Palladium-catalyzed 2-(Neopentylsulfinyl)aniline Directed C-H Acetoxylation and Alkenylation of the arylacetamides

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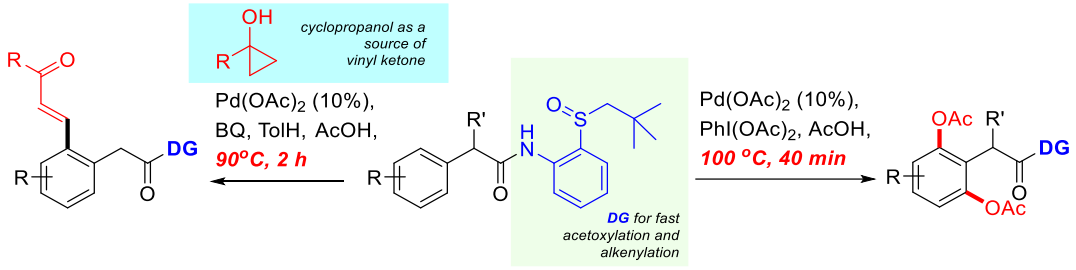


ABSTRACT

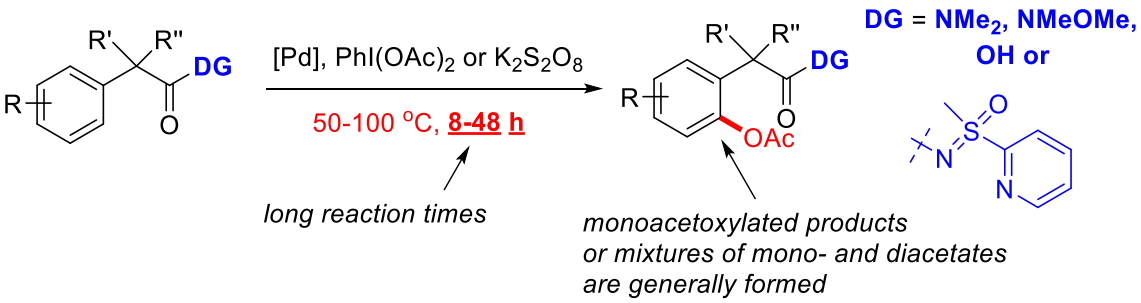
In this article, we report the 2-(neopentylsulfinyl)aniline directing group that promotes rapid palladium-catalyzed C-H acetoxylation and alkenylation of the arylacetamides. The acetoxylation reaches completion within only 40 min at 100 °C and leads to the bis-functionalized products. Alternatively, the reaction can be carried out at room temperature, which is beneficial for sensitive substrates. For the alkenylation with vinyl ketones, we developed a protocol in which easily available 1-substituted cyclopropanols are employed as equivlents of enones.

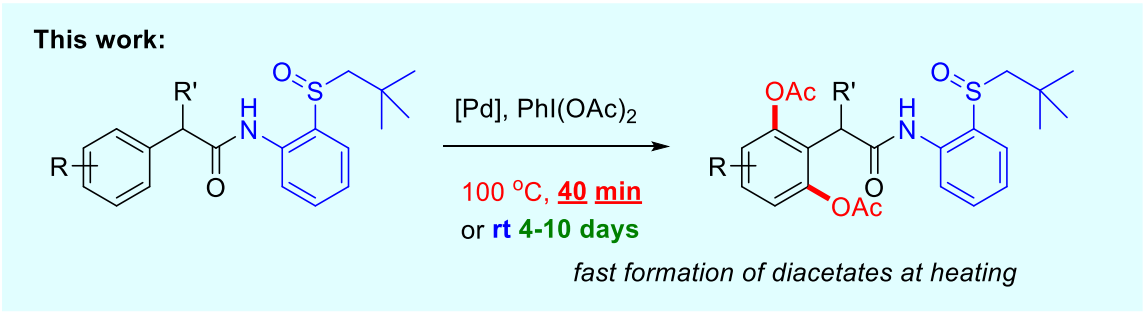
INTRODUCTION

C-H activation is a powerful tool for the functionalization of organic compounds and an important route to pharmaceuticals and natural products.[1] A large number of such transition metal-catalyzed transformations are enabled by directing groups.[2] These coordinating moieties are necessary to achieve a reasonable rate of the reaction and to control its regioselectivity.

However, even in the presence of a directing group, the transition metal-catalysed C-H functionalization requires an elevated temperature and a prolonged reaction time.[1,2] Examples of such transformations proceeding at room temperature or over a short period of time are scarce.[3] Herein, we report the 2-(neopentylsulfinyl)aniline auxiliary that promotes palladium-catalyzed acetoxylation and alkenylation of the arylacetamides with a very high reaction rate. Phenylacetic scaffold is featured in pharmaceuticals and other bioactive compounds.[4] For its functionalization, numerous C-H activation-based methods have been developed including arylation,[5] alkenylation,[6] alkylation,[7] alkynylation,[8] halogenation,[5b, d, 9] acylation,[10] deuteration,[11] lactonyzation[12] and acetoxylation.[5d, 6i, 12b, 13] Generally, the acetoxylation cannot be performed without a directing group and installation of dimethylamine,[13b] Weinreb amine,[6i] S-methyl-S-2-pyridylsulfoximine[13a] or quinolin-8-ylmethylamine[12b] auxiliary is required. Carried out at 50-160 ^{o}C, the functionalization of these arylacetamides reached completion within 8-48 h furnishing monoacetoxylated products or mixtures of mono- and diacetates. We found that in the presence of 2-(neopentylsulfinyl)aniline directing group, the acetoxylation proceeds within only 40 min at 100 ^{o}C giving diacetoxylated products. Previously, complete bis-acetoxylation was reported only for one substrate, Weinreb amide of ibuprofen,[6i] and general approach to such products remained elusive. Further investigations showed that the auxiliary also promotes the C-H alkenylation with electron-deficient olefins and easily available cycloropanols can be utilized as a convenient source of vinyl ketones.

Palladium-catalyzed C-H acetoxylation of arylacetic acids:



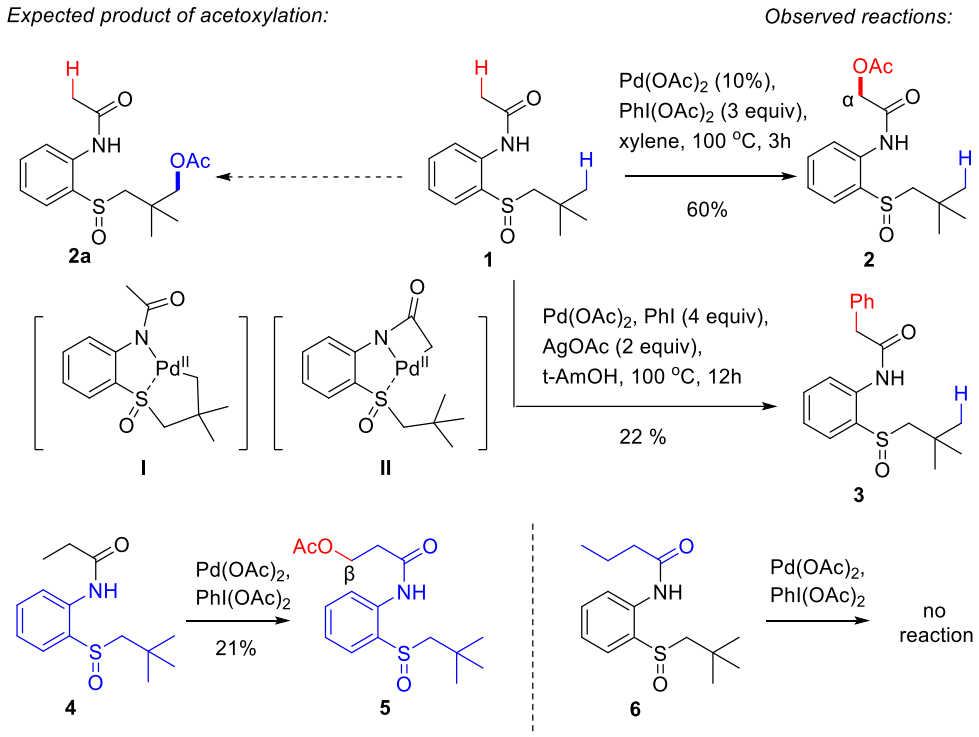


Scheme 1. C-H acetoxylation of the arylacetic acid scaffold

RESULTS AND DISCUSSION

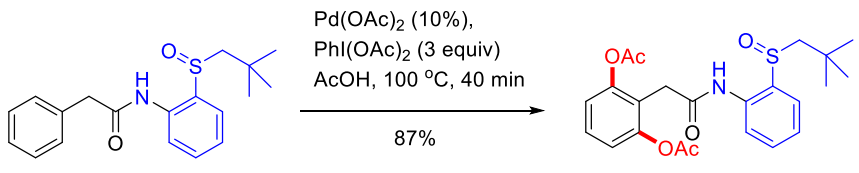
Our research commenced with an attempt to engage compound **1** in palladium-catalyzed acetoxylation (Scheme 2).[14] Although we were hoping that the reaction would lead to functionalization of the neopentyl unit in **1** proceeding through the 5-membered palladacyclic intermediate **I** and giving product **2a**,[14] we observed smooth formation of acetate **2** in a good yield. Presumably, this unexpected transformation proceeded through intermediate **II** that bears an atypical four-membered palladacyclic fragment.[15] In this reaction, the 2-(neopentylsulfinyl)aniline unit[16] of **1** serves as a directing group that promotes α-C-H activation of the acetamide moiety. To date, such a selectivity was reported only for acetoxylation of substrates bearing 1-aminoanthraquinone auxiliary.[15b] Encouraged by the obtained result, we performed additional experiments. The presence of a sulfoxide unit in the auxiliary was found to be crucial. When the sulfur atom was either non-oxidized or over-oxidized to sulfone, only decomposition or recovery of the starting material was observed, respectively. Next, we found that the directing group promotes α-C-H arylation furnishing phenylacetamide **3**,

though, in a low 22% yield. Disappointingly, these reactions were not general. The acetoxylation of propionamide **4** led to a usual product of β-C-H activation in a low yield, while *n*-butyramide **6** was completely non-reactive. Nevertheless, when phenylacetamide **3** was subjected to the reaction conditions, we were pleased to observe the facile and very fast functionalization of the aromatic *ortho*-C-H bonds and formation of diacetate **7** (Table 1).



Scheme 2. 2-(Neopentylsulfinyl)aniline-directed C-H functionalization

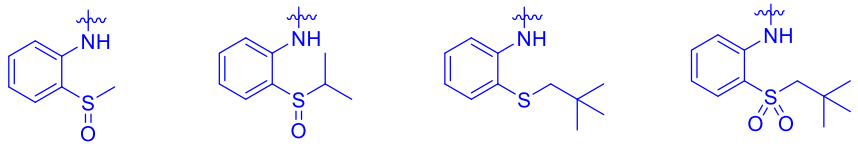
Table 1. Optimization of Pd-catalyzed sulfinylaniline-directed C-H acetoxylation of phenylacetamide 3.



3 7

entry	deviation from standard conditions	Yield of **7**, (%)
1	none	87%[a]
2	1 equiv of $PhI(OAc)_2$	36% of **7** + 53% of **3** [b]

3	**rt** instead of 100 °C (4 days)	75%[a]
4	**DG-I** instead of 2-(neopentylsulfinyl)aniline	76%[a]
5	**DG-II** instead of 2-(neopentylsulfinyl)aniline	50%[a]
6	**DG-III** instead of 2-(neopentylsulfinyl)aniline	complex mixture
7	**DG-IV** instead of 2-(neopentylsulfinyl)aniline (42 h)	28%[a] of the monoacetate
8	xylene instead of AcOH (2.5 h)	59%[b] of **7** + 18%[b] of **3**
9	*t*AmOH instead of AcOH	complex mixture

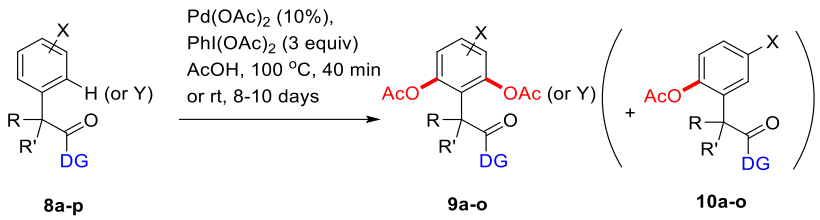


[a]Isolated yield. [b]Yield determined by ^{1}H NMR with CH_2Br_2 as an internal standard.

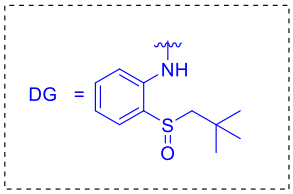
The highest yield of **7** was achieved when the reaction was carried out in acetic acid in the presence of 10% of $Pd(OAc)_2$ and 3 equivalents of $PhI(OAc)_2$ at 100 °C for 40 min (Table 1). Bis-acetate **7** was the only product of the functionalization even when one equivalent of the oxidant was used (entries 1 and 2). We also found that the directing group efficiently promotes the acetoxylation at ambient temperature. After 4 days, bis-acetate **7** was isolated in a good 75% yield (entry 3). Changing the neopentyl substituent in the directing group with either a smaller methyl (**DG-I**) or a bulkier isopropyl (**DG-II**) substituent caused a decrease of the yield (entries 4 and 5). Presence of the sulfinyl unit in the directing group was crucial for the reaction. The substrate bearing thioether auxiliary **DG-III** underwent decomposition under the acetoxylation conditions, while sulfone directing group **DG-IV** promoted the formation of the monoacetoxylated product in a low yield (entries 6 and 7). The reaction carried out in xylene

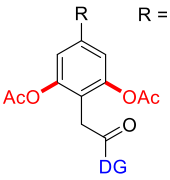
proceeded more slowly and its conversion was incomplete (entry 8). In *t*-AmOH, only a complex mixture was formed.

Table 2. Scope of the Pd-catalyzed sulfinylaniline-directed C-H acetoxylation of arylacetamides **8**.

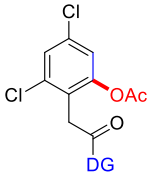


8a-p **9a-o** **10a-o**

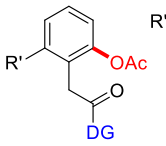




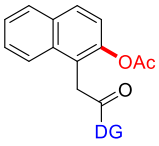
R = Me (**9a**), 75%
Cl (**9b**), 73%
I (**9c**), 79%
CF_3 (**9d**), 54%
OMe (**9e**), 28%
(77% at rt)[a]
NO_2 (**9f**), 23%
(39% at 60°C)[b]



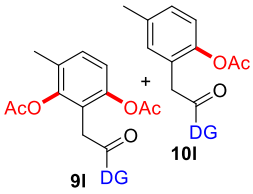
9g, 73%



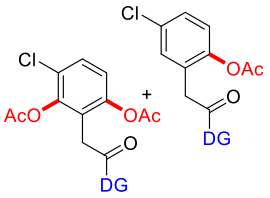
R' = Me (**9h**), 69%
Br (**9i**), 56%



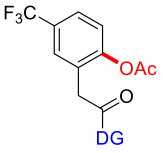
9j, 58%



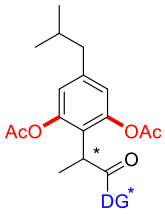
9k, 29%; **10k**, 45%
at rt:[c] **9k**, 44%; **10k**, 22%



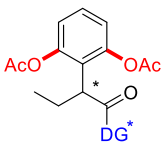
9l, 28%; **10l**, 32%
at rt:[c] **9l**, 42%; **10l**, 32%



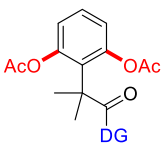
10m, 49%



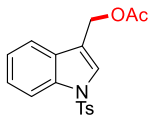
from the major diastereomer of **8n**:
9n, 14% (36% at rt)[c]



from the major diastereomer of **8o**:
9o, 35% (46 % at rt)[c]
from the minor diastereomer of **8o'**:
9o', 37%



9p, 0%



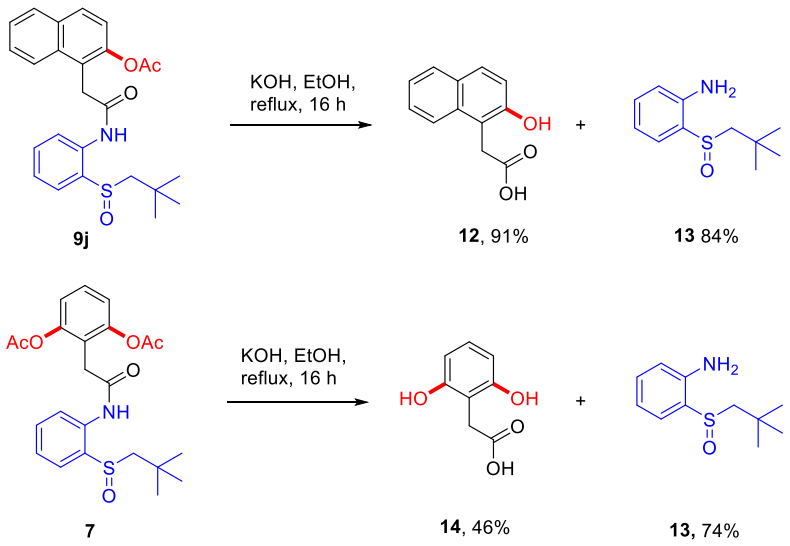
11, 23%

Reaction conditions: arylacetamide (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), $PhI(OAc)_2$ (0.3 mmol) in AcOH (0.41 mL) at 100 °C for 40 min or at room temperature for: [a]8 days; [b]3 h; [c] 10 days.

With the optimized conditions in hand, the scope of the reaction was investigated. Arylacetamides bearing methyl, chlorine, iodine or acceptor trifluoromethyl substituents in *para*-position were smoothly transformed to bis-acetates **9a-d**. Acetoxylation of p-methoxyphenylacetamide **8e** was accompanied by decomposition, and the product was isolated only in 28% yield. However, when the reaction was carried out at room temperature, the yield was significantly improved to 77%. Nitro-substituted bis-acetate **9f** was also obtained in a better yield when the reaction was carried out at lowered temperature. *Ortho*-substituted substrates **8h-i** and naphtalen-1-yl acetamide **8j** reacted smoothly yielding monoacetoxylated products **9h-j**. Generally, aromatic C-H bonds located between a directing group and a *meta*-substituent are protected from palladium-catalyzed activation.[17] Nevertheless, after acetoxylation of *meta*-methyl and *meta*-chloro arylacetamides **8k-l**, bis-acetoxylated products **9k-l** were isolated along with monoacetates **10k-l**. When the reaction was performed at room temperature, bis-acetoxylated products **9k** and **9l** became the major products, which can be attributed to better stability of the catalyst at ambient temperature. In the presence of a *meta*-trifluoromethyl substituent, the acetoxylation was surprisingly regioselective and led only to the monoacetoxylated product **10m**, even when the reaction time was increased. The room-temperature protocol was also beneficial for acetoxylation of the 2-alkylsubstituted arylacetamides **8n**, **8o** and **8o'**. Generally, alkyl substituents at this position cause decrease in the efficiency of the transformation. These amides, bearing a stereogenic centers at benzylic carbon and an asymmetric sulfur atom, were obtained as separable mixtures of diastereomers. When

the major diastereomer of ibuprofene derivative **8n** was reacted at 100°C, **9n** was formed in only 14% yield, but at room temperature the yield increased to 36% yield. Both diastereomers of 2-ethylsubstituted substrate **8o** and **8o'** were acetoxylated with a similar rate at 100 °C to give the products in 35% and 37% yields, respectively. At room temperature, the yield of **9o** was slightly improved to 46%. Unexpectedly, amide **8p** bearing two α-methyl groups was non-reactive, and only recovery of the starting material was observed. The amide **8q** prepared from 1-p-toluenesulfonylindolylacetic acid also did not react to form the expected acetates. Only the product of its decarboxylative acetoxylation **11** was isolated in a 23% yield.

Removal of the 2-(neopentylsulfinyl)aniline directing group from the product of acetoxylation was achieved by the alkaline hydrolysis of the amides. Acid **12** was isolated in a 91% yield along with amine **13** after heating a solution of **9j** in ethanolic KOH under reflux overnight. Dihydroxy acid **14** was also successfully obtained under the same reaction conditions.

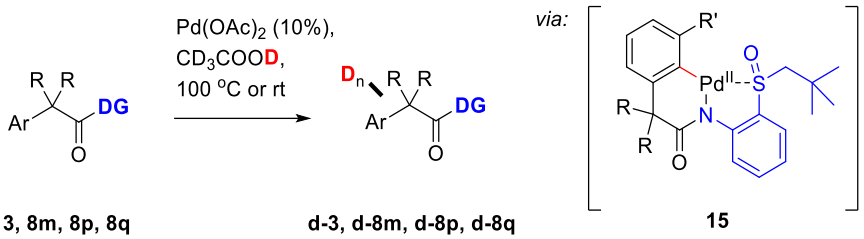


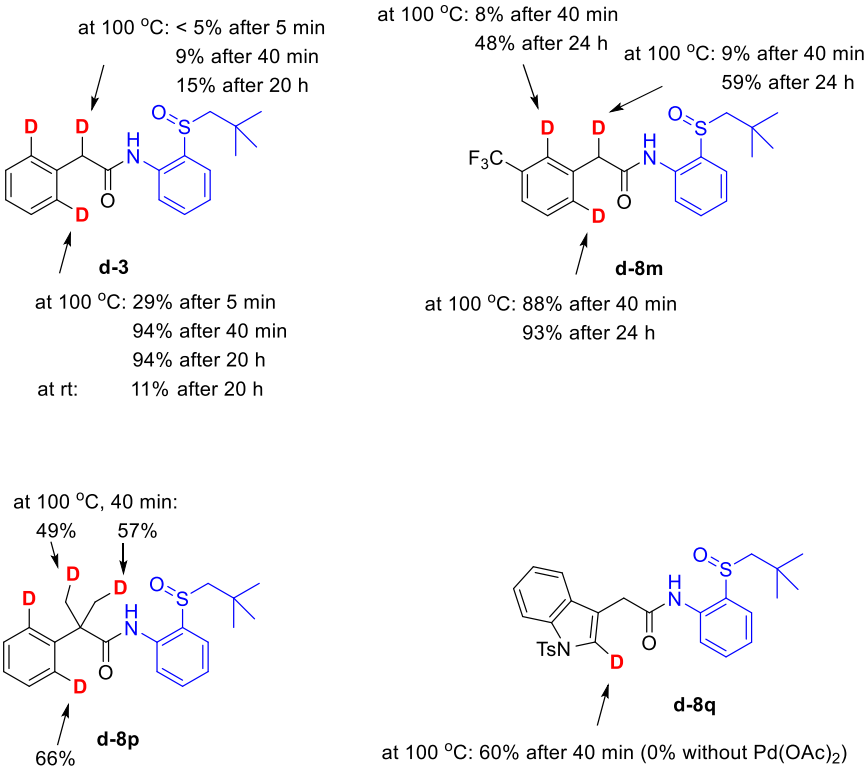
Scheme 3. Removal of the directing group from the products **9j** and **7**

In order to understand origin of high regioselectivity in the reaction of **8m**, inertness of **8p** and mechanism of decarboxylative acetoxylation of **8q**, deuterium studies were performed (Table 3).

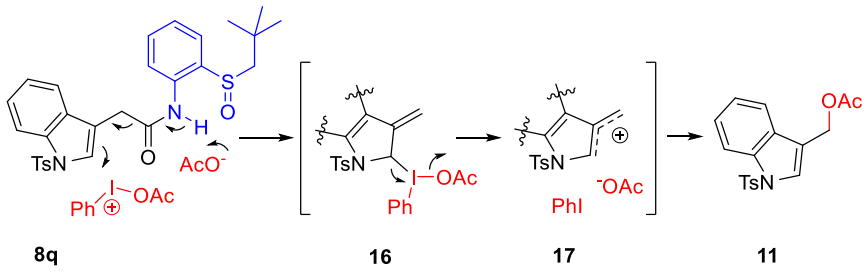
At first, we investigated deuteration of phenylacetamide **3**, which was found to be a good substrate in the acetoxylation reaction. After heating its solution in deuterated acetic acid at 100 °C in the presence of palladium acetate, 94% of *ortho*-protons in the substrate were substituted with deuterium after 40 min. At room temperature, deuteration of **3** was also observed, but it was significantly slower. Next, we studied deuterium exchange in *meta*-trifluoromethyl substituted amide **8m**, acetoxylation of which was mono-selective and led to the only product **10m**. While incorporation of acetoxy group into the *ortho*-position between two substituents in **8m** was not observed, its deuteration took place. This result suggests that the presence of *meta*-substituent prevents oxidation of the plausible intermediate **15** rather than C-H activation step. A similar result was observed in deuteration of α,α-dimethylphenylacetamide **8p**. While this substrate was totally inert under the acetoxylation conditions, its deuteration resulted in labelling of both *ortho*-positions and the methyl groups. Heating indolylacetic acid derivative **8q** in deuteroacetic acid in the presence of $Pd(OAc)_2$ resulted only in a regioselective C2-deuteration indicating that the product of decarboxylative acetoxylation **11** could be formed without participation of the catalyst. The competitive experiment carried out in the absence of palladium acetate confirmed this assumption. Presumably, this reaction proceeds similar to decarboxylative acetoxylation of β,γ-unsaturated acids.[18] The acetoxyiodobenzene cation, formed after dissociation of the reagent, reacts with the five-membered ring of **8q** with simultaneous decarboxylation assisted by acetate anion (Scheme 3). Next, dissociation of intermediate **16** followed by the reaction of the cation **17** with acetate anion gives product **11**.

Table 3. Deuterium studies[a]





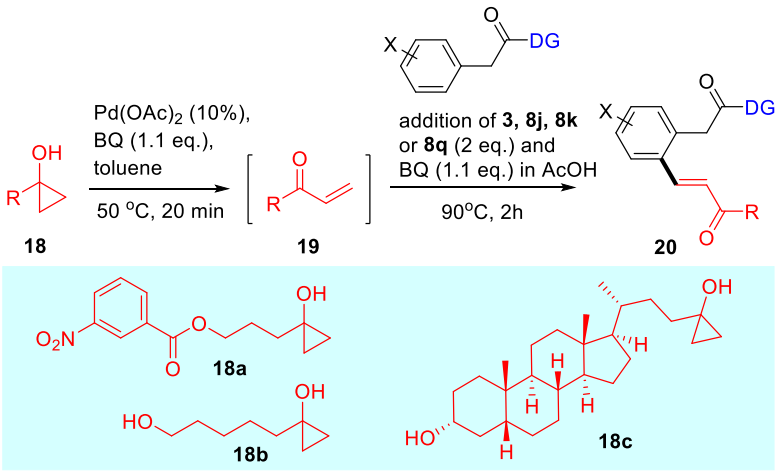
[a]Isotopic purity was determined from ^{1}H NMR spectra of the reaction mixtures.

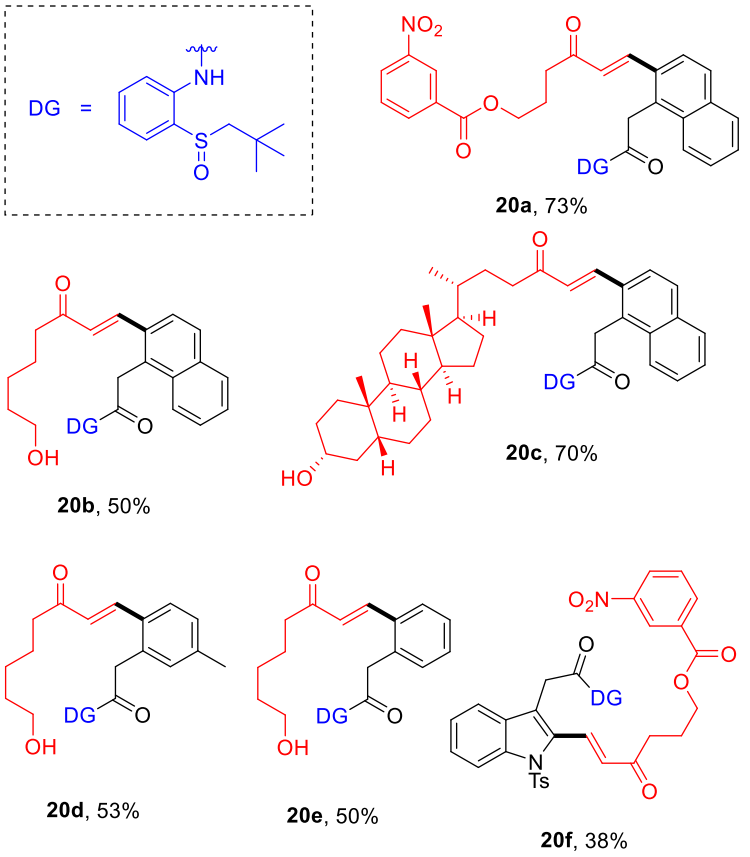


Scheme 4. Plausible mechanism of formation of **11**

Further investigations showed that 2-(neopentylsulfinyl)aniline auxiliary also assists the palladium-catalyzed reaction of arylacetamides **3** and **8** with electron-deficient olefins. Exploring this reaction, we also examined feasibility of using 1-monosubstituted cyclopropanols **18** as synthetic equivalents of vinyl ketones **19**. Under palladium catalysis, cyclopropanols undergo smooth transformation to enones in the presence of a stoichiometric oxidant.[19] Moreover, diverse cyclopropanols are easily available from esters by means of the Kulinkovich reaction.[20] However, they have never been utilized as coupling partners in reactions with C-H activated substrates under palladium catalysis.[21] Delightfully, our initial experiment showed that heating a solution of the arylacetamide, a cyclopropanol, palladium acetate and benzoquinone in acetic acid at 90 ^{o}C led to the desired product **20** (for details, see SI). Then, the yield of the reaction was improved by using two equivalents of the arylating reagent and by performing the stage of the vinyl ketone synthesis separately in toluene at 50 ^{o}C. Investigation of the scope of the reaction started with the preparation of enone **20a** from cyclopropanol **18a** and naphtylacetamide **8j** in a good 73% yield (Table 4). Unreacted arylating reagent **8j**, used in this reaction in excess, was recovered in 85% yield. Cyclopropanol **18b** bearing an unprotected hydroxyl group was also successfully transformed to the product **20b**, though its yield was lower. Starting from steroidal cyclopropanol, arylated enone **20c** was prepared in a 70% yield. The 2-(neopentylsulfinyl)aniline-promoted alkenylation was not as rapid as the acetoxylation and furthermore, bis-functionalized products did not form from ortho-unsubstituted substrates. The alkenylation of **8k** and **3** was mono-selective and corresponding products **20d** and **20e** were isolated in 53% and 50% yields, respectively. Finally, indolylacetic acid derivative **8j** was examined in the reaction. While the deuterium exchange in this substrate proceeded smoothly at C2, our attempt of its acetoxylation failed because of the side reaction with the oxidant (Table 2). Delightfully, the alkenylation proceeded successfully furnishing the expected enone **20f**.

Table 4. Scope of the Pd-catalyzed sulfinylaniline-directed C-H alkenylation of arylacetamides with vinyl ketones prepared in one pot from cyclopropanols.





Reaction conditions: cyclopropanol (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), benzoquinone (1.1 mmol) in toluene (1 ml) at 50 °C

for 20 min followed by addition of arylacetamide (0.2 mmol) and benzoquinone (1.1 mmol) in AcOH (1 mL), 90 °C, 2 h.

In conclusion, we have developed protocols for 2-(neopentylsulfinyl)aniline-directed palladium-catalyzed C-H acetoxylation and alkenylation of the arylacetamides. The acetoxylation proceeds within only 40 min at heating or alternatively, can be carried out at ambient temperature. We have also demonstrated that in the alkenylation, easily available 1-substituted cyclopropanols can be exploited as a souse of vinyl ketones. 2-(Neopentylsulfinyl)aniline auxiliary used in these transformation is removable by the simple hydrolysis with potassium hydroxide.

Experimental Section

General procedure for acetoxylation of 2-neopentylsulfinylacetamides

A 4 mL vial was charged with the substrate (0.1 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 10 mmol%), $PhI(OAc)_2$ (99.6 mg, 0.3 mmol, 3.0 equiv) and AcOH (0.41 mL, 0.25 M). The mixture was stirred at 100 °C, 60 °C or room temperature over indicated time. The reaction mixture then was filtered through a Celite pad and the solvent was evaporated. The crude product was purified on silica gel (petroleum ether/EtOAc or toluene/acetone).

General procedure for Pd-catalyzed alkenylation of 2-neopentylsulfinylacetamides

A 4 mL vial was charged with the cyclopropanol (0.1 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 10 mmol%), benzoquinone (11.9 mg, 1.1 mmol, 1.1 equiv.) and toluene (1 mL, 0.1 M). The mixture was stirred at 50 °C for 20 min followed by the addition of the arylacetamide (0.2 mmol, 2 equiv.) and benzoquinone (11.9 mg, 1.1 mmol, 1.1 equiv.) in AcOH (1 mL, 0.2 M). The reaction

mixture was stirred at 90 °C for 2 hours then filtered through a silica pad and the solvent was evaporated. The crude product was purified on silica gel (toluene/acetone or toluene/ EtOAc).

ASSOCIATED CONTENT

Supporting Information

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Notes

The authors declare no competing financial interest.

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