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Lewis Base Catalysis by Thiourea: *N*-Bromosuccinimide-Mediated Oxidation of Alcohols

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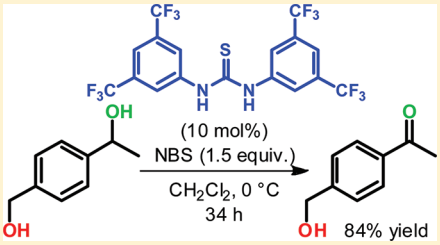
Supporting Information

ABSTRACT: In recent times, (thio)urea derivatives have become synonymous with hydrogen bonding owing to their extensive applicability as small molecule organocatalysts. In this paper, another activation mode by thiourea derivatives, namely via Lewis base catalysis, is disclosed for the NBS-mediated oxidation of alcohols. The mild reaction conditions employed here is suitable for chemoselective oxidation of secondary alcohol in the presence of primary alcohol.



During the past decade, (thio)urea derivatives have emerged as one of the most popular class of small molecule organocatalysts.[1] Initial reports have been confined to the direct activation of electrophilic substrates by means of double hydrogen bonding (Figure 1),[2] and a wide range of

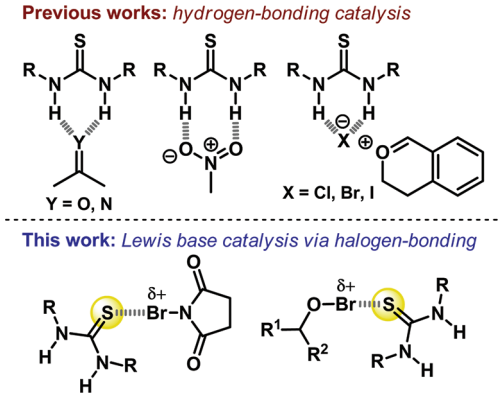


Figure 1. Hydrogen-bonding catalysis and Lewis base catalysis by thiourea.

asymmetric transformations have been accomplished using chiral (thio)urea derivatives.[3] More recently, the anion-binding property of (thio)ureas (Figure 1)[4] has been exploited in asymmetric catalysis.[5] Asymmetric counteranion-directed catalysis[6] of this type has already proven its potential for a number of challenging transformations.[7] Furthermore, the combination of (thio)urea-bound counteranion catalysis with other catalysis modes is rapidly gaining pace.[8] Although these newer activation modes by (thio)urea derivatives have added another dimension to (thio)urea catalysis, the foundation of these concepts is once again based on the hydrogen bond donor ability of (thio)urea derivatives.[9]

Herein we describe yet another activation mode of thiourea, namely Lewis base catalysis. The concept of Lewis base catalysis, particularly in asymmetric catalysis, has been thoroughly explored.[10] However, the application of thiourea derivatives as Lewis base catalyst remained rather scarce. One of the rare examples of thiourea as Lewis base catalyst was reported by Denmark et al. for halolactonization reactions.[11] We realized that the polarizable and Lewis basic sulfur center of thiourea can engage in an attractive interaction with suitable electrophilic halogen source (Figure 1). This interaction may be termed as halogen bonding,[12] which is commonly referred to the attractive noncovalent interaction between an electrophilic halogen atom and an electron-rich Lewis basic center. The proof of this concept is demonstrated here for the *N*-bromosuccinimide (NBS)-mediated oxidation of alcohols.

Very recently, chiral (thio)urea and thiocarbamate derivatives have been employed as catalyst for *N*-halosuccinimide-mediated asymmetric halolactonization and related transformations.[13,14] In all these cases, the catalytic activity of (thio)urea derivatives has been attributed to the hydrogen bonding from the catalysts. Only in the report of thiocarbamate-catalyzed halolactonizations and related reactions by Yeung and co-workers, in addition to the hydrogen bonding, an interaction of bromine with Lewis basic sulfur atom is proposed.[13b,c]

Oxidation of alcohols by NBS and other electrophilic halogen sources has been known for a long time, and the reactions proceed in rather demanding conditions in the absence of any catalyst.[15] At the outset of our investigation, the effect of (thio)urea derivatives on the oxidation of 1-phenylethanol **1a** by NBS was studied (Table 1). The oxidation of **1a** was indeed found to take place at ambient temperature with 1.5 equiv of NBS in the absence of any catalyst. However, the reaction was rather sluggish, and incomplete conversion to acetophenone **2a** was observed together with the formation of a significant amount of α-bromo and a trace of α,α-dibromo acetophenone (Table 1, entry 1). Consequently, to probe the

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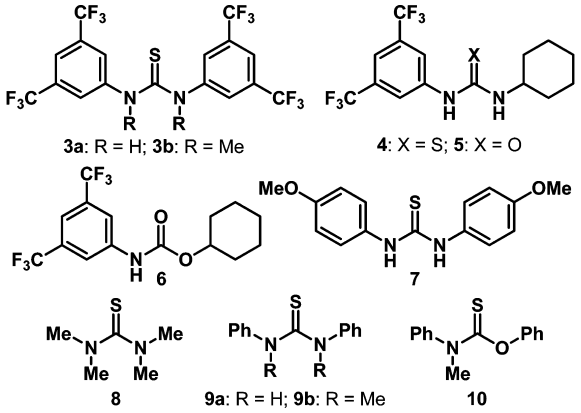
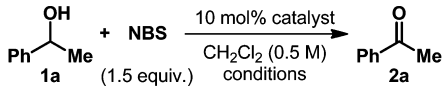
Table 1. Catalyst Screening for NBS-Mediated Alcohol Oxidation





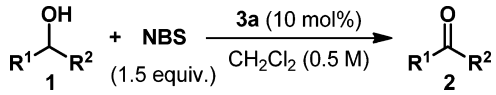
Entry	Catalyst	*T*/°C	*t*/h	Conversion (%)[a]
1	-	r.t.	24	-[b]
2	-	–35	90	<5
3	**3a**	–35	90	>95 (84)
4	**3b**	–35	72	>80
5	**4**	–35	90	90
6	**5**	–35	90	<10
7	**6**	–35	90	<10
8	**7**	–35	90	70
9	**8**	–35	90	72
10	**9a**	–35	90	63
11	**9b**	–35	90	>90 (80)
12	**10**	–35	90	>95 (84)
13[c]	**3a**	–35	90	25

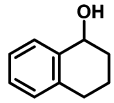
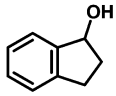
[a]Conversion as determined by ^{1}H NMR of the crude reaction mixture. The values in parentheses correspond to yields of the isolated products after column chromatography. [b]The reaction mixture consists of a mixture of **1a**, **2a**, α-bromoacetophenone, and α,α-dibromoacetophenone after 24 h. [c]The reaction was conducted in methanol.

catalytic activity of (thio)urea derivatives, the reaction conditions were chosen carefully so as to minimize the background as well as undesired side reactions. A quick temperature optimization revealed that the uncatalyzed reaction was completely suppressed at −35 °C, and no appreciable amount of **2a** was detected even after 90 h (entry 2). In contrast, only 10 mol % of the thiourea derivative **3a** is sufficient to catalyze nearly complete conversion within 90 h and **2a** was isolated in 84% yield (entry 3). Structurally related thiourea derivatives **4**, **7** and **9a** were also found to be potent catalysts for this reaction (entries 5, 8, and 10). Relatively less catalytic efficacy of **7**, despite having electron-rich *p*-methoxy substituents, is presumably due to its poor solubility in the reaction medium. The importance of Lewis basic sulfur center of thiourea derivatives in catalytic activity was established by catalytic incompetence of the corresponding urea **5** and carbamate **6** (entries 6 and 7): only trace amount of acetophenone was detected even after 90 h. Catalytic activity of thiourea derivatives was retained in spite of *N*-alkylation as exhibited by *N*-methylated thiourea and thiocarbamate derivatives **3b**, **8**, **9b**, and **10** (entries 4, 9, 11, and 12). These experiments clearly demonstrate that this NBS-mediated oxidation reaction does not proceed via hydrogen bonding activation of substrate/reagent. Particularly noteworthy is the catalyst pair **3a** and **3b**, where both thiourea derivative and its *N*-methylated counterpart were found to be nearly equally efficient in catalyzing the aforementioned oxidation reaction. Among other solvents screened, substantial decrease in reaction rate was observed in polar protic methanol (entry 13).

Although catalyst **3b**, **4**, **9b**, and **10** are almost equally efficient as **3a**, the scope and limitation of this oxidation method was investigated using thiourea derivative **3a**, considering its easy accessibility and wide applicability. It is important to note that in each case, the reaction temperature was carefully adjusted to suppress the uncatalyzed reactions. As summarized in Table 2, the catalyst **3a** is effective for oxidation

Table 2. Substrate Scope for the Catalytic Alcohol Oxidation



Entry	R^1	R^2	Product	*T*/°C	*t*/h	Yield (%)[a]
1	Ph	Me	**2a**	–35	90	84
2	Ph	Et	**2b**	–20	90	80
3	Ph	*c*-Hex	**2c**	0	48	86
4	Ph	*t*-Bu	**2d**	10	90	51
5	4-ClC_6H_4	Me	**2e**	–20	90	80
6	4-MeC_6H_4	Me	**2f**	–20	44	90
7	4-FC_6H_4	Me	**2g**	0	16	85
8	2-MeC_6H_4	Me	**2h**	0	66	80
9	*c*-Hex	Me	**2i**	–20	48	84
10	-$(CH_2)_5$-		**2j**	–35	72	82
11			**2k**	–35	90	92
12			**2l**	–20	16	80
13	$PhCH_2CH_2$	Me	**2m**	10	90	40
14	Ph	H	**2n**	–20	90	60[b]

[a]Yield of isolated product after column chromatography. [b]Conversion as determined by 1H-NMR of the crude reaction mixture.

of a wide range of secondary alcohols with different steric and electronic environment. Thus, benzylic alcohols with sterically diverse substituents underwent smooth oxidation to the corresponding ketones in very high yield (entries 1–3), except for *tert*-butyl phenyl methanol (**1d**), where only moderate yield of the *tert*-butyl phenyl ketone (**2d**) was obtained even after prolonged reaction time (entry 4). Equally efficient are secondary benzylic alcohols with both electron-rich and electron-withdrawing ring substituents (entries 5–8). The present method is not restricted to reactive benzylic alcohols as aliphatic secondary alcohols were also oxidized to the corresponding ketones in excellent yield (entries 9 and 10). Similar reaction conditions can also be employed to the oxidation of primary alcohol, albeit with diminished efficiency: benzyl alcohol was oxidized to benzaldehyde with 60% conversion after 90 h (entry 14).

We were intrigued by the striking reactivity difference between primary and secondary alcohols and realized that the

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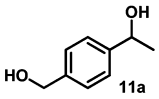
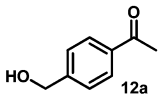
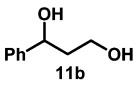
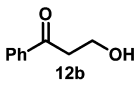
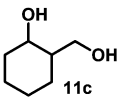
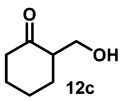
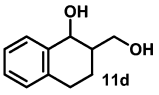
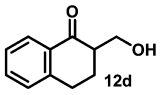
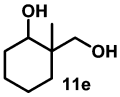
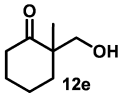
selective oxidation of secondary alcohols over primary alcohols could be achieved with our present method. Chemoselective oxidation of secondary alcohols in the presence of primary alcohols is a formidable challenge, particularly in the context of complex molecule synthesis. Even though a few methods are known for selective oxidation of secondary alcohols,[16] the protection−oxidation−deprotection strategy is still the method of choice. However, protecting-group free oxidation of secondary alcohols is highly desirable from the viewpoint of step-economic synthesis. Our oxidation method was indeed found to be selective for secondary alcohols. As depicted in Table 3, both benzylic as well as aliphatic secondary alcohols

Table 3. Chemoselective Oxidation of Secondary Alcohol Using 3a (10 mol %) as the Catalyst

Entry	Diol	Product	T/°C, t/h	Yield (%)[a]
1	 11a	 12a	0, 34	84
2	 11b	 12b	−20, 72	78
3	 11c	 12c	−20, 18	75
4	 11d	 12d	−20, 18	80
5	 11e	 12e	−30, 90	80

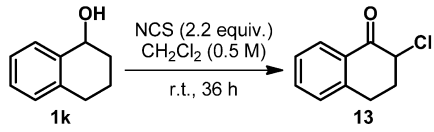
[a]Yields of the isolated products after column chromatography.

were oxidized to ketones under mild conditions in synthetically useful yields. Particularly remarkable is the diol **11a**, where the secondary benzylic alcohol was oxidized selectively leaving the primary benzylic alcohol untouched (Table 3, entry 1). The absence of any detectable aldehydes by ^{1}H NMR analysis of the crude reaction mixture demonstrates the synthetic utility of the present oxidation method.

Greater reactivity of secondary alcohols as compared to the primary alcohols is a clear indication of hydride abstraction mechanism since secondary alcohol would offer a greater stability to a carbocation generated at the α-position of alcohol after hydride abstraction.[16d] On the other hand, high catalytic efficiency of thiourea derivatives **3b**, **8**, and **9b** and thiocarbamate **10** (see Table 1) points toward the fact that hydrogen bonding by thiourea derivative **3a** is not responsible for its catalytic activity.On the basis of the above observations together with the striking difference in catalytic activity of urea and thiourea derivatives, it is reasonable to believe that the Lewis basic sulfur atom of thiourea is the catalytically active site and facilitates the hydride abstraction from alkyl hypobromide presumably by means of halogen bonding. Similar interaction might also be responsible in catalyzing the conversion of alcohol to the corresponding hypobromide. In the latter case, the possibility of nucleophilic catalysis by sulfur center cannot be ruled out at this stage. NBS mediated reactions are known to generate molecular bromine, which in principle can oxidize alcohols. However, the role of NBS itself as the oxidant was unambiguously established by independent experiments using molecular bromine as the reagent instead of NBS: no oxidation product of **1a** was detected using bromine under our standard reaction conditions either with or without catalyst **3a**.

To further illustrate the applicability of such Lewis base activation by thiourea, direct conversion of secondary alcohol to α-halo ketone was attempted. Preliminary experiments using *N*-chlorosuccinimide (NCS) as the electrophilic halogen source proved promising: thiourea **3a** catalyzed the facile conversion 1-tetralol **1k** to the corresponding α-chloro-1-tetralone **13** using 2.2 equiv of NCS with 56% isolated yield (Scheme 1). It is

Scheme 1. Direct Conversion of Alcohol 1k to α-Chloro Ketone 13



Catalyst	Yield
none	<5%
3a (10 mol%)	56%[a]

[a] Isolated yield

particularly notable that no conversion was observed in the absence of catalyst **3a** under the same conditions and the starting alcohol **1k** remained unreacted even after 36 h.

The wide range of transformations achieved since the turn of this century using (thio)urea derivatives as catalysts rely entirely on the hydrogen bond donor ability of (thio)urea NHs. In this paper, we described another activation mode of thiourea derivatives, namely Lewis base catalysis. NBS-mediated oxidation of alcohols is presented as a proof of this concept. The mild reaction conditions employed here are suitable for selective oxidation of secondary alcohols in the presence of primary alcohols. We are aware of the implication of this activation mode and strongly believe that the scope will not be restricted to the oxidation reaction reported herein. The successful conversion of alcohol to α-chloroketone also points toward a promising future of this activation mode. Investigations to explore the detailed mode of action by thiourea and the possibility of asymmetric halogenation reactions using chiral thiourea derivatives as catalyst are currently underway in our laboratory and will be the subject of future reports.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all reactions have been carried out with distilled and dried solvents under an atmosphere of N_2, and oven-dried (120 °C) glassware with standard vacuum line techniques were used. Dichloromethane was purified by distillation over CaH_2 under nitrogen. *N*-Bromosuccinimide was recrystallized from hot water followed by drying in high vacuum and stored in nitrogen atmosphere at −20 °C. All workups and purifications were carried out with reagent-grade solvents in air. Thin-layer chromatography was performed using Merck silica gel 60 F_{254} precoated plates (0.25 mm). Column chromatography was performed using silica gel (230−400 or 100−200 mesh). ^{1}H NMR and ^{13}C NMR were recorded on 400 and 100 MHz spectrometers, respectively. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ 7.26; CD_3OD, δ 3.31; DMSO-d_6, δ 2.50 for ^{1}H NMR and $CDCl_3$; δ 77.00, CD_3OD; δ 49.00, DMSO-d_6; δ 39.52 for ^{13}C NMR). For ^{1}H NMR, data are reported as follows: chemical shift, multiciplity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. Tetramethyl thiourea (**8**) is commercially available, and the commercial material was used without any further purification.

1,3-Bis-(3,5-bis(trifluoromethyl)phenyl)thiourea (3a). To a solution of 3,5-bis(trifluoromethyl)aniline (0.40 mL, 2.67 mmol) in 5 mL abs THF in a 25 mL round-bottom flask was added 3,5-

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bis(trifluoromethyl)phenyl isothiocyanate (0.50 mL; 2.70 mmol), and the resulting mixture was heated at 50 °C for 80 h. The reaction mixture was concentrated in vacuo to obtain a yellow oil. Purification by flash chromatography over silica gel (230−400 mesh) using CH_2Cl_2/petroleum ether (30:70 followed by 50:50) afforded a white solid (1.30 g, 2.59 mmol, 99%). FT-IR (KBr): 3207 (m), 3050 (m), 1557 (s), 1376 (s), 1290 (s). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 2H), 8.20 (s, 4H), 7.86 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.6, 141.2, 130.3 (q, J = 33 Hz), 124.1, 123.1 (q, J = 271 Hz), 117.8. HRMS (ESI+): calcd for $C_{17}H_9F_{12}N_2S$ ($[M + H]^+$) 501.0295, found 501.0296.

1,3-Bis(3,5-bis(trifluoromethyl)phenyl)-1,3-dimethylthiourea (3b). To the suspension of NaH (60% suspension in oil, 86.0 mg, 2.15 mmol) in THF (0.6 mL) was added a solution of 1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea (416 mg, 0.86 mmol) dropwise at rt. After 10 min, MeI (0.14 mL, 2.15 mmol) was added, and the resulting yellow solution was heated at 50 °C for 18 h. Water (5 mL) was added dropwise to the reaction mixture and extracted with DCM (15 mL × 4). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo to obtain a yellowish white solid. Recrystallization from a MeOH−DCM mixture afforded 1,3-bis(3,5-bis(trifluoromethyl)phenyl)-1,3-dimethylurea as a white crystalline solid (243 mg, 0.47 mmol, 55%). Mp: 149−151 °C. FT-IR (KBr): 3546 (m), 3098 (m), 1676 (s), 1386 (s), 1285 (s). ^{1}H NMR (400 MHz, CD_3OD): δ 7.52 (s, 2H), 7.43 (s, 4H), 3.35 (s, 6H). ^{13}C NMR (100 MHz, CD_3OD): δ 160.8, 148.2, 134.0 (q, J = 34 Hz), 127.5, 124.7 (q, J = 270 Hz), 120.1, 39.7. HRMS (ESI+): calcd for $C_{19}H_{13}F_{12}N_2O$ ($[M + H]^+$) 513.0836, found 513.0842. To the mixture of 1,3-bis(3,5-bis(trifluoromethyl)phenyl)-1,3-dimethylurea (50 mg, 0.10 mmol) and Lawesson's reagent (79.3 mg, 0.19 mmol) in a 10 mL round-bottom flask was added *o*-xylene (0.4 mL), and the resulting mixture was refluxed at 170 °C for 5 h. The reaction mixture was concentrated in vacuo to obtain a yellow solid. Purification by column chromatography over silica gel (100−200 mesh) using 5:95 EtOAc/petroleum ether afforded **3b** as a white solid (44 mg, 0.084 mmol, 84% yield). Mp: 172−174 °C. FT-IR (KBr): 3434 (m), 1472 (m), 1381 (s), 1278 (s), 1147 (s). ^{1}H NMR (400 MHz, CD_3OD): δ 7.57 (s, 2H), 7.30 (s, 4H), 3.61 (s, 6H). ^{13}C NMR (100 MHz, CD_3OD): δ 191.3, 149.7, 133.9 (q, J = 34 Hz), 126.8, 124.1 (q, J = 270 Hz), 120.0, 45.0. HRMS (ESI+): calcd for $C_{19}H_{12}F_{12}N_2S$ ($[M]^+$) 528.0530, found 528.1403.

***N*-Cyclohexyl-*N*′-(3,5-bis(trifluoromethyl)phenyl)thiourea (4).** To a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.34 mL, 1.85 mmol) in 2 mL of abs THF in a 10 mL round-bottom flask was added cyclohexylamine (0.21 mL, 1.85 mmol), and the resulting mixture was stirred at 30 °C for 2 h. The reaction mixture was concentrated *in* vacuo to obtain an off-white solid. The solid was triturated with petroleum ether (10 mL × 2) to obtain a white solid (600 mg, 1.62 mmol, 88%). FT-IR (thin film): 3272 (w), 2932 (w), 1527 (m), 1383 (m), 1274 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (br, 1H), 7.75 (s, 2H), 7.71 (s, 1H), 6.04 (br, 1H), 4.20 (br, 1H), 2.12−2.02 (m, 2H), 1.76−1.59 (m, 3H), 1.48−1.35(m, 2H), 1.28−1.12 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 138.9, 133.1 (q, J = 33 Hz), 123.8, 122.7 (q, J = 271 Hz), 119.3, 54.0, 32.3, 25.2, 24.5. HRMS (ESI+): calcd for $C_{15}H_{16}F_6N_2SNa$ ($[M + Na]^+$) 393.0836, found 393.0836.

***N*-Cyclohexyl-*N*′-(3,5-bis(trifluoromethyl)phenyl)urea (5).** To a solution of cyclohexyl isocyanate (0.51 mL, 3.99 mmol) in 4 mL of THF in a 10 mL round-bottom flask was added 3,5-bis-(trifluoromethyl)aniline (0.56 mL, 3.63 mmol), and the reaction mixture was stirred at 50 °C for 72 h. The reaction mixture was concentrated in vacuo to obtain an off-white solid. The solid was washed with cold CH_2Cl_2 (10 mL × 2) to obtain a white solid (600 mg, 1.69 mmol, 43%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.01(s, 2H), 7.49(s, 1H), 3.62−3.52 (m, 1H), 1.99−1.89 (m, 2H), 1.80−1.55 (m, 4H), 1.46−1.16 (m, 6H). ^{13}C NMR (100 MHz, CD_3OD): δ 156.4, 143.3, 132.9 (q, J = 33 Hz), 125.0 (q, J = 270 Hz), 118.7, 115.1, 34.6, 34.1, 26.5, 26.5, 25.9, 25.8.

Cyclohexyl (3,5-Bis(trifluoromethyl)phenyl)carbamate (6). To a solution of bis(trifluoromethyl)phenyl isocyanate (0.42 mL; 2.27 mmol) and cyclohexanol (250 mg; 2.50 mmol) in THF (10 mL) in 25 mL round-bottom flask was added NaH (60% suspension in oil; 132 mg, 5.50 mmol), and the reaction mixture was stirred at rt for 16 h. The reaction was diluted with EtOAc (10 mL), and H_2O (5 mL) was added dropwise to the reaction mixture, the organic layer was collected, and the aqueous layer was extracted with EtOAc (10 mL × 2). Combined organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo to obtain light yellow oil. Purification by column chromatography over silica gel (230−400 mesh) using petroleum ether and then 2:98 EtOAc/petroleum ether afforded a white solid (523 mg, 1.47 mmol, 65%). Mp: 107−110 °C. FT-IR (KBr): 3308 (s), 3120 (m), 2946 (s), 1703 (s), 1567 (s), 1272 (s), 1240 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 2H), 7.54 (s, 1H), 6.94 (s, 1H), 4.83−4.73 (m, 1H), 1.98−1.90 (m, 2H), 1.80−1.69 (m, 2H), 1.61−1.22 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 139.7, 132.40 (q, J = 33 Hz), 121.60 (q, J = 271 Hz), 118.1, 116.5, 74.8, 31.7, 25.2, 23.6. HRMS (ESI+): calcd for $C_{15}H_{17}F_6NO_2Na$ ($[M + Na]^+$) 378.0905, found 378.0901.

1,3-Bis-(4-methoxyphenyl)thiourea (7). A solution of 4-methoxyaniline (2.0 g; 16.24 mmol) in CH_2Cl_2 (100 mL) in a 250 mL round-bottom flask was cooled to 0 °C, and satd aqueous $NaHCO_3$ solution (100 mL) was added. Stirring was stopped, and thiophosgene (1.4 mL, 17.87 mmol) was added to the CH_2Cl_2 layer. The resulting mixture was stirred vigorously at rt for 30 min. The organic phase was separated, dried over anhyd Na_2SO_4, and concentrated in vacuo to obtain a yellow oil. To this oil in CH_2Cl_2 (35 mL) in a 100 mL round-bottom flask was added a solution of 4-methoxyaniline (1.82 g; 14.77 mmol) in CH_2Cl_2 (5 mL), and the resulting mixture was stirred at rt for 48 h. The reaction mixture was concentrated in vacuo to obtain a pale yellow solid. This solid was filtered and washed with cold CH_2Cl_2 (25 mL × 2) to obtain white solid (3.40 g, 11.79 mmol, 72%). FT-IR (KBr): 3221 (s), 1546 (s), 1512 (s), 1337 (s), 1246 (s). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.52 (s, 2H), 7.32 (d, J = 8.8 Hz, 4H), 6.88 (d, J = 8.8 Hz, 4H), 3.74 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.2, 156.5, 132.3, 126.0, 113.6, 55.2. HRMS (ESI+): calcd for $C_{15}H_{16}N_2O_2SNa$ ($[M + Na]^+$) 311.0830, found 311.0840.

1,3-Diphenylthiourea (9a). To the solution of phenyl isothiocyanate (742 mg, 5.49 mmol) in 10 mL of abs THF in a 25 mL round-bottom flask was added aniline (0.45 mL, 4.99 mmol), and the resulting mixture was stirred at rt for 40 h. The reaction mixture was concentrated in vacuo to obtain a yellow solid. Washing the crude with petroleum ether (25 mL × 4) afforded a white crystalline solid (1.1 g, 4.82 mmol, 88%). FT-IR (KBr): 3208 (s), 1551 (s), 1345 (s), 697 (s). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.94 (s, 2H), 7.52 (m, 4H), 7.34 (m, 2H), 7.13 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 179.6, 139.5, 128.4, 124.4, 123.6. HRMS (ESI+): calcd for $C_{13}H_{12}N_2SNa$ ($[M + Na]^+$) 251.0619, found 251.0611.

***N*,*N*′-Dimethyl-*N*,*N*′-diphenylthiourea (9b).** To a solution of *N*-methylaniline (0.41 mL; 3.73 mmol) in toluene (8 mL) in a 25 mL round-bottom flask were added thiophosgene (0.15 mL, 1.87 mmol) and Et_3N (0.53 mL, 3.73 mmol), and the resulting mixture was heated at 50 °C for 24 h. The resulting yellow solution was diluted with CH_2Cl_2 (20 mL) and then washed with 1 N HCl (10 mL × 2) and brine (5 mL × 1). The organic layer was dried over anhtd Na_2SO_4 and concentrated in vacuo. Purification by column chromatography on silica gel (230−400 mesh) using 1.5:98.5 and then 3:97 EtOAc/petroleum ether afforded a white solid (42 mg, 0.19 mmol, 5%). FT-IR (KBr): 3422 (br), 2924 (m), 1595 (m), 1492 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05−6.99 (m, 4H), 6.98−6.92 (m, 2H), 6.66 (d, J = 7.8 Hz, 4H), 3.51 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8, 147.5, 128.7, 125.4, 125.3, 45.2. HRMS (ESI+): calcd for $C_{15}H_{16}N_2SNa$ ($[M + Na]^+$) 279.0932, found 279.0934.

***O*-Phenyl-*N*-methyl-*N*-phenylthiocarbamate (10).** To a solution of thiophosgene (0.30 mL, 3.99 mmol) in CH_2Cl_2 (22 mL) in a 100 mL two-neck round-bottom flask was added a solution of phenol (250 mg, 2.66 mmol) in 0.3 M NaOH (8.87 mL, 2.66 mmol), and the resulting mixture was stirred at rt for 1 h. The reaction was diluted by CH_2Cl_2 (10 mL). The organic phase was separated, washed with brine (8 mL × 1), and concentrated in vacuo to obtain a yellow oil. CH_2Cl_2 (22 mL) was added to this oil followed by addition of *N*-methylaniline

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(0.58 mL, 5.32 mmol). The reaction mixture was stirred at rt for 30 min. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with brine (10 mL × 1), and the organic phase was dried over anhyd Na_2SO_4 and concentrated in vacuo to obtain a yellow oil. Purification by column chromatography on silica gel (230−400 mesh) using 20:80 and then 30:70 CH_2Cl_2/petroleum ether afforded a white solid (460 mg, 1.89 mmol, 76%). FT-IR (KBr): 1591 (m), 1480 (s), 1385 (s), 1208 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.40 (m, 2H), 7.40−7.29 (m, 6H), 7.01 (d, J = 7.3 Hz, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.0, 154.0, 143.5, 129.4, 129.1, 127.7, 125.9, 125.6, 122.5, 44.7. HRMS (ESI+): calcd for $C_{14}H_{13}NOSNa$ ($[M + Na]^+$) 266.0616, found 266.0614.

Typical Procedure for Thiourea-Catalyzed Oxidation of 1-Phenylethanol 1a (Table 2, Entry 1). In an oven-dried 10 mL two-neck round-bottom flask were added NBS (109.3 mg, 0.62 mmol) and **3a** (20.5 mg, 0.041 mmol). The flask was cooled to −35 °C, and a solution of alcohol **1a** (50 mg; 0.41 mmol) in CH_2Cl_2 (1.0 mL) was added. The resulting mixture was stirred at −35 °C for 90 h. The reaction was quenched with satd aq $Na_2S_2O_3$ solution (1 mL) at reaction temperature followed by brine (1 mL). The aqueous layer was extracted with CH_2Cl_2 (4 mL × 3). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (230−400 mesh) using 2:98 Et_2O/petroleum ether to obtain the desired product **2a** as a colorless oil (42 mg, 0.35 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98−7.94 (m, 2H), 7.60−7.53 (m, 1H), 7.50−7.43 (m, 2H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 137.0, 133.1, 128.5, 128.3, 26.6.

Propiophenone 2b (Table 2, Entry 2). The typical experimental procedure as above was followed in CH_2Cl_2 at −20 °C for 90 h with 0.37 mmol of 1-phenylpropan-1-ol (**1b**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 3:97 Et_2O/pentane to obtain a colorless oil (40 mg, 0.30 mmol, 80%). ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.00−7.94 (m, 2H), 7.59−7.52 (m, 1H), 7.50−7.43 (m, 2H), 3.01 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 136.8, 132.8, 128.5, 127.9, 31.7, 8.2.

Cyclohexyl(phenyl)methanone 2c (Table 2, Entry 3). The typical experimental procedure as above was followed in CH_2Cl_2 at 0 °C for 48 h with 0.26 mmol of cyclohexyl(phenyl)methanol (**1c**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 4:96 Et_2O/pentane to obtain a colorless oil (43 mg, 0.23 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 7.7 Hz, 2H), 7.57−7.50 (m, 1H), 7.49−7.41 (m, 2H), 3.30−3.21 (m, 1H), 1.93−1.80 (m, 4H), 1.78−1.68 (m, 1H), 1.56−1.2(m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.9, 136.3, 132.7, 128.5, 128.2, 45.6, 29.4, 25.9, 25.8.

2,2-Dimethyl-1-phenylpropan-1-one 2d (Table 2, Entry 4). The typical experimental procedure as above was followed in CH_2Cl_2 at 10 °C for 90 h with 0.30 mmol of 2-methyl-1-phenylpropan-1-ol (**1d**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 1:99 Et_2O/petroleum ether to obtain a colorless oil (25 mg, 0.154 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 7.12, 2H), 7.45−7.36 (m, 3H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.3, 138.6, 130.8, 128.0, 127.8, 44.2, 28.0.

4-Chloroacetophenone 2e (Table 2, Entry 5). The typical experimental procedure as above was followed in CH_2Cl_2 at −20 °C for 90 h with 0.32 mmol of 1-(4-chlorophenyl)ethanol (**1e**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 2:98 EtOAc/petroleum ether to obtain a colorless oil (40 mg, 0.26 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 139.5, 135.4, 129.7, 128.9, 26.5.

4-Methylacetophenone 2f (Table 2, Entry 6). The typical experimental procedure as above was followed in CH_2Cl_2 at −20 °C for 44 h with 0.37 mmol of 1-(*p*-tolyl)ethanol (**1f**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 2:98 Et_2O/pentane to obtain a colorless oil (45 mg, 0.34 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8 Hz, 2H), 2.59 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 143.9, 134.6, 129.2, 128.4, 26.5, 21.6.

4-Fluoroacetophenone 2g (Table 2, Entry 7). The typical experimental procedure as above was followed in CH_2Cl_2 at 0 °C for 16 h with 0.36 mmol of 1-(4-fluorophenyl)ethanol (**1g**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 2:98 Et_2O/pentane to obtain a colorless oil (42 mg, 0.31 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.95 (m, 2H), 7.16−7.09 (m, 2H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 165.7 (d, J = 253 Hz), 133.5, 130.9 (d, J = 9 Hz), 115.6 (d, J = 22 Hz), 26.5.

2-Methylacetophenone 2h (Table 2, Entry 8). The typical experimental procedure as above was followed in CH_2Cl_2 at 0 °C for 66 h with 0.37 mmol of 1-(*o*-tolyl)ethanol (**1h**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 3:97 Et_2O/pentane to obtain colorless oil (40 mg, 0.30 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 7.6 Hz, 1H), 7.40−7.34 (m, 1H), 7.30−7.21 (m, 2H), 2.58 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 138.4, 137.6, 132.0, 131.5, 129.3, 125.6, 29.5, 21.5.

1-Cyclohexylethanone 2i (Table 2, Entry 9). The typical experimental procedure as above was followed in CH_2Cl_2 at −20 °C for 48 h with 0.39 mmol of 1-cyclohexylethanol (**1i**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 4:96 Et_2O/pentane to obtain colorless oil (42 mg, 0.33 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38−2.28 (m, 1H), 2.14 (s, 3H), 1.91−1.84 (m, 2H), 1.82−1.74 (m, 2H), 1.73−1.63 (m, 1H), 1.34−1.25 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.4, 51.4, 28.4, 27.9, 25.8, 25.6.

Cyclohexanone 2j (Table 2, Entry 10). The typical experimental procedure as above was followed in CH_2Cl_2 at −35 °C for 72 h with 0.50 mmol of cyclohexanol (**1j**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 2:98 Et_2O/pentane to obtain a colorless oil (41 mg, 0.42 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (t, J = 6.6 Hz, 4H), 1.88−1.80 (m, 4H), 1.74−1.65 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.4, 41.9, 27.0, 24.9.

3,4-Dihydronaphthalen-1(2*H*)-one 2k (Table 2, Entry 11). The typical experimental procedure as above was followed in CH_2Cl_2 at −35 °C for 90 h with 0.34 mmol of 1,2,3,4-tetrahydronaphthalen-1-ol (**1k**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 5:95 Et_2O/petroleum ether to obtain a colorless oil (46 mg, 0.32 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.35−7.23 (m, 2H), 3.00 (t, J = 6.0 Hz, 2H), 2.67 (t, J = 6.0 Hz, 2H), 2.15 (quintet, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 144.5, 133.4, 132.5, 128.7, 127.1, 126.6, 39.1, 29.6, 23.2.

2,3-Dihydro-1*H*-inden-1-one 2l (Table 2, Entry 12). The typical experimental procedure as above was followed in CH_2Cl_2 at −20 °C for 16 h with 0.378 mmol of 2,3-dihydro-1*H*-inden-1-ol (**1l**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 4:96 Et_2O/petroleum ether to obtain a colorless oil (40 mg, 0.303 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.7 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 3.14 (t, J = 5.8 Hz, 2H), 2.69 (t, J = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3): δ 207.0, 155.1, 137.0, 134.5, 127.2, 126.6, 123.6, 36.1, 25.7.

4-Phenylbutan-2-one 2m (Table 2, Entry 13). The typical experimental procedure as above was followed in CH_2Cl_2 at 10 °C for 90 h with 0.67 mmol of 4-phenylbutan-2-ol (**1m**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 5:95 Et_2O/pentane to obtain a colorless oil (36 mg, 0.27 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.20 (m, 5H), 2.97 (t, J = 7.5 Hz, 2H), 2.84 (t, J = 7.8 Hz, 2H), 2.21 (s, 3H).

Benzaldehyde 2n (Table 2, Entry 14). The typical experimental procedure as above was followed in CH_2Cl_2 at 10 °C for 90 h with 0.5 mmol of benzyl alcohol (**1n**). The conversion was determined to be 60% by ^{1}H NMR analysis of the crude reaction mixture.

General Procedure for Chemoselective Oxidation of Secondary Alcohols. In an oven-dried 10 mL two-neck round-

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bottom flask were added NBS (1.5 equiv) and **3a** (10 mol %). The flask was cooled to the specified temperature, and a solution of diol **11** (1.0 equiv) in CH_2Cl_2 was added. The resulting mixture was stirred at the specified temperature until complete consumption of the starting material. The reaction was quenched with satd aqueous $Na_2S_2O_3$ solution at the reaction temperature followed by brine. The aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to obtain the desired hydroxyketone **12**.

4′-(Hydroxymethyl)acetophenone 12a (Table 3, Entry 1). The general experimental procedure as above was followed in CH_2Cl_2 at 0 °C for 34 h with 0.164 mmol of 1-(4-(hydroxymethyl)phenyl)-ethanol (**11a**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 10:90 EtOAc/petroleum ether to obtain a colorless oil (20.8 mg, 0.14 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 4.78 (s, 2H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 146.2, 136.3, 128.6, 126.6, 64.5, 26.6.

3-Hydroxy-1-phenyl-1-propanone 12b (Table 3, Entry 2). The general experimental procedure as above was followed in CH_2Cl_2 at −20 °C for 72 h with 0.33 mmol of 1-phenylpropane-1,3-diol (**11b**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 15:85 EtOAc/petroleum ether to obtain a colorless oil (39 mg, 0.26 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 7.8 Hz, 2 H), 7.60−7.54 (m, 1H), 7.50−7.43 (m, 2 H), 4.02 (t, J = 5.3 Hz, 2 H), 3.22 (t, J = 5.3 Hz, 2 H), 2.87 (br, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.4, 136.6, 133.5, 128.6, 128.0, 58.0, 40.3.

2-(Hydroxymethyl)cyclohexanone 12c (Table 3, Entry 3). The general experimental procedure as above was followed in CH_2Cl_2 at −20 °C for 18 h with 0.38 mmol of 1-phenylpropane-1,3-diol (**11c**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 15:85 EtOAc/petroleum ether to obtain a colorless oil (37 mg, 0.29 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76−3.69 (m, 1H), 3.63−3.56 (m, 1H), 2.67 (br, 1H), 2.56−2.45 (m, 1H), 2.45−2.25 (m, 2H), 2.15−2.06 (m, 1H), 2.06−1.96 (m, 1H), 1.95−1.88 (m, 1H), 1.73−1.64 (m, 2H), 1.53−1.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.8, 62.7, 52.2, 42.2, 30.0, 27.5, 24.7.

2-(Hydroxymethyl)-3,4-dihydronaphthalen-1(2*H*)-one 12d (Table 3, Entry 4). The general experimental procedure as above was followed except for the fact that NBS was added in two portions (0.75 equiv followed by another 0.75 equiv. after 6 h) in CH_2Cl_2 at −35 °C for 18 h with 0.28 mmol of 2-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (**11d**). The crude product was purified by column chromatography on silica gel (230−400 mesh) using 14:86 EtOAc/petroleum ether to obtain a colorless oil (40 mg, 0.225 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 7.8 Hz, 1H), 7.85 (t, J = 7.4 Hz, 1H), 7.34−7.22 (m, 2H), 3.97−3.89 (m, 1H), 3.87−3.77 (m, 1H), 3.21 (br, 1H), 3.15−2.95 (m, 2H), 2.75−2.65 (m, 1H), 2.18−2.08 (m, 1H), 2.01−1.92 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.6, 144.3, 133.8, 132.3, 128.8, 127.1, 126.7, 63.6, 49.4, 28.9, 26.1.

2-Hydroxymethyl-2-methylcyclohexanone 12e (Table 3, Entry 5). The typical experimental procedure as above was followed in CH_2Cl_2 at −30 °C for 90 h with 0.35 mmol of 2-(hydroxymethyl)-2-methylcyclohexanol (**11e**). The crude product was purified by column on silica gel (100−200 mesh) by using 3:97 Et_2O/CH_2Cl_2 to obtain a colorless oil (40 mg, 0.28 mmol; 80%). *Note: The product decomposes upon longer exposure on silica gel; therefore, a quick purification is required.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.53−3.47 (m, 2H), 2.63−2.45 (m, 2H), 2.30−2.22 (m, 1H), 2.08−1.97 (m, 1H), 1.90−1.52 (m, 5H), 1.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.2, 69.1, 50.1, 38.9, 35.5, 27.3, 20.7, 20.2.

Experimental Procedure for Thiourea-Catalyzed Direct Conversion of 1-Tetralol (1k) to α-Chloro Tetralone (13). In an oven-dried 10 mL two-neck round-bottom flask were added NCS (100.0 mg, 0.75 mmol) and catalyst (**3a**) (16.9 mg, 0.034 mmol). The flask was degassed in vacuum, and solution of α-tetralol (**1k**) (50 mg, 0.34 mmol) in CH_2Cl_2 (1.0 mL) was added. The resulting mixture was stirred at rt for 36 h. The reaction was monitored by TLC and quenched with satd aqueous $Na_2S_2O_3$ solution (1 mL) followed by brine (1 mL). The aqueous layer was extracted with CH_2Cl_2 (4 mL × 3). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo. Conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (230−400 mesh) using 2:98 Et_2O/petroleum ether to obtain a colorless oil (34 mg, 0.19 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 7.9 Hz, 1H), 7.56−7.49 (m, 1H), 7.38−7.31 (m, 1H), 7.31−7.24 (m, 1H), 4.66−4.61 (m, 1H), 3.34−3.23 (m, 1H), 3.05−2.95 (m, 1H), 2.63−2.53 (m, 1H), 2.51−2.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8, 143.1, 134.1, 130.4, 128.7, 128.5, 127.1, 59.8, 32.4, 26.3.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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