Pd-Catalyzed Intramolecular Acylation of Aryl Bromides via C—H Functionalization: A Highly Efficient Synthesis of Benzocyclobutenones

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · JANUARY 2010

Impact Factor: 12.11 · DOI: 10.1021/ja909811t · Source: PubMed

J|A|C|S COMMUNICATIONS

Published on Web 12/28/2009

Pd-Catalyzed Intramolecular Acylation of Aryl Bromides via C−H Functionalization: A Highly Efficient Synthesis of Benzocyclobutenones

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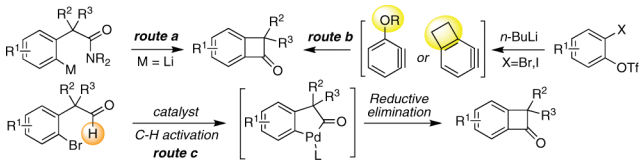
Benzocyclobutenones (BCBs) are an intriguing class of four-membered-ring ketones.[1] Their large ring strain and the great electrophilicity of their carbonyl unit make them highly susceptible to further manipulation. As a result, they have been successfully used as powerful intermediates in a wide variety of remarkable synthetic transformations,[1a,2] even in the context of the total synthesis of complex molecules.[3] Surprisingly, however, a limited number of methods have been developed for the selective formation of BCBs. Indeed, their synthesis is usually accomplished by intramolecular cyclization of stochiometric organolithium reagents (route a, Scheme 1)[4] or [2 + 2] cycloadditions (route b, Scheme 1).[1a,5] In the latter, the regioselectivity can be nicely controlled by the elegant approach of Suzuki using either proximal ring strain[5a] or α-alkoxybenzynes.[5b,c] However, the need for such *ortho*-directing groups as well as the use of highly reactive organolithium species might become important issues when preparing backbones with sensitive functional groups. Therefore, more general and direct routes to BCBs, particularly the design of regioselective strategies with the metal source being catalytic, would be highly desirable.

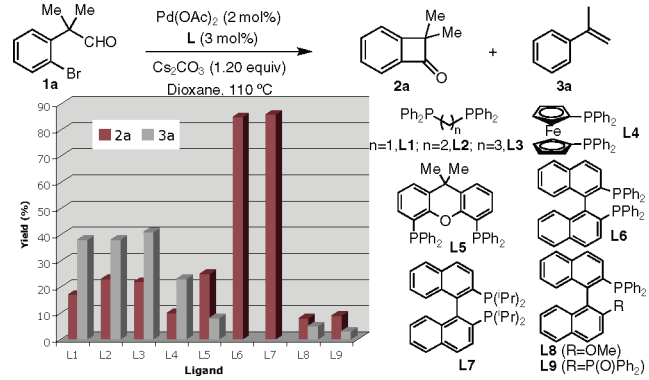
Scheme 1



In recent years, metal-catalyzed acylation of π systems such as alkenes and alkynes have become powerful tools in organic synthesis.[6] Despite the advances realized,[7−9] particularly the Heck-type process recently reported by Xiao,[10,11] direct acylation of aldehydes with aryl halides via metal-catalyzed C−H bond functionalization remains less explored.[12,13] As part of our investigations into Pd chemistry,[14] we present herein a versatile intramolecular acylation of aryl bromides via a C−H bond-functionalization event for the synthesis of BCBs (route c, Scheme 1).[15,16] The protocol is distinguished by its wide scope, thus opening access to functionalized BCB cores with a diverse set of substitution patterns that are beyond reach otherwise.

We began our study using readily available **1a** as the model substrate (Table 1).[17] A variety of experimental variables, such as the Pd precatalyst, ligand, base, and solvent, were systematically examined. After several rounds of optimization, we found that the best results were accomplished using $Pd(OAc)_2$, Cs_2CO_3, and a bidentate diarylphosphine in dioxane at 110 °C. Under these reaction conditions, we obtained variable amounts of **2a** and **3a**. While low conversions to **2a** were found for commonly employed **L1**−**L5**, the use of the binaphthyl-type ligands **L6** and **L7** *exclusively* afforded **2a** with *not even a trace* of **3a** detected in the crude reaction mixtures. At present, we have no explanation for this

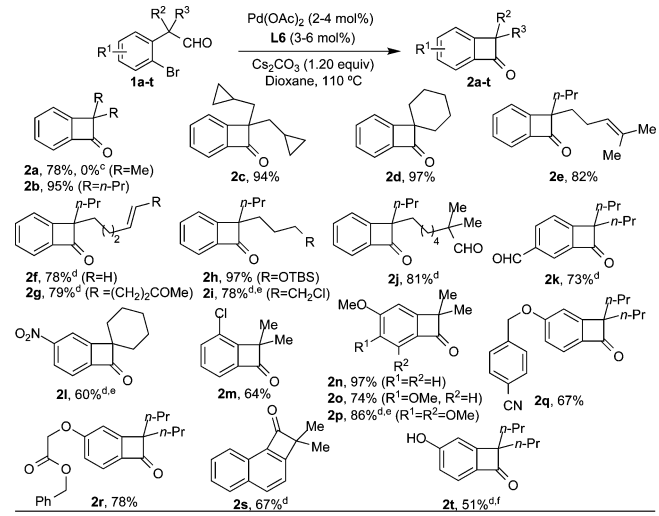
Table 1. Optimization of Reaction Conditions



behavior. Importantly, **L8** and **L9** gave low conversions to either **2a** or **3a**, thus indicating that the nature of the diarylphosphine backbone is crucial to the reactivity of the catalyst system. It is worth mentioning that at the same time we conducted our work, Larock reported the synthesis of styrene derivatives **3a** in modest yields;[18] interestingly, **2a** was not formed under their reaction conditions.

Having established the optimized reaction conditions, we set out to explore the scope of this reaction. As shown in Table 2, a host of aryl bromides with *ortho*, *meta*, or *para* electron-donating or electron-withdrawing substituents reacted with good to excellent

Table 2. Pd-Catalyzed Synthesis of Benzocyclobutenones[a,b]



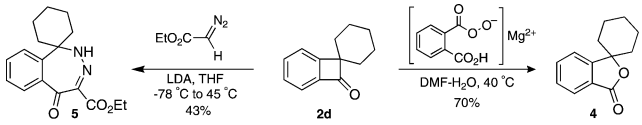
[a] Conditions: ArBr (0.5 mmol), $Pd(OAc)_2$ (2 mol %), **L6** (3 mol %), Cs_2CO_3 (0.6 mmol), dioxane (2 mL), 110 °C. [b] Isolated yields, average of two runs. [c] From ArCl. [d] $Pd(OAc)_2$ (4 mol %). [e] Using **L7**. [f] Cs_2CO_3 (2.40 equiv).

10.1021/ja909811t

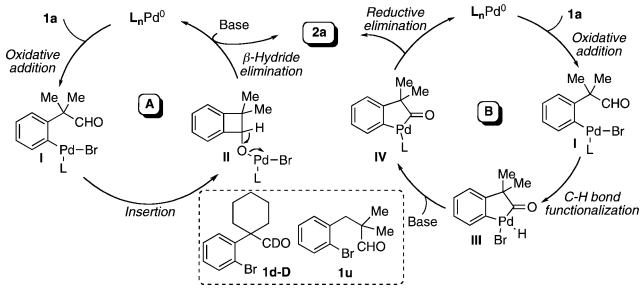
yields. Unlike other [2 + 2] cycloaddition approaches, the regioselectivity is totally controlled for unsymmetrical substrates, thus avoiding the need for directing-group methodologies.[5] Particularly significant is the chemoselectivity profile of this new protocol, as alkenes (**2e**, **2f**), esters (**2r**), nitriles (**2q**), aldehydes (**2j**, **2k**), ketones (**2g**), free hydroxy (**2t**), silyl groups (**2h**), alkyl halides (**2i**), and nitro groups (**2l**) all were perfectly accommodated. These results are noteworthy, as classical methods are not suitable for highly functionalized substrates.[1] As clearly shown by the formation of **2s**, this protocol could be extended to naphthyl derivatives as well. Furthermore, aryl chlorides were found to be inert (**2m**), thus providing a convenient functional handle for further functionalization. Although *o*-methoxy substituents did not hinder the reaction (**2p**), it was necessary to use the more bulky and electron-rich ligand **L7**. Gratifyingly, the acidic α-protons in **1g** and **1r** did not interfere with productive formation of **2g** and **2r**, respectively.[19] Finally, although the overall NMR data unambiguously identified the BCB core, we independently confirmed it by X-ray analysis of **2t**.[17]

Next, we turned our attention to the synthetic applicability of the resulting BCBs obtained using our method. As shown in Scheme 2, lactone **4** and benzodiazepine **5** could be easily obtained in one step by Baeyer−Villiger oxidation[2g] and diazomethylene insertion[2b] from **2d** in 70 and 43% yield, respectively.

Scheme 2. Synthetic Applicability of Benzocyclobutenones



Scheme 3. Proposed Catalytic Cycles



In principle, two mechanisms are conceivable for the results highlighted in Table 2 (Scheme 3): (1) 4-*exo*-trig-type insertion across the C=O bond from the oxidative addition complex **I**[20] followed by β-hydride elimination (mechanism **A**) or (2) C−H functionalization, loss of HBr from Pd(IV) intermediate **III**,[21] and a *challenging reductive elimination* from the five-membered metallacycle **IV** (mechanism **B**). As the available data do not allow us to distinguish between these two mechanisms, we reasoned that we could gather indirect evidence by studying the cyclization of **1u**. While **1u** would be expected to react faster via a 5-*exo*-trig-type cyclization in mechanism **A**,[22] a mechanism of type **B** would deal with a less favorable six-membered palladacycle. We found that **1u** did not cyclize under our optimized protocol; although this is not conclusive, we believe this experiment supports mechanism **B**. More interestingly, a kinetic isotope effect ($k_H/k_D = 2.8$) was observed when comparing the reaction rates of **1d** and the monodeuterated substrate **1d-D** (Scheme 3). This result implies that C−H bond cleavage is rate-limiting, thus providing further experimental evidence for mechanism **B**.[23]

In summary, we have developed a new protocol for the intramolecular acylation of aryl bromides via C−H functionalization. The practicality of the method, as well as the vast array of functionalized substrates with diverse substitution patterns that can be accessed, renders this method a powerful alternative to other approaches for the synthesis of BCBs. Further investigations of related processes are ongoing in our laboratories.

Acknowledgment. We thank the ICIQ Foundation and Consolider Ingenio 2010 (CSD2006-0003) for financial support. Johnson Matthey and Umicore are acknowledged for a gift of metal sources. We thank Dr. Benet-Buchholz and Dr. Bozoglian for obtaining the X-ray structure of **2t** and kinetic data. R.M. and A.F.-G. thank MICINN for a RyC and predoctoral fellowship (FPU).

Supporting Information Available: Experimental procedures, spectral data for all compounds, and crystallographic data for **2t** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA909811T