Homogeneous Catalysis

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Palladium-Catalyzed Intramolecular *ipso*-Friedel–Crafts Alkylation of Phenols and Indoles: Rearomatization-Assisted Oxidative Addition**

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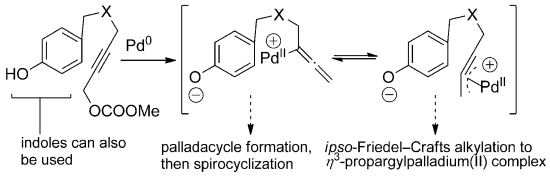
Spirocyclohexadienones are recognized as versatile intermediates for complex molecule syntheses. Functionalization of the cyclohexadienone unit provides efficient and rapid access to multicyclic molecular frameworks.[1] A number of natural product syntheses have been achieved using spirocyclohexadienones as key intermediates.[2] The development of an innovative method for synthesizing spirocyclohexadienones is therefore in high demand because of its potential impact on synthetic organic chemistry.

Dearomatization of phenols is one of the most straightforward approaches to the synthesis of spirocyclohexadienones. Among such methods, transition-metal-catalyzed intramolecular nucleophilic dearomatization of phenols has attracted recent attention.[3,4] Key to the success of this dearomatization process is whether the intramolecular C alkylation can be preferentially promoted over the competitive intermolecular O alkylation. We recently demonstrated that the present chemoselectivity issue was successfully controlled in a palladium-catalyzed intramolecular *ipso*-Friedel–Crafts allylic alkylation of *para*-substituted phenols with an allylic carbonate unit to give spiro[4.5]cyclohexa-dienones in excellent yield.[3a]

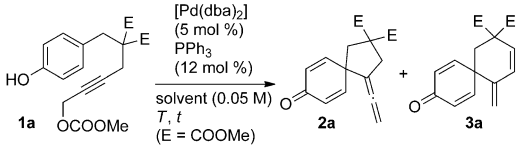
Reaction of propargyl carbonates with a palladium catalyst provides an equilibrium mixture of η^1-allenyl-palladium(II) complexes and η^3-propargyl-palladium(II) complexes.[5] Various catalytic transformations have been developed based on the electrophilic reactivity of these palladium complexes.[6] We envisioned that these complexes would be adaptable to palladium-catalyzed intramolecular nucleophilic dearomatization of phenols, thus providing novel access to functionalized spirocyclohexadienones (Scheme 1). Moreover, the use of indole variants in the same catalytic process would result in the formation of aza-spirocycles.[7] Herein, we report a novel synthetic method for spirocyclic molecules based on palladium-catalyzed intramolecular *ipso*-Friedel–Crafts alkylation of phenols and indoles. Mechanistic studies revealed that the reaction proceeds through an unprecedented rearomatization-assisted oxidative addition.



Scheme 1. Reaction design.

Our studies began with the model substrate **1a** (Table 1).[8] We first examined the reaction using 5 mol% $[Pd(dba)_2]$ and 12 mol% PPh_3 in CH_2Cl_2, which are the optimum reaction conditions for the palladium-catalyzed intramolecular *ipso*-Friedel–Crafts allylic alkylation of phenols.[3a] The reaction proceeded sluggishly to afford a mixture of spirocyclic adducts, **2a** and **3a** in a ratio of 94:6, in 15% yield. The use of other common solvents failed to improve the yield of spirocyclic adducts, and **2a** was mainly obtained in all cases (entries 1–4). The reactivity increased when the reaction was performed in a CH_2Cl_2/MeOH solvent mixture, and the ratio of **2a** and **3a** changed to 61:39 (entry 5). A prolonged reaction time resulted in consumption of most of the starting material, and interestingly, the ratio of **2a** and **3a** changed to

Table 1: Optimization of the reaction conditions.



Entry	Solvent	*T* [°C][a]	*t* [h]	Yield [%][b] (**2a**/**3a**)
1	CH_2Cl_2	RT	18	15 (94:6)
2	THF	RT	18	no reaction
3	DMF	RT	18	15 (88:12)
4	MeOH	RT	18	22 (94:6)
5	CH_2Cl_2/MeOH (4:1)	RT	18	78 (61:39)
6	CH_2Cl_2/MeOH (4:1)	RT	48	96 (13:87)
7	CH_2Cl_2/MeOH (4:1)	40	10	100 (4:96)
8	$(CH_2Cl)_2$/MeOH (4:1)	60	4	100 (95)[c] (0:100)

[a] RT: 20–25 °C. [b] Yield of the mixture of **2a** and **3a**, which are inseparable by chromatography. Yield and ratio were determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of isolated product. dba = dibenzylideneacetone, DMF = *N*,*N*′-dimethylformamide, THF = tetrahydrofuran.

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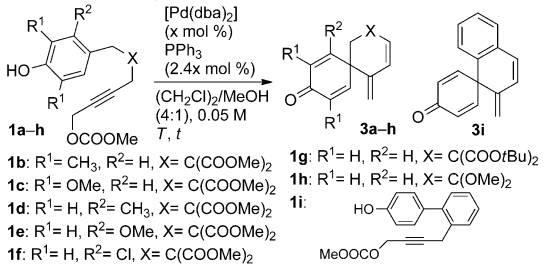
13:87 (entry 6). Similar results were obtained when the reaction was performed at 40 °C (entry 7). The best result was obtained when the reaction was performed at 60 °C in a $(CH_2Cl)_2$/MeOH solvent mixture, and **3a** was isolated in 95 % yield as the sole product (entry 8).[9]

We next examined the scope and limitations of different substrates under the optimized reaction conditions. Spirocyclization of **1a** could be performed even in the presence of 1 mol % of the palladium catalyst, thus giving **3a** in 97 % yield (Table 2, entry 1). The *ortho*-disubstituted phenol derivatives

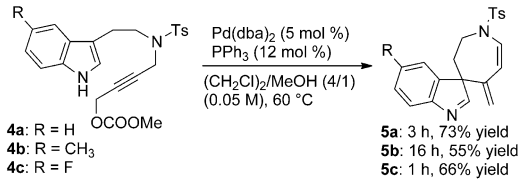
Table 2: Substrate scope.



Entry	Substrate	Pd cat. (mol %)	T [°C][a]	t [h]	Product	Yield [%][a]
1[b]	**1a**	1	60	21	**3a**	97
2	**1b**	5	80	5	**3b**	99
3	**1c**	5	80	5	**3c**	93
4	**1d**	5	60	4	**3d**	85
5	**1e**	5	80	21	**3e**	94
6	**1f**	5	60	18	**3f**	72
7	**1g**	5	60	2	**3g**	93
8	**1h**	5	60	6	**3h**	92
9	**1i**	5	60	0.5	**3i**	91

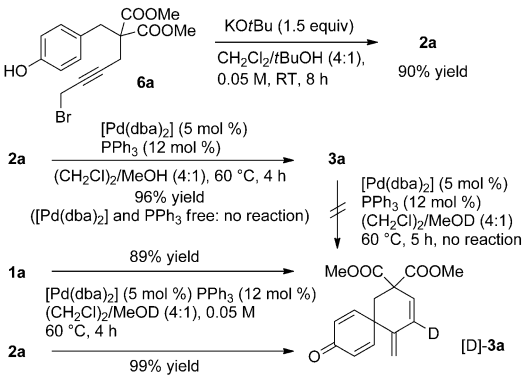
[a] Yield of isolated product. [b] [**1a**] = 0.1 M.

1b and **1c**, as well as the *meta*-substituted phenol derivatives **1d–f**, were also effective substrates for this reaction, and products having a spiro[5.5]cyclohexadieneone skeleton (**3b–f**) were obtained in 72–99 % yield (entries 2–6). Moreover, spirocyclization of **1g** and **1h**, bearing a bulky di(*tert*-butyl)malonate tether and a dimethyl acetal tether, respectively, proceeded smoothly to give the corresponding products **3g** and **3h** in high yield (entries 7 and 8). The biphenyl-type substrate **1i** was also applicable to this reaction, thus providing the corresponding product **3i** in 93 % yield (entry 9). Furthermore, this catalytic system was effective for nucleophilic dearomatization of indoles (Scheme 2). When the tryptamine derivatives **4a–c** were treated under the optimized reaction conditions, aza-spirocyclic adducts with a diene motif (**5a–c**) were obtained in good yield.



Scheme 2. Indole-type substrates.

As shown in Table 1, characteristic reaction profiles were observed in this spirocyclization. We performed the following experiments to gain preliminary insight into the reaction mechanism (Scheme 3). First, to elucidate the reactivity, **2a**



Scheme 3. Experiments for elucidating the reaction mechanism.

was prepared from **6a** in 90 % yield using a base-promoted nucleophilic dearomatization. Although no reaction occurred when **2a** was heated in a $(CH_2Cl)_2$/MeOH solvent mixture, clean transformation of **2a** into **3a** was observed in the presence of a palladium catalyst. When either **1a** or **2a** were treated with the palladium catalyst in a $(CH_2Cl)_2$/MeOD solvent mixture, [D]-**3a** was obtained in excellent yield. In addition, **3a** was not converted into [D]-**3a** under the same reaction conditions. These results indicated that both **1a** and **2a** were converted into **3a** through the same η^3-propargylpalladium(II) intermediate. A time-course experiment using the optimized conditions revealed interesting reaction profiles (Figure 1).[8] In the initial stage, **1a** was preferentially

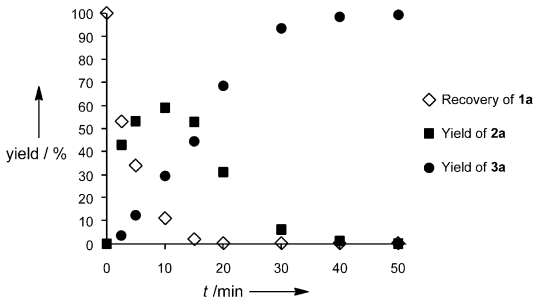


Figure 1. Time-course experiments using **1a**.

transformed into **2a**, and then **3a** gradually formed in proportion to the increase in the production of **2a**. In the second half of the reaction, **3a** was mainly produced from **2a**.

These findings led us to propose a plausible reaction pathway for this process (Scheme 4). First, oxidative addition of **1a** to Pd^0 forms the η^1-allenylpalladium(II) species **A**. The formation of the palladacycle intermediate **B** and subsequent reductive elimination, proceeds rapidly to give **2a** as an initial product. A rearomatization-assisted oxidative addition of **2a** to Pd^0 subsequently occurs to afford an equilibrium mixture

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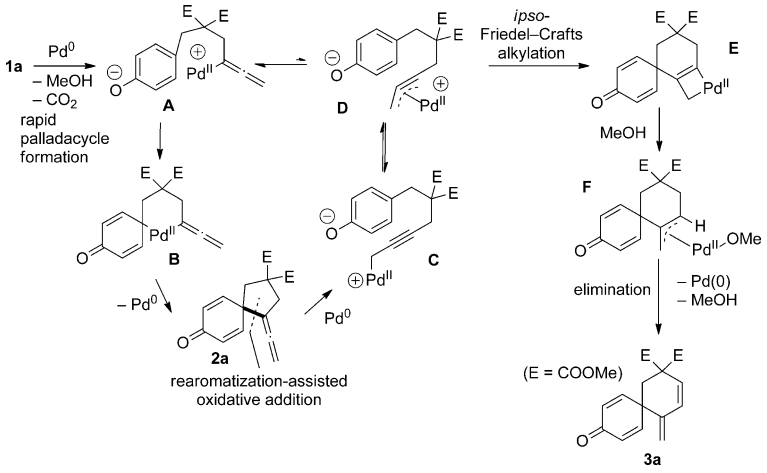
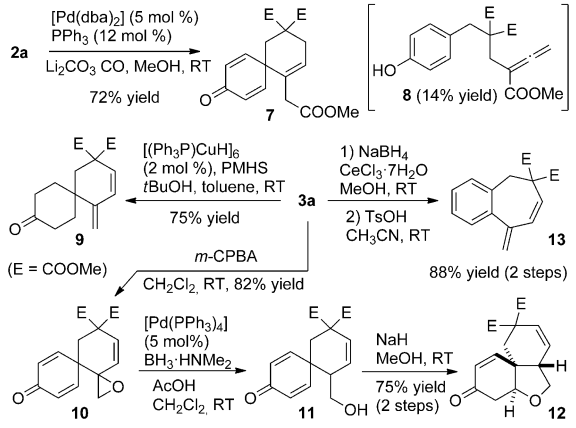


Scheme 4. Proposed reaction mechanism.

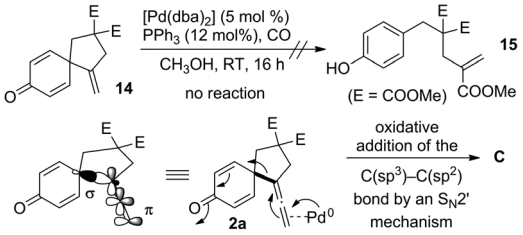
of the η^1- and η^3-propargylpalladium(II) complexes **C** and **D**. Intramolecular *ipso*-Friedel–Crafts alkylation of the phenol proceeds on the central carbon atom of the η^3-propargylpalladium(II) moiety to affords the palladacyclobutene intermediate **E**.[10] Subsequent protonation by MeOH generates the π-allylpalladium(II) complex **F**, which is finally converted into **3a**.

2a and **3a** could be utilized as versatile intermediates for synthesizing multicyclic molecules (Scheme 5). When **2a** was treated with a palladium catalyst in MeOH under a CO atmosphere, **7** was obtained in 72% yield, accompanied by the formation of **8**.[8] A copper-catalyzed conjugate reduction of **3a** provided the spirocyclohexanone derivative **9** in 75% yield, and epoxidation of **3a** preferentially occurred at the exocyclic olefin, thus affording **10** in 82% yield. A palladium-catalyzed reductive epoxide-opening reaction of **10**[11] and subsequent base-promoted intramolecular conjugate addition gave the tricyclic fused heterocycle **12** in 75% yield (2 steps). Luche reduction of **3a** and subsequent treatment with *p*-toluenesulfonic acid, gave the bicyclic compound **13** in 88% yield (2 steps). These results demonstrate the high potential of the developed method in organic synthesis.



Scheme 5. Derivatization of **2a** and **3a**. *m*CBPA = *meta*-chloroperbenzoic acid, PMHS = poly(methylhydroxysilane).

In striking contrast to **2a**, no reaction occurred when compound **14**, which was prepared using Buchwald's method,[3c,8] was treated with a palladium catalyst in MeOH under a CO atmosphere. This finding clearly indicated that the allenyl spirocyclohexadienone motif in **2a** is essential for oxidative addition (Scheme 6). The π orbital on the terminal double bond of the allene is coplanar with the σ orbital of the C_{sp^3}–C_{sp^2} bond, which is cleaved during the oxidative addition process. We speculate that this coplanarity would facilitate the electron transfer from Pd^0 to the cyclohexadienone moiety, thus promoting oxidative addition of the C_{sp^3}–C_{sp^2} bond to the palladium catalyst through an S_N2' mechanism. To the best of our knowledge, this is the first example of an oxidative addition of C–C bond based on the rearomatization of spirocyclohexadienones.[12]



Scheme 6. The mode of oxidative addition.

In conclusion, we developed a novel method for synthesizing spirocycles based on a palladium-catalyzed intramolecular *ipso*-Friedel–Crafts alkylation of phenols and indoles to η^3-propargylpalladium(II) complexes. Preliminary mechanistic studies revealed that the reaction proceeds through an unprecedented rearomatization-assisted oxidative addition. Further studies of an asymmetric version of this process, as well as a more detailed mechanistic investigation, are in progress.

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