Palladium-Catalyzed S_N1 Reactions of Secondary Benzylic Alcohols: Etherification, Amination, and Thioetherification

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Keywords: Homogeneous catalysis / Palladium / Phosphane ligands / Alcohols / Nucleophilic substitution

The reaction of various secondary benzylic alcohols in the presence of Pd^{II} catalysts provides ethers in good to high yields. Unsymmetric ethers could also be obtained with good selectivity by coupling two different alcohols. Direct amination is observed with electron-deficient anilines, and thioethers are prepared conveniently in high yields by the direct action of thiols on *sec*-phenylethyl alcohol.

Catalytic chemistry plays a central role in the development of efficient, selective, and environmentally friendly organic transformations. A wide variety of synthetic methods have been noted for the preparation of ethers from alcohols, but not without limitations. The most widely used Williamson ether synthesis requires the conversion of alcohols to halides or tosylates, resulting in excessive salt waste byproduct.[1] Alternative routes include, but are not limited to, acid catalysis,[2] UV irradiation[3] and refluxing in dimethyl sulfoxide.[4] However, the harsh conditions under which these processes are conducted and the mixture of products that often result limit their utility. Worthy of special mention is the work of Boyer and co-workers, in which $BiBr_3$ is employed in the benzylation of aliphatic alcohols.[5] Even though transition metal catalysts seem ideal for the selective etherification of alcohols, only a small number of metals have been investigated.[6] In this paper, we report on a facile and direct method for preparing symmetric and unsymmetric ethers under mild conditions employing cationic palladium phosphane catalysts. Moreover, we have extended the catalytic reaction to include direct amination of alcohols and preparation of thioethers form thiols and alcohols. The advantages of the Pd-catalysts described herein over the use of $FeCl_3$ [6c] are high selectivity for secondary benzylic alcohols, low catalyst loading, lack of elimination side products, and versatility in amination and thioetherification reactions.

Results and Discussion

Several palladium(II) complexes containing nitrogen- and phosphorus-based bidentate ligands were investigated (Table 1) with *sec*-phenylethyl alcohol as substrate. The active form of the catalyst was generated in situ by the action of two equivalents of silver triflate (AgOTf). As evidenced by the result in entry 3 of Table 1, an available coordination site is a prerequisite for catalysis. The reaction proceeds in a number of solvents: toluene, dichloromethane, 1,2-dichloroethane, 1,4-dioxane and THF; but due to the high solubility of the catalysts in nitromethane, it is the solvent of choice. Other organic solvents such as toluene require the use of the more exotic and expensive $AgBAr^F_4$ {BAr^F_4 = $[(3,5\text{-}(CF_3)_2C_6H_3)_4B]^-$} to give soluble Pd catalysts.[7] Control reactions employing the silver salts AgOTf or $AgBAr^F_4$ alone afford no ether formation under the employed reaction conditions (entry 9). The efficiency of a given Pd catalyst is dependent on the steric bulk of the ligand (entries 1 & 2, and 6 & 7). It is interesting to note that nitrogen- and phosphorus-based ligands exhibit similar reactivities. However, catalysts with nitrogen-based ligands such as Phen were less stable under catalytic conditions than their phosphorus counterparts, giving palladium mirrors. For this reason, the diop ligand was employed in defining the scope of these catalytic systems with different substrates.

While chiral ligands were employed with most of the studied catalysts (Table 1), mixtures of diastereomers and enantiomers were obtained consistently. This suggested the involvement of a carbocation intermediate. Supporting evidence for such a mechanism was provided by 1,2,3,4-tetrahydro-1-naphthol, which gave 1,2-dihydro-1-naphthalene (E1 product), and the ether in a 1:1 ratio. This was the only substrate, however, that gave detectable E1 product. Furthermore, when the enantiomerically pure (*S*)-(−)-*sec*-phenylethyl alcohol was employed, we recovered a diastereomeric and racemic mixture of bis-*sec*-phenylethyl ether (**1a**). To elucidate the rate determining step (RDS) in the catalytic reaction, we determined the kinetic dependence of the alcohol (benzhydrol) at a given catalyst — [{(*R*,*R*)-diop}$PdCl_2$] + 2AgOTf — concentration (Figure 1). The reaction is first order in concentration of al-

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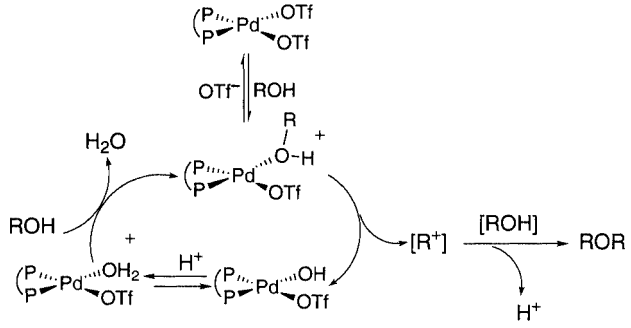
Table 1. $[Pd^{II}Cl_2(L\text{-}L)]$ catalysts for the etherfication of *sec*-phenylethyl alcohol[a]

Entry	Catalyst[b]	Yield (%)
1	[{(*R*,*R*)-Me-duphos}$PdCl_2$] + 2AgOTf	9
2	[{(*R*,*R*)-diop}$PdCl_2$] + 2AgOTf	83
3	[{(*R*,*R*)-diop}$PdCl_2$]	0
4	[(dppe)$PdCl_2$] + 2AgOTf	49
5	[{(*S*,*S*)-chiraphos}$PdCl_2$ + 2AgOTf	80
6	[{(*S*)-*iPr*)pyox}$PdCl_2$] + 2AgOTf	80
7	[{(*S*)-*iPr*)Phpyox}$PdCl_2$] + 2AgOTf	66
8	[(phen)$PdCl_2$] + 2AgOTf	75
9	AgOTf or $AgBAr^F{}_4$	0

[a] Conditions: [*sec*-phenylethyl alcohol] = 1.0 M, [Pd] = 0.020 M, and [AgOTf] = 0.040 M in CH_3NO_2 (V_T = 0.80 mL) at 50 °C for 24 hours. [b] Me-duphos = (−)-1,2-bis[(*2R,5R*)-2,5-dimethylphospholano]benzene; diop = (*4R,5R*)-(+)-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphanyl)butane; dppe = 1,2-bis(diphenylphosphanyl)ethane; chiraphos = (*2S,3S*)-(−)-bis(diphenylphosphanyl)butane; pyox = (*S*)-2-[4,5-dihydro-4-(1-methylethyl)-oxazol-2-yl]pyridine; Phpyox = (*S*)-2-[4,5-dihydro-4-(1-methylethyl)oxazol-2-yl]-6-phenylpyridine; phen = (1,10)-phenanthroline.

cohol and not second order; hence, carbocation formation is the RDS, Scheme 1. The racemization of the ether product is due to the fact that the etherification is reversible (vide infra per thiol reaction).



Scheme 1. Proposed catalytic sequence of reactions

Given its high reactivity, ease of preparation, and high stability, the [{(*R*,*R*)-diop}$PdCl_2$]/AgOTf catalyst was used in exploring symmetric ether formation from various alcohols. We discovered that only secondary benzylic alcohols are suitable and selective for ethers (Table 2). The ether yields varied from moderate (35%) to excellent (99%) depending on the nucleophilicity of the alcohol. The ether products are easily purified and isolated by flash chromatography. For example, ethers **3** and **1a** were isolated in 75% and 70% yield, respectively. Even though reactions were allowed to stand for one day, most reactions were complete within 3−4 hours. The success of secondary benzylic alcohols is related to the stability of their respective carbo-

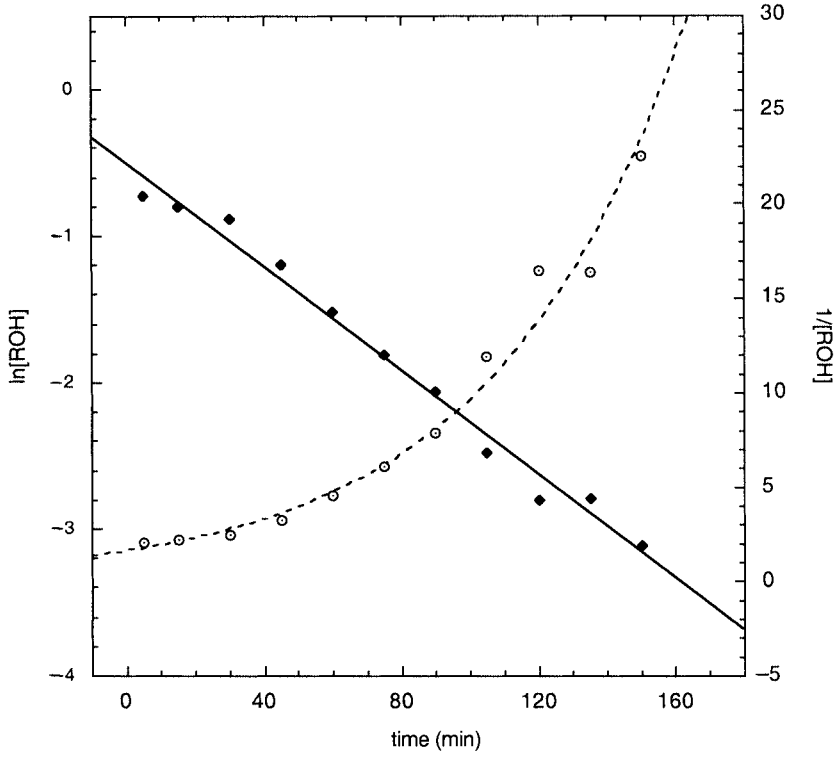
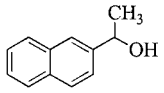
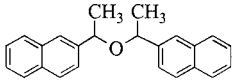
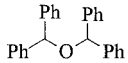
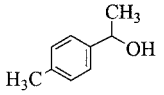
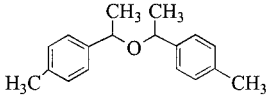
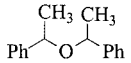
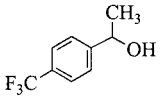
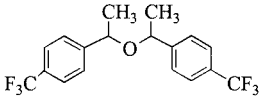
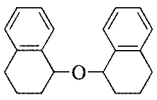


Figure 1. Plot of ln[ROH] (◆) and 1/[ROH] (⊙) versus time for the etherification of benzhydrol by [{(*R*,*R*)-diop}$PdCl_2$]/2AgOTf; conditions: [ROH] = 0.50 M, [{(*R*,*R*)-diop}$PdCl_2$] = 0.01 M, and [AgOTf] = 0.02 M in CH_3NO_2 at 50 °C

cation. As for tertiary benzyl alcohols such as 2-phenyl-2-butanol, a mixture of products was obtained with no evidence of ether formation.

Table 2. Formation of symmetric ethers from secondary benzylic alcohols catalyzed by [{(*R*,*R*)-diop}$PdCl_2$]/2AgOTf

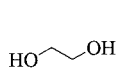
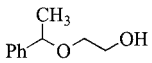
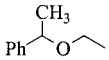
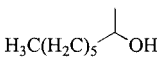
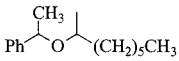
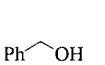
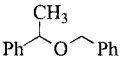
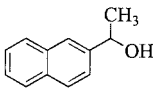
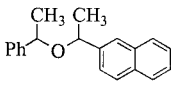
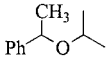
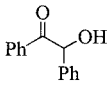
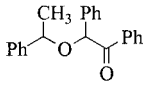
Entry[a]	Substrate	Product	Yield (%)[b]
1		 **2**	99[c]
2		 **3**	99[d]
3		 **1b**	99[c]
4		 **1a**	83[c,e]
5		 **1c**	35[e]
6		 **4**	55[c]

[a] Conditions: alcohol = 1.0 mmol, (*R*,*R*-(−)-(diop)$PdCl_2$ = 0.020 mmol, and AgOTf = 0.040 mmol in nitromethane (V_T = 0.80 mL) at 50 °C for 24 hours. [b] Determined by GC/MS and ^{1}H NMR spectroscopy. [c] All products were 1:1 mixtures of *dl* enantiomers and *meso* compounds. [d] 75% isolated yield. [e] 70% isolated yield.

Alkyl phenylethyl ethers such as phenylethyl ethyl ether and phenylethyl isopropyl ether are widely used in the perfume industry and are important oxygenates in reformulated gasoline.[8] Hence, we took advantage of our system's selectivity for secondary benzyl alcohols and explored its utility in the preparation of unsymmetrical aromatic ethers with a variety of primary and secondary alcohols, including diols (Table 3). Various benzylic and alkyl alcohols were used with phenylethyl alcohol to provide excellent to moderate yields of the unsymmetric ether. In every case, the conversion of *sec*-phenylethyl alcohol to ether products exceeded 90%. The only side product was the symmetric bis(*sec*-phenylethyl) ether; however, in most cases, the unsymmetric ether was the major product. In case of entry 5, since both substrates are secondary benzylic alcohols, symmetric ethers from both alcohols account for the balance in the yield.

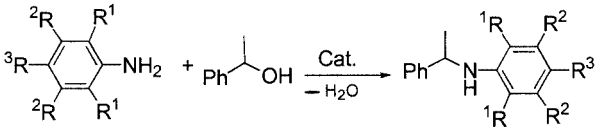
Amines have found uses as antioxidants in fuel oils, rubber stabilizers, medicinal drugs, detergents, and herbi-

Table 3. Formation of unsymmetric ethers by coupling *sec*-phenylethyl alcohol and benzylic or alkyl alcohols[a]

Entry	Substrate	Product	Conv. (%)[b]	Yield (%)[c]
1		 **5**	99	95
2	EtOH	 **6**	99	74
3		 **7**	97	73[d]
4		 **8**	92	68
5		 **9**	93	51[d]
6		 **10**	95	48
7		 **11**	93	36

[a] Conditions: *sec*-phenylethyl alcohol = 0.50 mmol, substrate = 0.50 mmol, (*R*,*R*-(−)-(diop)$PdCl_2$ = 0.020 mmol, and AgOTf = 0.040 mmol in nitromethane (V_T = 0.80 mL) at 50 °C for 24 hours. [b] Based on *sec*-phenylethyl alcohol concentration. [c] Determined by GC/MS and ^{1}H NMR spectroscopy; the remaining balance is the symmetric ether bis(*sec*-phenylethyl) ether. [d] Products were 1:1 mixtures of *dl* enantiomers and *meso* compounds.

Table 4. Formation of secondary amines from the direct amination of *sec*-phenylethyl alcohol with electron-deficient anilines[a]



Entry	Substrate	Product	Conv. (%)[b]	Yield (%)[c]
1	$R^1 = R^2 = R^3 = F$	**12**	95	64
2	R^2 = H, $R^1 = R^3$= F	**13**	86	39
3	R^2 = H, $R^1 = R^3$ = Cl	**14**	94	45

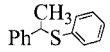
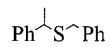
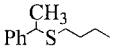
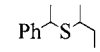
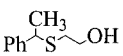
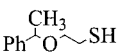
[a] Conditions: *sec*-phenylethyl alcohol = 0.50 mmol, substrate = 0.50 mmol, (*R*,*R*)-(−)-(diop)$PdCl_2$ = 0.020 mmol, and AgOTf = 0.040 mmol in nitromethane (V_T = 0.80 mL) at 50 °C for 24 hours. [b] Based on *sec*-phenylethyl alcohol concentration. [c] Determined by GC/MS; the remaining balance is the symmetric ether bis(*sec*-phenylethyl) ether.

cides.[9] Generally, alcohol aminations require the conversion of the alcohol to a halide. The method described herein is a direct one that employs anilines and *sec*-phenylethyl alcohol. Since palladium(II) has a high affinity for amine ligands,[10] anilines are problematic in that they bind irreversibly to our Pd^{II} complexes, inhibiting catalysis. Hence, only electron-deficient anilines reacted with *sec*-phenylethyl alcohol to yield the secondary amine in moderate to good yields (Table 4). Another limitation of this method is that the symmetric ether from *sec*-phenylethyl alcohol is always a side product. A study of 2,6-diisopropylaniline with the hope of blocking coordination to Pd was not successful as only starting materials were recovered.

Bis(diphenylphosphanyl)methane complexes of platinum(II) have been shown to catalyze the formation of thioethers from thiols and alkyl halides or geminal dihalides.[11] The procedure described here is direct and more convenient. The reaction of *sec*-phenylethyl alcohol with aromatic, benzylic, and alkyl thiols proceeds smoothly to give exclusively the thioether product (Table 5). One exception is the reaction with 2-mercaptoethanol (entry 5) in which both the ether and thioether are formed. Thioether **17** was isolated in 98% yield (entry 3) to illustrate the high efficiency of this method on a preparative scale.

An interesting observation was the conversion of any bis(*sec*-phenylethyl) ether formed during the reaction to the thioether product. In fact, when bis-*sec*-phenylethyl ether (**1a**) and 1-butanethiol in a 1:2 ratio, respectively, were combined in the presence of [{(*R*,*R*)-diop}$PdCl_2$]/2AgOTf, after two hours (*sec*-phenylethyl) *n*-butyl thioether **17** was observed as the exclusive product in solution. Control reactions without catalyst showed no reaction over days under the same conditions. Hence, we propose that the ether reacts with palladium to form an alkoxide complex of Pd^{II} along with a carbocation intermediate. The latter is captured by the thiol, yielding the thioether and a proton. The palladium alkoxide complex is protonated to regenerate the starting palladium catalyst and *sec*-phenylethyl alcohol.

Table 5. Formation of thioethers from the direct reaction of *sec*-phenylethyl alcohol with thiols[a]

Entry	Substrate	Product	Conv. (%)[b]	Yield (%)[c]
1		 **15**	99	99
2		 **16**	99	99
3		 **17**	99	99[d]
4[e]		 **18**	99	99[f]
5		 **19**	99	43
		 **20**		34

[a] Conditions: *sec*-phenylethyl alcohol = 0.50 mmol, substrate = 0.50 mmol, (*R*,*R*)-(−)-(diop)$PdCl_2$ = 0.02 mmol, and AgOTf = 0.04 mmol in nitromethane (V_T = 0.80 mL) at 50 °C for 24 hours. [b] Based on *sec*-phenylethyl alcohol concentration. [c] Determined by GC/MS and ^1H NMR spectroscopy. [d] 98% isolated yield. [e] Starting material was a racemic mixtures. [f] Products were 1:1 mixtures of *dl* enantiomers and *meso* compounds.

Conclusion

In summary, we have developed an efficient Pd^{II} catalytic system for the direct preparation of symmetric and unsymmetric aromatic ethers, for the amination of secondary benzylic alcohols, and for the direct formation of thioethers.

Experimental Section

General Remarks: Solvents and reagents for all reactions were used as received from commercial suppliers unless noted otherwise. (*S*)-2-[4,5-dihydro-4-(1-methylethyl)oxazol-2-yl]-6-phenylpyridine,[12] (*S*)-2-[4,5-dihydro-4-(1-methylethyl)oxazol-2-yl]-pyridine[13,14] and all palladium dichloride complexes[15] were prepared according to literature methods. GC/MS analyses were performed on an Agilent 6890 GC equipped with a medium polarity bonded-phase fused silica capillary column (30 m × 0.25 mm, DB5, J & W Assoc. Folsom, Ca., injector port and GCMS transfer line at 250 °C, oven 50 °C for 3 min following injection then increased linearly at 15 °C/min to a plateau of 300 °C) the end of which was inserted directly into the EI source (70 eV, 180 °C) of a TOF mass spectrometer (Micromass GCT). Chromatographic purification was performed using columns packed with EM Silica Gel 60 Å (200−400 mesh) that had been dried overnight at 100 °C. CH_3NO_2 was distilled from CaH_2 immediately before use. NMR spectra were obtained with a Bruker 400 or 500 MHz spectrometer and referenced to TMS; the solvent is specified for each of the compounds.

A Typical Catalytic Procedure: In a vial equipped with a stir bar, [{(*R*,*R*)-diop}$PdCl_2$] (0.0108 g, 0.016 mmol) and AgOTf (0.0081 g, 0.032 mmol) were dissolved in 0.7 mL of dry CH_3NO_2. The solution was allowed to stir at room temperature for a couple of minutes to allow for the formation of the active catalyst as indicated by the color change from a pale to bright yellow. (±)-*sec*-Phenylethyl alcohol (98 μL, 0.8 mmol) was then added via a syringe. The solution (V_T = 0.8 mL) was capped and placed in a 50 °C sand bath for 24 hours. Afterwards, the solvent was removed under vacuum. The organic residue was purified by flash chromatography on silica gel (1:1, hexanes and diethyl ether) and characterized by GC/MS, ^1H and ^{13}C NMR spectroscopy.

Bis(α-methyl-2-naphthalene)methyl Ether (2):[16] (0.32 g, 99%). ^1H NMR ($CDCl_3$): δ = 7.87−7.80 (m, 16 H), 7.51−7.41 (m, 12 H),

4.74 (q, 2 H)*, 4.45 (q, 2 H)*, 1.58−1.51 (2m, 12 H)* ppm. ^{13}C NMR ($CDCl_3$): δ = 141.54, (141.38), 133.20, (133.13), 132.95, (132.74), 128.33, (127.94), 127.73(2), 127.63, (127.50), 126.00(2), 125.65(2), 125.12, (124.77), 124.20(2), 74.70, (74.50), 24.45, (22.78) ppm. GC/MS: t_R = 14.85 & 15.10 min (*dl* and meso), obs. MS: *m/z* = $M^{+\cdot}$ (not observed), 172.10 [M − $C_{12}H_{10}$]$^+$, 154.07 [M − $C_{12}H_{12}O$]$^+$; calcd.: 326.44 ($C_{24}H_{22}O$), 172.23 ($C_{12}H_{12}O$), 154.21 ($C_{12}H_{10}$) Da. * diastereomeric pairs.

Bis(diphenyl)methyl Ether (3):[6a] (0.35 g, 99%). ^{1}H NMR ($CDCl_3$): δ = 7.38−7.25 (m, 20 H), 5.40 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 142.11, 128.30, 127.35, 127.12, 79.90 ppm. GC/MS: t_R = 14.80 min, obs. MS: *m/z* = $M^{+\cdot}$ (not observed), 183.09 [M − $C_{13}H_{11}$]$^+$, 167.08 [M − $C_{13}H_{11}O$]; calcd.: 350.46 ($C_{26}H_{22}O$), 183.23 ($C_{13}H_{11}O$), 167.23 ($C_{13}H_{11}$) Da.

Bis-1-(4-methylphenyl)ethyl Ether (1b): (0.25 g, 99%). ^{1}H NMR ($CDCl_3$): δ = 7.26−7.16 (m, 8 H), 7.12 (m, 8 H), 4.51 (q, 2 H)*, 4.24 (q, 2 H)*, 2.36 (s, 6 H)*, 2.33 (s, 6 H)*, 1.45 (d, 6 H)*, 1.38 (d, 6 H)* ppm. ^{13}C NMR ($CDCl_3$): δ = 141.08, (141.24), 136.90, (136.63), 129.09, (128.85), 126.21, (126.11), 74.16, (73.83), 24.63, (22.79), 21.07, (21.01) ppm. GC/MS: t_R = 10.82 min, obs. MS: *m/z* = $M^{+\cdot}$ (not observed), 239.17 [M − CH_3]$^+$; calcd.: 254.37 ($C_{18}H_{22}O$), 239.34 ($C_{17}H_{19}O$) Da. * diastereomeric pairs.

Bis-1-[4-(trifluoromethyl)phenyl]ethyl Ether (1c): (0.13 g, 35%). ^{1}H NMR ($CDCl_3$): δ = 7.62 (d, 4 H)*, (d, 4 H)*, 7.46 (d, 4 H)*, 7.40 (d, 4 H)*, 4.56 (q, 2 H)*, 4.28 (q, 2 H)*, 1.40 (d, 12 H)* ppm. ^{13}C NMR ($CDCl_3$): δ = 147.92(2), 126.46, 126.35, 125.56(2), 125.27(2), 74.65, 74.62, 24.50, 23.14 ppm. GC/MS: t_R = 6.38 min, obs. MS: *m/z* = $M^{+\cdot}$ (not observed), 189.06 [M − $C_9H_8F_3$]$^+$, 173.05 [M − $C_9H_8OF_3$]$^+$; calcd.: 362.31 ($C_{18}H_{16}F_6O$), 189.16 ($C_9H_8OF_3$), 173.16 ($C_9H_8F_3$) Da. * diastereomeric pairs.

Bis(1,2,3,4-tetrahydro-1-napthyl) Ether (4):[6e] (0.15 g, 55%). ^{1}H NMR ($CDCl_3$): δ = 7.17−7.14 (m, 12 H), 7.12−7.11 (m, 4 H), 3.73 (br. t, 4 H), 2.21 (q, 4 H)*, 2.15 (q, 4 H)*, 1.98 (m, 8 H)*, 1.84 (q, 4 H)*, 1.77 (q, 4 H)* ppm. ^{13}C NMR ($CDCl_3$): δ = 145.56, (137.85), 137.63, (134.05), 129.18, (128.99), 127.09, (126.24), 125.90, (125.56), 125.51, (125.06), 47.23, 29.75, 28.49, (28.47), (21.37) ppm. GC/MS: t_R = 13.50 min, obs. MS: *m/z* = $M^{+\cdot}$ (not observed), 260.16 [M − OH_2]$^+$; calcd.: 278.39 ($C_{20}H_{22}O$), 260.38 ($C_{20}H_{20}$) Da. * diastereomeric pairs.

(1-Hydroxy)ethyl (±)-*sec*-Phenylethyl Ether (5):[17] (0.078 g, 95%). ^{1}H NMR ($CDCl_3$): δ = 7.34−7.25 (m, 5 H), 4.45 (q, 1 H), 3.67 (m, 2 H), 3.41 (m, 2 H), 3.28 (br. s, 1 H), 1.42 (d, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.32, 128.45, 127.30, 126.22, 78.41, 69.64, 61.87, 24.00 ppm. GC/MS: t_R = 7.87 min, obs. MS: *m/z* = 166.11 ($M^{+\cdot}$); calcd.: 166.22 ($C_{10}H_{14}O_2$) Da.

Ethyl (±)-*sec*-Phenylethyl Ether (6):[6a] (0.056 g, 74%). ^{1}H NMR ($CDCl_3$): δ = 7.35−7.25 (m, 5 H), 4.41 (q, 1 H), 3.35 (q, 2 H), 1.45 (d, 3 H), 1.17 (t, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.93, 128.07, 126.99, 125.79, 77.42, 63.58, 24.32, 15.09 ppm. GC/MS: t_R = 5.57 min, obs. MS: *m/z* = $M^{+\cdot}$ (not observed), 135.08 [M − CH_3]$^+$; calcd.: 150.22 ($C_{10}H_{14}O$), 135.19 ($C_9H_{11}O$) Da.

1-Methylheptyl (±)-*sec*-Phenylethyl Ether (7):[5b] (0.086 g, 73%). ^{1}H NMR ($CDCl_3$): δ = 7.37−7.25 (m, 5 H), 4.53 (q, 1 H)*, 3.38 & 3.28 (2sextet, 1 H)*, 1.42 & 1.41 (2d, 3 H)*, 1.29 (m, 10 H), 1.12 & 1.04 (2d. 3 H)*, 0.88 (t, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 145.04, (144.51), 128.19, (128.15), 127.19, (127.06), 126.41, (126.14), 75.38, (73.10), 71.83, (68.20), 39.28, 37.50, 36.02, 31.79(2), 29.48, 29.27, 29.20, 25.68, 25.60, 25.25, 24.68, 24.33, 22.57, 19.23, 14.04 ppm. GC/MS: t_R = 5.90 min, obs. MS: *m/z* = $M^{+\cdot}$ (not observed), 219.19 [M − CH_3]$^+$; calcd.: 234.38 ($C_{16}H_{26}O$), 219.35 ($C_{15}H_{23}O$) Da. * diastereomeric pairs.

Benzyl (±)-*sec*-Phenylethyl Ether (8):[18] (0.072 g, 68%). ^{1}H NMR ($CDCl_3$): δ = 7.40−7.26 (m, 10 H), 4.54 (q, 1 H), 4.49 (d, 1 H), 4.36 (d, 1 H), 1.51 (d, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.50, 138.41, 128.29, 128.14, 127.49, 127.29, 126.13, 125.08, 70.08, 24.01 ppm. GC/MS: t_R = 10.77 min, obs. MS: *m/z* = $M^{+\cdot}$ (not observed), 197.11 [M − CH_3]$^+$; calcd.: 212.29 ($C_{15}H_{16}O$), 197.26 ($C_{14}H_{13}O$) Da.

1-(2-Naphthyl)ethyl (±)-*sec*-Phenylethyl Ether (9): (0.070 g, 51%). ^{1}H NMR ($CDCl_3$): δ = 7.89−7.26 (4m, 12 H), 4.76 (q, 1 H), 4.55 (q, 1 H), 1.49 (d, 3 H), 1.42 (d, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 141.54, (141.40), 133.23, (132.97), 128.42, 128.39, 128.18, 127.98, 127.80, 127.76, 127.60, 127.39, 127.34, 127.11, 126.25, 126.17, 126.08, 126.04, 126.02, 125.72, 125.69, 125.67, 125.32, 125.18, 125.15, 124.49, 124.25, 74.61, (74.55), 24.52, (24.50), 22.81, 22.78 ppm. GC/MS: t_R = 14.20 min, obs. MS: *m/z* = $M^{+\cdot}$ (not observed), 154.07 [M − $C_{12}H_{12}O$]$^+$, 105.07 [M − $C_{16}H_{13}O$]$^+$; calcd.: 276.38 ($C_{20}H_{20}O$), 154.21 ($C_{12}H_{10}$), 105.16 (C_8H_9) Da.

Isopropyl (±)-*sec*-Phenylethyl Ether (10):[19] (0.039 g, 48%). ^{1}H NMR ($CDCl_3$): δ = 7.37−7.26 (m, 5 H), 4.54 (q, 1 H), 3.49 (sept, 1 H), 1.41 (d, 3 H), 1.16 (d, 3 H), 1.10 (d, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 144.81, 128.27, 127.12, 126.07, 74.55, 68.44, 24.74, 23.25, 21.30 ppm. GC/MS: t_R = 5.90 min, obs. MS: *m/z* = $M^{+\cdot}$ (not observed), 149.10 [M − CH_3]$^+$; calcd.: 164.25 ($C_{11}H_{16}O$), 149.21 ($C_{10}H_{13}O$) Da.

1,2-Diphenyl-2-(1-phenylethoxy)-1-ethanone (11): (0.057 g, 36%). ^{1}H NMR ($CDCl_3$): δ = 7.80 (d, 2 H), 7.40−7.26 (m, 13 H), 5.53 & 5.47 (2s, 1 H)*, 4.59 & 4.48 (2q, 1 H)*, 1.52−1.50 (2d, 3 H)* ppm. ^{13}C NMR ($CDCl_3$): δ = 198.65, 142.67, (142.41), 134.84, 133.12, 132.87, 129.82, 129.14, (129.04), 128.72, (128.67), 128.54(2), 128.39, 128.18, 127.85(2), 127.34, 127.05, 126.70, 126.41, 125.31, 82.35, (81.41), 24.14, (23.83) ppm. GC/MS: t_R = 15.50 min, obs. MS: *m/z* = $M^{+\cdot}$ (not observed), 211.13 [$M^{+\cdot}$ − C_8H_9], 105.07 [$M^{+\cdot}$ − $C_{14}H_{11}O_2$]; calcd.: 316.40 ($C_{22}H_{20}O_2$), 211.24 ($C_{14}H_{11}O_2$), 105.16 (C_8H_9) Da. *diastereomeric pairs

***N*-(±)-α-methyl-benzyl-*N*-pentafluorobenzylamine (12):** (0.092 g, 64%). ^{1}H NMR ($CDCl_3$): δ = 7.42−7.27 (m, 5 H), 4.96 (q, 1 H), 3.74 (br. s, 1 H), 1.61 (d, 3 H) ppm. ^{13}F NMR ($CDCl_3$): δ = −158.3 (d, 2 F), −164.8 (t, 2 F), −170.9 (t, 1 F) ppm. GC/MS: t_R = 9.92 min, obs. MS: *m/z* = 287.08 [$M^{+\cdot}$]; calcd.: 287.23 ($C_{14}H_{10}F_5N$) Da.

***N*-(±)-α-methylbenzyl-*N*-2,4,6-trifluorobenzylamine (13):** (0.049 g, 39%). ^{1}H NMR ($CDCl_3$): δ = 7.37−7.26 (2m, 5 H), 6.55 (t, 2 H), 4.71 (q, 1 H), 3.74 (br. s, 1 H), 1.55 (d, 3 H) ppm. ^{19}F NMR ($CDCl_3$): δ = −120.59 (s, 2 F), −124.15 (s, 1 F) ppm. GC/MS: t_R = 9.85 min, obs. MS: *m/z* = 251.11 [$M^{+\cdot}$]; calcd.: 251.25 ($C_{14}H_{12}N F_3$) Da.

***N*-(±)-α-methylbenzyl-*N*-2,4,6-trichlorobenzylamine (14):** (0.068 g, 45%). ^{1}H NMR ($CDCl_3$): δ = 7.38−7.20 (2 m, 5 H), 7.19 (s, 2 H), 5.02 (q, 1 H), 4.16 (br. s, 1 H), 1.58 (d, 3 H)ppm. GC/MS: t_R = 13.65 min, obs. MS: *m/z* = 299.09 [$M^{+\cdot 35}Cl_3$], 301.09 [$M^{+\cdot 35}Cl_2$, ^{37}Cl], 303.09 [$M^{+\cdot 35}$Cl, $^{37}Cl_2$], & 305.9 [$M^{+\cdot 37}Cl_3$]; calcd.: 299 ($C_{14}H_{12}N^{35}Cl_3$), 301 ($C_{14}H_{12}N^{35}Cl_2$ ^{37}Cl), 303 ($C_{14}H_{12}N^{35}Cl^{37}Cl_2$), 305 ($C_{14}H_{12}N^{37}Cl_3$) Da.

Phenyl (±)-*sec*-Phenylethyl Thioether (15):[20] (0.11 g, 99%). ^{1}H NMR ($CDCl_3$): δ = 7.30−7.20 (m, 10 H), 4.35 (q, 1 H), 1.63 (d, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.12, 135.04, 132.33, 128.61, 128.31, 127.19, 127.06, 127.03, 47.86, 22.24 ppm. GC/MS: t_R =

10.45. min, obs. MS: *m*/*z* = 214.11 [$M^{+\cdot}$]; calcd.: 214.33 ($C_{14}H_{14}S$) Da.

Benzyl (±)-*sec*-Phenylethyl Thioether (16):[21] (0.11 g, 99%). ^1H NMR ($CDCl_3$): δ = 7.40−7.27 (m, 10 H), 3.88 (q, 1 H), 3.60 (d, 1 H), 3.50 (d, 1 H), 1.60 (d, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.70, 138.33, 128.80, 128.59, 128.42, 128.32, 127.94, 127.37, 127.00, 126.95, 126.76, 43.47, 35.63, 28.88, 22.46 ppm. GC/MS: t_R = 12.13 min, obs. MS: *m*/*z* = 228.10 ($M^{+\cdot}$), calcd.: 228.35 ($C_{15}H_{16}S$) Da.

***n*-Butyl (±)-*sec*-Phenylethyl Thioether (17):**[22] (0.096 g, 99%). ^1H NMR ($CDCl_3$): δ = 7.35−7.23 (m, 5 H), 3.94 (q, 1 H), 2.36−2.27 (m, 2 H), 1.57 (d, 3 H), 1.50−1.46 (m, 2 H), 1.40−1.32 (m, 2 H), 0.85−0.83 (t, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 144.20, 128.48, 127.30, 127.00, 44.09, 31.51, 31.02, 22.68, 22.09, 13.71 ppm. GC/MS: t_R = 9.25 min, obs. MS: *m*/*z* = 194.13 ([$M^{+\cdot}$]; calcd.: 194.33 ($C_{12}H_{18}S$) Da.

***sec*-Butyl (±)-*sec*-Phenylethyl Thioether (18):** (0.096 g, 99%). ^1H NMR ($CDCl_3$): δ = 7.37−7.22 (m, 5 H), 4.02 (2q, 1 H)*, 2.52 & 2.41 (2 sext, 1 H)*, 1.46 & 1.40 (quin, 2 H)*, 1.55 (d, 3 H), 1.24 & 1.11 (2d, 3 H)*, 0.92 & 0.86 (2t, 3 H)* ppm. ^{13}C NMR ($CDCl_3$): δ = 144.60, (144.57), 128.38(2), [128.36(2)], 127.17(2), [127.51(2)], 126.84, (126.83), 43.08, (42.82), 40.81, (40.80), 29.74, (29.47), 23.16, (22.94), 21.10, (20.26), 11.26, (10.97) ppm. GC/MS: t_R = 8.63 & 8.70 min (*dl* and meso), obs. MS: *m*/*z* = 194.12 ($M^{+\cdot}$), calcd.: 194.33 ($C_{12}H_{18}S$) Da. * diastereomeric pairs.

(1-Hydroxy)ethyl (±)-*sec*-Phenylethyl Thioether (19): (0.039 g, 43%) ^1H NMR ($CDCl_3$): δ = 7.37−7.22 (m, 5 H), 3.98 (q, 1 H), 3.60−3.51 (m, 2 H), 2.70−2.66 (m, 2 H), 2.27 (br. s., 1 H), 1.56 (d, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.34, 128.12, 126.94, 125.80, 60.36, 43.62, 34.24, 24.48 ppm. GC/MS: t_R = 9.75 min, obs. MS: *m*/*z* = 182.07 [$M^{+\cdot}$], 137.03 [M − C_2H_5O]$^+$, & 105.06 [M − C_2H_5OS]$^+$; calcd.: 182.28 ($C_{10}H_{14}OS$), 137.22 (C_8H_9S), & 105.16 (C_8H_9) Da.

1-Mercaptoethyl (±)-*sec*-Phenylethyl Ether (20): (0.031 g, 34%). ^1H NMR ($CDCl_3$): δ = 7.33−7.25 (m, 5 H), 4.41 (q, 1 H), 3.42 (t, 2 H), 3.33 (t, 2 H), 1.52 (t, 1 H), 1.43 (d, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.34, 128.12, 126.94, 125.80, 77.89, 70.12, 23.85, 22.42 ppm. GC/MS: t_R = 14.08 min, obs. MS: *m*/*z* = 182.07 [$M^{+\cdot}$], 121.06 [M − C_2H_5S]$^+$, & 105.06 [M − C_2H_5OS]$^+$; calcd.: 182.28 ($C_{10}H_{14}OS$), 121.16 (C_8H_9O), 105.16 (C_8H_9) Da.

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