

Palladium-Catalyzed Highly Chemoselective Intramolecular C–H Aminocarbonylation of Phenethylamines to Six-Membered Benzolactams

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S Supporting Information

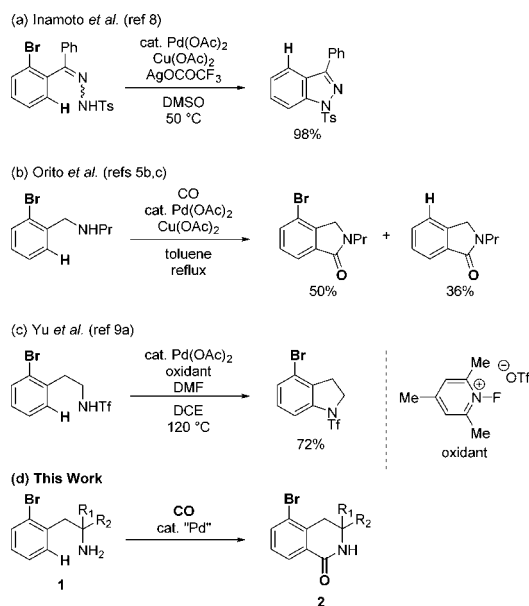
ABSTRACT: A palladium-catalyzed highly selective intramolecular C–H aminocarbonylation of Br-functionalized phenethylamines in the presence of CO was achieved while leaving the C–Br bond unreacted to afford six-membered benzolactams with good to high yields. The remaining C–Br group in the cyclized product was successfully used as a reactive center for further functionalization through various palladium-catalyzed coupling reactions.



Amides have received considerable attention in organic and medicinal chemistry because of their ubiquity in natural products, pharmaceuticals, and functional materials. Among the amide synthesis methods reported so far, the palladium-catalyzed aminocarbonylation of aryl halides (Ar–X, X = halogen atom) with amines in the presence of carbon monoxide (CO), first reported by Heck in 1974,¹ has demonstrated high versatility and efficiency.² A variety of palladium-based catalytic systems that successfully effect aryl C(sp²)–X bonds for aminocarbonylation have been developed to date.³ However, direct aminocarbonylation of aryl C(sp²)–H bonds with the aid of palladium catalysts provides a more straightforward and atom-economic route to the amide scaffold; several examples have been reported to date.^{4–6} In some cases, the intramolecular aminocarbonylation process allows for the facile synthesis of lactam compounds.^{5b–k}

The transition-metal-catalyzed C–H functionalization is a rapidly growing and intensive research area.⁷ Although the development of chemoselective processes is critical in modern organic synthesis, the control of chemoselectivity in transition-metal-catalyzed C–H functionalization processes is relatively unexplored. In particular, intramolecular selective C–H functionalization of substrates containing both C–H and C–X bonds still remains elusive. Thus, as previously reported by our group, the indazole synthesis via palladium-catalyzed intramolecular C–H amination of a substrate containing both C–H and C–Br bonds exclusively proceeded via C–Br functionalization, leading to a dehalogenated indazole compound [Scheme 1a].⁸ The Orito's palladium-catalyzed synthesis of benzolactam by intramolecular C–H aminocarbonylation utilizing CO yielded a mixture of products resulting from both C–H and C–Br functionalization (ca. 3:2) [Scheme 1b].^{5b,c} There have only been a few examples of palladium-catalyzed “C–H selective” cyclization while maintaining the reactive C–X

Scheme 1. Chemoselectivity (C–H vs C–Br) in Pd-Catalyzed C–H Functionalization



bond intact, which involve intramolecular C–N and C–O bond formation [Scheme 1c].⁹

Herein, we describe a highly chemoselective palladium-catalyzed intramolecular C–H aminocarbonylation. Thus, under the reaction conditions herein developed, cyclization of **1** (containing both C–H and C–Br reactive bonds) exclusively proceeded via C–H functionalization, thereby affording six-

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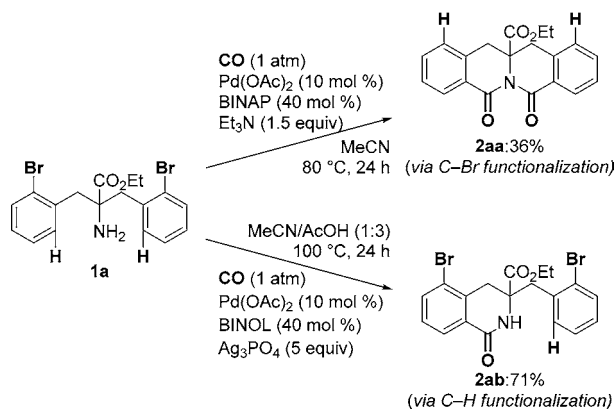
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membered benzolactam **2** with good to high yields [Scheme 1d].¹⁰ Further functionalization of **2** was conducted through various palladium-catalyzed coupling reactions involving the remaining C–Br bond.

In our continuous research on the transition-metal-catalyzed carbonylation reaction,¹¹ the carbonylative cyclization of substrate **1a** was investigated (Scheme 2). A twofold C–Br

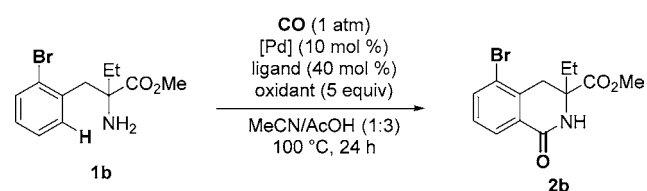
Scheme 2. Pd-Catalyzed Cyclization of Substrate **1a**



functionalization to benzolactam **2aa** was achieved in the presence of CO and Pd(OAc)₂/BINAP as a catalytic system. A change in the reaction conditions (i.e., by adding an oxidant such as Ag₃PO₄) allowed for the exclusive formation of benzolactam **2ab** retaining unreacted C–Br bonds with good yields.

Intrigued by this highly C–H selective cyclization process, further examination of the reaction parameters was conducted using the substrate **1b** (Table 1). Among the various palladium

Table 1. Optimization of Reaction Parameters for C–H Selective Intramolecular Aminocarbonylation^a

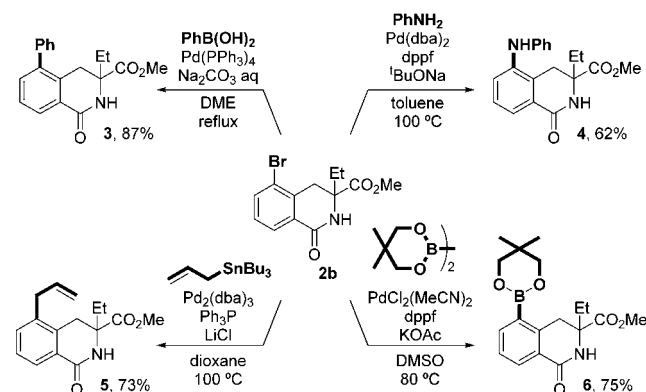


entry	Pd	ligand	oxidant	yield (%) ^{b,c}
1	Pd(dppe) ₂	BINOL	Ag ₃ PO ₄	67
2	[PdCl(allyl)] ₂	BINOL	Ag ₃ PO ₄	72
3	Pd(OAc) ₂	BINOL	Ag ₃ PO ₄	78
4	Pd(TFA) ₂	BINOL	Ag ₃ PO ₄	(99)
5	Pd(TFA) ₂	BINAP	Ag ₃ PO ₄	0
6	Pd(TFA) ₂	di ^t butyl tartrate	Ag ₃ PO ₄	11
7	Pd(TFA) ₂	IPr-HCl	Ag ₃ PO ₄	0
8	Pd(TFA) ₂	BINOL	AgOAc	35
9	Pd(TFA) ₂	BINOL	Ag ₂ CO ₃	41
10	Pd(TFA) ₂	BINOL	Cu(OAc) ₂	12
11	none	BINOL	Ag ₃ PO ₄	0
12	Pd(TFA) ₂	none	Ag ₃ PO ₄	4
13	Pd(TFA) ₂	BINOL	none	0
14 ^d	Pd(TFA) ₂	BINOL	Ag ₃ PO ₄	75 (79)

^aReactions were carried out on a 0.15 mmol scale. ^bDetermined by ¹H NMR using 1,1,2-trichloroethane as an internal standard. ^cIsolated yield in parentheses. ^d5 mol % of Pd(TFA)₂ and 20 mol % of BINOL.

sources tested (Table 1, entries 1–4), Pd(TFA)₂ was found to be a suitable catalyst as it achieved C–H functionalization to

Scheme 3. Further Functionalization of **2b** via Pd-Catalyzed Coupling Reactions



the desired cyclized product **2b** in quantitative yields (Table 1, entry 4). In contrast, the use of ligands other than BINOL led to a considerable decrease in yields (Table 1, entries 5–7). Ag₃PO₄ was found to be crucial for efficient C–H cyclization. Thus, the utilization of other oxidants such as AgOAc, Ag₂CO₃, and Cu(OAc)₂ resulted in lower yields (Table 1, entries 8–10). Essentially, in the absence of Pd(TFA)₂, BINOL, or Ag₃PO₄, little or no reaction occurred (Table 1, entries 11–13). Finally, lower catalyst loadings afforded **2b** with high yields, indicating the efficiency of the catalytic system (Table 1, entry 14).¹²

Once the reaction conditions were optimized, C–H selective intramolecular aminocarbonylation was studied for different substrates (Table 2). Phenethylamines **1c** and **1d** containing a bicyclic motif (i.e., naphthalene and 1,3-benzodioxole) afforded the desired products **2c** and **2d** in useful yields (Table 2, entries 1 and 2). In contrast, the introduction of a substituent at the *ortho*-position with respect to the C–H bond markedly inhibited the process (Table 2, entries 3 and 4). Substrates **1g** and **1h** containing a methyl (instead of an ethyl) group at the quaternary carbon gave benzolactams **2g** and **2h**, albeit in moderate yields (Table 2, entries 5 and 6). Substrates **1i** and **1j** with a silyl-protected alcohol moiety readily underwent the desired C–H cyclization under the optimized reaction conditions (Table 2, entries 7 and 8). With the aim to evaluate the steric influence of a substituent at the α -position with respect to the amine nitrogen atom, various α,α -dialkylamines **1k–o** were employed. Interestingly, the more sterically hindered the substrate becomes, the more efficiently the C–H cyclization proceeds (Table 2, entries 9–13). Additionally, the reactivity of the amine **1p** containing both C–H and C–Cl bonds was investigated. Exclusive formation of **2p** resulting from chemoselective C–H functionalization was observed (Table 2, entry 14).

With the aim of proving the applicability of the synthetic method herein proposed, further functionalization of the C–Br bond was conducted in the cyclized product **2b**. Various palladium-catalyzed coupling reactions were successfully carried out giving rise to further functionalized benzolactams **3–6** in good to high yields (Scheme 3).

In conclusion, we have developed a highly chemoselective aminocarbonylation methodology. Selective C–H cyclization of phenethylamines was efficiently carried out while leaving the reactive C–Br bond intact by using a palladium catalytic

Table 2. Effect of the Substrate in the C–H Selective Intramolecular Aminocarbonylation Process^a

entry	amine	1	product	2	yield (%) ^b
1		1c		2c	81
2		1d		2d	64
3		1e (R = F)		2e	29
4		1f (R = OMe)		2f	0
5		1g (R = Me)		2g	57
6		1h (R = Et)		2h	64
7		1i (Si = TIPS)		2i	61
8		1j (Si = TBDPS)		2j	79
		1k (R = Me)		2k	37
9		1l (R = Et)		2l	42
10		1m (R = Pr)		2m	52
11		1n (R = Bu)		2n	52 ^c
12		1o (R = Pentyl)		2o	60 ^c
13					
14		1p		2p	89

^aReactions were carried out on a 0.15 mmol scale. ^bIsolated yield. ^cYield based on ¹H NMR spectroscopy using 1,1,2-trichloroethane as an internal standard.

system. In addition, further functionalization of the C–Br bond in the cyclized benzolactam was successfully conducted making use of several palladium-catalyzed coupling strategies. Further studies on similar selective C–H transformations are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01171.

Experimental procedures, characterization data, and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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