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Pt-Catalyzed sp^3 C–H bond activation of *o*-alkyl substituted aromatic carboxylic acid derivatives for the formation of aryl lactones

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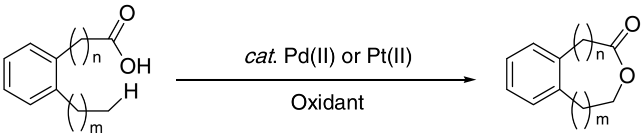
Abstract—Synthesis of aryl lactones from *ortho*-alkyl substituted aromatic carboxylic acids is described on the basis of sp^3 C–H bond activation using either palladium or platinum catalysts. Kinetic isotope studies reveal that the reaction takes place presumably by the chelation assistance of metal catalyst to the carboxylic group followed by the C–H bond activation.

Transition metal-catalyzed activation of carbon–hydrogen bonds has been perceived as challenging goals in organic synthesis owing to their robust nature.[1] In particular, selective functionalization of sp^3 C–H bonds is one of the most difficult targets, thus usually requiring stoichiometric amounts of metal complexes and/or harsh reaction conditions for that purpose.[2] As a result, finding a general method to make the unreactive bonds labile would have a significance impact. Thanks to the recent appearance of the active late transition metal catalyst systems, functionalization of certain types of aliphatic and aromatic C–H bonds has been possible via either a direct activation manner or a chelation-assisted strategy.[3]

Lactone is an important and ubiquitous building block in organic synthesis, materials science, polymer areas, and natural products chemistry.[4] Although various methods utilizing either the oxidation of benzylic C–H bond or insertion of carbon monoxide have been developed,[5] only a few direct approaches have been revealed for the construction of aryl lactones starting from *ortho*-alkyl substituted aromatic carboxylic acids or their derivatives via the sp^3 C–H bond activation (Eq. 1).[6] We describe herein our initial results on the Pd- and Pt-catalyzed direct lactonization of *o*-alkyl substituted carboxylates, and the preliminary mechanistic studies on the activation process are also presented.



(1)

For the one-step synthesis of aryl lactones from *o*-alkyl substituted aryl carboxylates, we initially investigated a wide range of metal catalyst systems in order to optimize reaction conditions.[7] Among the metal complexes examined, certain types of palladium(II) and platinum(II) catalysts exhibited discernable activities in the presence of additional oxidants or co-catalysts leading to the desired lactone product (Table 1).

When 2,4,6-trimethylbenzoic acid (**1**) was applied with the use of $Pd(OAc)_2$ (**3**, 20 mol %), 5,7-dimethylphthalide (**2**) was isolated in a moderate yield (44%) at 100 °C only in the presence of Na_2CO_3 (1.5 equiv) and MnO_2 (2.0 equiv, entry 3).[8] It was interesting to observe that atmospheric oxygen serves also as an oxidant although the efficiency of the reaction was lower compared to that of MnO_2 (entry 2). Use of toluene solvent

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Keywords: C–H Bond activation; Shilov catalyst system; Aromatic carboxylates; Lactones; Chelation assistance.

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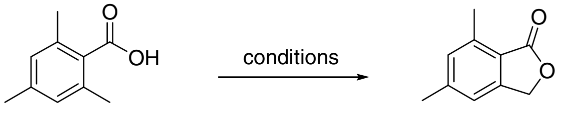
Table 1. Optimization of the catalyst system in the lactonization of 2,4,6-trimethylbenzoic acid (**1**)[a]



1 **2**

Entry	Catalyst	Additive	Base[b]	Solvent	Yield[c] (%)
1	$Pd(OAc)_2$ (**3**)	—	—	Chlorobenzene	0
2	**3**	O_2 (1 atm)	Na_2CO_3	Chlorobenzene	30
3	**3**	MnO_2[d]	Na_2CO_3	Chlorobenzene	44
4	**3**	MnO_2[d]	Na_2CO_3	Toluene	28
5	—	MnO_2[d]	Na_2CO_3	Chlorobenzene	<5
6	**3**	MnO_2[d]	—	Chlorobenzene	<5
7	**3**	MnO_2[d]	Et_3N	Chlorobenzene	<5
8	**3**	MnO_2[d]	Na_2CO_3	DMF	0
9	K_2PtCl_4 (**4**)	—	—	Water	0
10	—	K_2PtCl_6[e]	—	Water	0
11	**4**	K_2PtCl_6[e]	—	Water	60
12	**4**	$CuCl_2$ (1.0 equiv)	—	Water	23
13	**4**	$CuCl_2$ (3.0 equiv)	—	Water	56
14	—	$CuCl_2$ (3.0 equiv)	—	Water	0
15	$PdCl_2(PPh_3)_2$	—	Na_2CO_3	Chlorobenzene	13
16	$Pd(CH_3CN)_4BF_4$	—	Na_2CO_3	Chlorobenzene	31

[a] Palladium catalyst system: 20 mol % of **3**, 100 °C, 0.04 M and 9 h, and platinum catalyst system: 10 mol % of **4**, 150 °C, 0.01 M, and 24 h.

[b] 1.5 equiv of base was added.

[c] Isolated yield.

[d] 2.0 equiv were used.

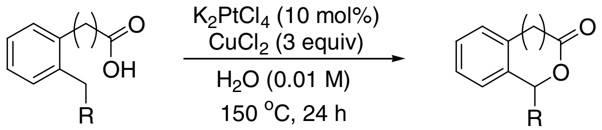
[e] 30 mol % was employed.

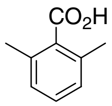
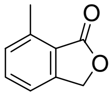
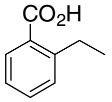
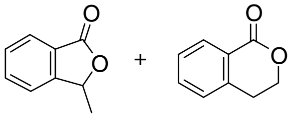
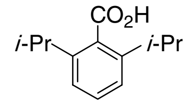
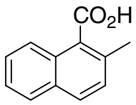
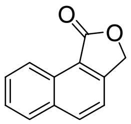
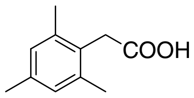
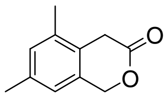
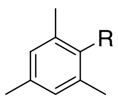
reduced the product yield mainly due to a side reaction, in which toluene itself is competitively activated to generate benzyl 2,4,6-trimethylbenzoate (20%) as a side product in addition to 5,7-dimethylphthalide (**2**, 28%, entry 4). Almost no desired product was observed in the absence of either a palladium catalyst (entry 5) or base (entry 6). Use of polar solvents such as 1,2-dimethoxyethane or DMF resulted in inhibition of the reaction (entry 8). Whereas $Pd(OAc)_2$ provided the highest yield (44%, entry 3) among various palladium catalysts examined, the use of others provided reduced yields under the same conditions, for example, $PdCl_2(PPh_3)_2$ in 13% and $Pd(CH_3CN)_4BF_4$ in 31%. It turned out that the lactonization suffered from decarboxylation under the palladium catalyst system, which limits the improvement on the yield and substrate scope. In addition, it was observed that the reaction has rather a narrow range of temperatures; if the temperature is below 90 °C, no reaction occurs. On the other hand, the substrates undergo complete decarboxylation at temperatures above 120 °C.[9]

Since a combination of $PtCl_4^{2-}/PtCl_6^{4-}$ in water (Shilov conditions) has been extensively investigated in the activation of unreactive bonds,[10] we next turned our attention to platinum catalyst system. With the platinum catalysis, decarboxylation seemed to be minimized to some degree compared to the corresponding palladium systems. In fact, when K_2PtCl_4 was applied in the presence of 0.30 equiv of K_2PtCl_6 in water, the desired lactone product was obtained up to 60% yield at 150 °C (entry 11). As expected, omission of any one platinum catalyst resulted in no conversion (entries 9 and 10). On the other hand, when the less expensive and more practical copper additive[11] was applied instead of a Pt(IV) cocatalyst, the reaction proceeded with an almost comparable efficiency (entry 13) compared to that obtained under the Shilov conditions. Although product yields were increased depending on the amounts of copper additive, the addition of $CuCl_2$ in more than 3.0 equiv did not improve the reaction efficiency.

To demonstrate the utility of the optimized lactonization protocol, a wide range of *o*-alkyl substituted aromatic carboxylic acid derivatives were then examined under the Pt(II)/Cu(II) systems (Table 2).[12] It was observed that *o*-toluic acid was also readily reacted under the conditions to afford phthalide (**5**) in acceptable yield (entry 1). When 2-ethylbenzoic acid was employed, both primary and secondary C–H bonds were activated, giving 3-methylphthalide (**6**, 10%) and 3,4-dihydridoisocoumarin (**7**, 35%), respectively. When an *iso*-propyl substituent is positioned *ortho* to the carboxylic acid group, the substrate was inert to the reaction conditions presumably due to steric reasons (entry 3). 2-Methylnaphthoic acid was subjected under the reaction condition to give 3(1*H*)-benzo[*e*]isobenzofuranone in 30% yield (entry 4). It should be mentioned that the lactonization protocol was also applied to arylacetic analogues in addition to benzoic acid derivatives. For example, 2,4,6-trimethylphenylacetic acid was subjected to the conditions and the corresponding substituted 3-isochromanone product was obtained in 35% yield (entry 5).[13] In addition, it is highly interesting to

Table 2. Lactonization of *o*-alkyl substituted aromatic carboxylates with the Pt catalyst system[a]



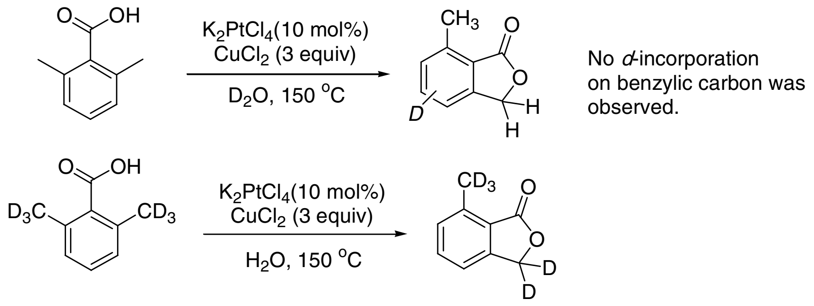
Entry	Substrate		Product(s)	Isolated yield (%)
1			 (**5**)	51
2			 (**6**) (**7**)	45 (**6**/**7** = 1:3.5)
3			No reaction	0
4				30
5				35
6		R = CO_2H	**2**	56
7		R = CO_2Et	**2**	43
8		R = $CONH_2$	**2**	65
9		R = CN	**2**	20

[a] See Ref. 12 for detailed experimental procedure.

note that the lactonization was achieved not only with carboxylic acids but also with their derivatives including esters, amides, and nitriles. For example, ethyl mestioate was converted to 5,7-dimethylphthalide (**2**) in 43% yield under the Pt(II)/Cu(II) system (entry 7). More significantly, the subject of corresponding benzamide and benzonitrile resulted in **2** although with lower yield in the later case (entries 8 and 9, respectively). This result suggests that the carboxylic derivatives are hydrolyzed in situ under the aqueous reaction conditions to the corresponding same carboxylic acid that is reacted to afford the lactone product.[14]

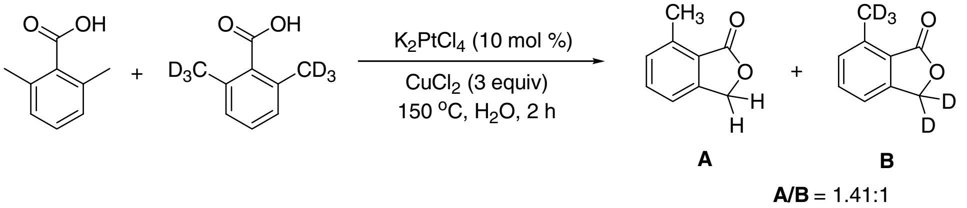
To gain insight into the mechanistic pathway in platinum catalysis, especially on the issue whether chelation of the catalyst to the carboxylic acid group occurs prior to the activation of C–H bond, we adopted both inter- and intra-molecular competitive reactions using deuterium-labeled 2,6-dimethylbenzoic acids.[15] It is assumed that, analogous to the conclusion of the recent reports on the kinetic isotope studies for the elucidation of chelation effects,[16] the measured k_H/k_D values would be nearly the same in both competitive reactions provided that C–H bond cleavage proceeds without coordination of the metal to the carboxylic acid group. On the other hand, if the present reaction involves the coordination of carboxyl group to the metal center prior to C–H bond cleavage, the k_H/k_D values in these labeling experiments should be different.

To make sure that this deuterium experiment is not complicated by H/D exchange reaction with water, 2,6-dimethylbenzoic acid was applied to the reaction condition under D_2O. It was found that the deuterium was not incorporated into methyl group of the substrate although *d*-incorporation was observed on the aromatic ring, thus suggesting that this reaction may proceed via electrophilic substitution with Pt(II) species. On the other hand, no deuterium was incorporated on the aromatic ring when 2,6-bis(trideuteriomethyl)benzoic acid was subjected to the reaction conditions in H_2O.

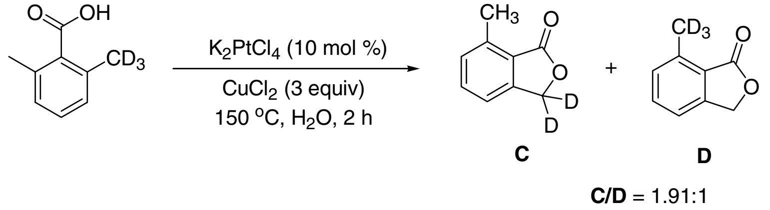


(2)

Values of kinetic isotope effects (KIE) were next measured in both inter- and intramolecular competition reaction. When 2,6-bis(trideuteriomethyl)benzoic acid and 2,6-dimethylbenzoic acid were applied at the same time to the reaction conditions,[17] the kinetic isotope effects value of the intermolecular competitive reaction was measured to be $k_H/k_D = 1.41 \pm 0.01$ (Eq. 3). This is significantly different from that of intramolecular reaction with 6-methyl-2-trideuteriomethylbenzoic acid ($k_H/k_D = 1.91 \pm 0.04$, Eq. 4). In each case, the extents of the deuterium incorporation were determined to be more than 95% based on the ^{1}H NMR integration. This result may support that the chelation of platinum metal to carboxylic group takes place prior to the C–H bond cleavage on the basis of the previous relevant mechanistic studies.[16] As a consequence, it is presumed that activation of C–H is considerably assisted by the chelation effects although the detailed pathway of the activation itself is not clear at the present stage.[18]



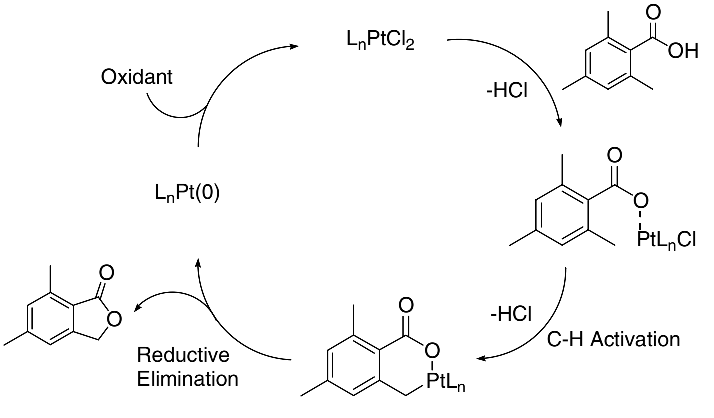
(3)



(4)

Based on the KIE results, a plausible mechanism is tentatively presented in Scheme 1. After initial chelation of metal center to carboxylic acid oxygen, it is assumed that the metal activates the adjacent benzylic C–H bond. Subsequent reductive elimination of the putative intermediate is presumed to complete the catalytic cycle with concomitant reoxidation of metal from zero oxidation state to metal(II) state.

In summary, we have demonstrated that either platinum or Pd catalysts can activate sp^3 carbon–hydrogen bond, converting aromatic benzoic acid derivatives to the corresponding lactones in moderate yield. On the basis of



Scheme 1. Plausible mechanism for the present transdormation.

the isotope studies, the lactonization is presumed to occur via C–H activations. Although the present results show that it has a rather limited substrate scope with modest selectivity for the formation of lactones, it is believed that further studies would lead to better catalysts system.

Acknowledgements

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8. *Representative experimental procedure using a palladium catalyst system*: To a solution of 2,4,6-trimethylbenzoic acid (**1**, 20.0 mg, 0.12 mmol), Na_2CO_3 (26 mg, 0.18 mmol) and MnO_2 (16 mg, 0.24 mmol) in chlorobenzene (3.0 mL, 0.04 M) was added 20 mol % of $Pd(OAc)_2$ (5.4 mg, 0.024 mmol). The reaction mixture was stirred for 9 h at 100 °C and the product was isolated by a silica gel chromatography (hexane) to give 5,7-dimethylphthalide (**2**) in 44% yield.
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13. Interestingly, when *o*-tolylacetic acid was employed as a substrate, we only obtained phthalide in 13% yield instead of either 3-isochromanone or 4-methyl-3*H*-benzofuran-2-one.
14. In the absence of catalyst, benzamide, benzoate and benzonitrile are completely hydrolyzed to benzoic acid in water at 150 °C within 1 h.
15. Intermolecular competition experiments: a mixture of 2,6-bis(trideuteriomethyl)benzoic acid (44 mg), 2,6-dimethylbenzoic acid (44 mg, 1 equiv), K_2PtCl_4 (12 mg, 10 mol %) and $CuCl_2$ (120 mg, 3 equiv) in H_2O (6 mL) was heated for 2 h at 150 °C (ca. half conversion was made). The crude products were analyzed by H NMR using an internal standard (1,4-dimethoxybenzene) to reveal that the lactone product is 41% deuterium-incorporated meaning that $k_H/k_D = 1.41 \pm 0.01$.
   Intramolecular competition experiments: a mixture of 6-methyl-2-trideuteriomethylbenzoic acid (44 mg, 0.3 mmol), K_2PtCl_4 (6 mg, 10 mol %) and $CuCl_2$ (60 mg, 3 equiv) in H_2O (3 mL) was heated for 2 h at 150 °C (ca. half conversion was made) to reveal that $k_H/k_D = 1.91 \pm 0.04$ (average of three time experiments).
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