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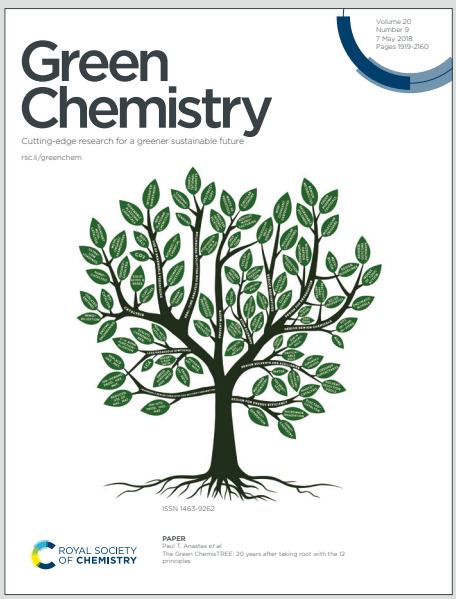

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ARTICLE

Catalytic O-H Bond Insertion Reactions Using Surface Modified Sewage Sludge as Catalyst

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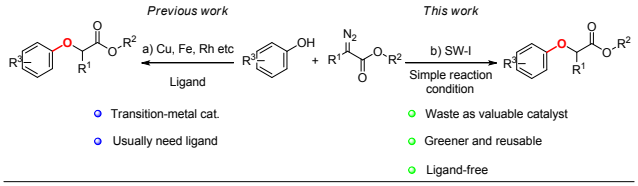
Developing greener, sustainable catalyst is very important but challenging task in organic synthesis. Herein, for the first time, we choose more economically and greener surface modification of sewage sludge-derived carbonaceous materials (SW) by perchloric acid as new catalyst for carbene insertion of α-aryl α-diazoacetates into O-H bond of phenols with good yields and high functional group tolerance. Significantly, we explored the scope of natural phenols with compelling biological activity, successfully afforded the O-H insertion and *meta* C-H functionalization products. Their structures have been confirmed by single-crystal X-ray crystallography. Further, the bioactivities (anti-tumor and anti-inflammatory) of majority O-H insertion products are better than the natural phenols themselves. The IC_{50} values indicated that the remarkable compounds **7a** (IC_{50}=16.80 μM) and **7c** (IC_{50}=16.48 μM) had better inhibition for tumor cell A-549 than positive control **DDP** (IC_{50}=20.62 μM). It should be noted that these transformations may provide a new strategy to derivative natural products and discover new drugs.

Introduction

Sewage sludge is an inevitable by-product during wastewater treatment, which exists in cities around the world and causes major handling and disposal environmental problems.[1] Carbonization of sewage sludge under the pyrolysis to produce sewage sludge-derived carbonaceous materials (SW) has been a sustainable strategy for beneficial use of sewage sludge, because of its low cost, environmentally friendly and catalytically active characteristics[2] which could reduce sewage sludge and turn solid waste into useful material for environment remediation. Significantly it also provides adsorbents for air pollution, organic pollutants and heavy metals, as catalysts for degradation of organic wastewater (like catalytic wet air oxidation (CWAO), catalytic ozone oxidation and Fenton-like oxidation), and it could even be used for preparing of surfactants, microplastics, sewage sludge biochar (SSBC) and nanoparticles.[3] However, the use of SW as catalysts for organic synthesis have not been reported. Thus, we wondered if SW can be used as a carrier to prepare a low-cost and high-activity catalyst for organic synthesis, it will have broad application prospects. With this context, the study of SW catalyzed O-H insertion of phenols with diazo compounds will carry out.



Scheme 1. Transformations of phenols with diazo compounds

Diazo compounds are widely used and essential reactive substrates which can achieve a series of transformations, such as X-H insertion (X = O,[4] N,[5] S,[6] Si,[7] B[8] etc.), C-H bond functionalization,[9] alkene cyclization,[10] ylide formation[11] and catalytic asymmetric dearomatization (CADA) reactions.[12] Among these transformations, O-H insertion is more favorable in the presence of various transition-metal catalysts. Like Iron complexes of spiro-bisoxazoline ligands,[13] Copper salts or Copper complexes,[14] Palladium complexes with chiral spiro-bisoxazoline ligands,[15] Rhodium complexes,[16] Ruthenium complexes.[17] Furthermore, Burtoloso's groups recently reported that perchloric acid could also be used for O-H insertion of alcohols with diazo compounds.[18] So far, transition-metal catalytic insertion of diazo compounds into O-H bond has been a useful and efficient method for C-O bond formation and constructing complex chemical molecules,[14a] but complex ligands are often required. This work, the waste will be as valuable catalyst for carbene insertion into O-H bond of phenols under mild reaction conditions (Scheme 1). (See the SI for details, SW treated by $HClO_4$, HCl, H_2SO_4, H_3PO_4, HNO_3 and NaOH respectively, we called SW-Ⅰ ($HClO_4$), SW-Ⅱ (HCl), SW-Ⅲ (H_2SO_4),

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SW-Ⅳ (H_3PO_4), SW-Ⅴ (HNO_3) and SW-Ⅵ (NaOH);[2c] Common soil treated by $HClO_4$ and Cu-loaded SW, we called Soil-Ⅰ ($HClO_4$) and SW-Cu).[2c]

Phenols are widely discovered in natural products and pharmaceutics, with their low price and wide availability as well as common versatile synthons in organic chemistry.[19] Yet, the Zhou[12,14a,15] and Zhang,[16] Shi[20] groups have developed elegant methods for O-H bond insertion and C-H bond functionalization of phenols, but usually requires complex ligands. In this work, ligand-free, SW-Ⅰ will be used as catalyst for insertion of *α*-aryl *α*-diazoacetates into the O-H bond of phenols, which provides a reliable and efficient method for the preparation of α-aryl-α-aryloxyacetates **3** with good yields under simple reaction conditions. The phenoxypropionate functionality is ubiquitous in pharmaceuticals (MBX-102, clofibrate),[21] pesticide (diclofopmethyl),[22] biologically active compounds (GSK183390A),[23] or as a chiral solvating agent for NMR spectroscopy [15,24] (Fig. 1).

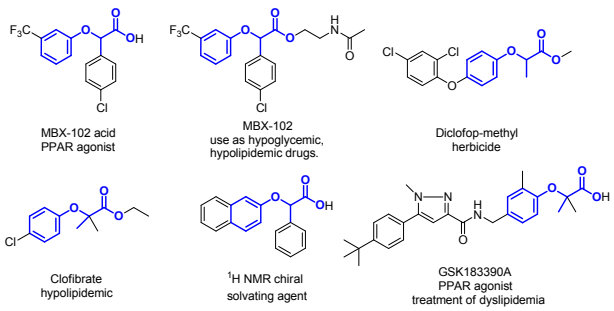

Fig. 1 Phenoxyacetate group in biologically active compounds

Herein, we first showed that more economically and greener surface modification of SW treated by perchloric acid (SW-Ⅰ) as new catalyst for O-H insertion reaction of phenols with good yields and high functional group tolerance. A gram-scale reaction and the synthesis of biologically active compound MBX-102 acid (a PPAR agonist) further enhanced the overall practical utility and demonstrated the potential value of the catalyst. It may provide an alternative strategy for the selection of catalysts in organic chemistry. Notably, natural phenols were also applicable in this catalytic model of SW-I, affording the O-H insertion and C-H functionalization products. The results of anti-tumor and anti-inflammatory bioactivities in vitro showed that the bioactivities of majority O-H insertion products are better than the natural phenols themselves. Moreover, the IC_{50} values indicated that some remarkable compounds showed better inhibition for specific tumor cell than positive control **DDP**. Finally, this work may provide a new strategy for the selection of catalysts in organic chemistry, even for the derivatization of natural products and drugs discovery.

Results and discussion

SW-catalyzed O-H insertion reaction. In this work, the reaction of ethyl 2-diazo-2-phenylacetate **1a** with phenol **2a** was selected as a prototype reaction (Table 1). We found that the formation of **3a** hardly occurred in the absence or presence of SW in DCE at 70 °C (entries 1-2). A variety of SWs (SW-Ⅱ-SW-Ⅴ) produced the desired O-H insertion product **3a** (entries 4-7) with lower yield (less than 15%). Ligand-free, even if SW-Cu (Cu

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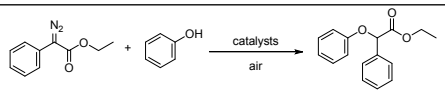
Table 1. Screening the optimum conditions for the synthesis of **3a**.[a]



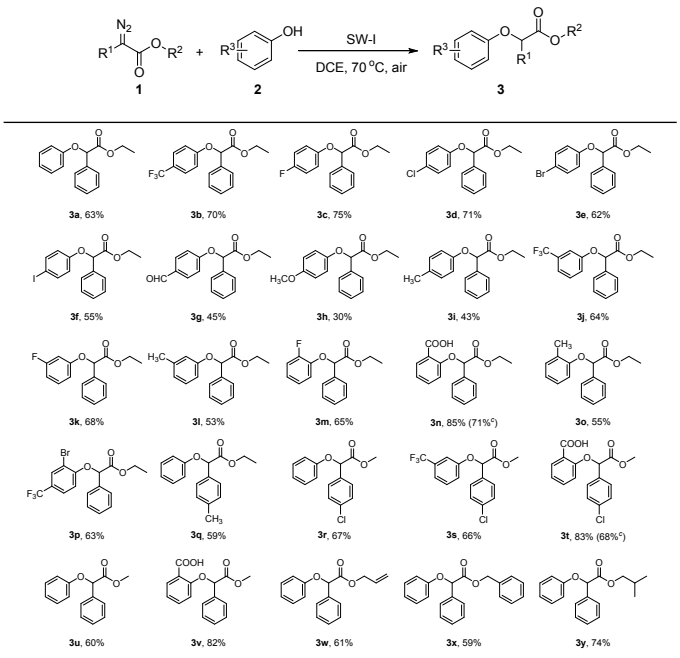
1a 2a 3a

Entry	Catalyst	**1a**:**2a** (equiv)	Solvent	Temp. (°C)	Yield[b] (%)
1	—	1:1.5	DCE	70	trace
2	SW[c]	1:1.5	DCE	70	8
3	SW-Ⅰ[c]	1:1.5	DCE	70	87
4	SW-Ⅱ[c]	1:1.5	DCE	70	10
5	SW-Ⅲ[c]	1:1.5	DCE	70	13
6	SW-Ⅳ[c]	1:1.5	DCE	70	12
7	SW-Ⅴ[c]	1:1.5	DCE	70	10
8	SW-Cu[c]	1:1.5	DCE	70	71
9	Soil-Ⅰ[c]	1:1.5	DCE	70	70
10	$HClO_4$[d]	1:1.5	DCE	70	64
11	SW[c]+$HClO_4$[d]	1:1.5	DCE	70	75
12	SW-Ⅰ	1:1.5	DCE	70	94
13	SW-Ⅰ[e]	1:1.5	DCE	70	89
14	SW-Ⅰ	1:1.5	DMF	70	16
15	SW-Ⅰ	1:1.5	Toluene	70	26
16	SW-Ⅰ	1:1.5	1,4-dioxane	70	31
17	SW-Ⅰ	1:1.5	CH_3CN	70	35
18	SW-Ⅰ	1:1.5	DCE	60	70
19	SW-Ⅰ	1:1.5	DCE	reflux	47
20	**SW-Ⅰ**	**1:1.6**	**DCE**	**70**	**95(63[f])**
21	SW-Ⅰ	1:1.7	DCE	70	95
22	SW-Ⅰ	1:1.4	DCE	70	94
23[g]	SW-Ⅰ	1:1.6	DCE	70	90(54[f])

[a]Conditions: **1a** (0.5 mmol), **2a**, catalyst (50 mg), solvent (5 mL), 0.1 MPa air, 4 h; symbol "-" means no catalyst. [b]GC yield with mesitylene as the internal standard. [c]75 mg. [d]$HClO_4$ (3 μL). [e]25 mg. [f]Isolated yield given in parentheses. [g]Catalyst recycling, 7 h.

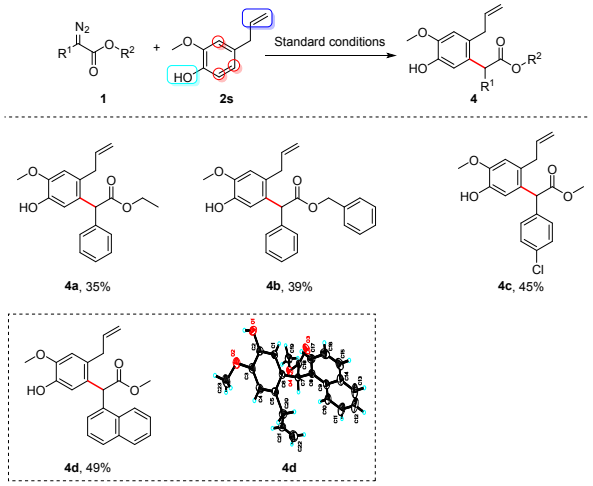
-loaded SW) was used as a catalyst also could not give satisfactory yield (entry 8). By contrast, when SW-Ⅰ (SW treated by $HClO_4$) was used as a catalyst could markedly improve the yield up to 87% in DCE at 70 °C for 4 h (entry 3). It should be noted that no additional transition-metal-catalyst and ligand were required—the reaction proceeded simply by heating both reagents in DCE and SW-Ⅰ. To learn more about this catalytic system, other factors will be considered (entries 9-11). When Soil-Ⅰ (common soil treated by $HClO_4$) was used as a catalyst could improve the yield of **3a** to 70% (entry 9), but lower than SW-Ⅰ. Based on the characterization and comparison of the Soil catalysts and SW-Ⅰ (see the SI for more details), we could infer that the elements and surface structure might be the main factors due to the difference catalytic activity of this two catalysts. Further, when $HClO_4$ was used, the yield could be improved to 64% (entry 10), and the result was supported by the article that $HClO_4$ could be used for O-H insertion of alcohols.[18] Whatsmore, when SW and $HClO_4$ were

directly added together, the yield of **3a** up to 75% (entry 11) , which higher than $HClO_4$, but also lower than SW-Ⅰ. The results revealed that $HClO_4$ or SW and $HClO_4$ simply mixed together could not give the satisfactory yield, but SW-Ⅰ (SW has been surface modified by $HClO_4$) could do it, which further indicated the importance of SW surface modification to the reaction. Meanwhile, the above result motivated us to screen the other reaction variables (entries 12-19), the yield was improved to 94% when the amount of the catalyst was reduced to 50 mg (entry 12). However, the amount was reduced continuously to 25 mg did not improve the yield (entry 13). Then, a solvent screen showed that DCE is best for this transformation (entry 12). The reaction also proceeds at lower or higher temperatures (entries 18-19), but with a noticeable decrease in the percentage conversions. Moreover, increasing the quantity of **2a** (1.6 equiv) could improve the yield to 95% (isolated yield: 63%, entry 20), and the further increase of **2a** equivalents did not improve yield (entry 21). However, the yield was slightly decreased when the amount of **2a** was reduced (entry 22). Based on the above results (see the SI for more details: Table S1), the optimum conditions for the O-H insertion reaction were identified as DCE at 70 °C for 4 h, SW-Ⅰ (50 mg) as catalyst, **1a**:**2a** (equiv = 1:1.6, entry 20). To our delight, the catalyst could be reused and give the desired product **3a** in 90% yield (isolated yield: 53%, entry 23, see the SI for more details).



Scheme 2. Substrate scope of O-H insertion reactions[a,b,c]. [a]Conditions: **1** (0.5 mmol), **2** (0.8 mmol), SW-Ⅰ (50 mg), DCE (5 mL), 70 °C ,0.1 MPa air, 4-24 h. [b]Isolated yields. [c]CH_3CN as the solvent (5 mL).

The scope of the reaction under the optimized conditions was studied using a set of diazo compounds **1** and phenols **2**, the results are summarized in Scheme 2. Significantly, a wide range of phenols were compatible, affording the desired O-H insertion products in moderate to good yields. For example, a series of *para*-substituted groups, electron-withdrawing groups gave the products in moderate to good yields (**3b**, **3g**), whereas electron-donating groups inhibited the transformation (**3h**, **3i**); halide groups (F, Cl, Br and I) were compatible, providing the products in good yields (**3c**-**3f**). Meanwhile, a series of *meta*-substituted and *ortho*-substituted phenols also afforded the corresponding products in moderate to excellent yields (**3j**–**3o**). Formation of the **3k** (68%), **3m** (65%) and **3l** (53%), **3o** (55%) indicated that steric hindrance had no obvious effect on the yield of the reaction. To our delight, *ortho*-carboxy substituted phenol **2n** (salicylic acid) could work well to give corresponding product in excellent yield (**3n**). Interestingly, CH_3CN could be used as the greener solvent and give the desired product **3n** in good yield (71%). In addition, polysubstituted phenol was also tolerated (**3p**). To further examine the robustness of this O-H insertion reactions, we evaluated a series of diazo compounds under the optimal reaction conditions. The results showed that electron-abundant and deficient α-aryl-α-diazoacetates were usable in the O-H insertion, furnishing the products (**3q**-**3t**) in good to excellent yields (59-83%). When CH_3CN was used as the greener solvent, furnishing the corresponding product **3t** in good yield (68%). Moreover, other esters such as methyl, allyl, even benzyl and isobutyl ester variants were also compatible and afforded the products (**3u**-**3y**) in good to excellent yields (59-82%).

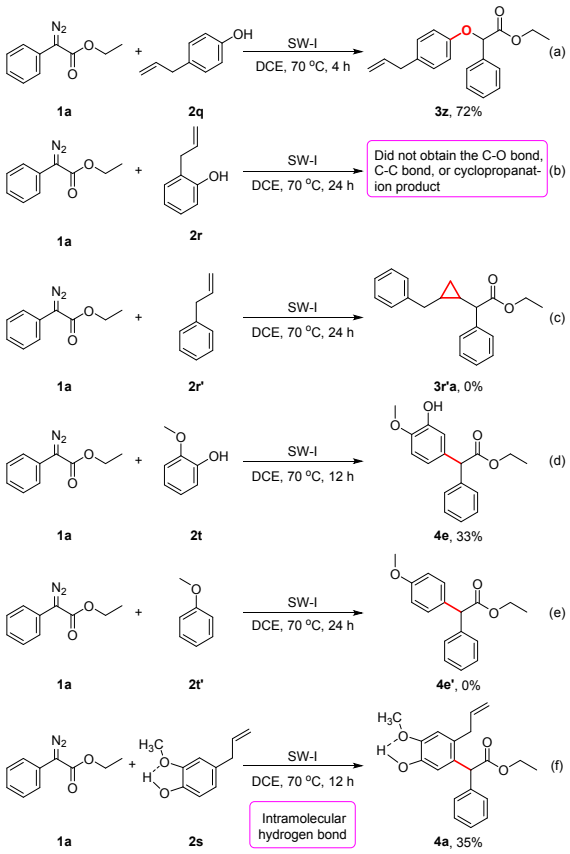


Scheme 3. *Meta* C-H bond functionalization of diazo compounds **1** with natural phenol **2s**[a,b]. [a]Conditions: **1** (0.5 mmol), **2s** (0.8 mmol), SW-Ⅰ (50 mg), DCE (5 mL), 70 °C, 0.1 MPa air, 12-24 h. [b]Isolated yields.

With its rich structural diversity, complexity and broad biological activities, natural products have inspired numerous innovations in synthetic chemistry, many drugs used today are natural products or natural product derivatives.[25] Herein, our aim is to select natural phenols of compelling biological activity and then attempt to insertion into O-H bond in such compounds bearing multiple functional substituents. With the optimal reaction conditions in hand, we next investigated the scope of natural phenols. Such as eugenol[26] **2s** (a phytogenic bioactive phenolic component, which could be used for inflammation, hyperglycemia and antimicrobial),[27] magnolol[28] **5a** and honokiol[29] **5b** (numerous recent studies have shown that they are used clinically for anti-microbial, anti-inflammatory, anti-

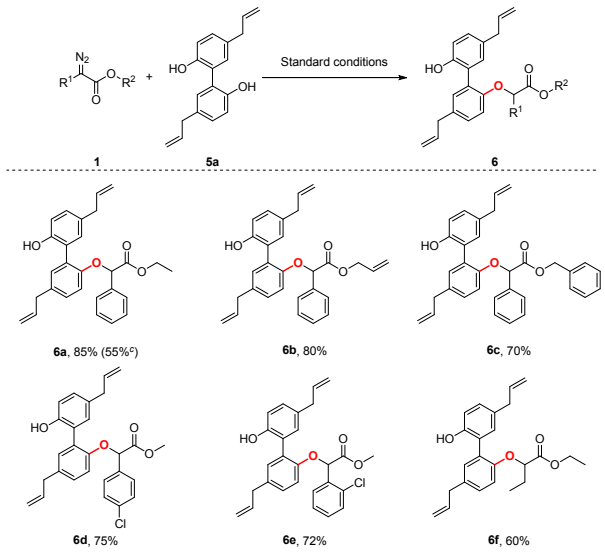
oxidative, anti-tumorigenic, anti-diabetic, anti-anxiety, anti-depressant properties and anti-neurodegenerative).[30] These selected natural phenols which all equipped with an allyl substituent, which might achieve a series of transformations, such as O-H insertion, C-H bond functionalization or alkene cyclopropanation.

The reactions of various substituted diazo compounds with eugenol **2s** were examined, as shown in Scheme 3. The structure of **4d** was confirmed by single-crystal X-ray crystallography (see Fig. S3, Supporting Information). It should be noted that the reactions afforded the *meta* C-H bond functionalization products (**4a**-**4d**) without formation of product via cyclopropanation or O-H insertion, indicating that this SW-I catalyst prefers to promote the C-H bond functionalization rather than the cyclopropanation of an alkene and the O-H insertion.



Scheme 4. Control experiments (to know the reason for C–H bond functionalization of eugenol **2s**, see the SI for more details).

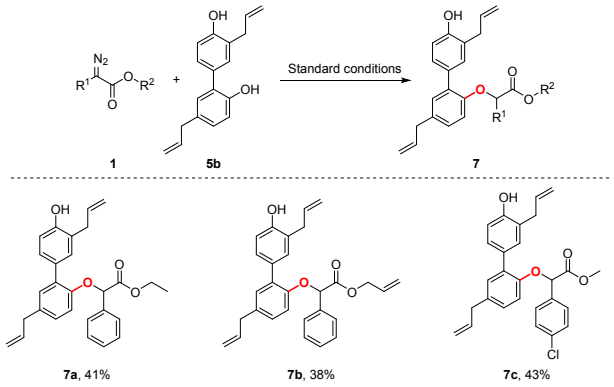
To gain further insight into the reason of the C-H bond functionalization, several control experiments were carried out under the optimal reaction conditions (Scheme 4). As shown in Scheme 4a, the use of *para*-allylphenol **2q** could furnish the desired O-H insertion product **3z** without formation of product via cyclopropanation or C-H bond functionalization. However, *ortho*-allylphenol **2r** did not give the product of O-H insertion, C-H bond functionalization or cyclopropanation (Scheme 4b). The results suggested that a remarkable substituent effect of allyl might work on the formation of O-H insertion product. Meanwhile, allylbenzene **2r'** (Scheme 4c) also could not provide cyclopropanation product, which revealed that might due to the lower selectivity of SW-I for cyclopropanation than O-H insertion. Then, the cyclopropanation of an alkene was more difficult to achieve than O-H insertion. Fascinatingly, when *ortho*-methoxyphenol **2t** was employed, C-H bond functionalization product **4e** could be isolated, without formation O-H insertion product (Scheme 4d), but *ortho*-methylphenol **2o** could provide the O-H insertion product **3o** instead of the C-H bond functionalization product (Scheme 2). Then we surmised that the oxygen of methoxy in eugenol might due to its strong electronegativity, SW-I easy to activate the C-H bond. Unfortunately, anisole **2t'** did not afforded the C-H bond functionalization product **4e'** (Scheme 4e). Thus, we inferred that the C-H bond functionalization product of eugenol may due to the result of intramolecular hydrogen bond between methoxy and hydroxyl,[31] which probably led SW-I to easily activate the C-H bond of eugenol (Scheme 4f). Significantly, *para*-methoxyphenol **2h** had no possibility of forming an intramolecular hydrogen bond,[31b] and it furnished the product of O-H insertion **3h** instead of C-H bond functionalization (Scheme 2), which could also demonstrate our inference that the intramolecular hydrogen bond probably led SW-I to easily activate the C-H bond of eugenol. Moreover, in eugenol the intramolecular hydrogen bond protects the hydroxyl group against strong intermolecular interactions,[31a,32b] and this might reveal that why did not give the O-H insertion product.



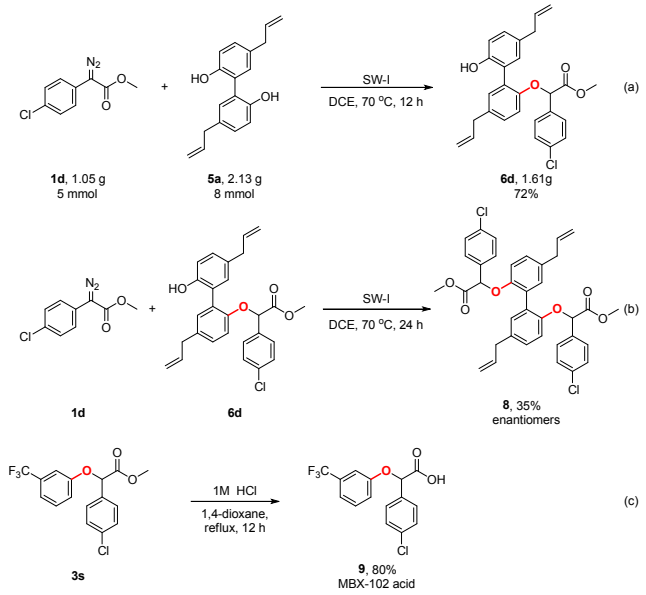
Scheme 5. O-H insertion of diazo compounds **1** with natural phenol **5a**[a,b,c]. [a]Conditions: **1** (0.5 mmol), **5a** (0.8 mmol), SW-I (50 mg), DCE (5 mL), 70 °C, 0.1 MPa air, 4-12 h. [b]Isolated yields. [c]CH_3CN as the solvent (5 mL).

The reactions of various substituted diazo compounds with magnolol **5a** were then explored, as shown in Scheme 5. Under the standard conditions, the reactions proceeded smoothly and gave good to excellent yields (60-85%) of the desired O-H insertion products (**6a**-**6f**). When CH_3CN was used as the solvent, affording the O-H insertion product **6a** in moderate yield (55%).

The structure of **6d** was confirmed by single-crystal X-ray crystallography (see Fig. S4, SI). This result also agreed that *para*-allylphenol furnished corresponding O-H insertion product **3z** without formation of product via cyclopropanation or C-H bond functionalization (Scheme 4a). It should be noted that aside from α-aryl diazo esters, even α-alkyldiazo esters (ethyl 2-diazobutanoate **1f**) could also be used in this transformation and gave the O-H insertion product **6f** in good yield (60%). As well as honokiol **5b**, the reactions of various substituted diazo compounds summarized in Scheme 6. The honokiol might due to the steric hindrance, providing the O-H insertion products in reduced yields (**7a**-**7c**). The molecular structures of the target products of type **7** could be also confirmed by the control experiments that *para*-allylphenol could give the O-H insertion product **3z**, but *ortho*-allylphenol could not afford the O-H insertion product (Scheme 4a and 4b).



Scheme 6. O-H insertion of diazo compounds **1** with natural phenol **5b**[a,b]. [a]Conditions: **1** (0.5 mmol), **5b** (0.8 mmol), SW-Ⅰ (50 mg), DCE (5 mL), 70 °C, 0.1 MPa air, 12-24 h. [b]Isolated yields.



Scheme 7. A gram scale reaction and transformations of O-H insertion products.

To evaluate the scalability of SW-Ⅰ catalyzed O-H insertion reaction, a gram-scale reaction of 1.05 g of **1d** and 2.13 g of **5a** was carried out with a much lower catalyst loading (500 mg) under the optimized reaction condition, affording 1.61 g of the desired product **6d** in 72 % isolated yield (Scheme 7a). In addition, the hydroxyl of **6d** is another versatile group for further transformation. Here, diazo compound **1d** successfully insertion into O-H bond of **6d** and gave the enantiomers product **8** in 35% yield, achieving the secondary O-H insertion of natural phenol **5a** (Scheme 7b). It should be noted that these products could be regarded as versatile precursors to synthesize useful bioactive compounds. Such as the hydrolysis of methyl 2-(4-chlorophenyl)-2-(3-(trifluoromethyl) phenoxy) acetate (**3s**) in acidic media produced MBX-102 acid **9** (Scheme 7c), a PPAR agonist.[4f,21a]

Mechanism researches. Since a precise reaction mechanism of SW-Ⅰ-catalyzed O-H insertion reaction is unclear. At the beginning of the experiments, we wondered whether the breaking of the phenolic O-H bond and H^+ migration were related to hydrogen bonding interactions. With this mind, NMR titration experiments were carried out.[32] The results showed that the single ^{1}H resonance of phenol was shifted downfield when more SW-Ⅰ was mixed (Fig. 2a-c), further indicating that the predominant interaction between phenol and SW-Ⅰ was hydrogen bonding. Thus, we hypothesized that the O-H insertion reaction of phenol probably due to the hydrogen bond between SW-Ⅰ and the hydroxy group. To our delight, the hypothesis also can be supported by the results that anisole did not provide the C-O bond or C-C bond product (control experiments: Scheme 4e). To further demonstrate that the O-H insertion reaction of phenol was not caused by the protonation of $HClO_4$ in this SW-Ⅰ catalytic system. Then, NMR titration experiments of different acids were carried out (see the SI for details: Fig. S6). The results showed that the single ^{1}H resonance of phenol was shifted upfield when HCl or $HClO_4$ was added. Compared with SW-Ⅰ, it just shifting in the opposite direction, which further supported that the O-H insertion reaction of phenol might cause by hydrogen bond between SW-Ⅰ and phenol in this catalytic system. Further, based on the results of NMR titration experiments of SW-Ⅰ and acids, we wondered if the SW-Ⅰ might act as a Lewis or Bronsted base. Then, NMR titration experiments of different bases were carried out (see the SI for details: Fig. S7). The results revealed that the single ^{1}H resonance of phenol was shifted downfield when NEt_3 or NaOH was added. The single ^{1}H resonance of phenol was shifted in consistent with SW-Ⅰ, which all could be shifted in the opposite direction with acids. The results supported our hypothesis that SW-Ⅰ might act as a Lewis or Bronsted base.

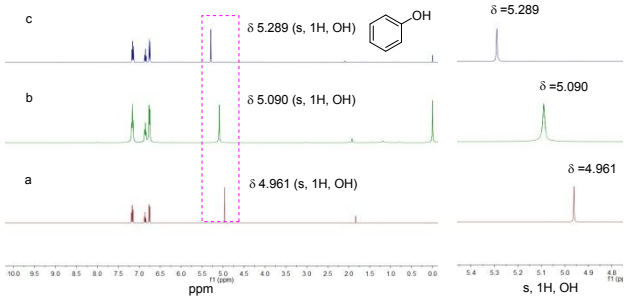
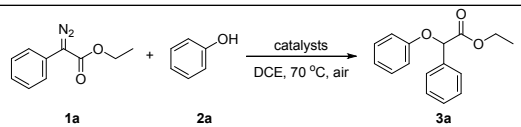


Fig. 2 ^{1}H NMR spectra of the phenol signals in $CDCl_3$ (a) phenol. (b) Phenol (0.3 mmol) with SW-Ⅰ (20 mg). (c) Phenol (0.3 mmol) with SW-Ⅰ (40 mg)

To gain mechanistic insight, we should get a better understanding of SW catalysts. XRF (X-ray fluorescence) was used to analyze the element content of SW catalysts (see the SI for details: Table S6). We found that large amount of SiO_2 and Al_2O_3 are contained in SW-Ⅰ. Apart from C and Cl atoms, the traditional-metals Fe and Cu which could be used for O-H insertion reaction also in it. As well as other metals, like Zn, Mn, Mg etc. Further, HRTEM (high resolution transmission electron microscope) and SEM (scanning electron microscopy) gave the overall image (see the SI for details: Fig. S8aⅡ) and microscopic morphology (Fig. S8bⅡ) of SW-I, presenting the particle and roughness surface. HAADF-STEM (high-angle annular darkfield scanning transmission electron microscopy) and EDS mapping images of the bright dot indicate that C, O, Al, Cl and Fe atoms are homogeneously distributed within the whole granule of SW-I (Fig. S8cⅡ). The O and Cl atoms could be found in SW-I suggested that the ClO_4^- may exist, which agreed that SW-Ⅰ was prepared with SW treated by $HClO_4$. We wondered whether this transformation followed the general mechanism of metal carbene insertion reaction.[4c,10b,11b,33] If some metals are suitable catalysts for this transformation. Next, based on the result of XRF, we have screened the ClO_4^- and part of the major metals in SW-I to find out the potential catalytic sites (Table 2). Meanwhile, the results of NMR titration experiments of SW-Ⅰ and bases revealed that SW-Ⅰ might act as a Lewis or Bronsted base. Therefore, we have also screened different bases (Table 2).

Table 2. Screening of catalytic sites for **3a**.[a]



1a 2a 3a

Entry	Catalyst	Wt (mg)	Yield[b](%)
1	Al_2O_3	7.05	62
2	Fe_2O_3	1.15	64
3	$FeCl_3$	1.15	71
4	$FeCl_2$	1.15	60
5	$CuCl_2$[c]	1.0	57
6	$MnCl_2$[c]	1.0	51
7	$ZnCl_2$[c]	1.0	60
8	$NaClO_4$	1.90	70
9	$NaClO_4$+ Al_2O_3	1.90+7.05	63
10	$NaClO_4$+ Fe_2O_3	1.90+1.15	65
11	$NaClO_4$+$FeCl_3$	1.90+1.05	73
12	Al_2O_3+ Fe_2O_3+ $FeCl_3$+ $FeCl_2$+$MnCl_2$+$ZnCl_2$+$CuCl_2$	7.05+1.15+1.15 +1.15+1.0+1.0 +1.0	47
13	NaOH	10	65
14	Et_3N	10	51
15	Py	10	61
16	SW-Ⅵ	50	71
17	SW+ NaOH	50+10	68
18[d]	SW-Ⅰ	50	95

[a]Conditions: **1a** (0.5 mmol), **2a** (0.8 mmol), DCE (5 mL), air (1.01 Mpa), 70 °C, 12 h. [b]GC yield with mesitylene as the internal standard. Wt less than 1 milligram are unified in 1 milligram. [d]Reaction for 4 h.

The results showed that the formation of **3a** occurred in the presence of a variety of metals (entries 1-7), $NaClO_4$ (entry 8) or $NaClO_4$ added with other metals together (entries 9-11), but the yield lower than SW-Ⅰ (entry 18). However, the yield was reduced when all metals added together (entry 12). The above results showed that various metals could successfully catalyzed O-H insertion reaction. This led us to speculate that a preferred multi-component cooperatively catalytic action might presence in this SW-Ⅰ catalytic system, but not means all metals worked together could provide excellent yield. Interestingly, besides Fe[13] and Cu[14] which could be used as catalyst for carbene insertion into O-H bond of phenol (entries 2-5). The other metals like sodium, zinc, manganese and aluminium salts could also give the positive results (entries 1, 6-8), but those metals are not good to generate metal carbenes. We wondered whether the results could be caused by SW-I, which might act as a Lewis or Bronsted base. With this mind, we have screened different bases (entries 13-15), the positive results supported our inference. Whatsmore, when SW-Ⅶ (entry 16, SW treated by NaOH) or SW and NaOH (entry 17) was added, the yield could be improved. but also lower than SW-I (entry 18). The results also revealed that SW-I might act as a base, causing the reaction.

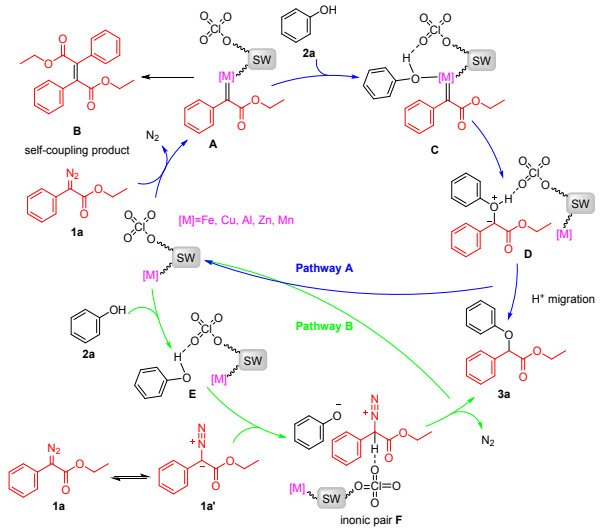


Fig. 3 Proposed mechanism. (The wavy bond between [M] and SW-Ⅰ means [M] (various metals) are attached to the surface of SW-Ⅰ).

Combined with the above results, two plausible mechanisms were proposed for the formation of **3a** (Fig. 3). Pathway A: at the beginning of the reaction, when the SW-Ⅰ was added, diazo compound **1a** will release nitrogen and form metal-carbene **A**. Then, the highly active metal-carbene **A** inserted into O-H bond of **2a** to give the intermediate **C** and self-coupling product **B**[34] (see the SI for details). Because the breaking of metal-carbon bond, the intermediate **D** was formed. Might due to the hydrogen-bonding between SW-Ⅰ and O-H bond or deprotonation of O atom,[35] H^+ easy

to migrate and afford the O-H insertion product **3a**, releasing SW- I and achieving catalytic cycle. Pathway B: Since the SW- I catalyst might act as a Lewis or Bronsted base, it can enhance the acidity of the phenol. Then, phenol may have the proper acidity to protonate the diazo compound **1a** and form the inonic pair **F**.[36] Next, phenolate ion could attack the protonated diazo, releasing molecular nitrogen as the leaving group, and furnishing product **3a**.

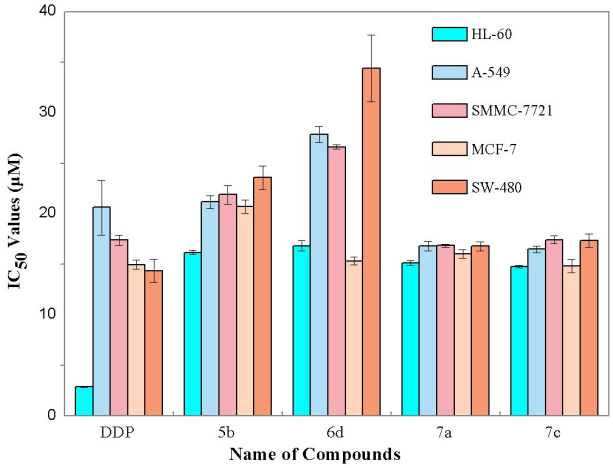


Fig. 4 IC_{50} values of **DDP** and compounds inhibiting the growth of the cancer cells

Study on pharmacological activity. Natural products have been an important role in the drug discovery and development since their wide range of bioactivities, low toxicity and few side effects.[37] Drug-discovery efforts around natural products have been ongoing, diazo compounds successfully insertion into O-H bond of natural phenols (**5a** and **5b**) which might provide a new strategy to derivative natural products and discover new drugs. Herein, to compare the bioactivities of O-H insertion products with natural phenols, compounds **6a**-**6f**, **7a**-**7c** (the O-H insertion products of magnolol **5a** and honokiol **5b**) were evaluated for anti-tumor and anti-inflammatory bioactivities in vitro.

Anti-tumor: in vitro antiproliferative activity assay. The antiproliferative activity in vitro of compounds **5a**, **5b**, **6a**-**6f** and **7a**-**7c** were tested on the tumor cells: HL-60 (leukemia carcinoma cells), SMMC-7721 (liver carcinoma cells), A-549 (lung carcinoma cells), MCF-7 (breast carcinoma cells) and SW480 (colon carcinoma cells) using the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfopheny)-2H-tetrazolium (MTS) assay. Most compounds exhibited moderate to good antiproliferative activity against HL-60, SMMC-7721, A-549, MCF-7 and SW-480 cell lines (see Table S7, Supporting Information).

After comparison of the bioactivity data, compounds **6b**, **6d**, **6e** showed better inhibition for five selected tumor cell lines than compound **5a**. Besides HL-60, compounds **6a**, **6f** showed better inhibition for the others cell lines than compound **5a**. Unfortunately, compounds **6c** showed no distinct inhibition. Compounds **7a** and **7c** (except cell SW-480) had better inhibition for five selected tumor cell lines than compound **5b**, but compounds **7b** had no distinct inhibition. In order to gain anti-tumor insight, compounds **5b**, **6d**, **7a** and **7c** were evaluated by their values of the concentration causing 50% inhibition of cell growth (IC_{50}) of inhibiting the growth of HL-60, SMMC-7721, A-549, MCF-7 and SW-480 tumor cell lines (see Table S8, Supporting Information). Then, compared the IC_{50} values with positive control **DDP** (Fig. 4).

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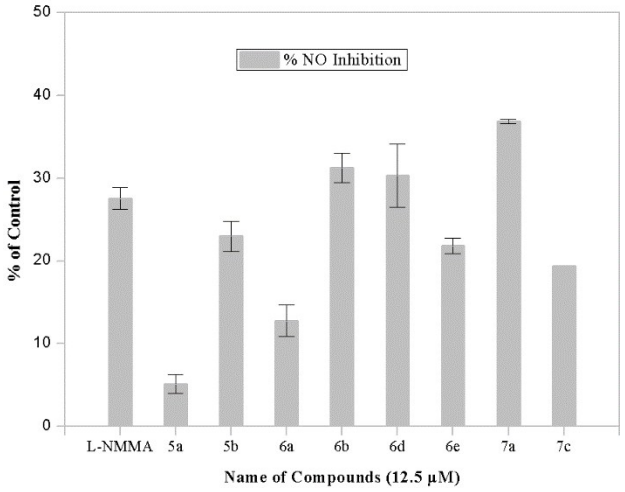

Fig. 5 NO inhibition (%) of compounds at a concentration of 12.5 μM.

For the growth inhibition of the five tumor cell lines, we found that these compounds exhibited effective in vitro anti-proliferation action. The IC_{50} values showed that the in vitro anti-proliferation activities of **6d** is lower than **5b** (besides tumor cell MCF-7). It should be noted that for the five selected tumor cell lines, the in vitro anti-tumor efficacy of **7a** and **7c** are higher than that of **5b**. Moreover, the inhibition of A-549 tumor cell lines, **7a** and **7c** are higher than the positive control **DDP**, **7c** showed highest inhibition than others. Simultaneously **7a** showed slightly better inhibition for tumor cell SMMC-7721 than **DDP**, and **7c** also showed slightly better inhibition for tumor cell MCF-7 than **DDP**. Collectively, our results revealed that **7a** and **7c** (O-H insertion products of honokiol) might become potential novel anti-tumor agents.

Anti-inflammatory: Measurement of Cell Viability and Nitrite. Compounds **5a**, **5b**, **6a**-**6f** and **7a**-**7c** were evaluated for anti-inflammatory activity by using LPS-stimulated RAW 264.7 murine macrophage cells to produce iNOS and trigger NO production. The cells were treated with test compounds at a concentration of 50 μM to 12.5 μM, and then stimulated with LPS (1 μg/mL) for an additional 24 h. Among the compounds tested (see Table S9, Supporting Information), compound **6c** showed weak inhibition (less than positive control **LNMMA**), **6f** and **7b** showed no distinct inhibition on LPS-induced NO production at 50 μM. Compounds **5a**, **5b**, **6a**, **6b**, **6d**, **6e**, **7a** and **7c** exhibited cytotoxicity at a concentration of 50 μM or 25 μM, but did not exhibited cytotoxicity at a concentration of 12.5 μM. Then, evaluated the compounds with cytotoxicity at a concentration of 12.5 μM, and compared the inhibition rate of NO production with positive control (**L-NMMA**) at 12.5 μM. As shown in Fig. 5.

Significantly, compounds **6a**, **6b**, **6d**, **6e** showed inhibition on LPS-induced NO production stronger than **5a**, especially compounds **6b** and **6d** even stronger than positive control **L-NMMA**. Meanwhile, compound **7a** exhibited inhibition of NO production stranger than **5b**

and **L-NMMA** respectively, but compound **7c** showed weak inhibition (less than **5b** and **L-NMMA**). Above results suggested that most O-H insertion products of magnolol and honokiol might have practical value in anti-inflammatory.

Conclusion

In summary, to the best of our knowledge, this is the first example about surface modification of sewage sludge-derived carbonaceous materials by perchloric acid as new catalyst for carbene insertion of α-aryl α-diazoacetates into O-H bond of phenols: mild conditions, good substrate scope, and ease in further transformation. Moreover, natural phenols with compelling biological activity were also applicable in this catalytic system, affording the O-H insertion and C-H functionalization products. The test of anti-tumor and anti-inflammatory in vitro showed that the bioactivities of majority O-H insertion products are better than the natural phenols themselves. Further, some remarkable compounds even showed better bioactivities than the positive control, which further indicated that this transformation may provide a new strategy to derivative natural products and discover new drugs.

Experimental

Preparation of SW catalysts.

The surface of SW was modified by different kinds of acids or bases to gain SW catalysts. SW was prepared by using municipal sewage sludge from wastewater treatment plant (WWTP) in China. Sewage sludge was dried to constant weight at 105 °C and carbonized at 600 °C for 4 h under a heating rate of 3 °C min^{-1} and a high purity nitrogen (99.999 wt%) flow of 500 mL min^{-1}. After the furnace had cooled to room temperature, SW was obtained. Different kinds of acids or bases were used to treat the SW. In the acid or base treatment process, 50 mL of SW were produced by immersing carbonized SW with the same volume of $HClO_4$ (35.4 wt%), HCl (20.5 wt%), H_2SO_4 (63.4 wt%), H_3PO_4 (45.4 wt%), HNO_3 (40.5 wt%) and NaOH (39.5 wt%) for 24 h for 24 h, respectively. Then, SW-Ⅰ ($HClO_4$), SW-Ⅱ (HCl), SW-Ⅲ (H_2SO_4), SW-Ⅳ (H_3PO_4), SW-Ⅴ (HNO_3) and SW-Ⅵ were washed with deionized water until the pH of the washing water reached 6-7 and the recovered solids were dried at room temperature. Soil-Ⅰ (common soil treated by $HClO_4$) was prepared by the same method of SW-Ⅰ. SW-Cu (Cu-loaded SW) was prepared via adding 10 g SW to 20 mL of a 0.08 mol/L $CuCl_2$ solution and stirred for 18 h at room temperature, then, after filtrating, the sludge residue was carbonized at 600 °C for 4 h under a heating rate of 3 °C min^{-1}in a high purity nitrogen (99.999 wt%, 500 mL/min) atmosphere. When the furnace was cooled to room temperature, the SW-Cu was obtained.

Catalyst characterization.

X-ray Fluorescence (XRF, Magix 601) was used to analyse the element content in the SW catalysts. The morphology and microstructure of SW-Ⅰ catalyst were examined by scanning electron microscope (SEM, HITACHI S4800), high-resolution transmission electron microscopy (HRTEM, JEOL JEM-2010 UHR) and transmission electron microscopy (TEM, JSM7500F).

General experimental procedures.

A typical procedure for the synthesis of α-diazoesters[38] **(1)** – *Synthesis of **1a***: DBU (2.24 mL, 15 mmol) was added slowly to a stirred solution of ethyl 2-phenylacetate (**sm1a**, 1.59 mL, 10.0 mmol) and tosylazide (**sm2**, 2.42 mL, 11.0 mmol) in the CH_3CN (20 mL) at 0 °C. Then, it was placed in microwave reactor that was heated to 40 °C (400 W, monitored by IR temperature sensor) and maintained at this temperature for 30 min. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl (5 mL), extracted with CH_2Cl_2 (3×30 mL), washed with brine (3×10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the product. The residue was purified by flash chromatography (petroleum ether (60-90 ºC)/AcOEt, 10:1) to afford the corresponding ethyl-2-diazo-2-phenylacetate **1a** as a yellow oil (1.65 g, 87%).

A typical procedure for the synthesis of O-H insertion procedures (3, **6**, **7**, **8)**. *Synthesis of **3a**:* A mixture of SW-Ⅰ (50 mg), phenol (**2a**, 75 mg, 0.8 mmol) and ethyl 2-diazo-2-phenylacetate (**1a**, 95 mg, 0.5 mmol) in DCE (5 mL) was stirred at room temperature under 0.1 Mpa air for 1 h, then the resulting mixture was stirred at 70 °C for 4 h. After filtrating and removing solvent in vacuum the product was purified by flash chromatography with petroleum ether (60-90 ºC)/AcOEt (10:1) to afford the corresponding **3a** as a Colorless oil (80 mg, 63%).

A typical procedure for the synthesis of C-H insertion procedures (**4**). *Synthesis of **4a**:* A mixture of SW-Ⅰ (50 mg), eugenol (**2s**, 131 mg, 0.8 mmol) and ethyl 2-diazo-2-phenylacetate (**1a**, 95 mg, 0.5 mmol) in DCE (5 mL) was stirred at room temperature under 0.1 Mpa air for 1 h, then the resulting mixture was stirred at 70 °C for 12 h. After filtrating and removing solvent in vacuum the product was purified by flash chromatography with petroleum ether (60-90 ºC)/AcOEt (5:1) to afford the corresponding **4a** as a Colorless oil (57 mg, 35%).

Procedure for anti-tumor: In vitro antiproliferative activity assay. The human tumor cell lines HL-60, SMMC-7721, A-549, MCF-7, and SW-480 were used in the cytotoxic assay. Cells were cultured in RMPI-1640 or DMEM medium supplemented with 10% fetal bovine serum at 37 °C in a humidified atmosphere with 5% CO_2. The cytotoxicity assay was evaluated by the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (MTS) assay. Briefly, cells were seeded into each well of a 96-well cell culture plate. After 12 h of incubation at 37 °C, the test compound (40 μM) was added. After incubated for 48 h, cells were subjected to the MTS assay. Most compounds exhibited moderate to good antiproliferative activity against HL-60, SMMC-7721, A-549, MCF-7 and SW-480 cell lines (Table S7). Then, compounds (**5b**, **6d**, **7a** and **7c**) with a growth inhibition rate of 50% were further evaluated at concentrations of 0.064, 0.32, 1.6, 8, and 40 μM in triplicate, with cisplatin as positive controls. The IC_{50} values were shown in Table S8.

Procedure for anti-inflammatory: Measurement of Cell Viability and Nitrite.

RAW 264.7 cells were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 100 units/mL penicillin, 100 μg/mL streptomycin, 2 mM L- glutamine, and 1 mM nonessential amino acids. Then, cells (4×10^5 cells/well) were seeded and incubated in 96-well culture plates at 37 °C, 5% CO_2 in humidified air for 24 h. test compounds, drug-free group and L-NMMA (positive control) dissolved in 0.1% DMSO, with the final concentrations ranging from 12.5 μM to 50 μM, were added to the plates. Following

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by LPS stimulation (1 μg/mL) for 18 h. NO production in the supernatant was assessed by Griess reagents. The absorbance at 570 nm was measured with a microplate reader (Thermo, Waltham, MA, USA). N^G-Methyl-L-arginine acetate salt (L-NMMA, Sigma), a well-known nitric oxide synthase (NOS) inhibitor, was used as a positive control. The viability of RAW264.7 cells was evaluated by the MTS assay simultaneously to exclude the interference of the cytotoxicity of the test compounds. All samples were assayed in at least triplicate. The NO inhibition (%) of compounds on NO production in LPS-stimulated RAW 264.7 cells were showed in Table S9.

Data availability. The X-ray crystallographic structures for compounds **4d** and **6d** reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), CCDC 1917686 for **4d** and CCDC 1869826 for **6d**. (http://www.ccdc.cam.ac.uk/data_request/cif). The authors declare that all other relevant data supporting the findings of this study are available within the article and its Supplementary Information files.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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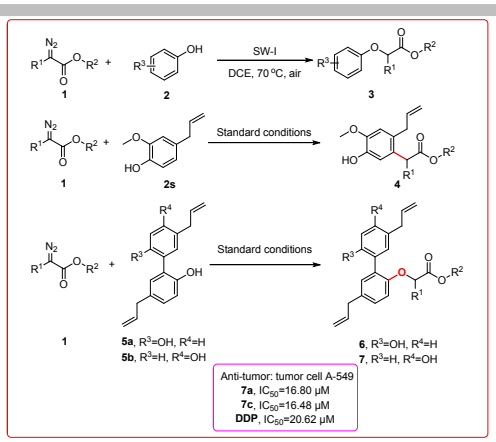
More economically and greener surface modified sewage sludge for carbene insertion of diazo compounds into O-H bond of phenols with good yields and high functional group tolerance. Significantly, natural phenols were also applicable, affording the O-H insertion and C-H functionalization products. The results of anti-tumor and anti-inflammatory bioactivities in vitro showed that the bioactivities of majority O-H insertion products of natural phenols are better than the natural phenols themselves. These transformations may provide a new strategy to derivative natural products and discover new drugs.



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