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Incorporation of norbornene moiety onto the arene of diaryl substituted amides through C-H functionalization

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ABSTRACT

In the presence of norbornene, Pd(OAc)$_2$ smoothly catalyzed the *meta*-C-H activation process of N-phenylbenzamide (**4**) and yielded a norbornene fused product, (1*R*,4*S*,4a*R*,8b*S*)-N-phenyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene-5-carboxamide (**5a**). The employment of Ag(OAc) is crucial to the success of this reaction. Norbornene related compounds, dicyclopentadiene and norbordiene, were used as the reagents and structurally similar compounds, **5b** and **5c** were formed although with much lower yields. Similar reaction was carried out for using N-benzylbenzamide (**9**) as starting reagent. The resulted norbornene fused product (1R,4S,4aR,8bS)-N-benzyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene-5-carboxamide (**10**) shows that the C-H activation indeed took place at the phenyl ring of acetophenone part rather than the benzyl side. Crystal structures of **5a**, **5c** and **10** were determined by X-ray diffraction methods. A reaction mechanism is proposed to account for the formation of **5a**, which could be extended to describe the generation of other structurally related compounds as well.

1. Introduction

For the past few decades, the subject of the C-H activation on the *ortho*- and *meta*-sites of the substituted arene has attracted much attention from both experimental and computational perspective [1]. Many thrilling *ortho*-site C-H activation methods have been so far developed for this task [2]. Among those reactions, Catellani type reaction is generally regarded as one of the most competent means for carrying out C-H activation on the *ortho*-site of the starting arylhalide [3]. Nevertheless, the C-H activation on the *meta*-site of the substituted aryl ring remains a solemn challenge due to the fact that the *meta*-position is located farther away from the major active center [4]. Normally, *meta*-C-H activation requires the assistance of an elaborately designed directing group longer enough to support the weak coordinated transition metal moiety to reach the proximity of the targeted C-H bond [5]. Regardless of these foreseeable difficulties, a number of methods with variation on directing groups were pursued and some successful results were achieved [6].

Recently, Yu reported an interesting *meta*- C-H activation pathway by employing compound embedded amide group as the executing directing group.[7, 5(d)] The reaction was started with *N*,2-diphenylacetamide, **1**, and the addition of ethyl iodide. It was allowed to be carried out in the presence of norbornene and with other active ingredients. There are two major products, **2** and **3**, being observed and identified later (Scheme 1). The formation of the targeted compound **3** obviously showed that C-H activation process indeed took place at the *meta*-site of the originally substituted aryl ring. Moreover, the observation of **2** indicates the C-H activation process took place at both the *ortho*- and *meta*-sites. Interestingly, a benzocyclobutene skeleton was formed in the framework of **2** which is the consequence of the incorporation of norbornene moiety onto the phenyl ring of **1**.

Yu also proposed that the transition states for the formations of **2** and **3** are palladium-containing six-membered ring precursor thus greatly enhances the C-H activation rate [7]. We were wondering whether the formation of a five-membered ring precursor in the transition state, rather than a six-membered ring, is still workable for this reaction. Thereby, the original starting material *N*,2-diphenylacetamide was modified from both sides of the amide framework by extending or shrinking one carbon framework. Similar reactions starting with *N*-phenylbenzamide and *N*-benzylbenzamide were pursued and some absorbing results are reported herein.

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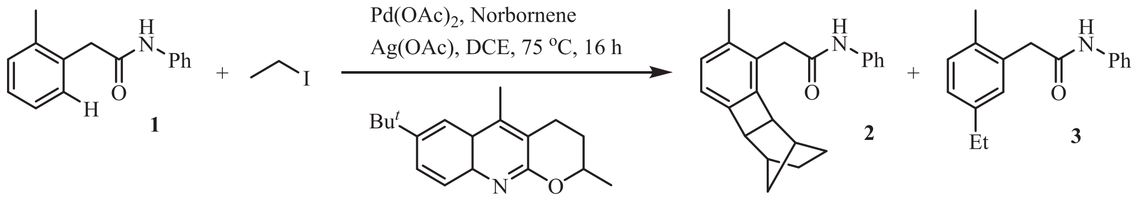


Scheme 1. Observation of *ortho*- and *meta*-C-H activations of *N*,2-diphenylacetamide reported in Yu's work.

2. Results and discussion

The reaction of *N*-phenylbenzamide (**4**) with norbornene in the presence of $Pd(OAc)_2$ and 4-phenylpyridine led to the formation of (1*R*,4*S*,4a*R*,8b*S*)-*N*-phenyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene-5-carboxamide (**5a**) (Scheme 2). The identity of **5a** was firstly characterized by spectroscopic methods. To our delight, suitable crystals for **5a** were obtained and the crystal structure of it was determined by X-ray diffraction methods. The crystal structure of **5a** indeed reveals that a benzocyclobutene skeleton was formed (Fig. 1). Four atoms, C(12), C(13), C(14), C(15), are almost coplanar which is indicated by the sum of their corresponding four angles (359.9°). The fact that the norbornene moiety incorporated into the phenyl ring in **5a** implies that the formation of a presumed five-membered ring intermediate could indeed take place *via* the reaction starting with **4**.

Subsequently, various combined reaction conditions to optimize the production yield of **5a** were pursued and results are listed in Table 1. Firstly, the combinations of base (K_2CO_3) with various oxidants were examined. It shows that the utilization of Ag(I) ion is better than Cu(I) ion (Entries 2 & 3 vs. 4, 5 & 6); and, Ag(OAc) is better than Ag_2CO_3 (Entry 2 vs. 3) in terms of yield. Recently, Larrosa [8] and Sanford [9] mentioned that carboxylate framework is beneficial to the formation of transition state and activation of C-H bond in arene through a Concerted Metalation Deprotonation (CMD) mechanism [10]. Moreover, the reaction was not able to execute without the employment of Ag(I).

The reaction mechanism for the formation of **5a** is proposed as shown below (Scheme 3) [5(d),11]. Initially, Ag(I) source acts as an oxidant as well as an inducing agent to polarize the carbonyl group of **4** which facilitates the removal of proton on amine while experiencing the attack by a Pd(II) species to form intermediate **I**. The formation of a five-membered ring **II** and the subsequent norbornene insertion to form **III** are the keys to the success of this reaction. It is followed by the acidification of **III** by HX in **IV**. The presence of carboxylate is also crucial for the CMD mechanism which might take place from **V** to **VI**. The final product **5a** is the result of the reductive elimination process from **VI**. Obviously, this process will be unlikely to take place at the N-phenyl side since a four-membered ring, having severe internal strain, will be formed.

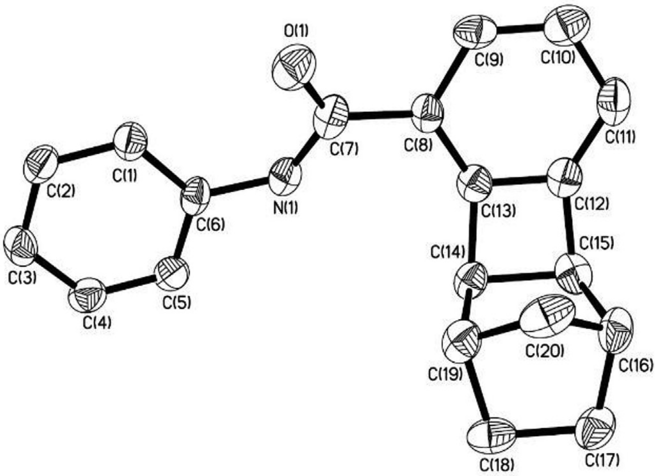


Fig. 1. ORTEP drawing of compound **5a**. Hydrogen atoms are omitted.

Table 1
Various reaction conditions for the production of **5a**.[a]

Entry	Oxidant	Yield[b] (%)
1	–	–
2	Ag(OAc)	92
3	Ag_2CO_3	55
4	CuI[c]	2
5	CuI	4
6	$Cu(OAc)_2$	Trace[d]

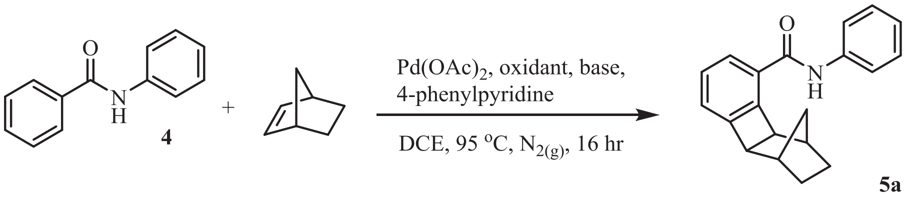
[a] Conditions: N-phenylbenzamide (0.5 mmol), norbornene (0.75 mmol), $Pd(OAc)_2$ (10.0 mol%), oxidant (1.5 mmol), 4-phenylpyridine (20.0 mol%), dichloroethane (5.0 mL), 95 °C, 16 h.

[b] Isolated yield.

[c] With 1.0 mmol K_2CO_3.

[d] Observed from TLC against standard compound.

The major structural motif of dicyclopentadiene can be regarded as a counterpart of norbornene [12]. Their chemical reactivities were often compared in ring-opening metathesis polymerization (ROMP) [13]. However, the extended fragment of dicyclopentadiene, compared to norbornene, might provide the steric repulsion which is needed for its extrusion from the catalytic cycle, a compelling factor for Catellani reaction [14]. Besides, norbornadiene can also be regarded as a derivative of norbornene with one



Scheme 2. The synthesis of compound **5a** from **4** and norbornene.