Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201500839

Direct Use of Benzylic Alcohols for Gold(III)-Catalyzed *S*-Benzylation of Mercaptobenzoic Acids in Water

Hidemasa Hikawa,[a,*] Ayaka Tada,[a] Shoko Kikkawa,[a] and Isao Azumaya[a,*]

[a] Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan
Fax: (+81)-47-472-1595; phone: (+81)-47-472-1591; e-mail: hidemasa.hikawa@phar.toho-u.ac.jp or isao.azumaya@phar.toho-u.ac.jp

Received: September 8, 2015; Revised: November 5, 2015; Published online: January 26, 2016

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500839.

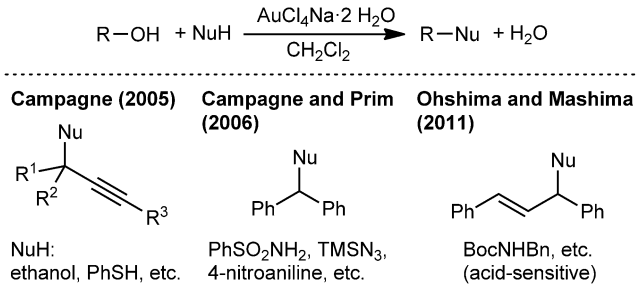
Abstract: We demonstrate the gold(III)-catalyzed direct substitution of benzylic alcohols in water. These atom economic and environmentally benign protocols afford *S*-benzylated products in moderate to excellent yields. In contrast, common Lewis or Brønsted acids as catalyst, and organic solvents such as dichloromethane or toluene were ineffective for the *S*-benzylation of mercaptobenzoic acids. Water can be an attractive tool for new transition metal-catalyzed reactions. A Hammett study for the rate constants with various substituted alcohols shows a good correlation ($R^2 = 0.97$) between the $\log(k_X/k_H)$ and the σ^+ value of the respective substituents. From the slope negative ρ values of 2.35 are obtained, suggesting that there is a build-up of positive charge in the transition state. Our catalytic system can be performed with the use of only 2 mol% of gold(III) catalyst without any other additives in water, and scaled up to 10 mmol scale (85% isolated yield). Notably, the present method can accomplish the *S*-benzylation of unprotected mercaptobenzoic acids, which is chemoselective and leaves the carboxyl group intact. Furthermore, the direct substitution of allylic and propargylic alcohols also proceeded smoothly in good yields.

Keywords: benzhydryl alcohol; benzylation; gold; mercaptobenzoic acid; water

Introduction

Gold(III)-catalyzed direct substitution of hydroxy groups affords a powerful methodology for the formation of C–C, C–S or C–N bonds.[1] These reactions occur through an attractive salt-free and atom-economic process, which affords the desired products along with water as the sole co-product. Such an efficiency is mainly due to the Lewis acidic character of the gold(III) catalyst for the activation of several sp^3 C–O bonds. It is worth noting that these efficient atom-economical transformations have been developed utilizing $AuCl_4Na{\cdot}2H_2O$ in CH_2Cl_2 as a standard protocol (Scheme 1). Campagne et al. reported the nucleophilic substitution of propargylic alcohols by a gold(III) catalyst, which acted as a propargylic alcohol-activating agent through coordination to a π-bond.[2] Campagne and Prim developed the direct amination of benzhydryl alcohols.[3] Ohshima and Mashima reported the direct substitution of allylic alcohols with Boc-, Bus-, and Dios-protected amine nucleophiles.[4] Although the direct substitution of benzylic alcohols benefits from high atom and step economies, further progress is needed to develop more environmentally friendly conditions. Water can be an attractive tool for new transition metal-catalyzed reactions. However, most gold-catalyzed reactions are usually conducted in organic solvents.[5] Furthermore, the dehydration reaction in water is one of the most challenging research topics.

We have been developing a unique strategy for the direct substitution of benzyl alcohols using a water-soluble gold catalyst Au(III)/TPPMS (sodium diphe-



Scheme 1. Gold(III)-catalyzed direct substitution of hydroxy groups.

nylphosphinobenzene-3-sulfonate) in water.[6] Notably, water activates the sp^3 C–O bond by hydrogen bonds between water and the hydroxy group of the alcohols. Theoretical calculations by Shinokubo and Oshima have elucidated the importance of hydration of the hydroxy group for the smooth generation of the π-allylpalladium species.[7] Cozzi et al. proposed that the direct generation of carbocations in water from alcohols is driven by the formation of hydrogen bonds between water and the hydroxy group of the alcohol.[8] Furthermore, the hydrophobic effect would also accelerate the benzylation in our catalytic system. Since water molecules have unusual chemical and physical properties compared to organic solvents, water should play an important role in the development of new and efficient reactions.

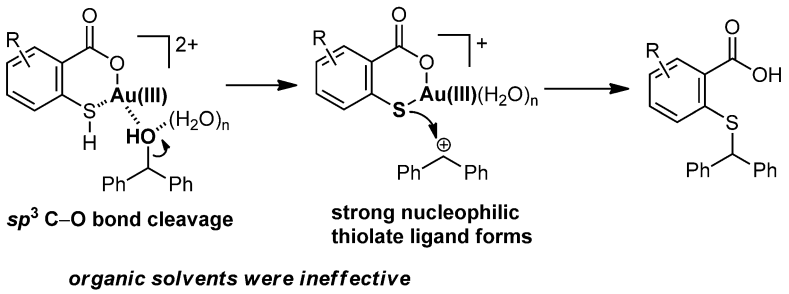
In light of our ongoing efforts to develop efficient methods for direct substitution reactions of benzylic alcohols, we hypothesize that the Lewis acidic gold(III) catalyst performs dual activation of the sp^3 C–O bond of alcohols and thiols as nucleophiles, generating the corresponding *S*-benzylated products, which have the potential to be powerful tools for direct transformations in water (Scheme 2). Consequently, we herein report an efficient method for the gold(III)-catalyzed direct substitution reaction of benzylic alcohols with unprotected mercaptobenzoic acids in water.[9] Notably, organic solvents such as CH_2Cl_2 or toluene were ineffective. Furthermore, when using protocols based on traditional methods such as using Lewis or Brønsted acids, the substrate scope was difficult to extend to strong nucleophilic thiols. Thus, the key to the success of this strategy is to avoid the deactivation of catalysts in the presence of strong nucleophiles.[10]

Additionally, gold complexes with thiolate ligands have been investigated not only for the development of synthetic methods but also as antiarthritic and cancerostatic drugs. For example, Auranofin is a well-known drug used to treat rheumatoid arthritis. Furthermore, Henderson et al. reported that gold(III) complexes containing a chelated thiosalicylate dianionic ligand showed high antitumor activity.[11] Thiolate-protected gold nanoclusters have also attracted much interest due to their fascinating size-dependent electronic properties. Recently, Kornberg and coworkers reported the crystallization and X-ray structure determination of *p*-mercaptobenzoic acid-protected gold nanoparticles.[12] Therefore, investigation into reactions using our catalytic system would provide new insights for biological chemistry and gold nanoclusters.

Results and Discussion

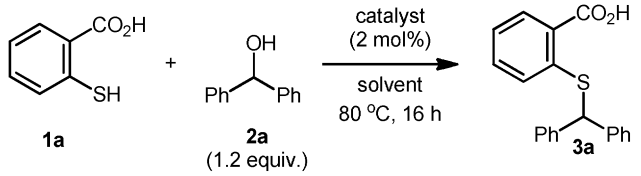
Effects of Catalysts and Solvents

First, we heated a mixture of 2-mercaptobenzoic acid (**1a**) and benzhydrol (**2a**) (1.2 equiv.) in the presence of $AuCl_4Na{\cdot}2H_2O$ (2 mol%) in CH_2Cl_2 at 80 °C for 16 h in a sealed tube. *S*-Benzylated **3a** was obtained in only 18% yield (Table 1, entry 1). As expected, the use of water as a solvent selectively afforded the desired **3a** in 70% yield, despite the possibility of forming the benzyl ester or disulfide (entry 2).[13] Using the water-soluble phosphine ligand TPPMS did not enhance the reaction (entry 3). In the absence of catalyst, no reaction occurred (entry 4). With regard to the gold catalyst, the use of $AuBr_3$ also gave the product **3a** in good yield (entry 5, 64%). In contrast, using $AuCl_3$ or Au(III)-picolinate complex resulted in lower yields (entries 6 and 7). A less Lewis acidic gold(I) catalyst, AuCl, was ineffective (entry 8). Recently, Morita and Tamura reported that the use of oxophilic (hard) gold(III) and π-philic (soft) gold(I) catalysts provided access to two types of cyclic ethers from propargylic alcohols, and these observations can be explained by the hard and soft acids and bases (HSAB) principle.[14] Thus, we decided to use more stable and easier to handle $AuCl_4Na{\cdot}2H_2O$ as the catalyst for further investigations. To compare the gold(III) catalyst with other efficient catalysts, we tested the reaction using Brønsted acids such as HCl and $TsOH{\cdot}H_2O$, and Lewis acids such as $Sc(OTf)_3$ and $CuBr_2$. However, the reactions resulted in low yields (entries 9–11), clearly showing the superiority of $AuCl_4Na{\cdot}2H_2O$ for the *S*-benzylation. Furthermore,



Scheme 2. Our strategy for dual activation of alcohols and thiols by Lewis acidic gold(III) catalyst in water.

Table 1. Effects of catalysts and solvents.[a]



Entry	Catalyst	Solvent	Conv. [%][b]
1	$AuCl_4Na{\cdot}2H_2O$	CH_2Cl_2	18
2	$AuCl_4Na{\cdot}2H_2O$	H_2O	70
3	$AuCl_4Na{\cdot}2H_2O$/TPPMS	H_2O	70
4	none	H_2O	trace
5	$AuBr_3$	H_2O	64
6	$AuCl_3$	H_2O	42
7	Au(III)-picolinate[c]	H_2O	28
8	AuCl	H_2O	37
9	HCl or $TsOH{\cdot}H_2O$	H_2O	25–26
10	$Sc(OTf)_3$	H_2O	25
11	$CuBr_2$	H_2O	26
12	$AuCl_4Na{\cdot}2H_2O$	EtOH or DMF	0
13	$AuCl_4Na{\cdot}2H_2O$	toluene	11
14	$AuCl_4Na{\cdot}2H_2O$	dioxane	13
15	$AuCl_4Na{\cdot}2H_2O$	DMF/H_2O (1:1)	0

[a] *Reaction conditions:* 2-mercaptobenzoic acid **1a** (1 mmol), catalyst (2 mol%), benzhydrole **2a** (1.2 equiv.), solvent (4 mL), 80 °C, 16 h in sealed tube, air.

[b] The conversion was determined by ^{1}H NMR analysis of the crude product using *p*-nitroanisole as an internal standard.

[c] Dichloro(2-pyridinecarboxylato)gold.

no reaction or low yields occurred when using organic solvents such as EtOH, DMF, toluene, or 1,4-dioxane instead of water (entries 12–14). The reaction also did not proceed in DMF/H_2O (entry 15). Thus, the hydrophobic effect in water could be observed in our catalytic system.[15]

Reaction Scope

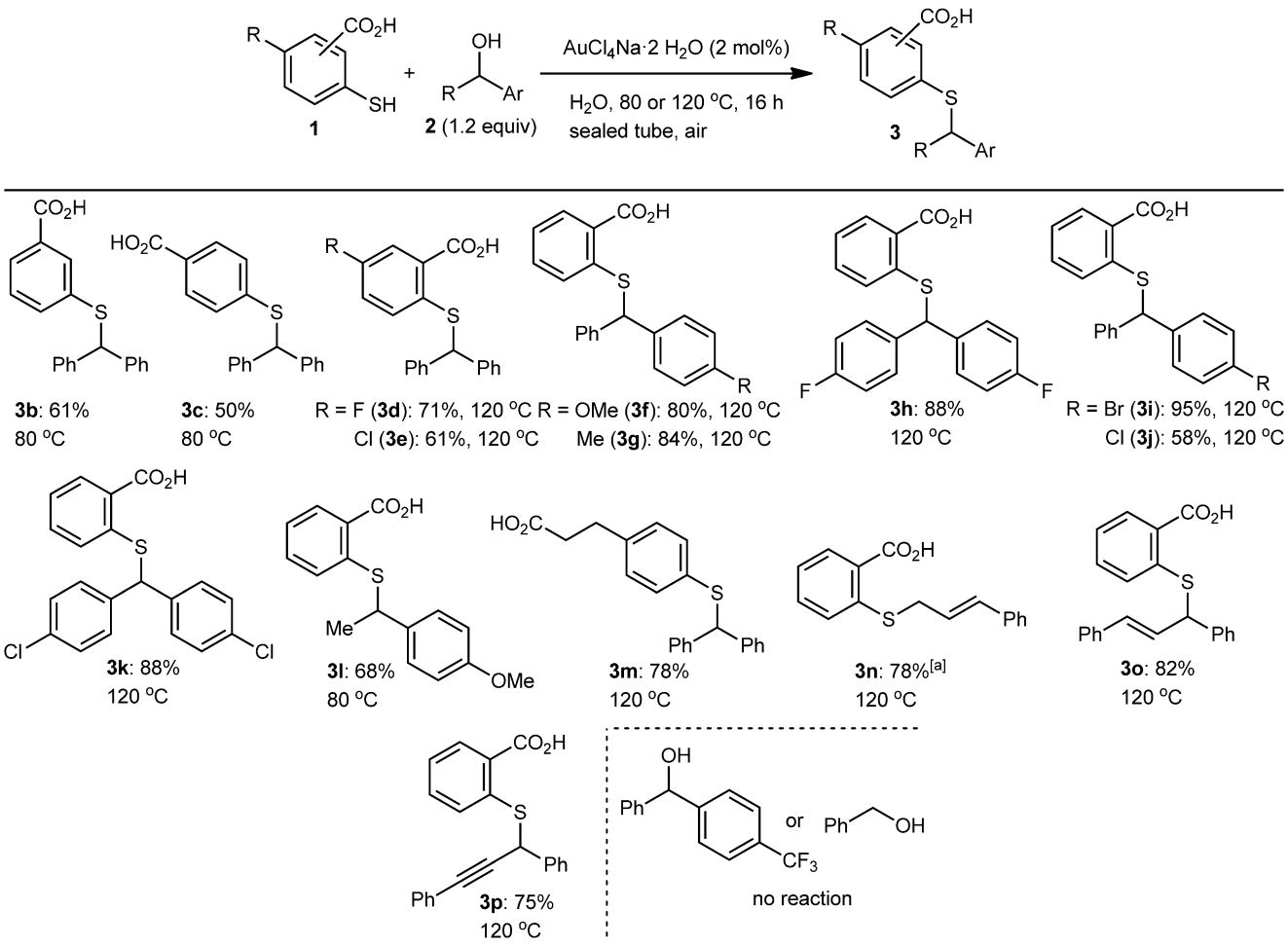
Results for the *S*-benzylation reactions of several mercaptobenzoic acids **1** with benzylic alcohols **2** using $AuCl_4Na{\cdot}2H_2O$ in water are summarized in Scheme 3. The reaction of 3-mercaptobenzoic acid gave almost the same result as **3a** (**3b**, 74% *vs.* **3a**, 70% NMR yield). In contrast, 4-mercaptobenzoic acid resulted in lower yield (**3c**, 50%). The 2-mercaptobenzoic acids with fluoro and chloro groups produced *S*-benzylated products in moderate to good yields (**3d**, 71%; **3e**, 61%). As expected, the benzhydryl alcohols with electron-donating methoxy and methyl groups resulted in good yields (**3f**, 80%; **3g**, 84%), and these observations can be explained by the stabilization of the benzyl cation intermediates. The benzhydryl alcohols with fluoro, bromo and chloro groups produced *S*-benzylated products in moderate to excellent yields (**3h**, 88%; **3i**, 95%; **3j**, 58%; **3k**, 88%). This reaction afforded **3i** with the carbon-bromine moiety left intact, which could be employed for further manipulation.[16] Furthermore, *S*-benzylation with α-methylbenzyl alcohol afforded the desired product **3l** in 68% yield. In contrast, no reaction occurred when using simple benzyl alcohol. Not only mercaptobenzoic acids but also benzenethiol with an aliphatic carboxylic acid, 4-mercaptohydrocinnamic acid, gave the desired **3m** in 78% yield. Allylic and propargylic alcohols also resulted in good yields (**3n**, 78%; **3o**, 82%; **3p**, 75%).

Hammett Studies

To demonstrate the electronic effect of substituents on the rates of the C–O bond cleavage and C–S bond formation reactions, a Hammett study was conducted for the gold-catalyzed *S*-benzylation (see the Supporting Information). From these studies, summarized in Figure 1, the ratio of rate constants can be obtained. The relative rates of coupling of 2-mercaptobenzoic acid (**1a**) with *para*-substituted benzhydryl alcohols **2** (X = diOMe, Me, diF, and Cl groups) were examined. Figure 1A shows a good correlation ($R^2 = 0.97$) between the $\log(k_X/k_H)$ and the σ^+ value of the respective substituents that resulted in a ρ value of −2.35, which suggested that the C–O bond cleavage process involved a build-up of positive charge in the transition state. Thus, this pathway should be favored by electron-donating groups on the long-lived benzyl cation, since these will stabilize the positive charge on the appropriate electrophilic carbon. Furthermore, the relative rates of coupling of 5-substituted thiosalicylic acid **1** (X = F and Cl groups) with benzhydrol (**2a**) showed that the reaction was decelerated by electron-withdrawing groups on the benzene ring of **1** (Figure 1B, ρ value of −1.20, $R^2 = 0.98$).

Mechanistic Considerations

These results and our previous report suggest the following mechanism for the *S*-benzylation of mercaptobenzoic acids **1** with benzhydryl alcohols **2** using $AuCl_4Na{\cdot}2H_2O$ in water (Scheme 4). First, thiol-Au(III) complex **A** ligates with alcohol **2** to form intermediate **B**.[12,17] Lewis acidic Au(III) cation **B** and water activate the sp^3 C–O bond of alcohol **2** for the smooth generation of benzylic cation **D**. Indeed the reaction does not occur in organic solvents (see Table 1). These processes should be favored by electron-donating R groups of intermediate **B**, since these could stabilize the positive charge on benzylic carbocation **D**. A negative Hammett ρ value in the reaction



[a] Cinnamyl alcohol (2 equiv.) was used.

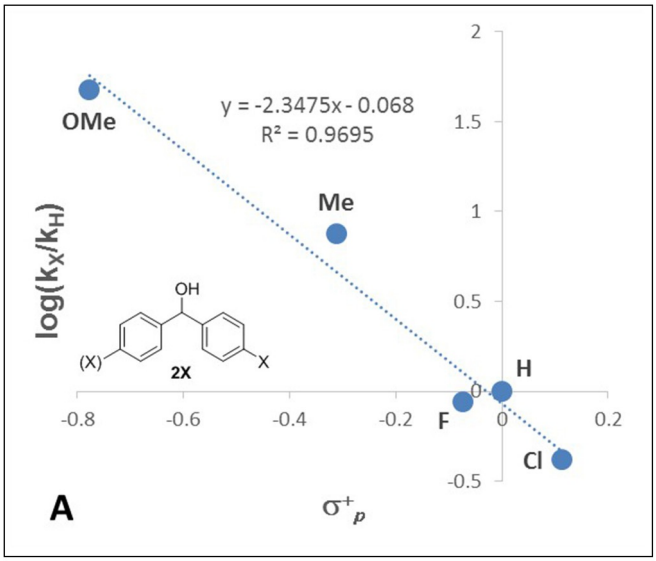
Scheme 3. Scope of benzhydryl alcohols **3**. *Reaction conditions:* mercaptobenzoic acids **1** (1 mmol), benzhydryl alcohols **2** (1.2 equiv.), $AuCl_4Na·2H_2O$ (2 mol%), H_2O (4 mL), 80–120 °C, 16 h in sealed tube, air. Yield of isolated product.

of *p*-substituted benzhydryl alcohols **2** with thiols **1** clearly shows the formation of a positive charge on the benzylic position in the transition state (see Figure 1A). Indeed the benzylation using 3-trifluoromethylbenzhydrol or decafluorobenzhydryl alcohol does not occur, since these alcohols cannot form cationic intermediates **D**. The strong nucleophilic thiolate anion ligand **C** attacks the electrophilically active benzyl cation **D** to afford the desired product **3**. The negative ρ value in the Hammett analysis (**B**) is consistent with the activation of thiol by cationic gold(III) being the rate-limiting step in our catalytic system (see Figure 1B).

Scale-Up Experiment

Finally, we examined the scalability of our catalytic system (Scheme 5). *S*-Benzylation of 2-mercaptobenzoic acid (**1a**) with benzhydrol (**2a**) could be performed on the 10 mmol scale. After 10 min, an insoluble gum-like substance of a yellowish brown color formed in water, which slowly turned into a white suspension. After 16 h, the reaction mixture was extracted with AcOEt, then crude **3a** could be purified simply by recrystallization from hexanes and AcOEt to give the desired product **3a** in 85% isolated yield. Notably, the developed process avoids using column chromatography.

Thiolate anions and benzyl halides with base are generally used for *S*-benzylation. However, benzyl halides are chemically unstable and their synthesis from benzyl alcohols is achieved by halogenation, which is undesirable from an environmental point of view. Furthermore, the use of excess benzyl halides leads to over-reaction of reactive functional groups. For example, the reaction of 2-mercaptobenzoic acid with 4-methylbenzyl chloride (2 equiv.) affords benzyl



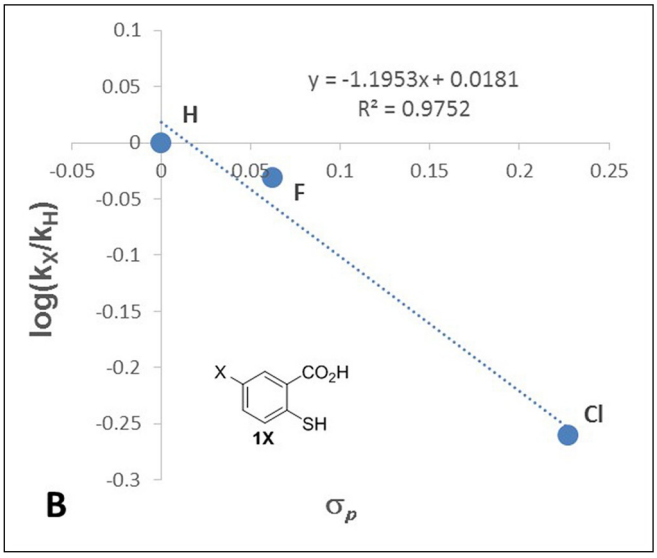


Figure 1. Hammett plot for the rate constants of benzylation by various substituted benzhydryl alcohols **2** (X = diOMe, Me, diF and Cl groups) (A), and in the benzylation of 5-substituted thiosalicylic acid **1** (X = F and Cl groups) (B).

esters as undesired products.[18] In contrast, our present method can accomplish the *S*-benzylation of unprotected mercaptobenzoic acids with benzylic alcohols in water, which is chemoselective and leaves the carboxyl group intact. Additionally, protection of reactive functional groups such as amino, hydroxy, or carboxyl groups is essential in organic synthesis, not only for suppressing side reactions, but also for easy handling by decreased polarity. However, protection sometimes causes serious problems, e.g., increasing the number of synthetic steps and difficulty in deprotecting unstable compounds. Therefore, the development of syntheses without protecting groups should lead to breakthroughs in organic synthesis.[19]

Conclusions

We have demonstrated an efficient and environmentally benign procedure for direct substitution of benzylic alcohols using a gold(III) catalyst in water. A negative Hammett ρ value indicated a build-up of positive charge on the benzylic carbon in the transition state. Our proposed strategy provided a scope for the development of gold(III)-catalyzed reactions for the direct modification of unprotected mercaptobenzoic acids, which would be utilized for pharmaceuticals[20] and materials.

Experimental Section

General Procedure

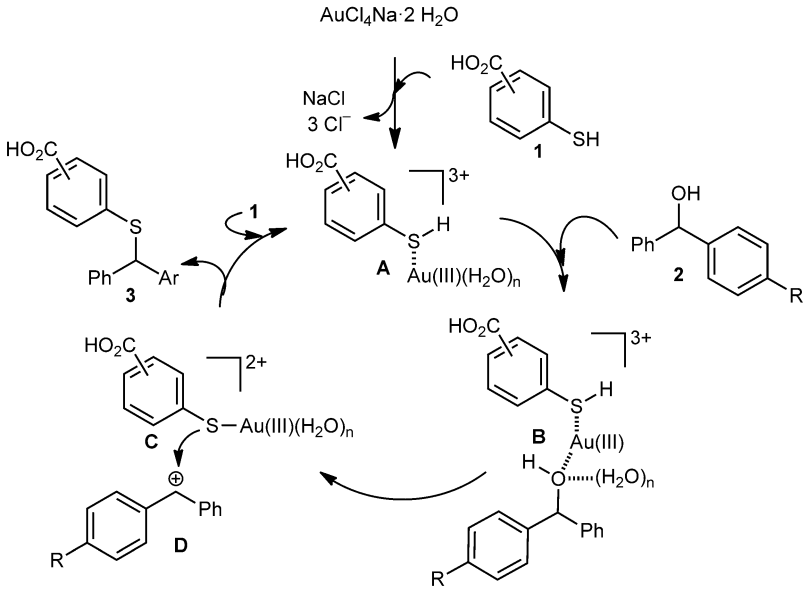
A mixture of mercaptobenzoic acids **1** (1 mmol), $AuCl_4Na{\cdot}2H_2O$ (8 mg, 0.02 mmol), and benzylic alcohols **2** (1.2 mmol) in H_2O (4 mL) was heated at 80 or 120 °C for 16 h in a sealed tube under air. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was washed with hexanes, then purified by flash column chromatography (silica gel, hexanes/EtOAc) to give the desired product **4**.

2-(Benzhydrylthio)benzoic acid (3a):[9a] Following the scale-up experiment (see the Supporting Information), **3a** was obtained as a white solid; mp 210–212 °C; IR (KBr): ν = 3437, 1681 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 5.60 (s, 1H), 7.14 (dd, J = 7.2 Hz, 2H), 7.17 (dt, J = 7.6, 0.8 Hz 1H), 7.27–7.33 (m, 6H), 7.40 (dt, J = 8.8, 2.0 Hz, 2H), 7.43 (dd, J = 6.4, 2.0 Hz, 2H), 8.01 (dd, J = 8.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.9, 124.2, 126.8, 127.2, 128.2, 128.7, 130.8, 132.0, 140.2, 140.8, 167.5; MS (FAB): m/z = 321 $[M+H]^+$.

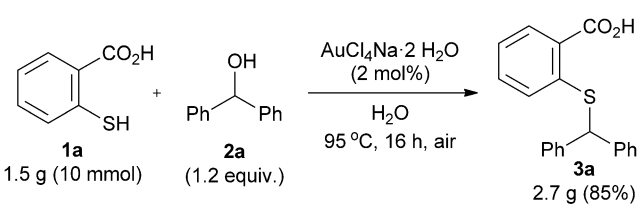
3-(Benzhydrylthio)benzoic acid (3b):[9a] Following the general procedure, **3a** was obtained as a white solid; yield: 196 mg (61%); mp 127–129 °C; IR (KBr): ν = 2559, 1693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 6.02 (s, 1H), 7.22 (dd, J = 7.3, 7.3 Hz, 2H), 7.28–7.38 (m, 5H), 7.50 (d, J = 7.3 Hz, 4H), 7.54 (dt, J = 8.7, 0.9 Hz, 1H), 7.69 (dt, J = 7.8, 1.1 Hz, 1H), 7.82 (t, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.5, 127.2, 127.3, 128.0, 128.6, 129.1, 129.9, 131.4, 133.5, 136.3, 140.7, 166.7; MS (FAB): m/z = 321 $[M+H]^+$.

4-(Benzhydrylthio)benzoic acid (3c):[9a] Following the general procedure, **3c** was obtained as a pale yellow solid; yield: 159 mg (50%); mp 188–190 °C; IR (KBr): ν = 3081, 1682 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 5.72 (s, 1H), 7.22 (dd, J = 7.3, 7.3 Hz, 2H), 7.28–7.38 (m, 5H), 7.50 (d, J = 7.3 Hz, 4H), 7.54 (dt, J = 8.7, 0.9 Hz, 1H), 7.69 (dt, J = 7.8, 1.1 Hz, 1H), 7.82 (t, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.8, 126.6, 127.9, 128.5, 129.2, 130.1, 130.9, 141.1, 142.8, 167.3; FAB-MS: m/z = 321 $[M+H]^+$.

2-(Benzhydrylthio)-5-fluorobenzoic acid (3d):[9a] Following the general procedure, **3d** was obtained as a pale yellow solid; yield: 239 mg (71%); mp 163–166 °C; IR (KBr): ν = 3067, 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.60 (s, 1H), 6.99 (ddd, J = 8.8, 7.6, 2.8 Hz, 1H), 7.14 (dd, J = 8.8,



Scheme 4. Plausible mechanism.



Scheme 5. Scale-up experiment.

5.2 Hz, 1H), 7.23–7.27 (m, 2H), 7.30 (dd, J=7.2, 7.2 Hz, 4H), 7.41 (dd, J=7.2, 1.6 Hz, 4H), 7.76 (dd, J=9.2, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=53.9, 117.6 (d, J=23.9), 119.7 (d, J=21.9 Hz), 127.9, 128.7, 129.2, 130.1 (d, J=7.7 Hz), 131.4 (d, J=7.7 Hz), 135.5, 141.1, 159.6 (d, J=242.2), 167.1; MS (FAB): m/z=339 $[M+H]^+$.

2-(Benzhydrylthio)-5-chlorobenzoic acid (3e): Following the general procedure, **3e** was obtained as a white solid; yield: 218 mg (61%); mp 166–168 °C; IR (KBr): ν=3082, 1683 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=6.04 (s, 1H), 7.23–7.49 (m, 13H), 7.80 (d, J=2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=53.4, 127.9, 128.8, 129.2, 129.4, 130.6, 132.2, 139.6, 140.9, 166.9; FAB-MS: m/z=355 $[M+H]^+$, 357 $[M+H+2]^+$.

2-{[(4-Methoxyphenyl)(phenyl)methyl]thio}benzoic acid (3f): Following the general procedure, **3f** was obtained as a white solid; yield: 283 mg (80%); mp 184–187 °C; IR (KBr): ν=3080, 1683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.78 (s, 3H), 5.61 (s, 1H), 6.83 (dd, J=6.8, 2.4 Hz, 2H), 7.13–7.35 (m, 8H), 7.42 (s, 1H), 7.44 (s, 1H), 8.06 (dd, J=8.0, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=53.1, 55.6, 114.6, 124.8, 127.6, 127.7, 128.7, 129.1, 129.9, 140.6, 141.7, 158.9, 168.0; MS (FAB): m/z=351 $[M+H]^+$; anal. calcd. for $C_{21}H_{18}O_3S$: C 71.98, H 5.18, N 0; found: C 71.87, H 5.13, N 0.

2-{[Phenyl(*p*-tolyl)methyl]thio}benzoic acid (3g): Following the general procedure, **3g** was obtained as a white solid; yield: 283 mg (84%); mp 176–179 °C; IR (KBr): ν=3080, 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.31 (s, 3H), 5.61 (s, 1H), 7.10–7.33 (m, 10H), 7.42 (dd, J=8.8, 7.2 Hz, 2H), 8.06 (dd, J=8.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=21.1, 53.5, 124.8, 127.6, 128.7, 129.2, 129.7, 131.2, 132.4, 136.9, 140.5, 141.6, 168.0; MS (FAB): m/z=335 $[M+H]^+$; anal. calcd. for $C_{21}H_{18}O_2S$: C 75.42, H 5.43, N 0; found: C 75.44, H 5.38, N 0.

2-{[Bis(4-fluorophenyl)methyl]thio}benzoic acid (3h): Following the general procedure, **3h** was obtained as a white solid; yield: 313 mg (88%); mp 197–200 °C; IR (KBr): ν=3081, 1684 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=6.05 (s, 1H), 7.13 (dd, J=8.8, 2.4 Hz, 5H), 7.25 (dd, J=7.2 Hz, 1H), 7.31 (dt, J=7.2, 1.6 Hz, 1H), 7.48 (dd, J=8.4, 5.2 Hz, 4H), 7.81 (dd, J=7.2, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=51.9, 116.0 (d, J=22.0 Hz), 125.1, 127.8, 129.3, 130.7 (d, J=7.6 Hz), 131.2, 132.5, 137.4 (d, J=2.8 Hz), 139.8, 161.8 (d, J=243.1 Hz), 168.0; MS (FAB): m/z=357 $[M+H]^+$; anal. calcd. for $C_{20}H_{14}F_2O_2S$: C 67.40, H 3.96, N 0; found: C 67.03, H 4.15, N 0.

2-{[(4-Bromophenyl)(phenyl)methyl]thio}benzoic acid (3i):[1] Following the general procedure (1/2 scale), **3i** was obtained as a white solid; yield: 191 mg (95%); mp 206–208 °C; IR (KBr): ν=3080, 1683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.60 (s, 1H), 7.13–7.19 (m, 2H), 7.27–7.33 (m, 6H), 7.39–7.45 (m, 4H), 8.07 (dd, J=7.6, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=52.9, 120.9, 125.0, 126.5, 127.7, 129.2, 131.0, 132.1, 133.7, 140.9, 168.1; FAB-MS: m/z=399 $[M+H]^+$, 401 $[M+H+2]^+$.

2-{[(4-Chlorophenyl)(phenyl)methyl]thio}benzoic acid (3j): Following the general procedure, **3j** was obtained as a white solid; yield: 207 mg (58%); mp 204–207 °C; IR (KBr): ν=3081, 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.62 (s, 1H), 7.14 (dd, 2H), 7.25–7.34 (m, 5H), 7.37–7.42 (m, 4H), 8.06 (dd, J=7.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=52.8, 125.0, 127.8, 128.8, 129.2, 130.6, 132.4, 140.0, 140.4, 140.9, 168.0; MS (FAB): m/z=355 $[M+H]^+$, 357 $[M+H+2]^+$.

2-{[Bis(4-chlorophenyl)methyl]thio}benzoic acid (3k): Following the general procedure, **3k** was obtained as a yellow solid; yield: 344 mg (88%); mp 190–192 °C; IR (KBr): ν = 3072, 1674, 1672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.60 (s, 1H), 7.16 (dt, J = 8.4, 1.2 Hz 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 4H), 8.06 (dd, J = 7.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 51.6, 125.0, 127.4, 129.3, 130.6, 131.4, 132.7, 140.1, 168.0; MS (FAB): m/z = 389 $[M+H]^+$, 391 $[M+H+2]^+$; anal. calcd. for $C_{20}H_{14}Cl_2O_2S$: C 61.71, H 3.63, N 0; found: C 61.71, H 4.08, N 0.

2-{[1-(4-Methoxyphenyl)ethyl]thio}benzoic acid (3l): Following the general procedure, **3l** was obtained as a white solid; yield: 195 mg (68%); mp 168–171 °C; IR (KBr): ν = 2966, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.66 (d, J = 6.8 Hz 3H), 3.78 (s, 3H), 4.39 (q, J = 6.8 Hz, 4H), 6.80 (dd, J = 6.8, 2.0 Hz 4H), 7.22 (dd, J = 24, 8.4 Hz, 1H), 7.33 (dd, J = 6.0, 1.2 Hz, 1H), 7.37 (dt, J = 7.2, 1.6 Hz, 1H), 8.15 (dd, J = 7.6, 1.2 Hz, 1H); ^{13}C NMR(100 MHz, DMSO-d_6): δ = 23.0, 40.4, 55.6, 114.4, 124.9, 128.2, 128.9, 132.3, 135.2, 140.0, 158.8, 168.1; MS (FAB): m/z = 289 $[M+H]^+$; anal. calcd. for $C_{16}H_{16}O_3S$: C 66.64, H 5.59, N 0; found: C 66.53, H 5.43, N 0.

3-[4-(Benzhydrylthio)phenyl]propanoic acid (3m): Following the general procedure, **3f** was obtained as a white solid; yield: 264 mg (78%); mp 108–110 °C; IR (KBr): ν = 3025, 1707 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.61 (t, J = 6.8 Hz, 2H), 2.87 (t, J = 3.6 Hz, 2H), 5.49 (s, 1H), 7.02 (d, J = 4.6 Hz, 2H), 7.14–7.42 (m, 14H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.3, 35.4, 55.6, 127.7, 128.5, 129.1, 129.3, 130.2, 133.2, 139.8, 141.8, 174.2; FAB-MS: m/z = 349 $[M+H]^+$.

2-(Cinnamylthio)benzoic acid (3n): Following the general procedure, **3n** was obtained as a white solid; yield: 211 mg (78%); mp 208–210 °C; IR (KBr): ν = 3031, 1672 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 3.82 (d, J = 6.8 Hz, 1H), 6.36 (dt, J = 15.6, 7.6 Hz, 1H), 6.70 (d, J = 15.6 Hz, 1H), 7.18–7.27 (m, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 7.47–7.56 (m, 2H), 7.87 (dd, J = 8.0, 1.6 Hz 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 34.2, 124.5, 125.1, 126.6, 126.7, 128.2, 128.9, 129.2, 131.4, 132.7, 133.5, 136.9, 140.9, 168.0; FAB-MS: m/z = 271 $[M+H]^+$; anal. calcd. for $C_{16}H_{14}O_2S$: C 71.09, H 5.22, N 0; found: C 70.91, H 5.19, N 0.

(*E*)-2-[(1,3-Diphenylallyl)thio]benzoic acid (3o): Following the general procedure, **3n** was obtained as a white solid; yield: 284 mg (82%); mp 164–166 °C; IR (KBr): ν = 3056, 1677 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 5.46 (d, J = 7.2 Hz, 1H), 6.58 (dd, J = 15.6, 6.4 Hz, 1H), 6.63 (d, J = 15.6 Hz, 1H), 7.19 (dt, J = 7.2, 0.8 Hz, 1H), 7.20–7.25 (m, 1H), 7.26–7.33 (m, 3H), 7.33–7.47 (m, 5H), 7.52–7.59 (m, 3H), 7.80 (dd, J = 8.0, 2.0 Hz 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.4, 125.3, 126.9, 128.0, 128.3, 128.7, 128.9, 129.1, 129.3, 129.5, 130.3, 131.0, 132.1, 132.3, 136.7, 139.3, 140.5, 168.2; FAB-MS: m/z = 347 $[M+H]^+$; anal. calcd. for $C_{22}H_{18}O_2S{\cdot}0.2H_2O$: C 75.49, H 5.30, N 0; found: C 75.26, H 5.19, N 0.

2-[(1,3-Diphenylprop-2-yn-1-yl)thio]benzoic acid (3p): Following the general procedure, **3o** was obtained as a yellow solid; yield: 258 mg (75%); mp 170–172 °C; IR (KBr): ν = 3078, 3021, 1683 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 5.89 (s, 1H), 7.30 (dt, J = 7.6, 0.8 Hz, 1H), 7.34–7.40 (m, 6H), 7.45 (t, J = 8.0 Hz, 2H), 7.60–7.70 (m, 3H), 7.84 (d, J = 8.0 Hz, 1H), 7.91 (dd, J = 8.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 5.4, 88.7, 122.5, 125.6, 128.3, 128.7, 128.9, 129.2, 129.3, 129.4, 131.3, 131.9, 132.7, 137.4, 139.9, 168.1; HR-MS-EI: m/z = 344.0871 (M^+), calcd. for $C_{22}H_{16}O_2S$: 344.0871.

References

[1] a) A. Corma, A. Leyva-Perez, J. S. Maria, *Chem. Rev.* **2011**, *111*, 1657–1712; b) P. Mukherjee, R. A. Widenhoefer, *Org. Lett.* **2011**, *13*, 1334–1337; c) P. Mukherjee, R. A. Widenhoefer, *Org. Lett.* **2010**, *12*, 1184–1187; d) Y. Lu, X. Fu, H. Chen, X. Du, X. Jia, Y. Liu, *Adv. Synth. Catal.* **2009**, *351*, 129–134; e) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; f) S. Guo, F. Song, Y. Liu, *Synlett* **2007**, 964–968.

[2] a) M. Georgy, M. Boucard, O. Debleds, C. D. Zotto, J.-M. Campagne, *Tetrahedron* **2009**, *65*, 1758–1766; b) M. Georgy, M. Boucard, J.-M. Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 14180–14181.

[3] V. Terrasson, S. Marque, M. Georgy, J.-M. Campagne, D. Prim, *Adv. Synth. Catal.* **2006**, *348*, 2063–2067.

[4] T. Ohshima, Y. Nakahara, J. Ipposhi, Y. Miyamoto, K. Mashima, *Chem. Commun.* **2011**, *47*, 8322–8324.

[5] Gold-catalyzed reactions in aqueous media, see: a) H. Kitahara, H. Sakurai, *Chem. Lett.* **2010**, *39*, 46–48; b) E. Feng, Y. Zhou, F. Zhao, X. Chen, L. Zhang, H. Jiang, H. Liu, *Green Chem.* **2012**, *14*, 1888–1895; c) A. Monopoli, P. Cotugno, G. Palazzo, N. Ditaranto, B. Mariano, N. Cioffi, F. Ciminale, A. Nacci, *Adv. Synth. Catal.* **2012**, *354*, 2777–2788; d) S. Sanz, L. A. Jones, F. Mohr, M. Laguna, *Organometallics* **2007**, *26*, 952–957.

[6] a) H. Hikawa, H. Suzuki, I. Azumaya, *J. Org. Chem.* **2013**, *78*, 12128–12135; b) H. Hikawa, H. Suzuki, Y. Yokoyama, I. Azumaya, *J. Org. Chem.* **2013**, *78*, 6714–6720.

[7] H. Kinoshita, H. Shinokubo, K. Oshima, *Org. Lett.* **2004**, *6*, 4085–4088.

[8] P. G. Cozzi, L. Zoli, *Angew. Chem.* **2008**, *120*, 4230–4234; *Angew. Chem. Int. Ed.* **2008**, *47*, 4162–4166.

[9] Pd-catalyzed *S*-benzylation; a) H. Hikawa, I. Azumaya, *Org. Biomol. Chem.* **2014**, *12*, 5964–5972; b) H. Hikawa, Y. Yokoyama, *Org. Biomol. Chem.* **2012**, *10*, 2942–2945.

[10] $Hf(OTf)_4$-catalyzed Friedel–Crafts reaction of 1,3-dimethoxybenzene with benzhydrol did not proceed in the presence of 1-methylindole, since the strong π nucleophile 1-methylindole suppressed the acidity of $Hf(OTf)_4$.

[11] a) W. Henderson, B. K. Nicholson, S. J. Faville, D. Fan, J. D. Ranford, *J. Organomet. Chem.* **2001**, *631*, 41–46; b) M. B. Dinger, W. Henderson, *J. Organomet. Chem.* **1998**, *560*, 233–243.

[12] a) Y. Levi-Kalisman, P. D. Jadzinsky, N. Kalisman, H. Tsunoyama, T. Tsukuda, D. A. Bushnell, R. D. Kornberg, *J. Am. Chem. Soc.* **2011**, *133*, 2976–2982; b) P. D. Jadzinsky, G. Calero, C. J. Ackerson, D. A. Bushnell, R. D. Kornberg, *Science* **2007**, *318*, 430–439.

[13] A. Corma, T. Rodenas, M. J. Sabater, *Chem. Sci.* **2012**, *3*, 398–404.

[14] N. Morita, A. Yasuda, M. Shibata, S. Ban, Y. Hashimoto, I. Okamoto, O. Tamura, *Org. Lett.* **2015**, *17*, 2668–2671.
[15] a) P. A. Grieco, K. Yoshida, P. Gaener, *J. Org. Chem.* **1983**, *48*, 3137–3139; b) D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.
[16] M. Ciobanu, B. Cojocaru, C. Teodorescu, F. Vasiliu, S. M. Coman, W. Leitner, V. I. Parvulescu, *J. Catal.* **2012**, *296*, 43–54.
[17] a) B. P. Jarman, B. K. Nicholson, *J. Organomet. Chem.* **2012**, *702*, 1–9; b) K. J. Kilpin, B. P. Jarman, W. Henderson, B. K. Nicholson, *Appl. Organomet. Chem.* **2011**, *25*, 810–814; c) K. J. Kilpin, W. Henderson, B. K. Nicholson, *Dalton Trans.* **2010**, *39*, 1855–1864.
[18] G. Flouret, T. Majewski, L. Balaspiri, W. Brieher, K. Mahan, O. Chaloin, L. Wilson Jr, J. Slaninova, *J. Pept. Sci.* **2002**, *8*, 314–326.
[19] a) H. Hikawa, Y. Yokoyama, *Org. Biomol. Chem.* **2011**, *9*, 4044–4050; b) H. Hikawa, Y. Yokoyama, *J. Org. Chem.* **2011**, *76*, 8433–8439.
[20] a) K. Islam, H. F. Chin, A. O. Olivares, L. P. Saunders, E. M. De La Cruz, T. M. Kapoor, *Angew. Chem.* **2010**, *122*, 8662–8666; *Angew. Chem. Int. Ed.* **2010**, *49*, 8484–8488; b) A. S. Mehanna, J. Y. Kim, *Bioorg. Med. Chem.* **2005**, *13*, 4323–4331; c) A. Zarghi, M. Faizi, B. Shafaghi, A. Ahadian, H. R. Khojastehpoor, V. Zanganeh, S. A. Tabatabai, A. Shafiee, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3126–3129.

