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COMMUNICATION

Palladium-catalyzed *S*-benzylation of unprotected mercaptobenzoic acid with benzyl alcohols in water†

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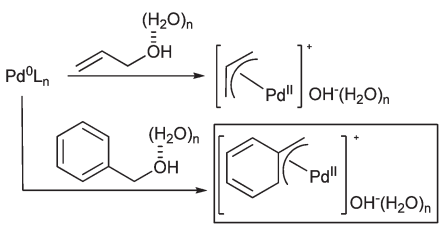
Palladium-catalyzed *S*-benzylation of unprotected mercaptobenzoic acids with benzyl alcohols gave only *S*-benzylated mercaptobenzoic acids in good yields. Water may play an important role for the smooth generation of the (η^3-benzyl) palladium species by activation of the hydroxyl group of the benzyl alcohol.

Palladium-catalyzed benzylations with benzylic alcohols are especially challenging because the reactivity of benzylic alcohols towards Pd(0) is poor compared with benzylic halides, carboxylates, carbonates and phosphates.[1] However, we discovered a direct catalytic substitution of benzylic alcohols with unprotected anthranilic acids without additives for activation of benzylic alcohols in water,[2] which was analogous to the palladium-catalyzed allylation of allyl alcohols.[3] Water may play an important role in the smooth generation of the (η^3-benzyl)palladium species by hydration of the hydroxyl group due to the structural similarity to allylic alcohols (Scheme 1).

Based on this work, we became interested in further expanding the substrate scope of this methodology to *S*-benzylation. *S*-Benzylated thiophenyl structures are key units in a wide range of relevant pharmacophores with a broad spectrum of activities.[4] The most traditional *S*-benzylation method is the reaction of thiolate anions with benzyl halides.[4b,c,5] However, 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.) gives benzyl esters as the undesired products (Scheme 2).[6]

Therefore, the development of a direct catalytic substitution of benzylic alcohols, which produces the desired products along with water as the sole coproduct, is also highly desired. *S*-Benzylation with benzyl alcohols, which are activated by boron trifluoride etherates,[7] yttrium triflates,[8] ZnI_2[9] and $ZrCl_4$[10] in organic solvents, have been reported. Herein, we report a palladium-catalyzed selective *S*-benzylation of unprotected mercaptobenzoic acids with benzylic alcohols in water, which is chemoselective and leaves the carboxyl group intact. To the best of our knowledge, the palladium-catalyzed *S*-benzylation with benzyl alcohols has not been described before.

The mixture of 4-mercaptobenzoic acid **1a** and benzyl alcohol (**2a**: 5 equiv.) in the presence of $Pd(OAc)_2$ (5 mol%) and sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 10 mol%) in water was heated at 120 °C for 24 h in a sealed tube proceeded to give the desired product **3a** in 88% yield (Table 1, entry 1). When the reaction carried out at 100 °C in open vessel, desired **3a** was not obtained. Since the reaction did not proceed in the absence of the palladium catalyst (entry 2), a S_N2 reaction mechanism was excluded in the formation of the *S*-benzylated product. The use of zero- or divalent palladium as the catalyst, $Pd_2(dba)_3$ or $PdCl_2$, gave the product in moderate to good yields (entry 3, 61%; entry 4, 87%). To our surprise, the use of $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ instead of a water-soluble ligand also resulted in the formation of **3a** in good yields (entry 5, 86%; entry 6, 87%). Since *S*-benzylated **3a** was not obtained in DMSO, EtOH, AcOH or DMSO–H_2O (1 : 1) (entry 7) but in water as the solvent, water must play an important role in the *S*-benzylation with benzyl alcohols. NaOH as an additive suppressed the benzylation (entry 8). In contrast, the reaction proceeded with addition of AcOH (4 equiv.) in good yield (entry 9, 86%). Basset and co-workers reported that the π-allyl palladium intermediate is unstable under strong basic conditions.[11] In contrast, Manabe and Kobayashi[12] and Yang *et al.*[13] reported that carboxylic acids enhance the formation of the π-allyl complex in aqueous media. Since our results are consistent with these reports on the palladium-catalyzed allylation with allylic alcohols, (η^3-benzyl)palladium may be an intermediate here in analogy to the allylic substitution reaction.



Scheme 1 Hydration of the hydroxyl group.

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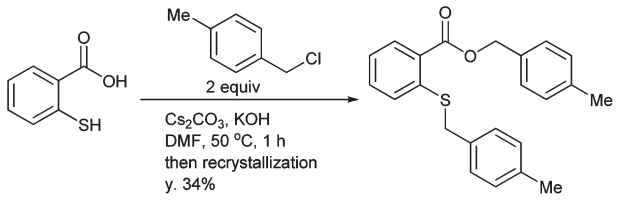
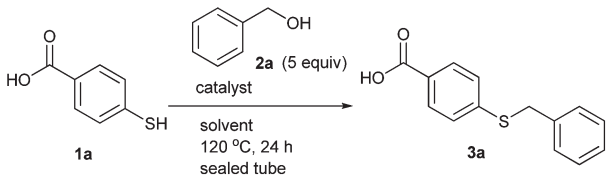
†Electronic supplementary information (ESI) available: Experimental procedures and characterization data. Copies of ^1H and ^{13}C NMR spectra of the new compounds. See DOI: 10.1039/c2ob25091h



Scheme 2 Reaction of 2-mercaptobenzoic acid with 4-methylbenzyl chloride.

Table 1 Effects of catalysts and solvents[a]



Entry	Catalyst	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$–TPPMS	H_2O	88 (trace)[c]
2	TPPMS	H_2O	0
3	$Pd_2(dba)_3$[d]–TPPMS	H_2O	61
4	$PdCl_2$–TPPMS	H_2O	87
5	$PdCl_2(PPh_3)_2$	H_2O	86
6	$Pd(PPh_3)_4$	H_2O	87
7	$Pd(OAc)_2$–TPPMS	DMSO, EtOH, AcOH or DMSO–H_2O (1 : 1)	Trace
8	$Pd(OAc)_2$–TPPMS	1 N $NaOH_{aq}$[e]	0
9	$Pd(OAc)_2$–TPPMS	H_2O–AcOH[e]	86

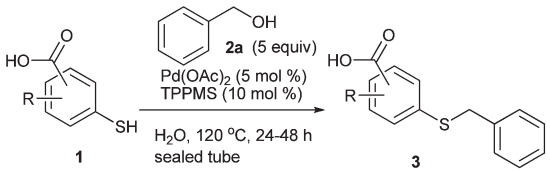
[a] Pd catalyst (5 mol%), ligand (10 mol%), benzyl alcohol **2** (5 equiv.), solvent (0.25 M), 120 °C, 24 h in sealed tube. [b] Yield of isolated product. [c] The reaction carried out at 100 °C in open vessel. [d] 2.5 mol%. [e] 4 equiv. was used.

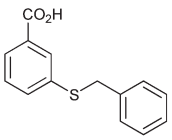
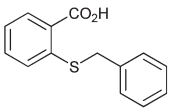
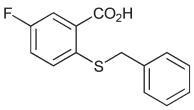
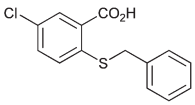
Results for the *S*-benzylation of several mercaptobenzoic acids using $Pd(OAc)_2$ and TPPMS in water are summarized in Table 2. 3-Mercaptobenzoic acid smoothly underwent *S*-benzylation with benzyl alcohol **2a** to give the corresponding *S*-benzylated mercaptobenzoic acid in 90% yield (entry 1). The reaction of 2-mercaptobenzoic acids also proceeded to give *S*-benzylated **3c–e** in overall yields ranging from 60 to 71% despite the steric effect of the carboxyl group at the *ortho*-position (entries 2–4).

Results for the *S*-benzylation of 4-mercaptobenzoic acid **1a** with a number of benzyl alcohols substituted by electron-withdrawing and electron-donating groups using $Pd(OAc)_2$ and TPPMS are summarized in Table 3. The benzyl alcohols with electron-donating methyl, ethyl and methoxy groups resulted in good yields (entry 1, 80%; entry 2, 77%; entry 3, 94%). A sterically demanding methyl group at the *ortho* position was tolerated in the *S*-benzylation (entry 4, 70%). The use of 4-fluorobenzyl alcohol also resulted in good yield (entry 5, 85%). The benzyl alcohols with bromo and chloro groups produced *S*-benzylated **3k–m** in good yields with the carbon–halogen moiety left intact, which could be employed for further manipulation (entry 6, 88%; entry 7, 76%; entry 8, 87%).

We next investigated the scope of different benzylic alcohols **2** (Table 4). *S*-Benzylation with α-alkyl benzyl alcohols proceeded smoothly to give the desired products **3n–o** in good yields in spite of the possible formation of a vinylarene through β-hydride elimination from the benzylpalladium intermediate (entry 1, 74%; entry 2, 77%).[14] The sterically demanding cyclic benzyl alcohols also gave good yields (entry 3, 75%; entry 4, 74%). Surprisingly, a hydrophobic benzyl alcohol such as diphenylmethanol, which is not soluble in water, gave the *S*-benzylated

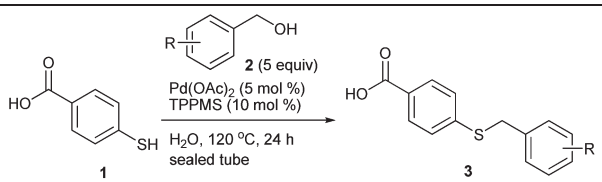
Table 2 *S*-Benzylation of several mercaptobenzoic acids **1**[a]



Entry	Time (h)	Product **3**		Yield (%)
1	24		**3b**	90
2	48		**3c**	60
3	48		**3d**	69
4	48		**3e**	71

[a] Reaction conditions: **1** (1 mmol), $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), benzyl alcohols **2** (5 equiv.), H_2O (4 mL), 120 °C, 24–48 h in sealed tube. Yield of isolated product.

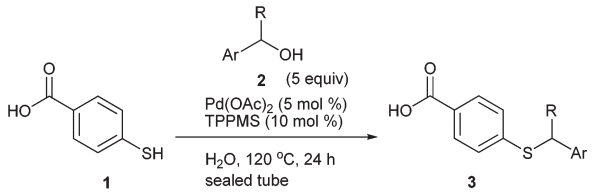
Table 3 *S*-Benzylation with substituted benzyl alcohols **2**[a]

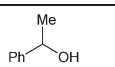
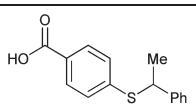
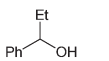
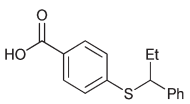
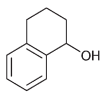
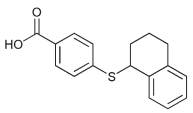
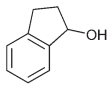
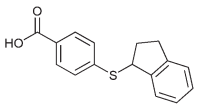
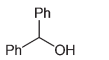
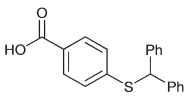
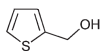
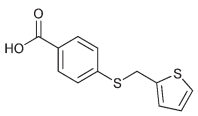


Entry	R =	Product **3**	Yield (%)
1	4-Me	**3f**	80
2	4-Et	**3g**	77
3	4-OMe	**3h**	94
4	2-Me	**3i**	70
5	4-F	**3j**	85
6	4-Br	**3k**	88
7	3-Br	**3l**	76
8	4-Cl	**3m**	87

[a] Reaction conditions: **1** (1 mmol), $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), benzyl alcohols **2** (5 equiv.), H_2O (4 mL), 120 °C, 24 h in sealed tube. Yield of isolated product.

Table 4 Scope of alcohols **2**[a]

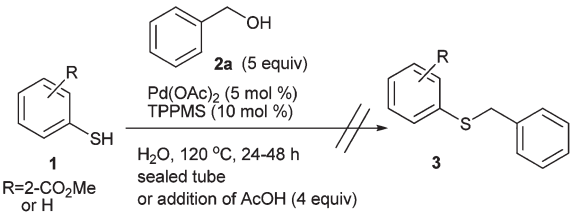


Entry	Alcohol **2**	Product **3**		Yield (%)
1			**3n**	74
2			**3o**	77
3			**3p**	75
4			**3q**	74
5			**3r**	83 (76)[b]
6			**3s**	87

[a] Reaction conditions: **1** (1 mmol), $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), benzyl alcohols **2** (5 equiv.), H_2O (4 mL), 120 °C, 24 h in sealed tube. Yield of isolated product. [b] $Pd(PPh_3)_4$ was used instead of TPPMS.

product **3r** in 83% yield (entry 5). In addition, the use of Pd $(PPh_3)_4$ as a non water soluble catalyst instead of TPPMS also resulted in good yield (76%). Thus, the reaction may proceed "on water" in our catalytic system. 2-Thiophenemethanol also resulted in good yield (entry 6, 87%), although palladium-catalyzed reactions with heteroaryl methyl alcohol derivatives are extremely rare.[15]

Finally, to evaluate the effect of the carboxyl group of mercaptobenzoic acids in our catalytic system, *S*-benzylation of 2-mercaptobenzoic acid methyl ester and benzenethiol was carried out (Scheme 3). The reaction with benzyl alcohol **2a** using $Pd(OAc)_2$ and TPPMS in water did not afford the *S*-benzylated products **3**. *S*-benzylated **3** was also not obtained with addition of AcOH (4 equiv.). These results suggested that the carboxyl group of the mercaptobenzoic acid plays a key role as an activator in our catalytic system. Our method also succeeds under neutral conditions in good yields. NaOH suppressed the *S*-benzylation. Therefore, pH plays a critical role in the palladium-catalyzed *S*-benzylation and the outcome of the *S*-benzylation can be controlled simply by changing the basicity of the reaction media.



Scheme 3 Effect of carboxyl group of mercaptobenzoic acid.

We are also interested in the development of unprotected syntheses and selective reactions towards various reactive functional groups in aqueous media.[16] Protection of reactive functional groups such as amino, hydroxyl, or carboxyl groups is often required 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 unprotected syntheses should lead to a breakthrough in organic synthesis.

Conclusions

In summary, we have developed a new synthetic methodology for achieving a palladium-catalyzed *S*-benzylation of unprotected mercaptobenzoic acids **1** with benzylic alcohols **2** in water without additives. In our catalytic system, the key is the use of water as a solvent. Water plays an important role in the activation of the benzylic alcohols to form the corresponding palladium complexes. Recently, organic reactions in water have attracted attention not only for their environmental and economical advantages, but also for their unique reactivity. Therefore, development of reactions in water is an important goal of synthetic methodology. We are currently investigating the scope of various nucleophiles on the benzylation, and are developing new reactions using (η^3-benzyl)palladium species from benzyl alcohols in aqueous media.

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