C-H Activation Hot Paper

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Remote Construction of N-Heterocycles via 1,4-Palladium Shift-Mediated Double C–H Activation

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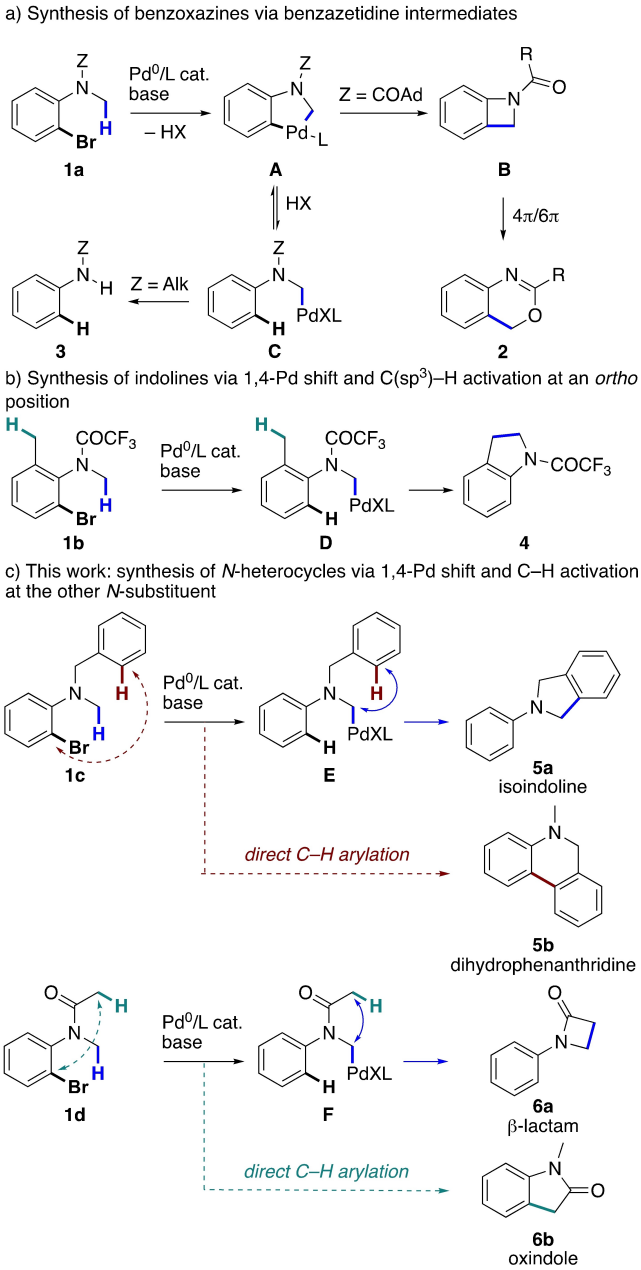
Abstract: *In the past years, Pd^0-catalyzed $C(sp^3)$–H activation provided efficient and step-economical methods to synthesize carbo- and heterocycles via direct $C(sp^2)$–$C(sp^3)$ bond formation. We report herein that a 1,4-Pd shift allows access to N-heterocycles which are difficult to build via a direct reaction. It is shown that o-bromo-N-methylanilines undergo a 1,4-Pd shift at the N-methyl group, followed by intramolecular trapping by $C(sp^2)$–H or $C(sp^3)$–H activation at another nitrogen substituent and remote C–C bond formation to generate biologically relevant isoindolines and β-lactams. The product selectivity is influenced by the employed ligand, with NHCs favoring the product of remote C–C coupling against products arising from direct C–C coupling and N-demethylation.*

Introduction

Nitrogen-containing heterocycles are privileged motifs in synthetic organic chemistry due to their abundance in nature and their prevalence in agrochemicals, functionalized materials, and pharmaceuticals.[1] In particular, they account for over 60% of small-molecule drugs approved by the FDA. Thus, many efforts have been devoted to the development of new synthetic routes towards the synthesis of these essential building blocks. Over the last two decades, C–H activation-based methods have been established as powerful tools for the atom- and step-economical de novo construction of diverse azacycles.[2] In particular, Pd^0-catalyzed $C(sp^3)$–H activation allows the direct formation of $C(sp^2)$–$C(sp^3)$ bonds and generation of nitrogen heterocycles from easily accessible $C(sp^2)$ (pseudo)-halides.[3] For instance, the reaction of 2-bromo-*N*-methyl anilines **1a** equipped with a bulky carbonyl substituent on the nitrogen atom was shown to produce benzoxazines **2** via $C(sp^3)$–H activation at the *N*-methyl group (Scheme 1a), giving rise to 5-membered palladacycle **A**, which upon reductive elimination generates benzazetidine **B**. The latter is unstable under the reaction conditions and undergoes a 4π/6π electrocyclic cascade to furnish product **2**.[4] In addition, N-demethylation was



Scheme 1. Pd^0-catalyzed $C(sp^3)$–H activation of 2-bromo-*N*-methyl-anilines for the synthesis of nitrogen heterocycles.

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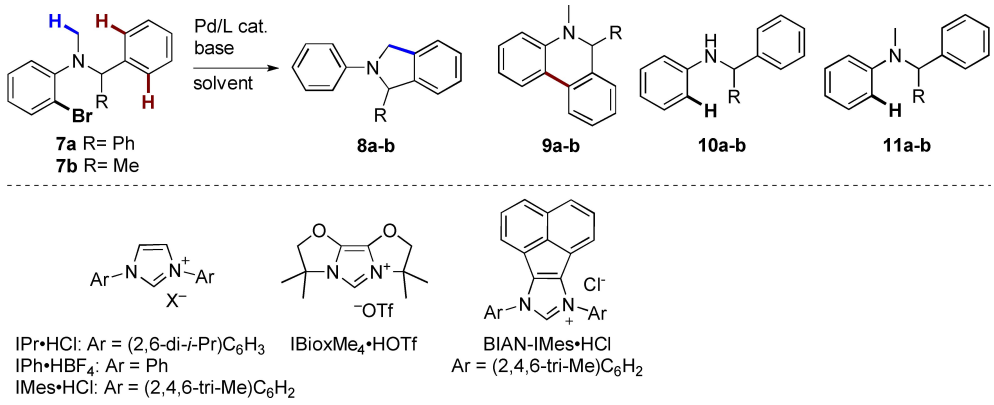
Table 1: Optimization of the isoindoline synthesis.[a]



Entry	Substrate	Pd/L	Temp [°C]/Solvent	Yield[b] **8a,b/9a,b/10a,b/11a,b**
1	**7a**	$[Pd(\pi\text{-allyl})Cl]_2$/IBioxMe$_4$	140/PhMe	99:0:0:0
2	**7a**	$[Pd(\pi\text{-allyl})Cl]_2$/IPr	140/PhMe	73:0:26:0
3	**7a**	Pd_2dba_3/PCy_3	140/PhMe	10:61:11:2
4	**7a**	Pd_2dba_3/PPh_3	140/PhMe	0:61:30:9
5[c]	**7a**	$Pd(PPh_3)_4$	140/PhMe/DMSO	0:43:18:9
6	**7b**	$[Pd(\pi\text{-allyl})Cl]_2$/IBioxMe$_4$	140/PhMe	68:0:32:0
7	**7b**	$[Pd(\pi\text{-allyl})Cl]_2$/IMes	140/PhMe	82:0:17:1
8	**7b**	$[Pd(\pi\text{-allyl})Cl]_2$/IMes	110/*m*-xylene[d,e]	94 (78)[f]:0:5:1
9	**7b**	$[Pd(\pi\text{-allyl})Cl]_2$/IPh	110/*m*-xylene[d,e]	2:0:trace:trace
10	**7b**	$[Pd(\pi\text{-allyl})Cl]_2$/BIAN-IMes	110/*m*-xylene[d,e]	80:0:9:4

[a] Reactions were performed on a 0.1 mmol scale using 10 mol% [Pd] and ligand, Cs_2CO_3 (1.5 equiv), CsOPiv (30 mol%), solvent (*c* 0.1 M) and 4 Å MS for 15 h. [b] NMR yield determined using trichloroethylene as internal standard. [c] Using KOPiv (2 equiv) instead of Cs_2CO_3/CsOPiv and toluene/DMSO 95:5. [d] *c* 0.067 M. [e] Using 5 Å MS. [f] Yield of the isolated product.

observed when an *N*-alkyl substituent was present instead of the carbonyl group, which presumably occurs through reversible reprotonation of palladacycle **A** to furnish σ-alkylpalladium intermediate **C** and demetallation via formation of an iminium species.[4,5] The formation of σ-alkylpalladium complex **C** from the oxidative addition complex arising from **1a** and the active Pd^0 catalyst formally results in a 1,4-Pd shift. 1,4-Palladium shifts were initially reported by Heck in 1972[6] and subsequently exploited to generate hard-to-reach $C(sp^2)$–$C(sp^2)$ and $C(sp^2)$–$C(sp^3)$ bonds remotely from $C(sp^2)$ halides.[7]

Inspired from seminal work by Dyker,[8] we showed that a 1,4-Pd shift onto an adjacent position to an oxygen or nitrogen atom gives rise to a σ-alkylpalladium complex which can effect further $C(sp^3)$–H activation on a substituent located at the next *ortho* position.[9] Accordingly, 2-bromo-*N*-methylanilines **1b**, wherein the lone pair of the nitrogen atom was deactivated by a trifluoroacetyl group to avoid the abovementioned demethylation process, gave rise to indolines **4** via σ-alkylpalladium intermediate **D** (Scheme 1b), albeit with a modest reaction scope. This 1,4-Pd shift-based strategy allowing the remote construction of $C(sp^3)$–$C(sp^3)$ bonds via twofold $C(sp^3)$–H bond cleavage was recently employed to synthesize cyclopropanes.[10] Of note, it was also shown that σ-alkylpalladium intermediates generated by 1,4-Pd shift can be trapped through a range of other processes.[11]

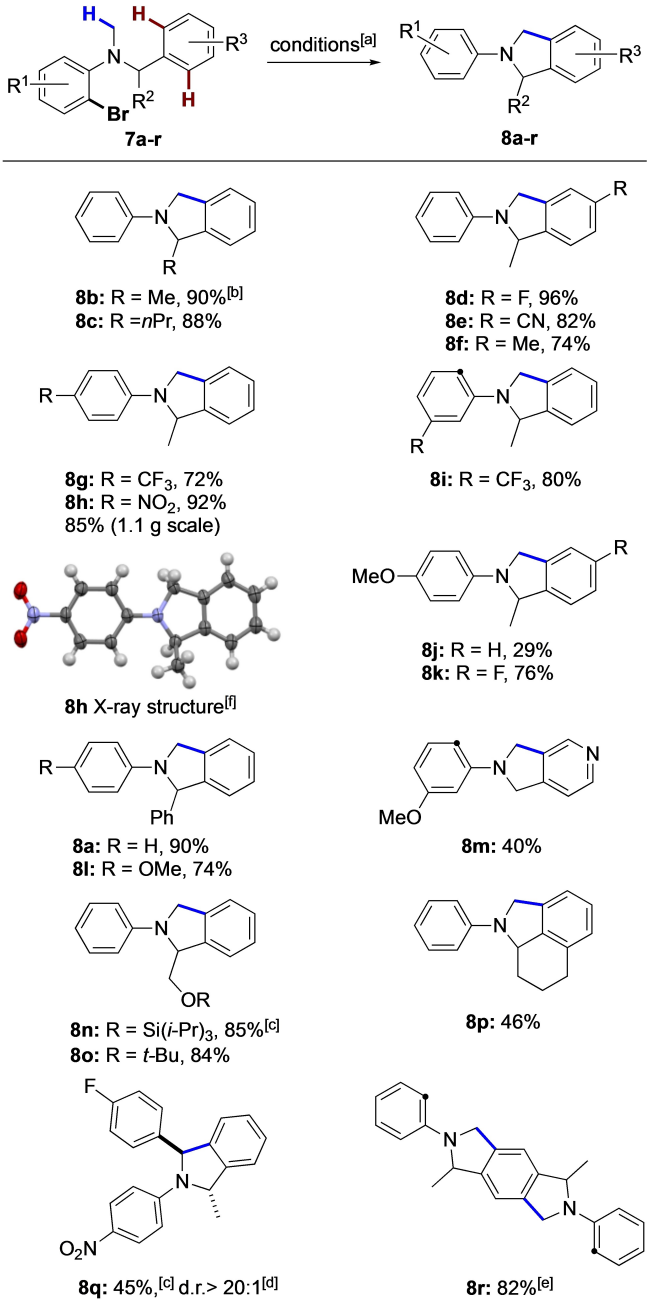
Following up on this work, we sought to expand the scope of this 1,4-Pd shift-based strategy to access valuable azacycles by installing a suitable N-substituent which would trap the transient σ-alkylpalladium intermediate **E** or **F** by $C(sp^2)$–H or $C(sp^3)$–H activation, respectively (Scheme 1c). Herein, we report the implementation of this strategy for the synthesis of isoindolines **5a** and β-lactams **6a**, which cannot be easily accessed by direct Pd^0-catalyzed $C(sp^3)$–H activation,[3] and are biologically relevant heterocycles.[12,13] At the onset of this work, we realized that developing such reactions would be challenging because 1. the desired migration pathway would compete with the direct C–H arylation leading to 5,6-dihydrophenanthridines **5b**[14] and oxindoles **6b**,[15] respectively, and 2. N-demethylation could occur in the absence of an electron-withdrawing group adjacent to the nitrogen atom. However, previous studies pointed at the effect of the base and the ligand to favor the 1,4-Pd shift pathway over the direct reaction,[9,10] and thus gave us confidence that the desired selectivity could be achieved by playing on these factors.

Results and Discussion

We set out to explore the reactivity of several *o*-bromoaniline substrates using three different catalytic systems, which proved successful in previous Pd^0-catalyzed $C(sp^3)$–H activa-

tion reactions, i.e. [Pd(π-allyl)Cl]$_2$/NHC (NHC = N-heterocyclic carbene),[16] Pd_2dba_3/PR_3[4,9] and $Pd(PPh_3)_4$[10] (Table 1, entries 1–5, see Table S1 for details). As a result, $IBioxMe_4$[16b,17] was identified as the optimal ligand to convert substrate **7a** to the desired indoline **8a** in 99% NMR yield, and minimize the formation of the direct C(sp^2)–H arylation product **9a**, N-demethylated product **10a**, and proto-dehalogenated product **11a** (entry 1). Interestingly, the previously developed conditions for 1,4-Pd shift-mediated double C–H activation reactions employing phosphine ligands provided **9a** as the major product (entries 3–5). In contrast, NHC ligands[18] seem to favor the 1,4-Pd shift on the *N*-Me group (entries 1 and 2). Motivated by these results, we turned to the more challenging substrate **7b** bearing a methyl instead of the second phenyl group at the α position to the nitrogen atom. Indeed, in this case, the trapping of the σ-alkylpalladium intermediate arising from 1,4-Pd shift (see **E**, Scheme 1c) by C(sp^2)–H arylation is less favorable than in **7a** since less C(sp^2)–H bonds are accessible. In addition, the direct C(sp^3)–H arylation at the α-Me group[19] could potentially be an additional competitive reaction. With substrate **7b**, IMes was found to be superior to the bis-oxazoline-based IBiox NHC to reduce the amount of N-demethylated product **10b** and increase the yield of isoindoline **8b** (entries 6 and 7, see also Tables S2–S3). Further optimizations led to identify *m*-xylene as the optimal solvent under slightly more diluted conditions, at 110 °C and in the presence of 5 Å MS (entry 8). Then, the effect of the ligand structure was further investigated (Table S12). No reaction occurred with IPh, bearing unsubstituted Ph groups (entry 9). The IMes analogue BIAN-IMes[20] also furnished isoindoline **8b**, but with a reduced yield (entry 10). Under the optimized conditions (entry 8), isoindoline **8b** was formed with a high yield (78% upon isolation) and selectivity.

With these optimized conditions in hand, the versatility of this 1,4-Pd shift-based isoindoline synthesis was investigated (Scheme 2). In addition to the aryl bromide precursor, the use of the electron-rich IMes ligand allowed the use of the corresponding aryl chloride with a similar efficiency (90%, **8b**). Another alkyl group could be introduced at the α position to the nitrogen atom without detrimental effect on the yield (**8c**). Electron-withdrawing or -donating groups on the remote aryl ring were well tolerated, affording the corresponding isoindolines in good to excellent yields (**8d–f**). In addition, substrates bearing electron-withdrawing groups in the *meta* or *para* position of the *N*-aryl ring also reacted in good yields (**8g–i**, 72–92%). Of note, the reaction providing isoindoline **8h** was successfully conducted on gram scale without significant impact on the efficiency. However, a significant drop of yield was observed upon introduction of an electron-donating group on the *N*-aryl ring (**8j**). This effect was nevertheless counterbalanced by installing either an electron-withdrawing group on the remote aryl ring (**8k**) or by employing a more reactive *gem*-diphenyl substrate (**8l**). Interestingly, trapping by C(sp^2)–H activation at a pyridine ring could be also realized, albeit in modest yield (**8m**). In addition to an alkyl group, a protected primary alcohol was well tolerated at the



Scheme 2. Scope of the isoindoline synthesis. [a] Aryl bromide (0.2 mmol), [Pd(π-allyl)Cl]$_2$ (5 mol%), IMes·HCl (10 mol%), Cs_2CO_3 (1.5 equiv), CsOPiv (30 mol%), *m*-xylene, 5 Å MS, 110 °C, 15 h. Yields refer to the isolated isoindoline product. Dots indicate the initial position of the bromine atom, when ambiguous. [b] Using the aryl chloride instead of the aryl bromide. [c] Performed at 140 °C. [d] Determined by ^{1}H NMR of the crude mixture. [e] Using 10 mol% [Pd(π-allyl)Cl]$_2$ and 20 mol% IMes·HCl. [f] Thermal ellipsoids shown at 50% probability.[23]

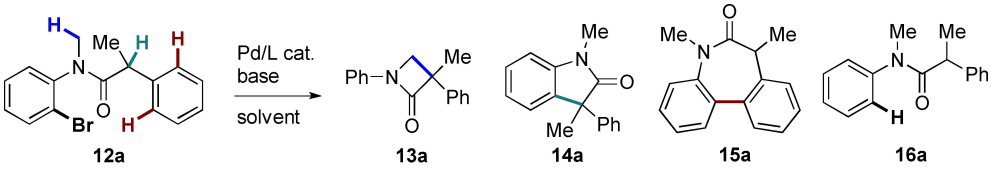
α position to the nitrogen atom (**8n**, **8o**). Interestingly, the strained hexahydrobenzoindole system (**8p**) could be constructed in moderate yield from the corresponding tetrahydronaphthalene precursor. To further increase the molecular complexity, the *N*-methyl group was replaced with a *para*-fluorobenzyl moiety, which enabled 1,4-Pd shift on a meth-

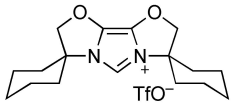
ylene position and afforded the trisubstituted isoindoline **8q** as a single *trans* diastereoisomer. Finally, the use of a symmetrical dibrominated substrate set the stage for a twofold reaction involving a fourfold C–H activation, which furnished hexahydropyrroloisoindole **8r** in 82 % yield.

After the implementation of the 1,4-Pd shift-based strategy for the selective synthesis of isoindolines, we endeavored to further expand this methodology to build other N-heterocycles. The tertiary amide **12a**, which contains multiple C–H functionalization sites, was already employed in the direct α-arylation resulting in oxindole **14a** (Table 2).[15] Alternatively, β-lactam **13a** would arise from 1,4-Pd shift onto the *N*-methyl substituent and trapping by C(sp^3)–H alkylation. Finally, dibenzazepinone **15a** might arise from direct C(sp^2)–H arylation.[21] Since we expected a strong influence of the ligand on the reaction selectivity similar to the above isoindoline synthesis, we set out to explore the influence of different classes of ligands on the reaction of the model amide **12a** (entries 1–3, see also Table S13). Interestingly, a different product distribution was again observed with the three displayed ligands. The common phosphine ligand PCy_3 resulted in the preferential formation of dibenzazepinone **15a** (entry 1), with only traces of β-lactam **13a** being formed. In contrast, IPr clearly favored the oxindole product **14a** (entry 2). These results are rather unsurprising in light of literature precedents.[15c,21] In contrast, we were pleased to discover that IBiox-type ligands, and in particular the spirocyclic IBiox6,[17,22] provided the β-lactam product **13a** in 30 % NMR yield, along with oxindole **14a** (31 %), dibenzazepinone **15a** (23 %), and the proto-dehalogenated product **16a** (26 %, entry 3). Building on this result, the reaction conditions were optimized. In the first round, trifluorotoluene ($PhCF_3$) was found to be the best solvent, improving the yield of the β-lactam to 37 % and completely suppressing the formation of the dibenzazepinone product (entry 4). Moreover, stoichiometric Cs_2CO_3 and catalytic CsOPiv were found to be the best basic system for this transformation (Tables S15, S17–S20). Expectedly, employing stronger bases such as LiHMDS or NaO*t*-Bu resulted in the selective formation of the oxindole, presumably via an enolate arylation mechanism (entry 5).[15] Replacing IBiox6 with the smaller $IBioxMe_4$ ligand (see structure in Table 1) further improved the yield of the β-lactam product to 44 % (entry 6). A second optimization round with additional solvents revealed cyclopentyl methyl ether (CPME) as the optimal reaction medium, yielding 50 % of the desired product **13a**, along with 35 % of oxindole **14a** and 12 % of proto-dehalogenated product **16a** (entry 7). While cesium salts provided the best results, the amount of Cs_2CO_3 could be reduced to 1 equivalent (entry 8). Interestingly, omitting CsOPiv only resulted in a small decrease of efficiency (Table S20). Despite extensive efforts, the reaction could not be further optimized.

Repeating the reaction on a 0.3 mmol scale furnished a separable 3:2 mixture of remote and direct C(sp^3)–H functionalization products **13a** and **14a**, from which β-lactam **13a** could be isolated in 51 % yield (Scheme 3). Then, we explored the scope of this reaction. Various electron-donating substituents in *meta* and *para* position to the *N*-aryl ring were well tolerated, affording the corresponding β-lactams **13b**–**13e** in moderate to good yields. In particular, starting from the 2-bromo-5-methylaniline derivative (**12c**), **13c** was isolated in moderate yield (53 %). However, when the 2-bromo-3-methylaniline isomer was engaged a lower

Table 2: Optimization of the β-lactam synthesis.[a]

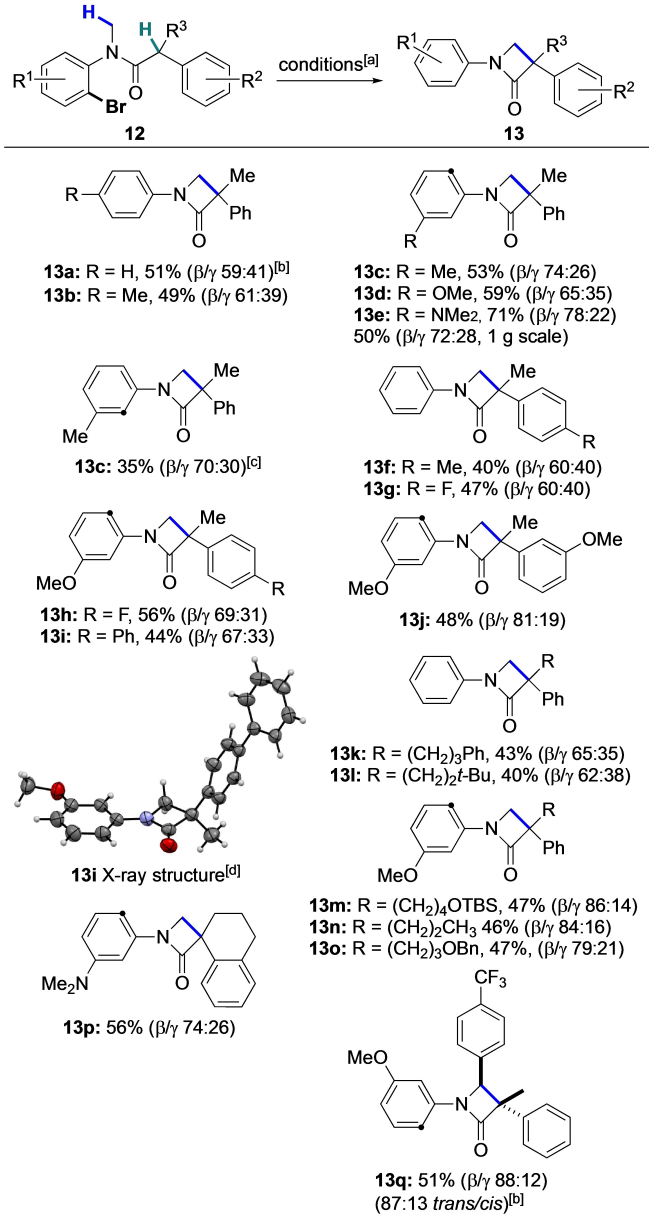




IBiox6•HOTf

Entry	Pd/L	Solvent	Base	Yield[b] **13a/14a/15a/16a**
1	$Pd(PCy_3)_2$	mesitylene	Cs_2CO_3	6:0:66:0
2	$[Pd(\pi\text{-cinnamyl})Cl]_2$/IPr[c]	mesitylene	Cs_2CO_3	2:84:0:8
3	$[Pd(\pi\text{-cinnamyl})Cl]_2$/IBiox6[d]	mesitylene	Cs_2CO_3	30:31:23:26
4	$[Pd(\pi\text{-cinnamyl})Cl]_2$/IBiox6[d]	$PhCF_3$	Cs_2CO_3	37:18:0:10
5	$[Pd(\pi\text{-cinnamyl})Cl]_2$/IBiox6[d]	$PhCF_3$	NaO*t*-Bu	0:95:0:0
6	$[[Pd(\pi\text{-cinnamyl})Cl]_2$/$IBioxMe_4$[d]	$PhCF_3$	Cs_2CO_3	44:25:0:19
7	$[Pd(\pi\text{-cinnamyl})Cl]_2$/$IBioxMe_4$[d]	CPME	Cs_2CO_3	50:35:0:12
8	$[Pd(\pi\text{-cinnamyl})Cl]_2$/$IBioxMe_4$[d]	CPME	Cs_2CO_3[e]	53:34:0:13

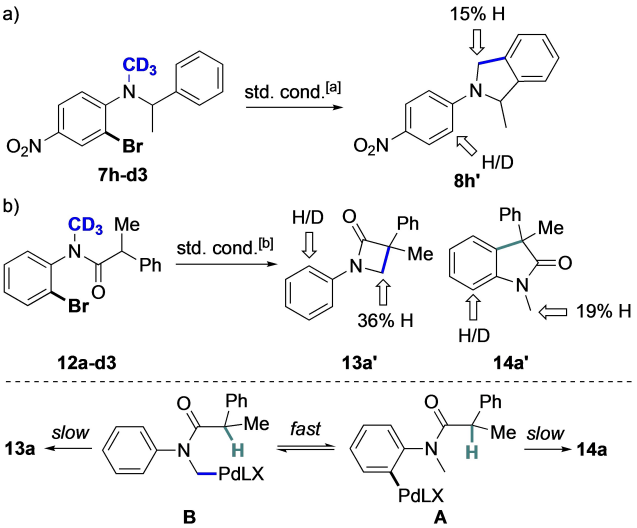
[a] Reactions were performed on a 0.1 mmol scale using 10 mol% [Pd] and ligand, base (1.5 equiv), CsOPiv (30 mol%), 160 °C, 18 h. [b] NMR yield determined using trichloroethylene as internal standard. [c] Using IPr·HCl (10 mol%). [d] Using IBiox·HOTf (10 mol%). [e] Using 1.0 equiv Cs_2CO_3.



Scheme 3. Scope of the β-lactam synthesis. [a] Reaction conditions: **12** (0.3 mmol), $[Pd(\pi\text{-cinnamyl})Cl]_2$ (5 mol%), IBioxMe$_4$·HOTf (10 mol%), Cs_2CO_3 (1 equiv), CsOPiv (30 mol%), CPME, 160 °C. Yields refer to the isolated β-lactam product. β/γ Ratios refer to the ratios of the β-lactam/oxindole products, as determined by GCMS, unless otherwise stated. Dots indicate the initial position of the bromine atom, when ambiguous. [b] Determined by ^{1}H NMR. [c] Starting from the 2-bromo-3-methylaniline derivative. [d] Thermal ellipsoids shown at 50% probability.[23]

yield of **13c** was observed (35%), probably due to a sterically challenging oxidative addition. A significant yield improvement was obtained by installing a strong electron-donating group (OMe, NMe_2) on the *N*-aryl ring (**13d**, **13e**). This result stands in contrast to the isoindoline case, for which electron-withdrawing substituents on the *N*-aryl ring provided a better yield. Electron-donating (**13f**, **13j**) and -withdrawing groups (**13g**, **13h**), as well as a phenyl substituent (**13i**) on the other aryl ring at the α position to the amide group were well tolerated, and provided yields in the range of 40–56%. Unfortunately, replacing this aryl group with an ester, amide, benzyl or alkyl substituent resulted in unproductive reactions. Moreover, different alkyl chains at the α position to the amide group were also compatible (**13k**–**13o**), and the corresponding products were isolated in 40–47% yield. Interestingly, a spirocyclic β-lactams (**13p**) was obtained in 56% yield from the corresponding tetrahydronaphthoic acid derivative. Gratifyingly, and similar to the isoindoline case, replacing the *N*-methyl with an *N*-(*p*-trifluoromethylbenzyl) substituent allowed the formation of highly substituted β-lactam **13q** in 51% yield and as the major *trans* diastereoisomer. This example further demonstrates the feasibility of 1,4-Pd shift onto an activated methylene position adjacent to a nitrogen atom. Finally, we successfully performed the reaction producing β-lactam **13e** on a gram scale.

Preliminary mechanistic investigations were conducted with deuterated substrates **7h-d3** and **12a-d3** (Scheme 4). The reaction of **7h-d3** under standard conditions showed significant proton incorporation on the newly formed methylene position of isoindoline **8h′** by ^{1}H NMR (Scheme 4a). Likewise, the methylene position of β-lactam **13a′** and the *N*-methyl group of oxindole **14a′** showed significant proton incorporation (Scheme 4b). Moreover, ^{2}H NMR experiments revealed deuterium incorporation on the *N*-aryl ring of the three C–H activation products **8h′**, **13a′** and **14a′**. These observations clearly indicate that the 1,4-Pd shift between the *N*-aryl and *N*-methyl groups is fast and reversible. As illustrated with **12a** (Scheme 4, bottom), a Curtin–Hammett scenario is likely at play in these reactions, whereby product selectivity is controlled by the trapping rate of the σ-aryl- and σ-alkylpalladium intermediates **A** and **B** by C–H functionalization at the α position to the amide.



Scheme 4. Deuterium-labeling experiments reveal H/D scrambling, indicating a reversible 1,4-Pd shift. [a] Standard conditions: see Scheme 2. [b] Standard conditions: see Scheme 3.

Conclusion

The synthesis of two types of nitrogen heterocycles from readily available *o*-bromo-*N*-methylaniline precursors is reported. These reactions proceed by a 1,4-Pd shift on the *N*-methyl group and intramolecular trapping via C(sp^2)–H or C(sp^3)–H activation at another nitrogen substituent, and allow the construction of C–C bonds remotely to the initial C–Br bond. N-Heterocyclic carbene ligands were found to be key to control the selectivity in favor of the remote vs. the direct C–H functionalization products. This method allows access to isoindolines and β-lactams, which are valuable nitrogen heterocycles found in numerous biologically relevant molecules.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: C–H Activation · Isoindolines · N-Heterocycles · Palladium · β-Lactams

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Research Articles

C-H Activation

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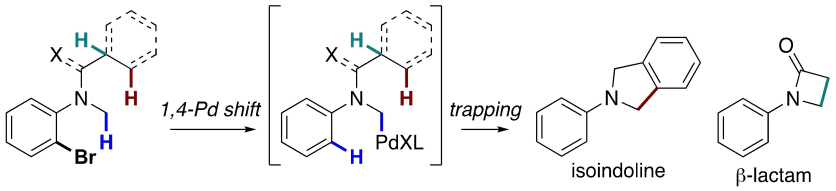
Remote Construction of N-Heterocycles via 1,4-Palladium Shift-Mediated Double C–H Activation



A ligand-controlled 1,4-palladium shift onto an *N*-methyl group enables the construction of C–C bonds in a remote position to the initial C–Br bond, leading to valuable isoindoline and β-lactam products. The reaction proceeds via trapping of the σ-alkylpalladium intermediate by C–H activation at another nitrogen substituent.