Received: January 17, 2015 | Accepted: February 5, 2015 | Web Released: February 17, 2015 CL-150041

$Pd(OAc)_2$-catalyzed Lactonization of Arylacetamides Involving Oxidation of C–H Bonds

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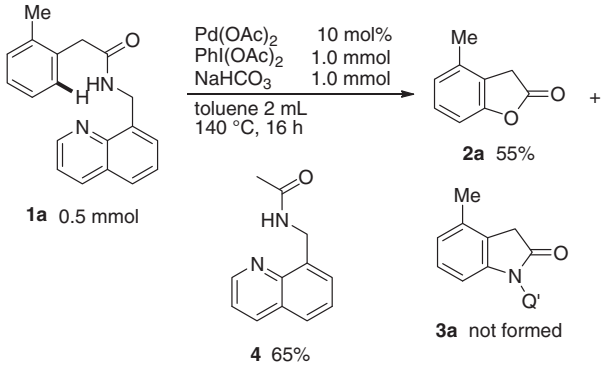
The reaction of arylacetamides that contain a quinolin-8-ylmethylamine as the directing group with $PhI(OAc)_2$, in the presence of $Pd(OAc)_2$ as the catalyst, results in lactonization to give γ-lactones, the formation of which involves activation of the *ortho* C–H bonds, with concomitant cleavage of the directing group.

Chelation-assisted functionalization of C–H bonds has become one of the most reliable methods for the regioselective functionalization of C–H bonds.[1] A wide variety of functional groups can be used as the directing group in this type of transformation. In most cases, the directing groups promote the functionalization of C–H bonds, but remain intact under the reaction conditions employed. In some cases, they can be easily elaborated to more synthetically useful functional groups after the complete functionalization of the C–H bond. A majority of such functionalizations can be included in this category. In another iteration of this reaction, the directing group is incorporated in the final product. In this case, the directing group promotes the functionalization of C–H bonds, and then reacts further with the introduced groups and is incorporated into the final product as a component of the final compound. We recently reported the Pd(II)-catalyzed synthesis of dibenzophosphole derivatives from diarylphosphines, in which the phosphorus atom promotes the activation of the C–H bond, followed by C–PPh bond cleavage.[2] In this type of reaction, the originally installed directing group becomes a part of the product. Because of this, the directing group cannot be recovered or be recycled. There are many examples of directing groups in this category.[3]

Recently, considerable attention has been focused on traceless removal directing groups in the catalytic functionalization of C–H bonds because of the synthetic utility of this procedure.[1j,4] A carboxylate directing group is an attractive and promising traceless directing group because of its ready availability and unique character.[5] It is known that a carboxylate directing group promotes the decarboxylative Mizoroki–Heck-type alkenylation of C–H bonds at the C2-position of indoles with acrylic esters and styrenes, but a C3-selective reaction took place when the indoles contained no carboxylate directing group.[6] The carboxylate group also promotes both ipso-decarboxylative arylation in benzoic acid derivatives with aryl halides[7] and *ortho*-decarboxylative arylation of C–H bonds in benzoic acid derivatives, depending on the catalytic system in use.[8]

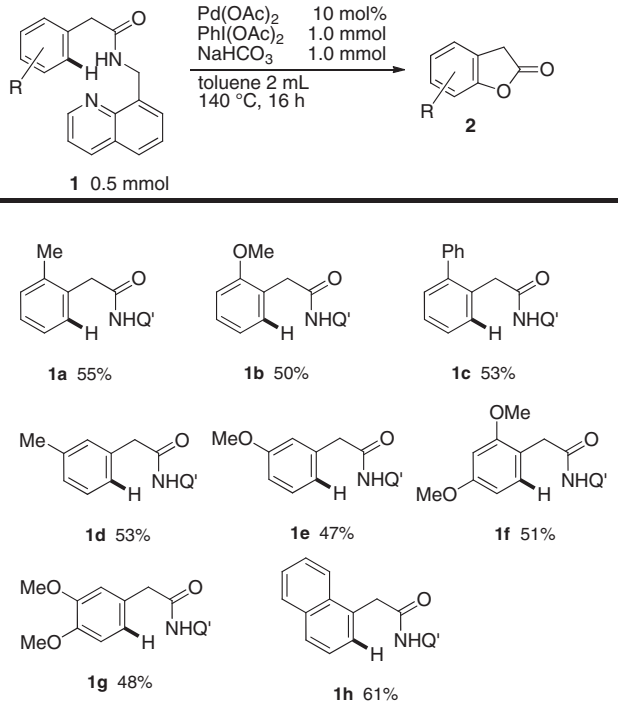
In another class of directing groups, the directing group spontaneously cleaved after the activation of the C–H bond, and could be recovered intact or as a derivative. Hirano and Miura recently reported the Cu(II)-catalyzed synthesis of carbazoles from 2-aminobiphenyl derivatives that contain a picolinamide-based directing group, in which the picolinamide moiety promotes C–H amination and is then spontaneously removed by hydrolysis after the final coupling event.[9] From the standpoint of atom economy, this type of reaction represents an ideal route to the functionalization of C–H bonds because the directing group can be recycled. However, examples of this type are rare. The design of new directing groups continues to be an important issue in terms of the development of new types of functionalizations that cannot be achieved using known directing groups. In this context, we report herein the first use of an quinolin-8-ylmethylamine moiety in the Pd(II)-catalyzed lactonization of arylacetamides with $PhI(OAc)_2$ as the oxidant.

The focus of our recent research has been on the use of *N*,*N*-bidentate directing groups, such as pyridinylmethylamine and 8-aminoquinoline in C–H functionalization reactions.[10,11] The reaction is significantly affected by the nature of the directing group. This encouraged us to design a new type of *N*,*N*-bidentate directing group.[12–14] We found that the reaction of **1a**, containing an quinolin-8-ylmethylamine moiety as the directing group, with $PhI(OAc)_2$ in toluene as the solvent in the presence of a catalytic amount of $Pd(OAc)_2$ gave 4-methylbenzofuran-2(3*H*)-one (**2a**). Chen recently reported the $Pd(OAc)_2$-catalyzed oxidation of arylacetamides containing 8-aminoquinoline as the directing group with $PhI(OAc)_2$ to give γ-lactam derivatives, in which an intramolecular C–N bond is formed and the directing group remains attached to the product.[15] Surprisingly, however, the expected lactam **3a** was not formed in our chelation system. The formation of **2a** involves the elimination of the directing group, which is recovered as acetamide **4**. Among the oxidants examined, $PhI(OAc)_2$ was found to be superior; $Cu(OAc)_2$ trace, AgOAc 0%, $K_2S_2O_8$ 0%, $PhI(OCOCF_3)_2$ 32%. After optimization of the reaction conditions, we determined that the following conditions were optimal for the reaction: **1a** (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), $NaHCO_3$ (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), toluene (2 mL) at 140 °C for 16 h (Scheme 1). Under the standard reaction conditions, lactone **2a** was obtained in 55% isolated yield, along with the directing group being recovered as acetamide **4** in 65% yield.

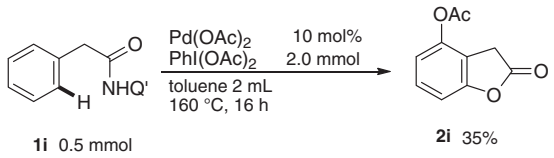


Scheme 1. $Pd(OAc)_2$-catalyzed reaction of **1a** with $PhI(OAc)_2$.

Table 1. $Pd(OAc)_2$-catalyzed lactone synthesis of **1** with $PhI(OAc)_2$[a]



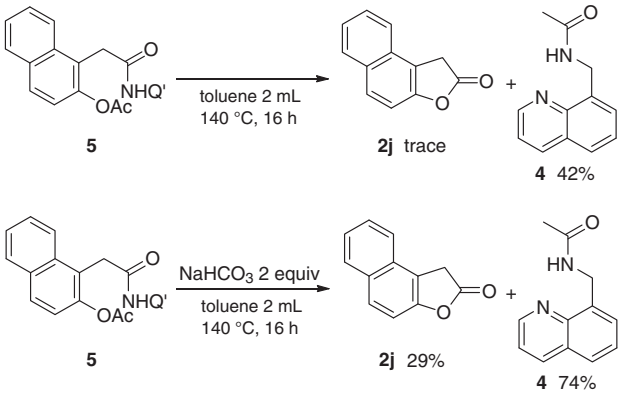
[a]Reaction conditions: **1** (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), $NaHCO_3$ (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), toluene (2 mL) at 140 °C for 16 h. Yields are isolated yields by column chromatography. Q′ refers quinolin-8-ylmethanamino group.



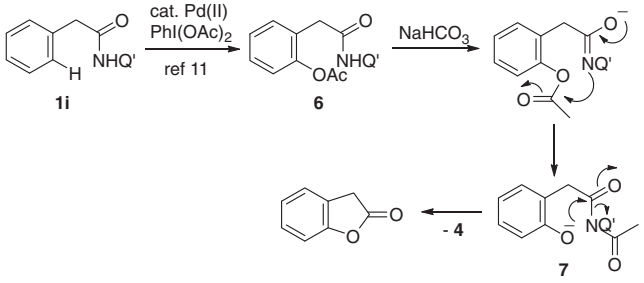
Scheme 2. $Pd(OAc)_2$-catalyzed reaction of **1i** with $PhI(OAc)_2$.

Some examples of this reaction are listed in Table 1. The reaction was highly dependent on the electronic nature of the substituent. Only electron-rich substrates gave the expected products. In the case of *meta*-methyl substrates **1d**, **1e**, and **1g**, only the less hindered C–H bonds were oxidized to give **2d**, **2e**, and **2g**. The reaction was not greatly affected by the steric effects of the substituents, as in **1c**.

The reaction of **1i** gave **2i**, the formation of which involves both lactonization and acetoxylation (Scheme 2). It is known that acetoxylation of C–H bonds does not occur when no directing group is present on the substrate, suggesting that the acetoxylation product is the initially produced, which then undergoes intramolecular cyclization under the reaction conditions to give lactones. To confirm the reaction mechanism involved in the formation of a lactone, some controlled experiments using acetoxy substrate **5** were carried out (Scheme 3). In the absence of $NaHCO_3$, lactone **2j** was not formed. However, **2j** was formed when $NaHCO_3$ was used. These results suggest that the acetoxylation product is an initial product and that the base promotes further intramolecular cyclization.



Scheme 3. Controlled experiments.



Scheme 4. Proposed mechanism.

A proposed mechanism for this transformation is shown in Scheme 4. The Pd(II)-catalyzed acetoxylation of C–H bonds in **1i** takes place by taking advantage of the use of a directing group, similar to the case of known reactions using another type of directing group, to afford **6**.[16] A base-promoted intramolecular acyl transfer then occurs to give **7**, which undergoes intramolecular cyclization to give a lactone, with the concomitant generation of **4**.

In summary, we report a new synthesis of benzofuran-2(3*H*)-one derivatives from arylacetamide derivatives. The reported synthesis of benzofuran-2(3*H*)-one derivatives through the activation of C–H bonds involves the cyclative formation of C–O bonds in arylacetic acids.[17] However, the presence of disubstituents at the α-carbon was required for the successful transformation. In contrast, in our system, the presence of a substituent is not required, which contradicts the previously reported reactions. Most importantly, the expected formation of C–N bonds with the cleavage of C–H bonds to lactams did not take place in our chelation system, in sharp contrast to the case of other similar *N*,*N*-chelation systems.[15] This result is an example of the importance of designing new directing groups for exploring new types of functionalizations of C–H bonds, which cannot be realized when using conventional directing groups. We are currently investigating the use of this new directing group in various functionalization reactions of C–H bonds.

This work was supported, in part, by a Grant-in-Aid for Scientific Research on Innovative Areas “Molecular Activation Directed toward Straightforward Synthesis” from Monbusho (The Ministry of Education, Culture, Sports, Science and Technology).

Supporting Information is available electronically on J-STAGE.

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