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Authors: Maryia Barysevich, Marharyta Laktsevich-Iskryk, Anastasiya Krech, Vladimir Zhabinskii, Vladimir Khripach, and Alaksiej L. Hurski

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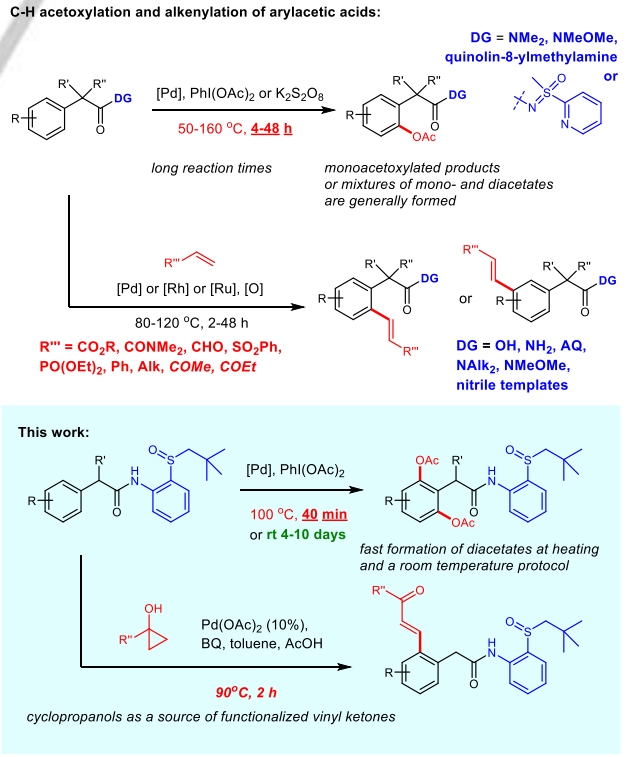
Palladium-catalyzed 2-(Neopentylsulfinyl)aniline Directed C-H Acetoxylation and Alkenylation of the Arylacetamides

Maryia V. Barysevich,[a] Marharyta V. Laktsevich-Iskryk,[a] Anastasiya V. Krech,[a] Vladimir N. Zhabinskii, [a] Vladimir A. Khripach[a] and Alaksiej L. Hurski[a]*

Abstract: The 2-(neopentylsulfinyl)aniline directing group that promotes rapid palladium-catalyzed C-H acetoxylation and alkenylation of the arylacetamides has been developed. 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, we have developed a protocol in which easily available 1-substituted cyclopropanols were employed as equivalents of vinyl ketones.

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 reaction rate and regioselectivity control. However, even in the presence of a directing group, the transition metal-catalyzed 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 a very fast C-H acetoxylation and alkenylation of the arylacetamides promoted by a sulfinylaniline auxiliariy.[4] Phenylacetic scaffold is featured in pharmaceuticals and other bioactive compounds.[5] For its functionalization, numerous C-H activation-based methods have been developed including arylation,[6] alkenylation,[7] alkylation,[8] alkynylation,[9] halogenation,[6b, f, 10] acylation,[11] deuteration,[12] lactonization [13] and acetoxylation.[6b, 7f, 13b, 14] Generally, the acetoxylation of arylacetic acids cannot be performed without installation of an amide directing group. Sanford reported the *ortho*-oxidation of simple dimethylamide of *m*-tolylacetic acid.[14b] Yu showed that the Weinreb amide moiety efficiently promotes the functionalization.[7f] Bidentate *S*-methyl-*S*-2-pyridylsulfoximine and quinolin-8-ylmethylamine auxiliaries were developed by Sahoo[14a] and Chatani[13b] groups, respectively. Carried out at 50-160 °C, these reactions proceeded within 4-48 h typically furnishing monoacetoxylated products or mixtures of mono- and diacetates.[15] We found that the acetoxylation promoted by the 2-(alkylsulfinyl)aniline directing groups reaches completion significantly faster leading to the diacetoxylated products over 40 min at heating. The highest yields were achieved when the alkyl unit in the auxiliary was the neopentyl group. Furthermore, this strong *N*,*S*-bidentate directing moiety enabled the functionalization even at room temperature. In addition to the acetoxylation, the 2-(neopentylsulfinyl)arylacetamides underwent palladium-catalyzed functionalization with electron-deficient olefins. In recent decade, C-H alkenylation of the phenylacetic scaffold was widely studied.[7] The acids were olefinated either directly[7a-c] or after installation of an appropriate amide auxiliary.[7d-n] In these *ortho*-[7a-d, 7f, 7h-j, 7m] and *meta*-selective[7e, 7g, 7k-l, 7n] reactions, alkenyl carboxylic acid derivatives,[7a-i, 7l-n] phenylvinylsulfone,[7i] diethyl vinylphosphonate,[7e, 7i] styrene or unactivated olefins,[7a-d, 7i-l] acrolein[7e] and simple alkyl vinylketones[7a-b,7e] were utilized as coupling partners. Exploring alkenylation promoted by the 2-(neopentylsulfinyl)aniline directing group, we developed a protocol, in which easily accessible 1-substituted cyclopropanols were employed as a convenient source of the functionalized enones.



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

[a] Maryia V. Barysevich, Marharyta V. Laktsevich-Iskryk, Anastasiya V. Krech, Dr. Vladimir N. Zhabinskii, Prof. Vladimir A. Khripach, Dr. Alaksiej L. Hurski
Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevich str. 5/2, Minsk 220141, Belarus
Institution
E-mail: ahurski@iboch.by

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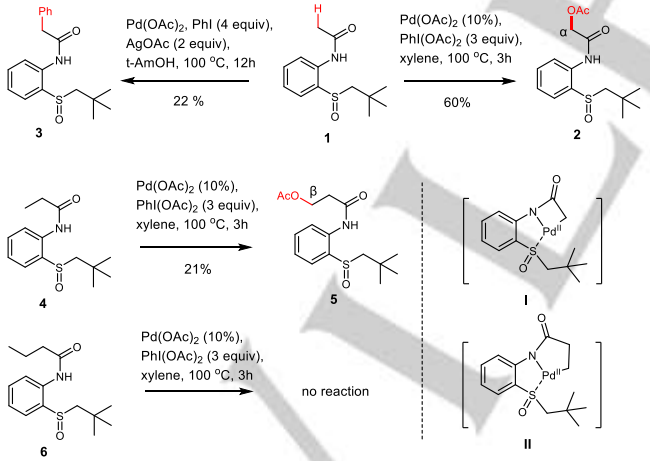
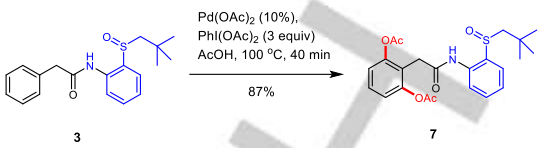
Results and Discussion

Previously, directing groups that simultaneously bear the sulfinyl and amide coordinating moieties were successfully employed in palladium-catalyzed C-H functionalization of the aliphatic acids,[4a-c] benzylamines[4d] and benzaldehydes.[4e] All of these reactions were β-selective and proceeded through the five-membered palladacyclic intermediates. Our studies commenced with the investigation of palladium-catalyzed acetoxylation of acetamide **1** (Scheme 2),[16] which unexpectedely led to the α-functionalization product **2** in a moderate 60% yield. The 2-(neopentylsulfinyl)-aniline unit in **1** served as a coordinating auxiliary that was also found to assist the α-arylation. Arylacetamide **3** was isolated in a 22% yield along with 60% of the recovered starting material. The presence of the sulfoxide moiety in the directing group was crucial for these reactions. When the unit was substituted with the sulfone moiety, the amide became non-reactive. The substrate bearing the thioether auxiliary was inert in the arylation and underwent decomposition when was subjected to the acetoxylation. Sensitivity of the reactions to the structure the auxiliary suggested that they could proceed through the unusual four-membered palladacycle **I**.[17] In the C-H functionalization of carboxylic acid derivatives, formation of such intermediates was reported when the 1-aminoanthraquinone was employed as a directing group.[17b] Disappointingly, we failed to improve the yield of the arylation and the α-C-H acetoxylation was not general. In fact, propanamide **4** was acetoxylatied with β-selectivity proceeding through the usual five-membered palladacycle **II**. Although the starting amide **4** was consumed completely, significant decomposition was observed and acetate **5** was isolated in a poor 21% yield. Butyramide **6** was inert under the reaction conditions. Nevertheless, we were pleased to find that the 2-(neopentylsulfinyl)-aniline auxiliary promotes a very fast γ-acetoxyltion of arylacetamide **2** affording difunctionalized product **7** in a high 87% yield (Table 1).

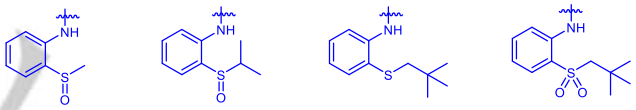


Scheme 2. 2-(Neopentylsulfinyl)aniline-directed C-H functionalization of the alkylacetamides.

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



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



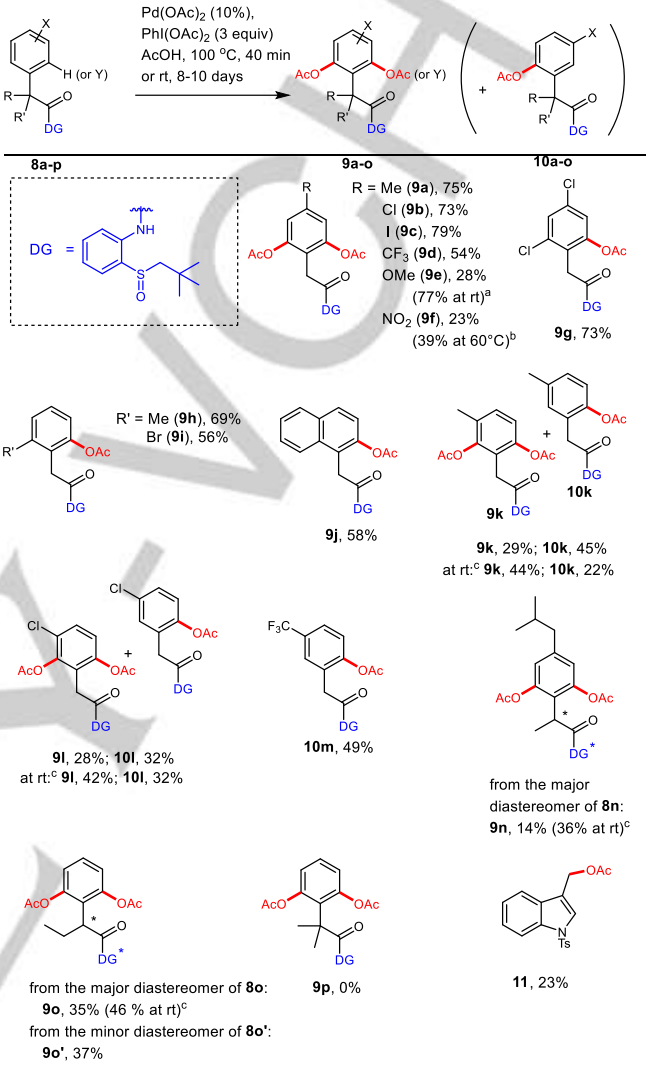
[a] Isolated yield. [b] Yield determined by ^1H NMR with CH_2Br_2 as an internal standard.

The diacetoxylation of **3** 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, entry 1). Bis-acetate **7** was the only product of the functionalization even when one equivalent of the oxidant was used (entry 2). Then, we found that the directing group efficiently promotes the reaction even at ambient temperature. After 4 days, bis-acetate **7** was isolated in a good 75% yield (entry 3). Surprisingly, even under these mild room-temperature conditions, we did not observe formation of the monoacetoxylated product. When the neopentyl unit in the auxiliary was changed with either a smaller methyl (**DG-I**) or a bulkier isopropyl (**DG-II**) substituents, the yields of the acetoxylation dropped to 76% and 50% respectively (entries 4 and 5). Taking into account that the starting material was consumed completely in both of the reactions, the observed results suggests that the neopentyl moiety increases stability of the unit during the functionalization. Presence of the sulfinyl moiety in the directing group was crucial for the reaction. The substrate containing thioether auxiliary **DG-III** underwent

decomposition under the acetoxylation conditions (entry 6). Directing group **DG-IV** bearing the sulfone unit promoted formation of the monoacetoxylated product with a very slow reaction rate and in a poor 28% yield (entry 7). In xylene, the reaction was slower than in AcOH and its conversion was incomplete (entry 8). In *t*-AmOH, only decomposition of the starting material was observed. Moreover, we tested alternative oxidants, but the results were unsatisfactory. When *tert*-butyl peroxyacetate was employed, a mixture of unidentified products was formed. Significant decomposition was also observed in the reaction with $K_2S_2O_8$ that led to diacetate **7** in a low 18% yield.

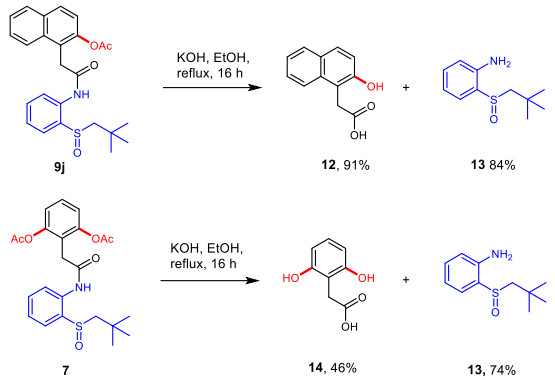
With the optimized conditions in hand, the scope of the reaction was investigated (Table 2). Arylacetamides bearing methyl, chlorine, iodine or acceptor trifluoromethyl substituents in *para*-position were smoothly transformed to bis-acetates **9a-d**. Acetoxylation of p-methoxyphenylacetamide **8e** was accompanied by decomposition, and the product was isolated in a poor 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 at decreased temperature. Although the yield of **9f** was low, we did not observe formation of the monoacetoxylated product. *Ortho*-substituted substrates **8h-i** and naphtalen-1-yl acetamide **8j** reacted smoothly yielding acetates **9h-j**. Generally, aromatic C-H bonds located between a directing group and a *meta*-substituent are protected from palladium-catalyzed activation.[18] Nevertheless, after the acetoxylation of *meta*-methyl and *meta*-chloro arylacetamides **8k-l**, we observed formation of the desired diacetates **9k-l**. These products became major when the reaction was run at ambient temperature, which can be attributed to the better stability of the catalyst under the milder conditions. *Meta*-trifluoromethyl group in **8m** prevented the diacetoxylation and the only isolated product was monoacetate **10m** regardless of the reaction time and temperature. Next, 2-alkyl substituted arylacetamides **8n-p** were tested. Both amides **8n** and **8o**, which bear two asymmetric atoms, were obtained as separable diastereomeric mixtures. The acetoxylation of the major diastereomer of ibuprofene derivative **8n**, and two diastereomers of 2-ethylsubstituted substrate **8o** and **8o'** led to diacetates **9n, 9o** and **9o'**. These reactions were accompanied by decomposition and their outcome was slightly better when the room temperature protocol was utilized. Unexpected results were observed in the reactions of 2,2-dimethylsubstituted amide **8p** and indolylacetamide **8q**. While **8p** was inert under the reaction conditions, **8q** underwent decarboxylative acetoxylation giving the only product, acetate **11** in a 23% yield.

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



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

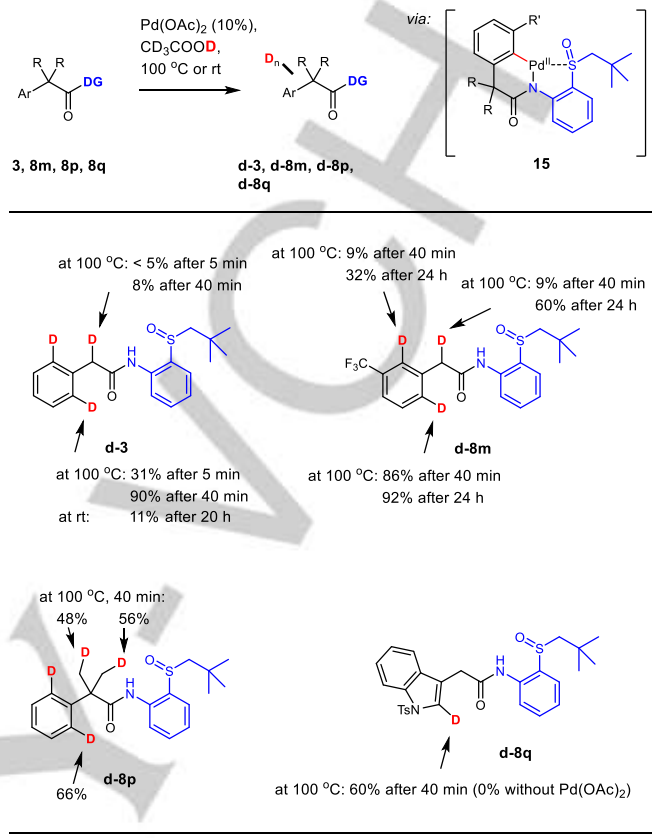
Removal of the 2-(neopentylsulfinyl)aniline directing group from the product of acetoxylation was achieved by simple alkaline hydrolysis (Scheme 3). Acid **12** was isolated in a 91% yield along with amine **13** after heating a solution of **9j** in ethanolic KOH under reflux overnight. Dihydroxy acid **14** was also successfully obtained under the same reaction conditions.



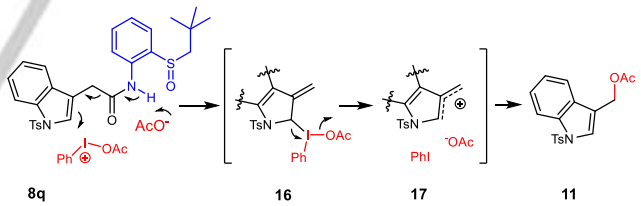
Scheme 3. Removal of the directing group from acetates **9j** and **7**.

In order to understand origin of high regioselectivity in the reaction of **8m**, inertness of **8p** and mechanism of decarboxylative acetoxylation of **8q**, we carried out deuterium studies (Table 3). At first, deuteration of phenylacetamide **3** that underwent smooth acetoxylation was investigated. After heating its solution in deuterated acetic acid in the presence of the palladium catalyst at 100 °C for 40 min, 90% of the *ortho*-protons were substituted with deuterium. At room temperature, the H-D exchange was also observed, but it was significantly slower. Next, deuteration of *meta*-trifluoromethyl substituted amide **8m** was studied. While the *ortho*-C-H bond located between two substituents was inert toward the acetoxylation, we observed its deuteration. A similar result was obtained in the labelling of α,α-dimethylphenylacetamide **8p**. Non-reactive in the acetoxylation, its *ortho*-positions and methyl groups were smoothly deuterated. These results suggest that although the directing group promotes the C-H activation stage, the plausible intermediates **15** are inert toward the oxidant. Presumably, their low reactivity can be attributed to the high steric hindrance in **15**. Finally, we investigated H-D exchange in indolylacetic acid derivative **8q**. The auxiliary efficiently assisted the deuteration and we did not observe any side reaction. This experiment suggested that decarboxylation product **11** could be formed without participation of the catalyst. The competitive experiment conducted in the absence of palladium acetate led to **11** in 20% yield supporting the assumption. Presumably, the mechanism of formation of **11** is similar to that for the decarboxylative acetoxylation of β,γ-unsaturated acids.[19] 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 cation **17** with acetate anion gives product **11.**

Table 3. Deuterium studies[a].

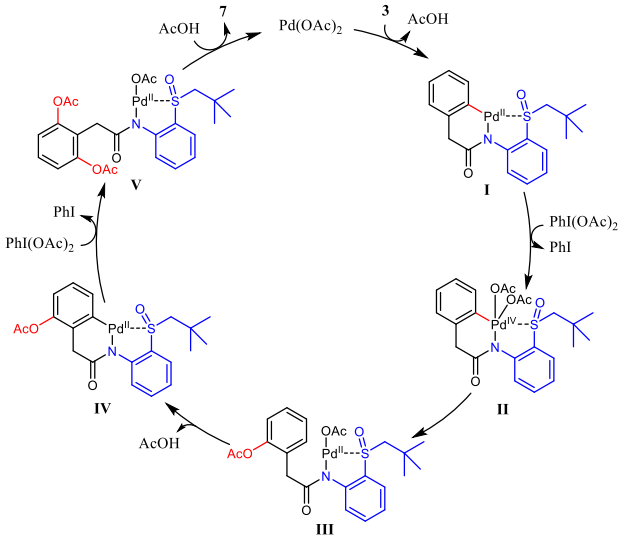


[a] Isotopic purity was determined from ^{1}H NMR spectra of the reaction mixtures.



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

A tentative reaction mechanism of the diacetoxylation is shown in **Scheme 5**. Coordination of substrate **3** with the catalyst followed by the C-H activation furnishes intermediate **I**. Next, oxidation of Pd^{II} to Pd^{IV} and reductive elimination from **II** gives monoacetoxylated comlex **III**. As far as we have never observed the monoacetoxylated products in the reaction of **3**, we speculated that **III** undergoes further C-H activation to form intermediate **IV**. Oxidation of **IV** followed by the reductive elimination furnishes complex **V**. Its decomposition leads to diacetoxylated product **7** and regeneration of $Pd(OAc)_2$. In intermediates **I-V**, the auxiliary is coordinated with palladium through both nitrogen and sulfur atoms. This assumption was made based on the vital role of the sulfinyl unit of the directing group (Table 1, entries 1, 6, 7).

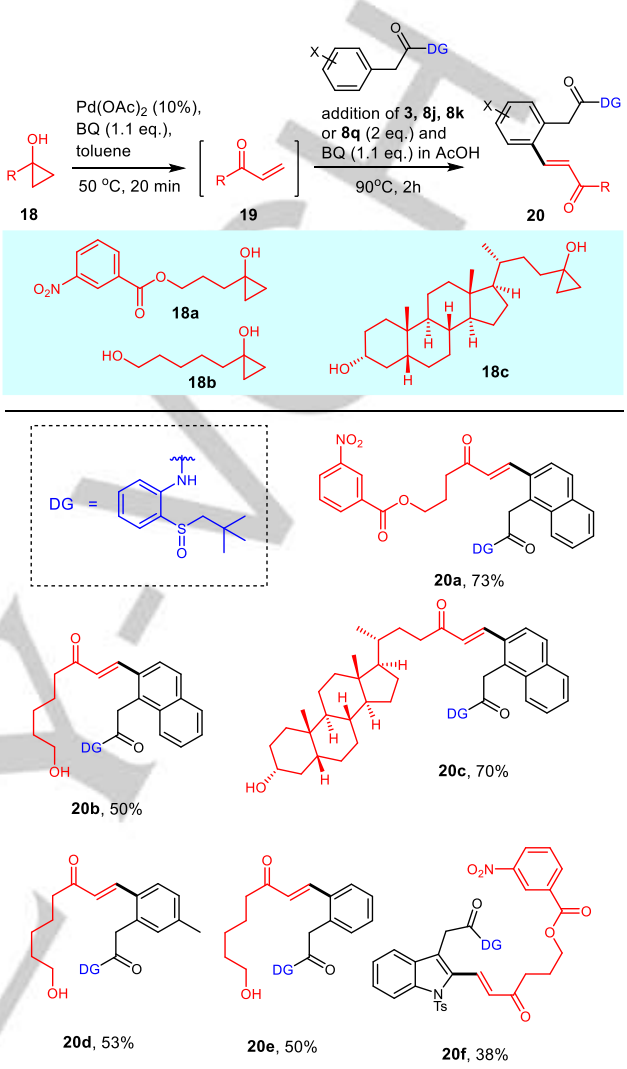


Scheme 5. Proposed catalytic cycle.

Further investigations showed that in addition to the acetoxylation, the 2-(neopentylsulfinyl)aniline auxiliary assists the alkenylation of the arylacetamides with electon-deficient olefins. Exploring alkenylation of 2-(neopentylsulfinyl)-arylacetamides **3**, **8j, 8k**, and **8q** we wondered whether 1-substituted cyclopropanols **18** could be employed in this reaction as a source of functionalized vinyl ketones **19**. Cyclopropanols are easily available from esters by means of the Kulinkovich reaction[20] and under the palladium catalysis, undergo smooth transformation to enones in the presence of an oxidant.[21] Successfully employed in the rhodium-catalyzed reactions,[22] cyclopopropanols have never been utilized as coupling partners in C-H functionalization under the palladium catalysis.[23] Delightfully, our initial experiment showed that heating a solution of the arylacetamide, cyclopropanol, palladium acetate and benzoquinone in acetic acid at 90 °C led to 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 °C.

Investigation of the reaction scope started with the preparation of enone **20a** from cyclopropanol **18a** and naphtylacetamide **8j** in a good 73% yield (Table 4). Unreacted arylating reagent **8j** was recovered in 85% yield. Cyclopropanol **18b** bearing an unprotected hydroxyl group was also successfully transformed to product **20b**, though its yield was lower. Starting from steroidal cyclopropanol, arylated enone **20c** was prepared in 70% yield. 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 position, our attempt of its acetoxylation failed because of the side reaction with the oxidant (Table 2). Delightfully, its alkenylation proceeded successfully furnishing the desired 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.

Conclusions

In conclusion, we have developed 2-(neopentylsulfinyl)aniline directing group that promotes palladium-catalyzed C-H acetoxylation and alkenylation of the arylacetamides. The acetoxylation proceeds significantly faster as compared to the previously reported approaches and can be carried out even at room temperature. Our approach is suitable for facile preparation of the diacetoxylatied products from *ortho*-unsubstituted substrates including those bearing a *meta*-substituent. We also demonstrated that in the alkenylation, 1-substituted cyclopropanols could be employed as a source of vinyl ketones. The advantage of this protocol is that diverse functionalized cyclopropanols are accessible in one step from easily available

esters. The 2-(neopentylsulfinyl)aniline auxiliary is removable by simple hydrolysis with potassium hydroxide.

Experimental Section

General procedure for acetoxylation of 2-neopentyl-sulfinylacetamides

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).

Acknowledgments

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Keywords: C-H acetoxylation • C-H alkenylation • arylacetic acids • cyclopropanols • ring-opening

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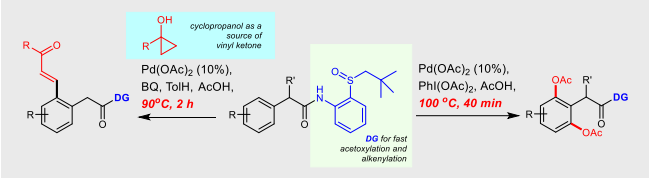

The 2-(neopentylsulfinyl)aniline-promoted rapid palladium-catalyzed C-H acetoxylation and alkenylation of the arylacetamides is reported. In the alkenylation, easily available cyclopropanols were employed as a source of functionalized vinyl ketones.

C–H Functionalization

*Maryia V. Barysevich, Marharyta V. Laktsevich-Iskryk, Anastasiya V. Krech, Vladimir N. Zhabinskii, Vladimir A. Khripach, Alaksiej L. Hurski**

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