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General Method for Synthesis of Salicylic Acids from Phenols via Pd-Catalyzed Silanol-Directed C–H Carboxylation

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Abstract

A silanol directed, palladium catalyzed C–H carboxylation reaction of phenols into 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 carboxylation of estrone and by the synthesis of a bis-unsymmetrically substituted phenolic compound via iterative C–H functionalizations.

Keywords

carboxylation; palladium; phenols; salicylic acids; C–H activation

Salicylic acids (SAs) are key motifs in pharmaceutically and biologically active compounds,^[1] useful synthetic intermediates,^[2] as well as important building blocks in material science.^[3] Due to the significance of SAs, a number of synthetic methods have been developed.^[4] The Kolbe-Schmitt reaction is the most commonly used route to SAs (Figure 1, path A).^[4a] Other routes include, *ortho*-formylation of phenols with subsequent oxidation (path B),^[4b,c] and, directed *ortho* metalation (DoM) of phenol, followed by quenching of the formed aryllithium species with CO₂ (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*

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C–H carboxylation reaction of phenols toward SAs synthesis. This efficient protocol is highly selective and demonstrates excellent functional group tolerance.

Transition metal catalyzed C–H^[5] carboxylation reactions^[6] employing cheap and abundant CO is attractive approach since it allows for introduction of valuable carboxyl functionality at inert, but ubiquitous in organic compounds, C–H bonds. Most reports for highly efficient and selective C–H carboxylation of arenes^[7] entail the use of directing groups (eq 1).^[8] Moreover, Yu, and later Shi and Cheng groups, reported a hydroxyl-directed Pd-catalyzed C–H carbonylation reactions of arenes leading to lactones and coumarins (eq 2 and 3).^[9] Since no general and selective methods for conversion of phenols into SAs exist (*vide supra*), we thought that development of such methodology is highly justified. Previously, our group developed silanol as a powerful traceless directing group^[10] for Pd-catalyzed *ortho*-alkenylation^[10a] and oxygenation^[10b] of phenols. Hence, we hypothesized that if the phenoxy silanol could undergo a Pd-catalyzed carbonylation reaction to generate intermediate *i*, the latter, upon a routine desilylation, would produce SAs in a regioselective manner from accessible phenols (Figure 1, path D).^[11]

(1)

(2)

(3)

We initially tested the carboxylation reaction of **1b** under Yu's modified procedure.^[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'** under the carboxylation conditions, along with the cleanness of the reaction encouraged us to focus on optimization studies. It was found that only trace amounts of product were detected in a control experiment without ligand (entry 2). Accordingly, we screened different MPAA ligands in this reaction. Notably, product yield increased to 37% with Ac-Val-OH as a ligand (entry 3), among many other ligands tested (entries 4 – 6, also see Supporting Information for the complete screening), Boc-Leu-OH exhibited the best reactivity, producing **2b'** in 90% yield (entry 6). Screening

other experiment parameters indicated that reducing palladium amount to 5 mol % had a deleterious effect on the yield (entry 7), and no carboxylation occurred in the absence of palladium (entry 8). Other oxidants and solvents were also examined. Cu(OAc)₂, BQ and O₂, which are commonly used oxidants in C–H functionalization, were ineffective (entries 9 – 11). Solvents other than DCE gave poorer results (entries 11 – 13).

Under the optimized conditions for carboxylation, followed by a routine desilylation step, silanol **1a** was converted into salicylic acid **2a** in 76 % yield (Table 1, entry 1). Substrates with electron donating groups produced the corresponding SAs (**2b**, **2c**, **2e**, **2h**) in good to excellent yields; whereas, those possessing electron neutral and deficient substituents generated products (**2d**, **2j**, **2i**) in slightly diminished yields. Remarkably, a number of useful functionalities, including ester (**2s**), nitrile (**2t**), aryl chlorides (**2g**, **2k**), alkyl chloride (**2u**), cyclopropyl (**2r**), and ketone (Scheme 2, **2w**) were tolerated under the reaction conditions. Notably, only desired products were isolated when other potential directing groups, such as methoxy- and acetoxo groups, were present (**2e**, **2f**, **2p**, **2q**).^[12] In the event where the silanol precursor contained two possible reactive sites, C–H carboxylation occurred preferentially at the sterically less demanding position (**2l-p**). Bis-silanol derivative **1v** produced mono-acid **2v** in excellent yield. Evidently, the newly installed carboxylic group electronically deactivates the aromatic ring thus preventing the second C–H carboxylation event. Importantly, substrates possessing a sensitive cinnamyl group at *para*- and *meta*-positions (**1w**, **x**) were also competent reactants producing the corresponding salicylic acids **2w**, **x** in reasonable yields. Likewise, carbazole derivative **1y** reacted smoothly to give **2y** in 64% yield. In contrast, ester-possessing phenol **1z** was much less reactive under these conditions (entry 26), whereas strongly electron-deficient 3-NO₂- and 4-CN-substituted phenols did not react at all. Notably, this method tolerates substituents at the *ortho* position, as demonstrated by carboxylation of **2h** (Me), **2i** (Ph), **2j** (naphthalene) and **2k** (chloro). This is in sharp contrast with our previous report on the silanol-directed C–H olefination reaction, which showed no reactivity toward substrates possessing substituents at the *ortho* position.^[10a]

Next, we were eager to clarify the reaction pathway. Hence, in our previously developed silanol-directed C–H oxygenation of phenols,^[10b] with the aid of ¹⁸O labeling study, we established that the silanol oxygen was not incorporated into the oxygenated product **C** (Scheme 1, a). Accordingly, we prepared **1b-¹⁸O** and subjected it to our C–H carboxylation reaction conditions. In contrast to the previous report, this study revealed complete retention of ¹⁸O label in the silacycle **2b'** (Scheme 1, b). Therefore, we propose that the key intermediate **D**, which was generated upon C–H activation of **1b** and migratory insertion of CO, undergoes reductive elimination to produce the ¹⁸O incorporated product **2b'-¹⁸O**.^[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 2, a). Considering the importance of multi-substituted phenols in bioactive compounds,^[14] we probed our method toward the synthesis of bis-unsymmetrically functionalized phenolic compound. Hence, after two iterative C–H functionalization operations, olefination^[10a] followed by carboxylation, the desired phenolic

compound **3b** was obtained in good overall yield (Scheme 2, b). To the best of our knowledge, this represents the first example of a stepwise unsymmetrical C–H functionalization of phenols.^[15]

In conclusion, a general method for synthesis of salicylic acids from phenols has been developed. This method features high efficiency, broad substrate scope, and high regioselectivity. Mechanistic study revealed the ester oxygen atom of the carboxylic group originates from silanol group. The feasibility for employment of this method for a late stage functionalization of Moreover, two iterative C–H functionalization reactions, olefination^[10a] and carboxylation, allowed for synthesis of *o,o'*-bis-unsymmetrically substituted phenolic compound. We envision that this approach will become a useful method toward synthesis of salicylic acids from phenols.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Existing Methods: **This work: D** **Figure 1.**

Methods for Synthesis of Salicylic Acid from Phenols.

Scheme 1.
 ^{18}O Labelling Studies.

Scheme 2.

C–H Carboxylation Reaction of Complex Phenols.

[a] $t\text{Bu}_2\text{SiBr}_2$ (1.1 eq.), imidazole (2.2 eq.), DMF, 18 h. Then, NaHCO_3 (aq), r.t., 1 h. [b] $\text{Pd}(\text{OAc})_2$ (10 mol %), Boc-Leu-OH (**L**, 20 mol %), AgOAc (3 eq.), $\text{CF}_3\text{CH}_2\text{OH}$ (3 eq.), CO/Ar (1:8, balloon), DCE (0.25 M), 95 °C, 18 h. Then, TBAF (0.4 mL, 1 M), THF (2 mL), r.t., 30 min. [c] alkene (1.2 eq.), $\text{Pd}(\text{OAc})_2$ (10 mol %), (+)Menthyl(O_2C)-Leu-OH (**L1**, 20 mol %), AgOAc (4 eq.), DCE (0.1 M), 100 °C, 48 h.

Table 1

Optimization of 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(O₂C)-Leu-OH; **L4** = Ac-Leu-OH; **L5** = Boc-Leu-OH.

^[b] GC yield, with ¹³C₁₅H₃₂ as internal standard.

^[c] 5 mol % Pd(OAc)₂ and 10 mol % ligand was used.

^[d] No Pd(OAc)₂.

^[e] O₂ balloon.

Table 2

Scope of Salicylic Acids.^{[a] [b]}

entry	silanol	product	yield, %
1			76
2			91
3			92
4			65
5			80
6			71

entry	silyl enol ether	product	yield, %
7			49
8			89
9			63
10			66
11			45

entry	silanol	product	yield, %
12			85[c]
13			98[d]
14			99
15			92
16			57
17			69
18			77

entry	silanol	product	yield, %	
19			76	
20			81	
21			79	
22			91	
23			62	
24			66	
25			64

entry	silanol	product	yield, %
26			(14) ^[e]

^[a] Reacton conditions: Silanol **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 eq.), CF₃CH₂OH (0.6 mmol, 3 eq.), CO/Ar (1:8, balloon), DCE (0.8 mL, 0.25 M), 95 °C, 18 h. See Supporting Information for details.

^[b] isolated yield.

^[c] major : minor = 2 : 1.

^[d] major : minor = 4 : 1.

^[e] NMR yield of silacycle after the first step.