Tetrahedron 69 (2013) 4479–4487

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Palladium-catalyzed ring-opening of cyclopropyl benzamides: synthesis of benzo[*c*]azepine-1-ones via C($sp^3$)–H functionalization

Carolyn L. Ladd, Daniela Sustac Roman, André B. Charette *

*Centre in Green Chemistry and Catalysis, Department of Chemistry, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, QC H3C 3J7, Canada*

ARTICLE INFO

*Article history:*
Received 30 November 2012
Received in revised form 18 February 2013
Accepted 22 February 2013
Available online 26 February 2013

*Keywords:*
Cyclopropane
Palladium catalysis
C–H functionalization
Benzoazepines
Silver

ABSTRACT

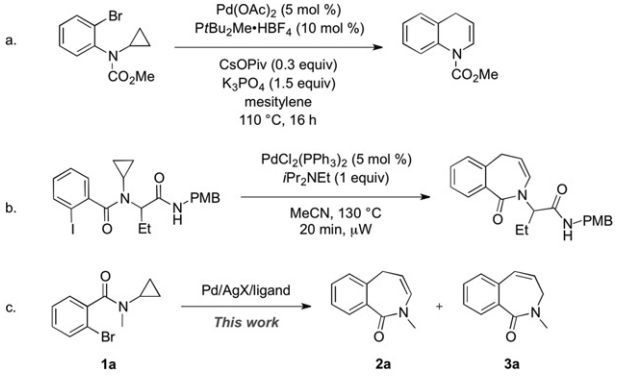
A variety of difficult to obtain benzo[*c*]azepine-1-ones are synthesized via a novel palladium-catalyzed, silver-promoted intramolecular cyclization of cyclopropyl benzamides. This biologically important class of molecules is prepared in an efficient and high-yielding manner from easily accessible starting materials. Both aryl bromides and iodides are effective substrates for the transformation. Mechanistic studies indicate that the reaction proceeds through a cyclopropyl C($sp^3$)–H cleavage step, followed by ring-opening, deprotonation, and reductive elimination.



## 1. Introduction

The transformation of C–H bonds via palladium catalysis has emerged as a reliable method for the design of complex chemical architectures.[1] In particular, the direct functionalization of $sp^2$ centers has been well established.[2,3] Lately, the activation of the more challenging $sp^3$ C–H bonds has gained considerable attention from the organic synthetic community.[4,5] The cyclopropyl unit is a predominant building block in medicinal chemistry, and considerable efforts have been directed toward its synthesis and functionalization.[6] Cyclopropanes have unique physical, chemical, and electronic properties as a result of ring strain; its carbon atoms display $sp^2$-like properties, which makes them an attractive target for C–H bond functionalization processes. The research program in our group has focused on developing novel methodologies aimed toward the enantioselective synthesis of a variety of substituted cyclopropanes, as well as their functionalization via metalation and cross-coupling reactions.[7] The opening of cyclopropyl rings is also a versatile transformation, as it can lead to the formation of complex molecules that are hard to obtain through other means.[8] However, the direct C–H functionalization of cyclopropanes remains largely undeveloped in organic synthesis.

More recently, Fagnou et al. have disclosed the elegant formation of quinoline and tetrahydroquinoline derivatives (Scheme 1a).[9] The reaction proceeds via Pd(0)-catalyzed cyclopropyl C–H bond functionalization mediated by pivalate via a concerted metalation–deprotonation (CMD) transition state. This is followed by ring-opening, deprotonation and finally C($sp^2$)–C($sp^3$) bond formation via reductive elimination. The proposed mechanism is supported by the lack of reaction in the absence of catalytic pivalate, a well-known additive in C–H bond activation pathways.[10] The tetrahydroquinolines thus formed were prone to decomposition; consequently, an aromatization protocol to the




**Scheme 1.** Pd-catalyzed intramolecular cyclopropane opening.

* Corresponding author. Tel.: +1 514 343 6283; fax: +1 514 343 7586; e-mail addresses: barbara.bessis@umontreal.ca, andre.charette@umontreal.ca (A.B. Charette).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.02.080

corresponding quinoline species employing 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant was developed.[9] Another recent report presents the palladium-catalyzed ring-opening of aminocyclopropyl Ugi adducts and their subsequent intramolecular cyclization (Scheme 1b), although it is believed that this reaction does not proceed through a C–H activation process.[11]

Other efforts toward the intermolecular activation of cyclopropanes have focused on the use of directing groups to guide the transition metal into the C–H bond.[12] A notable example is the Pd(II)-catalyzed enantioselective direct arylation of cyclopropanes with boronate esters in the presence of amino acid-derived chiral ligands, which was disclosed by Yu et al.[12b]

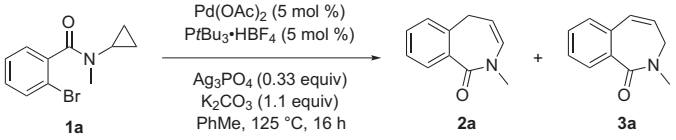
Due to our long-standing interest in both the synthesis and functionalization of cyclopropanes, our group has also been exploring various systems that would induce cyclopropyl C–H activation. In particular, we were interested in direct functionalization of cyclopropyl benzamides, such as **1a**, as its ring-opening would lead to the formation of novel seven-membered benzazepine-type products of particular significance in medicinal chemistry (Scheme 1c).[13] These products are not easily accessible through other routes;[14] furthermore, they may serve as precursors to other species, such as benzolactams.[15] Herein, we disclose the synthesis of novel benzo[*c*]azepine-1-ones via a palladium-catalyzed and silver-promoted ring-opening of cyclopropyl benzamides and present our mechanistic investigations that support a C($sp^3$)–H activation process.

## 2. Results and discussion

### 2.1. Reaction optimization

We chose cyclopropyl benzamide **1a** as our model substrate, as it is easily accessible from 2-bromobenzoic acid in two steps. We also hypothesized that the presence of the nitrogen lone pair would facilitate the opening of the cyclopropane. Screening of the catalyst, ligand, base and silver salt led to the optimal reaction conditions, which include $Pd(OAc)_2$ (5 mol %), $P^tBu_3 \cdot HBF_4$ (5 mol %), $K_2CO_3$ (1.1 equiv), and $Ag_3PO_4$ (0.33 equiv) in toluene at 125 °C (Table 1, entry 1). We observed the formation of two isomers, **2a** and **3a**[16] in

**Table 1**
Reaction optimization

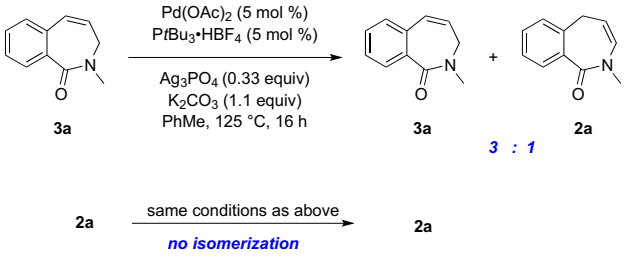



| Entry | Variation from standard conditions | Yield **2a**/**3a** (total)%[a] |
|---|---|---|
| 1 | None | 66/26 (92) |
| 2 | $PPh_3$ instead of $P^tBu_3 \cdot HBF_4$ | 18/15[b] (33) |
| 3 | $Ag_2CO_3$ instead of $Ag_3PO_4$ | 58/11 (69) |
| 4 | AgOAc instead of $Ag_3PO_4$ | 44/9 (53) |
| 5 | With 0.5 equiv $Ag_3PO_4$ | 47/27 (74) |
| 6 | Without $Ag_3PO_4$ | 0/0[c](0) |
| 7 | Without $Ag_3PO_4$, $K_3PO_4$ instead of $K_2CO_3$ | 5/1[c](6) |
| 8 | Without $Pd(OAc)_2$ | 0/0[c](0) |

[a] $^1H$ NMR yield using trimethoxybenzene as internal standard.
[b] Recovery of starting material (27%).
[c] Recovery of starting material (>80%).

a ratio of 2:1 and total yield of 92%. Replacing air-stable $P^tBu_3 \cdot HBF_4$ with other phosphine ligands, such as $PPh_3$ resulted in incomplete conversion (entry 2). One equivalent of silver was critical, as no reaction occurred in its absence (entry 6); also, increasing the silver loading resulted in diminished yields (entry 5). Other silver sources were also screened (entries 3 and 4), but $Ag_3PO_4$ gave the highest yield. Omitting $Ag_3PO_4$ and adding the phosphate ion in the form of $K_3PO_4$ resulted in trace amounts of the product (entry 7), thus, further establishing the crucial role of the silver additive. Finally, no reaction occurred in the absence of the palladium catalyst (entry 8).

Products **2a** and **3a** were easily separable by column chromatography.[17] When the reaction was stopped after 30 min, we observed the formation of **2a** in 17% yield, and **3a** in 30% yield, along with recovered starting material. Furthermore, when each isomer was separately re-submitted to the reaction conditions, benzo[*c*]azepine **3a** slightly isomerized to **2a** (3:1 after 16 h), while no change was observed for **2a** (Scheme 2). This suggests that **3a** is the kinetically favored isomer and that **2a** is the thermodynamic product.




**Scheme 2.** Isomerization study.

### 2.2. Scope of the cyclopropane ring-opening reaction

The scope of the transformation was explored using the optimized conditions at 125 °C for 16 h (Table 2). Both aryl bromides and iodides are efficient substrates for the reaction (entries 1 and 2). Aryl chlorides were not effective under these conditions.[18] Substitution on the aromatic ring was well-tolerated, as methyl groups in both *meta* and *para* positions gave excellent yields (entries 3 and 4). Notably, a disubstituted benzamide **1d** in both the *ortho* and *meta* positions produced the corresponding products in a total yield of 94%, demonstrating that steric hindrance adjacent to the bromide does not impede the reaction (entry 5). The corresponding mono- or difluorinated benzo[*c*]azepine-1-ones **2e**–**g** and **3e**–**g** were also obtained in 84–88% overall yields (entries 6–8), indicating that fluorinated aryl substrates are also accessible. Methoxy substitution on the aromatic ring also gave excellent conversion (entry 9, 94%). 3,4,5-Trimethoxybenazamide **1i** cyclized to give 17% of the major benzo[*c*]azepine **2i** and 10% of the minor isomer **3i** (entry 10). Starting material and reduced aryl bromide **1i** (30%) were isolated along with the two products (**2i**–**3i**). Finally, replacing the methyl protecting group with a benzyl protecting group is also viable, producing the corresponding benzo[*c*]azepines **2j** and **3j** in a total yield of 96% (entry 11). Interestingly, no product resulting from direct arylation of the benzyl group was observed, indicating that the present conditions favor the activation of a cyclopropane over an aryl ring. Substitution on the cyclopropane resulted in low yields as a mixture of isomers.[19]

### 2.3. Mechanistic studies

Our investigations into the reaction mechanism focused on determining if C–H activation of the cyclopropane occurs prior to ring-opening, or if the catalyst induces ring-opening.[20,21] When submitting benzamide **1a** to the reaction conditions previously developed by Fagnou et al.,[9] we isolated, along with benzo[*c*]azepine **2a**, dihydroisoquinoline **4a** in 50% yield and spirooxindole **5a** in 18% yield (Scheme 3a). Products **4a** and **5a** are believed to form via a pivalate-promoted CMD transition state, each involving C–H activation of a different cyclopropane bond, followed by reductive elimination to give either a five- or a six-membered ring.[9,22]