C–H Activation

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General Method for the Synthesis of Salicylic Acids from Phenols through Palladium-Catalyzed Silanol-Directed C–H Carboxylation**

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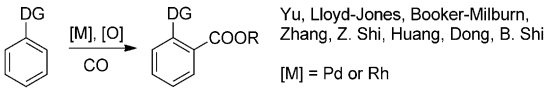
Abstract: *A silanol-directed, palladium-catalyzed C–H carboxylation reaction of phenols to give salicylic acids has been developed. This method features high efficiency and selectivity, and excellent functional-group tolerance. The generality of this method was demonstrated by the carboxylation of estrone and by the synthesis of an unsymmetrically o,o′-disubstituted phenolic compound through two sequential C–H functionalization processes.*

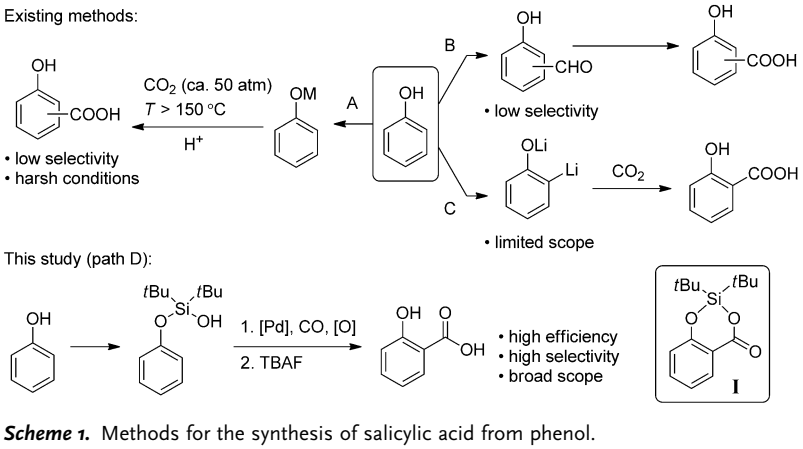
Salicylic acids (SAs) are key motifs in pharmaceutically and biologically active compounds,[1] useful synthetic intermediates,[2] and important building blocks in materials science.[3] Owing to the significance of SAs, a number of methods for their synthesis have been developed.[4] The Kolbe–Schmitt reaction is the most commonly used route to SAs (Scheme 1, path A).[4a] Other routes include the *ortho* formylation of phenols with subsequent oxidation (path B)[4b,c] and the directed *ortho* metalation (DoM) of phenol, followed by quenching of the formed aryl lithium species with CO_2 (path C).[4d] Though widely used, the aforementioned methods suffer from major limitations, such as harsh conditions, poor selectivity, and limited scope. Herein, we report a palladium-catalyzed silanol-directed *ortho*-C–H carboxylation reaction of phenols for the synthesis of SAs. This efficient protocol is highly selective and demonstrates excellent functional-group tolerance.

Transition-metal-catalyzed C–H[5] carboxylation reactions[6] with cheap and abundant CO is an attractive approach, since it enables the introduction of valuable carboxy functionality at inert C–H bonds, which are ubiquitous in organic compounds. Most reported methods for highly efficient and selective C–H carboxylation of arenes[7] entail the use of a directing group (DG) [Eq. (1)].[8] For example, the Yu



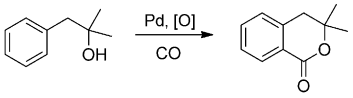
(1)

research group and later the groups of Shi and Cheng reported hydroxy-directed palladium-catalyzed C–H carbonylation reactions of arenes to give lactones and coumarins [Eq. (2) and (3)].[9] Since no general and selective methods for the conversion of phenols into SAs exist (see above), we found the development of such methodology highly justified. Previously, our research group introduced a silanol as a powerful traceless directing group[10] for the palladium-catalyzed *ortho* alkenylation[10a] and oxygenation[10b] of phenols. Hence, we hypothesized that if the phenoxy silanol could undergo a palladium-catalyzed carbonylation reaction to generate intermediate **I**, routine desilylation of this intermediate would produce SAs in a regioselective manner from accessible phenols (Scheme 1, path D).[11]



Scheme 1. Methods for the synthesis of salicylic acid from phenol.

We initially tested the carboxylation reaction of **1b** by a procedure modified from that described by Yu and co-workers.[9a] Under these conditions, **2b′** was obtained as a single product in 17% yield (Table 1, entry 1). Despite the low yield, the robustness of **2b′**



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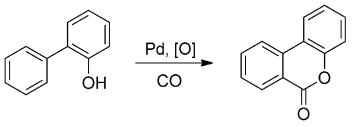

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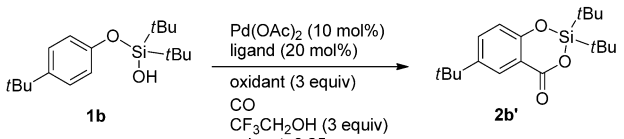
Table 1: Optimization of the reaction conditions.



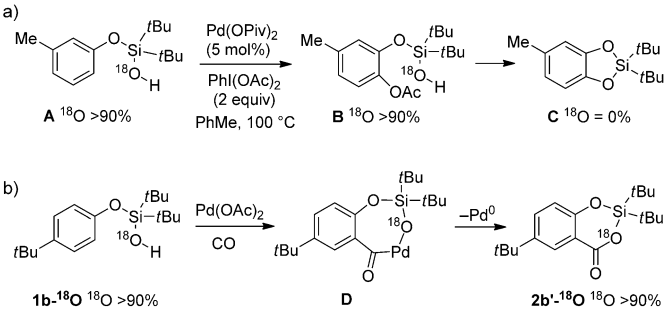
Entry	Ligand[a]	Oxidant	Solvent	Yield [%][b]
1	L3	AgOAc	DCE	17
2	/	AgOAc	DCE	<1
3	L1	AgOAc	DCE	37
4	L2	AgOAc	DCE	33
5	L4	AgOAc	DCE	42
6	**L5**	**AgOAc**	**DCE**	**90**
7[c]	L5	AgOAc	DCE	59
8[d]	L5	AgOAc	DCE	0
8	L5	$Cu(OAc)_2$	DCE	5
9	L5	BQ	DCE	3
10[e]	L5	O_2	DCE	7
11	L5	AgOAc	dioxane	<1
12	L5	AgOAc	EtCN	4
13	L5	AgOAc	xylene	20

[a] L1 = Ac-Val-OH; L2 = Boc-Val-OH; L3 = (+)-menthyl(O_2C)-Leu-OH; L4 = Ac-Leu-OH; L5 = Boc-Leu-OH. [b] The yield was determined by GC with $nC_{15}H_{32}$ as the internal standard. [c] The reaction was carried out with 5 mol% of $Pd(OAc)_2$ and 10 mol% of the ligand. [d] No $Pd(OAc)_2$ was added. [e] The reaction was carried out under an O_2 atmosphere (O_2 balloon). Boc = *tert*-butoxycarbonyl, DCE = 1,2-dichloroethane.

under the carboxylation conditions, along with the cleanness of the reaction, encouraged us to focus on optimization studies. Only a trace amount of the product was detected in a control experiment without a ligand (Table 1, entry 2). Accordingly, we screened a range of monoprotected amino acid (MPAA) ligands in this reaction. Notably, the product yield increased to 37% with Ac-Val-OH as the ligand (Table 1, entry 3). Among the other ligands tested (Table 1, entries 4–6; see the Supporting Information for the complete range of ligands screened), Boc-Leu-OH exhibited the best reactivity with the production of **2b′** in 90% yield (entry 6). A decrease in the amount of palladium used to 5 mol% had a deleterious effect on the yield (Table 1, entry 7), and no carboxylation occurred in the absence of palladium (entry 8). Other oxidants and solvents were also examined. $Cu(OAc)_2$, benzoquinone (BQ), and O_2, which are commonly used oxidants in C–H functionalization, were ineffective (Table 1, entries 9–11), and solvents other than DCE gave poorer results (entries 12–14).

Under the optimized conditions for carboxylation, followed by a routine desilylation step, silanol **1a** was converted into salicylic acid (**2a**) in 76% yield (Table 2, entry 1). Substrates with electron-donating groups were transformed into the corresponding SA derivatives (**2b**,**c**,**e**,**h**) in good to excellent yields, whereas those possessing electron-neutral and electron-deficient substituents were converted into the desired products (**2d**,**i**,**j**) in slightly diminished yields. Remarkably, a number of useful functionalities, including ester (product **2s**), nitrile (product **2t**), aryl chloride (products **2g**,**k**), alkyl chloride (product **2u**), cyclopropyl (product **2r**), and ketone groups (Scheme 3 and Table 2, product **2w**), were tolerated under the reaction conditions. Notably, only the desired product was isolated when other potential directing groups, such as a methoxy or acetoxy group, was present (Table 2, products **2e**,**f**,**p**,**q**).[12] When the silanol precursor contained two possible reactive sites, C–H carboxylation occurred preferentially at the sterically less demanding position (products **2l**–**p**). Bis(silanol) derivative **1v** was transformed into monoacid **2v** in excellent yield. Evidently, the newly installed carboxylic group electronically deactivates the aromatic ring, thus preventing a second C–H carboxylation event. Importantly, substrates possessing a sensitive cinnamyl group at the *para* or *meta* position (substrates **1w**,**x**) were also competent reactants: The corresponding salicylic acids **2w**,**x** were produced in reasonable yields. Likewise, the carbazole derivative **1y** reacted smoothly to give **2y** in 64% yield. In contrast, the ester-substituted phenol **1z** was much less reactive under these conditions (Table 2, entry 26), and strongly electron deficient 3-NO_2- and 4-CN-substituted phenols did not react at all. Notably, this method tolerates substituents at the *ortho* position, as demonstrated by the carboxylation of **1h** (Me), **1i** (Ph), **1j** (naphthalene), and **1k** (chloro). This result is in sharp contrast with our previous results for the silanol-directed C–H olefination reaction, in which case substrates possessing substituents at the *ortho* position showed no reactivity.[10a]

Next, we were eager to clarify the reaction pathway. In our previously developed silanol-directed C–H oxygenation of phenols,[10b] with the aid of a ^{18}O-labeling study, we established that the silanol oxygen atom was not incorporated into the oxygenated product **C** (Scheme 2a). Accordingly, we

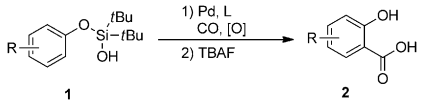


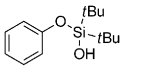
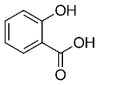
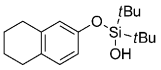
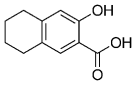
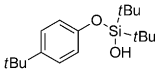
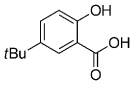
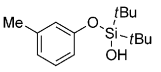
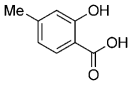
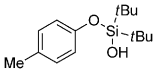
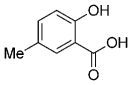
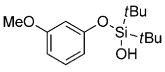
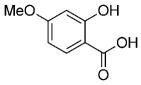
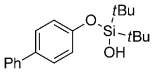
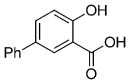
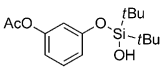
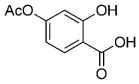
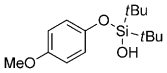
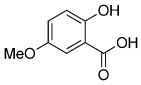
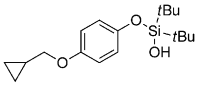
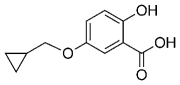
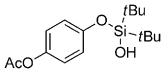
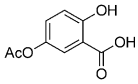
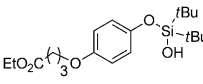
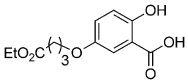
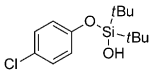
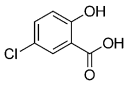
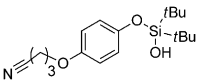
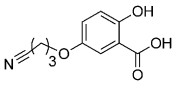
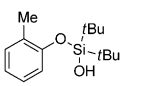
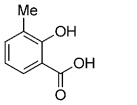
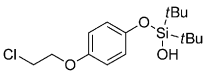
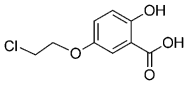
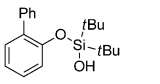
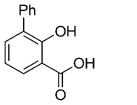
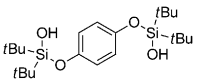
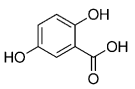
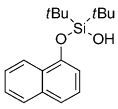
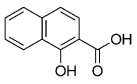
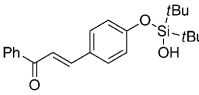
Scheme 2. ^{18}O-Labeling studies. Piv = pivaloyl.

prepared **1b-^{18}O** and subjected it to the conditions of our C–H carboxylation reaction. In contrast to the previous study, this experiment revealed complete retention of the ^{18}O label in the silacycle **2b′** (Scheme 2b). Therefore, we propose that the key intermediate **D** generated upon C–H activation of **1b** and migratory insertion of CO undergoes reductive elimination to produce the ^{18}O-containing product **2b′-^{18}O**.[13]

Finally, this novel carboxylation method was tested on more complex phenols. Thus, estrone was first converted into its silanol derivative **1aa** in almost quantitative yield. The latter underwent a smooth carboxylation/desilylation sequence to produce **2aa** as a single isomer in 89% yield (Scheme 3a). Considering the importance of multisubstituted

Table 2: Scope of the reaction for the formation of salicylic acids.[a]

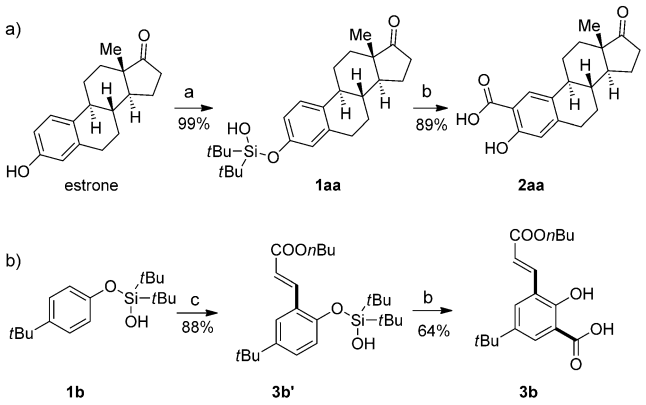


Entry	Silanol		Product		Yield [%][b]	Entry	Silanol		Product		Yield [%][b]
1		**1a**		**2a**	76	14		**1n**		**2n**	99
2		**1b**		**2b**	91	15		**1o**		**2o**	92
3		**1c**		**2c**	92	16		**1p**		**2p**	57
4		**1d**		**2d**	65	17		**1q**		**2q**	69
5		**1e**		**2e**	80	18		**1r**		**2r**	77
6		**1f**		**2f**	71	19		**1s**		**2s**	76
7		**1g**		**2g**	49	20		**1t**		**2t**	81
8		**1h**		**2h**	89	21		**1u**		**2u**	79
9		**1i**		**2i**	63	22		**1v**		**2v**	91
10		**1j**		**2j**	66	23		**1w**		**2w**	62
11		**1k**		**2k**	45	24		**1x**		**2x**	66
12		**1l**		**2l**	85[c]	25		**1y**		**2y**	64
13		**1m**		**2m**	98[d]	26		**1z**		**2z′**	(14)[e]

[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), Boc-Leu-OH (L; 0.04 mmol, 20 mol%), AgOAc (0.6 mmol, 3 equiv), CF_3CH_2OH (0.6 mmol, 3 equiv), CO/Ar (1:8, balloon), DCE (0.8 mL, 0.25 M), 95 °C, 18 h (see the Supporting Information for details). [b] Yield of the isolated product. [c] The product was formed as a 2:1 ratio of regioisomers. [d] The product was formed as a 4:1 ratio of regioisomers. [e] Yield of the silacycle after the first step, as determined by NMR spectroscopy. TBAF = tetrabutylammonium fluoride.

phenols in bioactive compounds,[14] we tested our method for the unsymmetrical bisfunctionalization of a phenolic compound. Thus, after two sequential C–H functionalization operations, olefination[10a] followed by carboxylation, the desired phenolic compound **3b** was obtained in good overall yield (Scheme 3b). To the best of our knowledge, this reaction sequence is the first example of a stepwise unsymmetrical C–H functionalization of phenols.[15]

In conclusion, a general method for the synthesis of salicylic acids from phenols has been developed. This method features high efficiency, broad scope, and high regioselectivity. A mechanistic study revealed that the ester oxygen atom



Scheme 3. C–H carboxylation reaction of complex phenols. [a] tBu_2SiBr_2 (1.1 equiv), imidazole (2.2 equiv), DMF, 18 h; then $NaHCO_3$ (aq), room temperature, 1 h. [b] $Pd(OAc)_2$ (10 mol%), Boc-Leu-OH (L; 20 mol%), AgOAc (3 equiv), CF_3CH_2OH (3 equiv), CO/Ar (1:8, balloon), DCE (0.25 M), 95 °C, 18 h. Then, TBAF (0.4 mL, 1 M), THF (2 mL), room temperature, 30 min. [c] alkene (1.2 equiv), $Pd(OAc)_2$ (10 mol%), (+)Menthyl(O_2C)-Leu-OH (L1; 20 mol%), AgOAc (4 equiv), DCE (0.1 M), 100 °C, 48 h. DMF = *N*,*N*-dimethylformamide.

of the carboxylic group originates from the silanol group. The feasibility of this method for the late-stage functionalization of complex molecules was demonstrated by the carboxylation of estrone. Moreover, two sequential C–H functionalization reactions, olefination[10a] and carboxylation, enabled the synthesis of an unsymmetrically *o*,*o*′-disubstituted phenolic compound. We envision that this approach will become a useful method for the synthesis of salicylic acids from phenols.

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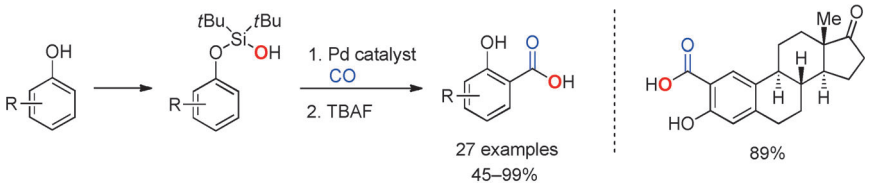
Communications

C–H Activation

Y. Wang, V. Gevorgyan* ——— ■■■–■■■

General Method for the Synthesis of Salicylic Acids from Phenols through Palladium-Catalyzed Silanol-Directed C–H Carboxylation



A strict director: The title reaction produced a wide range of salicylic acid derivatives with high efficiency and selectivity. The scope of this method was demonstrated by the carboxylation of estrone (see scheme; TBAF = tetrabutylammonium fluoride) and by the unsymmetrical bisfunctionalization of a phenolic compound through sequential C–H functionalization reactions.