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.7, 143.8, 131.3, 129.1, 124.4, 58.8, 39.7, 31.7, 29.3, 29.2, 29.1, 26.8, 22.6, 14.0; HRMS (EI) m/z (M^+) calcd for $C_{16}H_{25}NO_2S$ 295.1606, found 295.1600.

*N-Benzyl-2-(phenylsulfinyl)acetamide (**3ab**).*[28] Chromatographic purification on a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). Pale yellow liquid: 79 mg, 96% yield; ^{1}H NMR ($CDCl_3$) δ 7.49−7.40 (m, 5H), 7.25−7.13 (m, 5H), 4.35 (dd, J = 14.7 and 6 Hz, 1H), 4.27 (dd, J = 14.7 and 6 Hz, 1H), 3.69 (d, J = 14.4 Hz, 1H), 3.42 (d, J = 14.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 163.5, 141.3, 137.5, 129.4, 128.7, 131.5, 127.9, 127.5, 123.9, 58.3, 43.6; HRMS (EI) m/z (M^+) calcd for $C_{15}H_{15}NO_2S$ 273.0823, found 273.0811.

*N-(4-Phenylbutyl)-2-(phenylsulfinyl)acetamide (**3ac**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 88 mg, 93% yield; mp 55−59 °C; ^{1}H NMR ($CDCl_3$) δ 7.53−7.50 (m, 2H), 7.44−7.42 (m, 3H), 7.14−7.08 (m, 5H), 6.90−6.80 (m, 1H), 3.61 (d, J = 14.3 Hz, 1H), 3.38 (d, J = 14.3 Hz, 1H), 3.24−3.06 (m, 2H), 2.54 (t, J = 7.2 Hz, 2H), 1.59−1.36 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 163.9, 142.4, 141.9, 132.0, 129.8, 128.8, 128.7, 126.2, 124.3, 59.0, 39.9, 35.8, 29.4, 29.0; HRMS (EI) m/z (M^+) calcd for $C_{18}H_{21}NO_2S$ 315.1293, found 315.1283.

*N,N-Dibutyl-2-(phenylsulfinyl)acetamide (**3ad**).*[12a] Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 83 mg, 94% yield; mp 41−45 °C; ^{1}H NMR ($CDCl_3$) δ 7.76−7.73 (m, 2H), 7.52−7.50 (m, 3H), 3.98 (d, J = 13.9 Hz, 1H), 3.64 (d, J = 13.9 Hz, 1H), 3.29−3.00 (m, 4H), 1.46−1.15 (m, 8H), 0.87 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 163.7, 143.8, 131.3, 129.1, 124.5, 62.2, 48.2, 46.0, 31.0, 29.6, 20.0, 19.8, 13.7, 13.6; HRMS (EI) m/z (M^+) calcd for $C_{16}H_{25}NO_2S$ 295.1606, found 295.1593.

*2-(Phenylsulfinyl)-1-(pyrrolidin-1-yl)ethanone (**3ae**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 69 mg, 97% yield; mp 104−108 °C; ^{1}H NMR ($CDCl_3$) δ 7.69−7.66 (m, 2H), 7.47−7.41 (m, 3H), 3.93 (d, J = 13.2 Hz, 1H), 3.60 (d, J = 13.2 Hz, 1H), 3.45−3.32 (m, 3H), 3.09−3.01 (m, 1H), 1.86−1.63 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 162.3, 143.7,

129.2, 131.4, 124.2, 63.2, 47.3, 46.0, 25.9, 24.3; HRMS (EI) m/z (M^+) calcd for $C_{12}H_{15}NO_2S$ 237.0823, found 237.0814.

*1-Morpholino-2-(phenylsulfinyl)ethanone (**3af**).* Chromatographic purification on a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 74 mg, 98% yield; mp 146−150 °C; ^{1}H NMR ($CDCl_3$) δ 7.67−7.64 (m, 2H), 7.49−7.47 (m, 3H), 3.92 (d, J = 13.2 Hz, 1H), 3.66 (d, J = 13.2 Hz, 1H), 3.41−3.63 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 162.7, 143.3, 131.6, 129.3, 124.1, 66.6, 66.5, 60.9, 46.8, 42.3; HRMS (EI) m/z (M^+) calcd for $C_{12}H_{15}NO_3S$ 253.0773, found 253.0761

*N-(4-Methoxyphenyl)-2-(phenylsulfinyl)acetamide (**3ag**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 86 mg, 99% yield; mp 124−126 °C; ^{1}H NMR ($CDCl_3$) δ 7.58−7.54 (m, 2H), 7.46−7.44 (m, 3H), 7.28 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 3.84 (d, J = 14.4 Hz, 1H), 3.49 (d, J = 14.4 Hz, 1H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.4, 156.6, 140.8, 131.8, 130.4, 129.5, 123.9, 122.0, 114.1, 58.5, 55.4; HRMS (EI) m/z (M^+) calcd for $C_{15}H_{15}NO_3S$ 289.0773, found 289.0779.

*N-(4-Chlorophenyl)-2-(phenylsulfinyl)acetamide (**3ah**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 84 mg, 95% yield; mp 162−166 °C; ^{1}H NMR ($CDCl_3$) δ 7.56−7.52 (m, 2H), 7.46−7.44 (m, 3H), 7.34 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 9.0 Hz, 2H), 3.86 (d, J = 14.1 Hz, 1H), 3.52 (d, J = 14.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 161.6, 140.6, 135.9, 131.9, 129.6, 129.0, 123.8, 121.4, 58.5; HRMS (EI) m/z (M^+): calcd for $C_{14}H_{12}ClNO_2S$ 293.0277, found 293.0269

*(R)-2-(p-Tolylsulfinyl)-N-octylacetamide (**3ba**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 92 mg, 99% yield; mp 170−174 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 3.60 (d, J = 14.1 Hz, 1H), 3.35 (d, J = 14.1 Hz, 1H), 3.24−3.03 (m, 2H), 2.34 (s, 3H), 1.20 (m, 12H), 0.81 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.6, 142.1, 138.2, 130.1, 123.9, 58.5, 39.7, 31.8, 29.2, 29.1, 26.9, 22.6, 21.4, 14.1; HRMS (EI) m/z (M^+) calcd for $C_{17}H_{27}NO_2S$ 309.1762, found 309.1755; $[\alpha]_D^{25}$ +208.3 (c = 1, acetone), ee >99% (Chiralcel IA, hexane:2-propanol 95:5, flow 1 mL/min).

*(R)-2-(p-Tolylsulfinyl)-1-(pyrrolidin-1-yl)ethanone (**3be**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 70 mg, 93% yield; mp 121−125 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 3.91 (d, J = 12.9 Hz, 1H), 3.57 (d, J = 12.9 Hz, 1H), 3.49−3.05 (m, 4H), 2.35 (s, 3H), 1.86−1.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 162.4, 141.9, 140.4, 129.9, 124.2, 63.2, 47.3, 46.0, 25.9, 24.3, 21.4; HRMS (EI) m/z (M^+) calcd for $C_{13}H_{17}NO_2S$ 251.0980, found 251.0970; $[\alpha]_D^{25}$ +140.2 (c = 1, acetone), ee >99% (Chiralcel IA, hexane:2-propanol 96:4, flow 4 mL/min).

*(R)-2-(p-Tolylsulfinyl)-N-p-tolylacetamide (**3bi**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 82 mg, 96% yield; mp 170−172 °C. ^{1}H NMR ($CDCl_3$) δ 7.43 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 3.80 (d, J = 14.1 Hz, 1H), 3.49 (d, J = 14.1 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.6, 142.3, 137.6, 134.8, 134.2, 130.2, 129.4, 120.3, 60.3, 21.4, 21.0; HRMS (EI) m/z (M^+) calcd for $C_{16}H_{17}NO_2S$ 287.0980, found 287.0985; $[\alpha]_D^{25}$ +211.4 (c = 1, acetone), ee >99% (Chiralcel IA, hexane: 2-propanol 85:15, flow 3 mLl/min).

*1,3-Dioctylurea (**4a**).*[29] Chromatographic purification on a silica gel column with *n*-hexane−ethyl acetate (1:1). White solid: 81 mg, 95% yield; mp 89−90 °C; ^{1}H NMR ($CDCl_3$) δ 5.00−5.01 (bb, 2H), 3.03−3.09 (m, 4H), 1.42−1.37 (m, 4H), 1.30−1.10 (m, 20H), 0.80 (t, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 158.9, 40.2, 31.8, 30.4, 29.4, 29.3, 27.0, 22.6, 14.0; HRMS (EI) m/z (M^+) calcd for $C_{17}H_{36}N_2O$ 284.2827, found 284.2812.

*1,3-Dibenzylurea (**4b**).*[30] Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1). White solid: 67 mg, 93% yield; mp 170−171 °C; ^{1}H NMR ($CDCl_3$) δ 7.25−7.15 (m, 10H), 4.80 (bs, 2H), 4.26 (s, 2H), 4.24 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 158.0, 139.1, 128.6, 127.4, 127.3, 44.5; HRMS (EI) m/z (M^+) calcd for $C_{15}H_{16}N_2O$ 240.1263, found 240.1255.

*1,3-Bis(4-phenylbutyl)urea (**4c**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1). White solid: 90 mg, 93% yield; mp 76−80 °C; ^{1}H NMR ($CDCl_3$) δ 7.22 −7.12 (m, 4H), 7.10−7.07 (m, 6H), 4.33−4.30 (bb, 2H), 3.11−3.04 (m, 4H), 2.57−2.51 (m, 4H), 1.61−1.54 (m, 4H), 1.51−1.37 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 158.2, 142.2, 128.4, 128.3, 125.8, 40.3, 35.5, 29.8, 28.6; HRMS (EI) m/z (M^+) calcd for $C_{21}H_{28}N_2O$ 324.2216, found 324.2217.

*N^1,N^1,N^2,N^2-Tetrabutyloxalamide (**5a**).*[31] Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1). Colorless oil: 56 mg, 60% yield; ^{1}H NMR ($CDCl_3$) δ 3.38−3.13 (m, 8H), 1.63−1.50 (m, 8H), 1.39−1.21 (m, 8H), 0.95−0.88 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 165.0, 47.7, 43.5, 30.5, 29.2, 20.1, 20.0, 13.7, 13.6; HRMS (EI) m/z (M^+) calcd for $C_{18}H_{36}N_2O_2$ 312.2777, found 312.2766.

*1,2-Di(pyrrolidin-1-yl)ethane-1,2-dione (**5b**).*[32] Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1). White solid: 28 mg, 48% yield; mp 73−75 °C; ^{1}H NMR ($CDCl_3$) δ 3.49−3.42- (m, 8H), 1.90−1.83 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 163.1, 46.8, 45.0, 25.8, 24.1; HRMS (EI) m/z (M^+) calcd for $C_{10}H_{16}N_2O_2$ 196.1212, found 196.1199.

*1,2-Dimorpholinoethane-1,2-dione (**5c**).*[33] Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1). White solid: 38 mg, 55% yield; mp 181−185 °C; ^{1}H NMR ($CDCl_3$) δ 3.68−3.57 (m, 12H), 3.40−3.37 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 162.7, 66.7, 66.4, 46.4, 41.4; HRMS (EI) m/z (M^+) calcd for $C_{10}H_{16}N_2O_4$ 228.1110, found 228.1103.

*Ethyl 2-(Phenylsulfinyl)acetate (**8aa**).*[34] Chromatographic purification in a silica gel column with *n*-hexane− ethyl acetate 5:1). Colorless oil: 53 mg, 83% yield; ^{1}H NMR ($CDCl_3$) δ 7.63−7.61 (m, 2H), 7.48−7.46 (m, 3H), 4.08 (q, J = 6.9 Hz, 2H), 3.78 (d, J = 13.5 Hz, 1H), 3.60 (d, J = 13.5 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.0, 143.0, 131.7, 129.3, 124.1, 61.9, 61.6, 13.9; HRMS (EI) m/z (M^+) calcd for $C_{10}H_{12}O_3S$ 212.0507, found 212.0500.

*Butyl 2-(Phenylsulfinyl)acetate (**8ab**).* Chromatographic purification in a silica gel column with *n*-hexane− ethyl acetate 5:1). Colorless oil: 56 mg, 78% yield; ^{1}H NMR ($CDCl_3$) δ 7.64−7.62 (m, 2H), 7.48−7.46 (m, 3H), 4.03 (t, J = 6.6 Hz, 2H), 3.76 (d, J = 13.5 Hz, 1H), 3.60 (d, J = 13.5 Hz, 1H), 1.28−1.18 (m, 4H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.7, 143.1, 131.7, 129.3, 124.1, 65.8, 61.7, 30.3, 18.9, 13.6; HRMS (EI) m/z (M^+) calcd for $C_{12}H_{16}O_3S$ 240.08202, found 240.0806.

*2-Chloroethyl 2-(Phenylsulfinyl)acetate (**8ac**).* Chromatographic purification in a silica gel column with *n*-hexane− ethyl acetate 5:1). Colorless oil: 46 mg, 63% yield; ^{1}H NMR ($CDCl_3$) δ 7.65−7.62 (m, 2H), 7.50−7.47 (m, 3H), 4.27 (t, J = 5.7 Hz, 2H), 3.82 (d, J = 13.8 Hz, 1H), 3.67 (d, J = 13.8 Hz, 1H), 3.54 (t, J = 5.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 164.3, 142.8, 131.9, 129.4, 124.1, 65.2, 61.3, 40.9; HRMS (EI) m/z (M^+) calcd for $C_{10}H_{11}ClO_3S$ 246.0117, found 246.0110.

*2-Methoxyethyl 2-(Phenylsulfinyl)acetate (**8ad**).* Chromatographic purification in a silica gel column with *n*-hexane− ethyl acetate 5:1). Colorless oil: 44 mg, 61% yield; ^{1}H NMR ($CDCl_3$) δ 7.63−7.61 (m, 2H), 7.48−7.46 (m, 3H), 4.18 (t, J = 4.8 Hz, 2H), 3.83 (d, J = 13.8 Hz, 1H), 3.65 (d, J = 13.8 Hz, 1H), 3.47 (t, J = 4.8 Hz, 2H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.7, 143.0, 131.8, 129.4, 124.2, 69.9, 64.8, 61.5, 58.9; HRMS (EI) m/z (M^+) calcd for $C_{11}H_{14}O_4S$ 242.0613, found 0.242.0612.

*(Phenylsulfinyl)acetic Acid 2-Ethoxy-2-oxoethyl Ester (**8ae**).* Chromatographic purification in a silica gel column with *n*-hexane− ethyl acetate 5:1). Colorless oil: 48 mg, 59% yield; ^{1}H NMR ($CDCl_3$) δ 7.63−7.61 (m, 2H), 7.48−7.47 (m, 3H), 4.57 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 3.84 (d, J = 13.8 Hz, 1H),3.72 (d, J = 13.8 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.0, 164.2, 142.9, 133.1, 129.4, 124.1, 61.7, 61.6, 61.5, 14.0; HRMS (EI) m/z (M^+) calcd for $C_{12}H_{14}O_5S$ 270.0562, found 270.0554.

*Benzyl 2-(Phenylsulfinyl)acetate (**8af**).* Chromatographic purification in a silica gel column with *n*-hexane−AcOEt 5:1). Colorless oil: 21 mg, 25% yield; ^{1}H NMR ($CDCl_3$) δ 7.59−7.56 (m, 3H), 7.30−7.20 (m, 5H), 7.44−7.42 (m, 2H), 5.05 (s, 2H), 3.84 (d, J = 13.5 Hz, 1H), 3.64 (d, J = 13.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 164.5, 143.0, 134.7,

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131.8, 129.4, 128.7, 128.6, 128.5, 124.2, 67.7, 61.6; HRMS (EI) m/z (M^+) calcd for $C_{15}H_{14}O_3S$ 274.0664, found 274.0657.

*(R)-Ethyl 2-(p-Tolylsulfinyl)acetate (**8ba**).*[13] Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate 5:1). Colorless oil: 55 mg, 81% yield; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 8.1, Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 4.09 (q, J = 6.9 Hz, 2H), 3.80 (d, J = 13.5 Hz, 1H), 3.57 (d, J = 13.5 Hz, 1H), 2.36 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 14.0, 21.5, 61.7, 62.0, 124.2, 130.0, 139.8, 142.4, 164.8; HRMS (EI) m/z (M^+) calcd for $C_{11}H_{14}O_3S$ 226.0664, found 226.0660; ee> 99%, $[\alpha]_D^{25}$ +155.3 (c = 1, acetone). (Chiralcel OD-H, hexane:2-propanol 99:1, flow 2 mL/min).

*N-(2-Hydroxyethyl)-2-(phenylsulfinyl)acetamide (**10aa**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 65 mg, 96% yield; mp 101−104 °C; ^{1}H NMR ($CDCl_3$) δ 7.59−7.55 (m, 2H), 7.49−7.47 (m, 3H), 3.67 (d, J = 13.8 Hz, 1H), 3.60 (q, J = 4.8 Hz, 2H), 3.50 (d, J = 13.8 Hz, 1H), 3.33 (q, J = 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 164.2, 141.4, 131.7, 129.5, 124.0, 61.4, 59.9, 42.6; HRMS (EI) m/z (M^+) calcd for $C_{10}H_{13}NO_3S$ 227.0616, found 227.0626.

*N,N-Bis(2-hydroxyethyl)-2-(phenylsulfinyl)acetamide (**10ab**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 77 mg, 95% yield; mp 101−104 °C; ^{1}H NMR ($CDCl_3$) δ 7.65−7.63 (m, 2H), 7.47−7.45 (m, 3H), 4.20 (d, J = 14.1 Hz, 1H), 3.81 (d, J = 14.1 Hz, 1H), 3.71−3.47 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 166.1, 142.4, 131.6, 129.4, 124.4, 72.2, 61.6, 60.0, 52.6, 50.4; HRMS (EI) m/z (M^+) calcd for $C_{12}H_{17}NO_4S$ 271.0878, found 271.0885.

*(R)-2-(p-Tolylsulfinyl)-N-(2-hydroxyethyl)acetamide (**10ba**).* Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1 to 1:2). White solid: 73 mg, 99% yield; mp 123−125 °C; ^{1}H NMR ($CDCl_3$) δ 7.44 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 3.65−3.27 (m, 7H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.3, 142.3, 138.3, 130.1, 124.1, 61.1, 60.8, 42.5, 21.4; HRMS (EI) m/z (M^+): calcd for $C_{11}H_{15}NO_3S$ 241.0773, found 241.0771; $[\alpha]_D^{25}$ +198.1 (c = 1, acetone), ee >99% (Chiralcel IA, hexane:2-propanol 90:10, flow 2 mL/min).

*Oxazolidin-2-one (**11aa**).* Obtained under aerobic conditions. Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1). White solid: 41 mg, 78% yield; mp 86−91 °C; ^{1}H NMR ($CDCl_3$) δ 6.40−6.10 (br s, 1H), 4.37 (t, J = 7.9 Hz, 2H), 3.55 (t, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 160.7, 64.9, 40.6; HRMS (EI) m/z (M^+) calcd for $C_3H_5NO_2$ 87.0320, found 87.0299

*3-(2-Hydroxyethyl)oxazolidin-2-one (**11ab**).* Obtained under aerobic conditions. Chromatographic purification in a silica gel column with *n*-hexane−ethyl acetate (1:1). Colorless oil: 61 mg, 77% yield; ^{1}H NMR ($CDCl_3$) δ 4.32 (t, J = 7.9 Hz, 2H), 3.75−3.65 (m, 4H), 3.60−3.50 (br s, 1H), 3.36 (t, J = 5.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 159.3, 62.1, 59.9, 46.6, 45.4; HRMS (EI) m/z (M^+) calcd for $C_5H_9NO_3$ 131.0582, found 131.0611.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all compounds and HPLC chromatograms for chiral compounds. The crystallographic information file (CIF) contains the supplementary crystallographic data for this paper. 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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