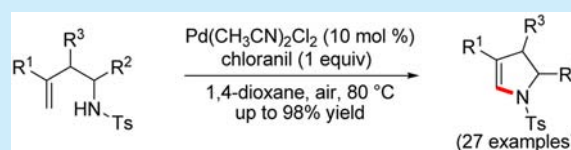


Palladium-Catalyzed Direct Intramolecular C–N Bond Formation:
Access to Multisubstituted DihydropyrrolesBing Jiang,[†] Fei-Fan Meng,[†] Qiu-Ju Liang,[†] Yun-He Xu,^{*,†,‡} and Teck-Peng Loh^{*,†,‡,§}[†]Department of Chemistry, University of Science and Technology of China, Hefei 230026, China[‡]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371

Supporting Information

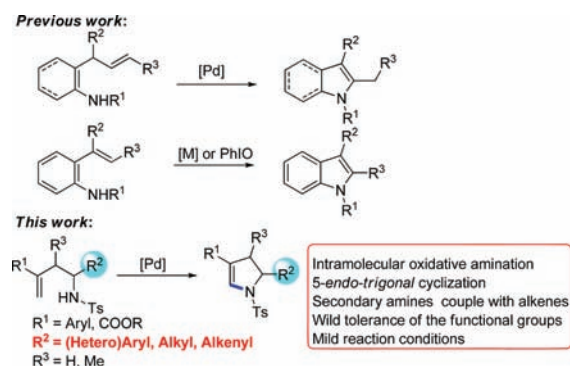
ABSTRACT: A palladium-catalyzed intramolecular amination of alkenes with retention of olefin functionalization was achieved under mild reaction conditions. In the presence of palladium catalyst, the tosyl-protected amine can directly couple with a double bond to provide versatile dihydropyrrole derivatives in moderate to excellent yields.



Development of economical and practical synthetic methods for the construction of a carbon–nitrogen (C–N) bond is an important goal in organic synthesis because nitrogen-containing compounds are featured prominently in many pharmaceuticals and functional materials.^{1,2} Therefore, many methods have been developed for the construction of a C–N bond especially in the area of palladium-catalyzed olefin amination.^{3,4} These methods usually involve the use of various nitrogen sources to couple with electrophilic or nucleophilic carbon compounds. Among these methods, transition-metal-catalyzed direct oxidative amination is the most efficient due to its atom economy in nature and the easy accessibility of the substrates (Scheme 1). It is important to note that pioneering works on oxidative amination (sp²) of *o*-allylaniline and olefinic tosamides to form indoles and non-aromatic nitrogen heterocycles were elegantly demonstrated by Hegedus.⁵ Another example of palladium-catalyzed cyclization of vinylanilines to indoles was reported by Stille and co-workers.⁶ Thereafter, Tamaru,⁷ Larock,⁸ Stahl,⁹ Chemler,¹⁰ Muñiz,¹¹ Obora,¹² Mizuno,¹³ and Jiménez¹⁴ et al.¹⁵ independently developed oxidative amination reactions. Simultaneously, Beller and colleagues also reported a Rh-catalyzed intermolecular oxidative amination of secondary amines with styrenes.¹⁶ Nonetheless, these methods are mainly limited to aniline with styrene derivatives and/or intermolecular amination processes. We envisage that an intramolecular amination of a double bond with simple amines will provide easy access to versatile dihydro-nitrogen-containing compounds. In this paper, we focus on the palladium-catalyzed intramolecular direct amination that provides easy access to multisubstituted dihydropyrroles.¹⁷

We initiated our study by investigating the Pd-catalyzed intramolecular sp² 5-*endo* cyclization of **1a** in THF at 50 °C under air atmosphere. It was found that the desired product could be obtained in 8% yield in the presence of BQ as oxidant (Table 1, entry 1) after being stirred for 24 h. Encouraged by this result, we screened a variety of oxidants (Table 1, entries 1–5), and it was found that the product yield could be improved to 28% when chloranil was used as the oxidant (Table 1, entry 3). After further

Scheme 1. Oxidative Amination Reactions of Alkenes



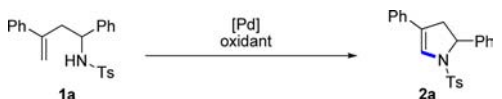
screening of different solvents, the results suggested that 1,4-dioxane was the most efficient solvent for this transformation, affording the desired product **2a** in 58% yield (Table 1, entry 6). Among the palladium catalysts screened in this reaction, Pd(CH₃CN)₂Cl₂ was found to be the most efficient when the reaction was conducted at 80 °C (Table 1, entry 13). Therefore, the optimal reaction conditions can be summarized as follows: 0.5 mmol substrate in 1,4-dioxane (2 mL) with Pd(CH₃CN)₂Cl₂ catalyst (10 mol %) and chloranil (1 equiv) at 80 °C for 24 h under air atmosphere.

Under the optimized reaction conditions, we next explored the substrate scope of this reaction. Initially, we studied the effect of the substituents on the double bond. A substrate with an electron-withdrawing group such as CF₃– on the phenyl ring could afford the desired product in 75% yield (**2b**, Chart 1).

Unfortunately, the presence of an electron-donating substituent such as Me– on the phenyl ring reduced the product's yield significantly (**2c**, Chart 1). Similar results were also observed in the formation of products **2d** and **2e** (which were generated via

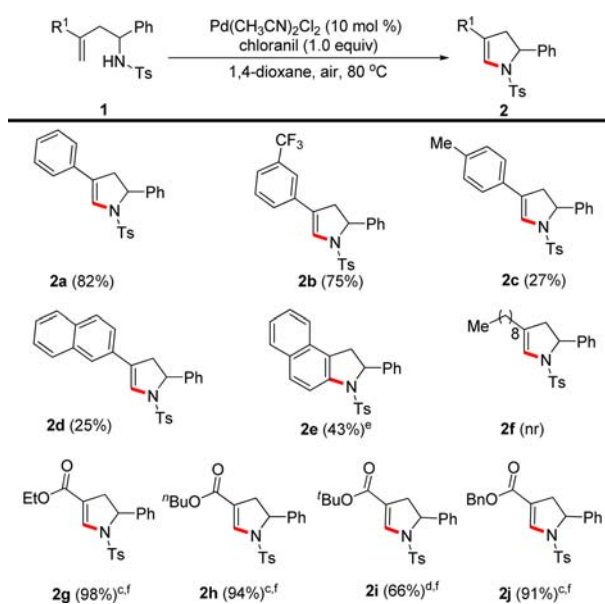
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Table 1. Optimization of Reaction Conditions for Palladium-Catalyzed 5-*endo-trig* Cyclization of **1a**^a


entry	catalyst (10 mol %)	oxidant (equiv)	solvent	temp (°C)	yield (%) ^b
1	Pd(CH ₃ CN) ₂ Cl ₂	BQ (2.0)	THF	50	8
2	Pd(CH ₃ CN) ₂ Cl ₂	<i>p</i> -toluquinone (2.0)	THF	50	22
3	Pd(CH ₃ CN) ₂ Cl ₂	chloranil (2.0)	THF	50	28
4	Pd(CH ₃ CN) ₂ Cl ₂	^t BuOO ^t Bu (2.0)	THF	50	17
5	Pd(CH ₃ CN) ₂ Cl ₂	dicumyl peroxide (2.0)	THF	50	20
6	Pd(CH ₃ CN) ₂ Cl ₂	chloranil (2.0)	1,4-dioxane	50	58
7	Pd(CH ₃ CN) ₂ Cl ₂	chloranil (2.0)	toluene	50	57
8	Pd(CH ₃ CN) ₂ Cl ₂	chloranil (2.0)	CH ₂ Cl ₂	50	48
9	Pd(CH ₃ CN) ₂ Cl ₂	chloranil (1.0)	1,4-dioxane	50	53
10	PdCl ₂	chloranil (1.0)	1,4-dioxane	50	38
11	Pd(PhCN) ₂ Cl ₂	chloranil (1.0)	1,4-dioxane	50	75
12	Pd(PhCN) ₂ Cl ₂	chloranil (1.0)	1,4-dioxane	80	69
13	Pd(CH ₃ CN) ₂ Cl ₂	chloranil (1.0)	1,4-dioxane	80	82

^aReaction conditions: To a mixture of 0.5 mmol **1a**, catalyst (10 mol %), and oxidant was added solvent (2 mL), and the mixture was allowed to stir for 24 h under air atmosphere. ^bYield was determined by ¹H NMR using mesitylene as internal standard. Chloranil is tetrachloro-1,4-benzoquinone.

Chart 1. Investigation of Substrates with Different Substituents on the Double Bond^{a,b}

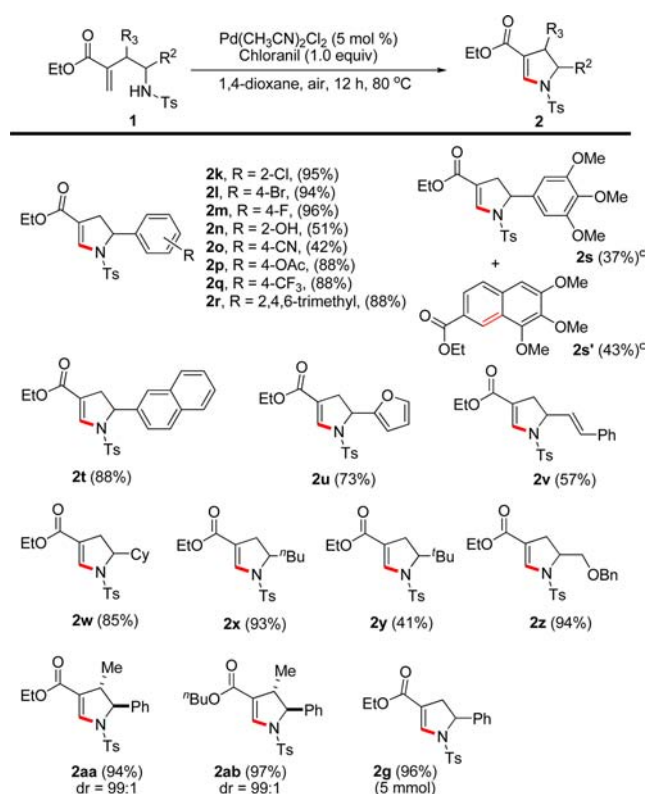
^aThe reaction was performed under the following reaction conditions: **1** (0.5 mmol), Pd(CH₃CN)₂Cl₂ (10 mol %), and chloranil (1.0 equiv) in 2 mL of dioxane at 80 °C under air atmosphere for 24 h. ^bIsolated yield. ^cReaction was run for 12 h. ^dReaction was run for 48 h. ^eStarting material is *N*-(2-(3,4-dihydronaphthalen-1-yl)-1-phenylethyl)-4-methylbenzenesulfonamide. ^f5 mol % of Pd(CH₃CN)₂Cl₂ was used.

cyclization and aromatization processes). No reaction took place when the substituent R¹ was replaced by a long-chain alkyl group (**2f**, Chart 1). When R¹ was changed to different ester groups, it was also found that all of the desired products could be obtained in excellent yields, except the *tert*-butyl ester substituted **2i**, possibly due to its steric hindrance. These results implied that electron-withdrawing functional groups at the R¹ position favor the 5-*endo-trig* cyclization.

Next, we turned our attention to expand the substrate scope with the R¹ group as ethyl ester. Expectedly, the desired products were obtained in moderate to excellent yields when the R² group was the

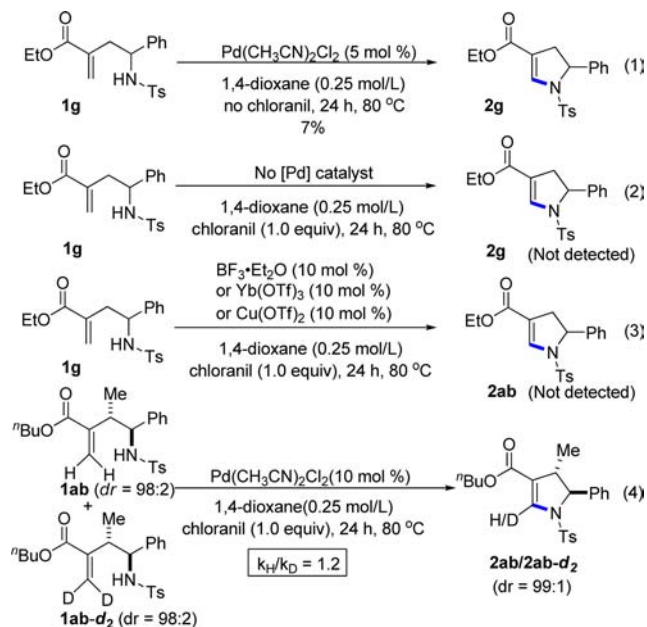
substituted phenyl ring. It was also observed that a wide scope of functional substituents on the phenyl ring could be well-tolerated, except for the cyano and hydroxyl groups, which afforded the desired products only in moderate yields, possibly due to their coordinative effect with the palladium catalyst. It should be noted that the reaction with the 2,4,6-trimethylphenyl ring proceeded smoothly to give the desired product in 88% yield. However, the electron-rich substrate **1n** with a 3,4,5-trimethoxyphenyl ring only afforded the desired product **2s** in 37% yield. Another product, **2s'**, formed via intramolecular oxidative coupling and aromatization processes, was isolated in 43% yield. Next, the substrates bearing other aryl groups such as naphthyl and furyl groups were tested in this cyclization reaction, and both provided the corresponding products in high yields. When the styryl-substituted substrate (**1v**, Chart 2) was subjected to the reaction, only a moderate yield was observed. Furthermore, all reactions proceeded smoothly to give the desired products in excellent yields when R² was changed to alkyl groups. However, the steric effect of R² for the product's yield was significant because only 41% yield of **2y** could be obtained using the substrate with a sterically demanding *tert*-butyl group. Finally, it was found that the substituents at the R³ position were less influential on the product's yield. Under the optimized reaction conditions, the 5-*endo-trig* cyclization reaction can be scaled up to 5 mmol without compromising the product yield (**2g**, Chart 2).

To explore the possible mechanistic pathway of this intramolecular oxidative amination reaction, the following experiments (Scheme 2, eq 1–4) were carried out. When the reaction was conducted without any oxidant, only about 7% of the desired product was detected according to crude ¹H NMR spectrum. However, reaction without palladium catalyst or those with other Lewis acids (10 mol %) instead of palladium, gave no desired product. Therefore, the hypothesis which suggests the role of palladium catalyst as mere Lewis acid could be omitted. Next, isotopically labeled experiments were conducted to gain some preliminary understandings of this coupling process. Intermolecular competition experiments between **1g** and its dideuterated analogue **1g-d₂** exhibited a kinetic isotopic effect value (KIE) of 1.2, which suggested that β-hydride elimination step was not the turnover limiting step in this catalytic cycle.

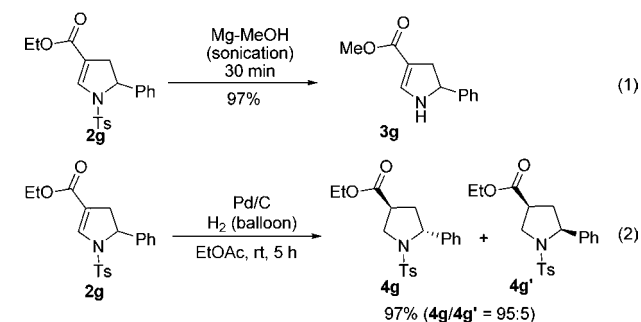
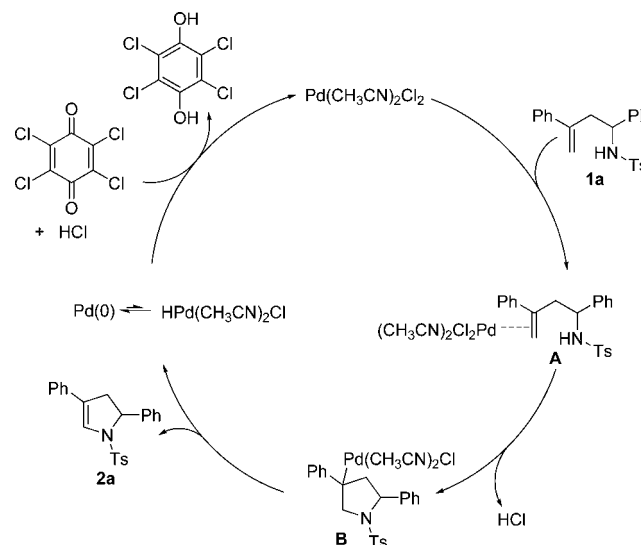
Chart 2. Scope of Different Substrates with an Ester Group on the Double Bond^{a,b}

^aThe reaction was run under the following reaction conditions: **1** (0.5 mmol), Pd(CH₃CN)₂Cl₂ (10 mol %), and chloranil (1.0 equiv) in 2 mL of dioxane at 80 °C under air atmosphere for 24 h. ^bIsolated yield. ^cStarting material is ethyl 2-methylene-4-(4-methylphenylsulfonamido)-4-(3,4,5-trimethoxyphenyl)butanoate.

Scheme 2. Control Experiments



Furthermore, derivatization reactions of compound **2g** were investigated. First, the tosyl protecting group could be easily removed using magnesium turnings in methanol solution under

Scheme 3. Derivation of Compound **2g**Scheme 4. Proposed Plausible Mechanism for the Palladium-Catalyzed *5-endo-trig* Cyclization

sonication (Scheme 3, eq 1). Moreover, hydrogenated product **4g** could be afforded in high yield with excellent stereoselectivity (Scheme 3, eq 2).

Based on the previous reports,^{7b} a possible mechanistic pathway is proposed (Scheme 4). First, the Pd(II) coordinates with a double bond followed by nucleophilic attack on the coordinated olefin to form the C–N and σ -Pd bonds. After β -hydride elimination of intermediate B, the desired product is formed together with the release of the palladium catalyst for the next catalytic cycle.

In conclusion, we have developed a palladium-catalyzed intramolecular oxidative amination of alkenes. In this work, various tosyl-protected amines can be coupled with multi-substituted vinylarene and acrylate fragments efficiently. The corresponding products can be obtained in moderate to excellent yields under simple reaction conditions. Application of the current methodology in organic synthesis of natural products is ongoing 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.7b00072.

Experimental procedures and spectral data for all new compounds (¹H NMR, ¹³C NMR, HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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