ChemPubSoc Europe

DOI: 10.1002/chem.201400084

CHEMISTRY A European Journal Communication

C–H Activation

# Palladium/Norbornene-Mediated Tandem C–H Amination/C–I Alkenylation Reaction of Aryl Iodides with Secondary Cyclic *O*-Benzoyl Hydroxylamines and Activated Terminal Olefins

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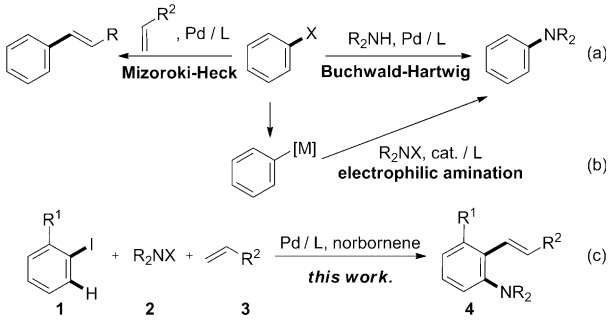
**Abstract:** A novel palladium-catalyzed norbornene-mediated three-component reaction for the construction of *ortho*-alkenyl aromatic tertiary amines has been achieved, which represents a useful extension of the Catellani-type tandem *ortho*-selective C–H amination transformations.

By using aryl halides or *pseudo* halides as readily available starting materials, great diversity of C–C or C–hetero bonds can be regioselectively generated through known palladium-catalyzed cross-coupling reactions. For example, the alkenylation of aryl iodide, as represented by Mizoroki–Heck reaction, is one of the most important C–C bond formation processes for the preparation of alkenyl aromatic derivatives.[1] Palladium-catalyzed Buchwald–Hartwig amination reaction of aryl halides with amines,[2] the current state of the art in nucleophilic amination, has been intensively studied as a prominent tactic for the generation of functional arylamines (Scheme 1a). Recently, electrophilic amination based on Umpolung strategy[3] of organometallic reagents with $R_2N^+$ synthons, such as chloro- and hydroxylamines,[4] has attracted significant interest in the synthetic organic community (Scheme 1b). Transition-metal-catalyzed electrophilic amination reaction enables not only organometallic reagents,[5] but also heteroaromatic C–H bonds[6] to be efficiently aminated, thus providing attractive alternatives to the previously established C–N bond formation protocols. While Pd-catalyzed C–C or C–N bond formation reactions have aroused significant interest even at industrial scale, the one-step preparation of *ortho*-alkenyl aromatic anilines using aryl halides as reliable substrates has been less developed, although such type of aromatic amines may find important applications as synthetic building blocks in the laboratory or industry,[7a] as bioactive drugs in medicinal chemistry,[7b] and organic light-emitting materials.[7c]

Recently, domino/tandem reactions have emerged as an efficacious synthetic tool because they could provide straightforward access to structurally diverse molecules in a one-pot reaction vessel.[8] Domino reactions that involve sequential C–H activation processes are of particular value, since these types of reactions do not require prefunctionalization of one or both of the substrates, thus significantly shortening the number of synthetic steps.[9,10] Inspired by the seminal work of Catellani,[11] Lautens,[12] and others,[13] who demonstrated a fascinating domino reaction of aryl iodides with alkyl bromides and alkenes by Pd/norbornene-mediated tandem C–H alkylation/C–I alkenylation sequences (the Catellani reaction),[11–14] we envisioned that a direct C–H amination/C–X alkenylation reaction based on the electrophilic amination strategy could be applied to the Catellani reaction process (Scheme 1c).[15]




**Scheme 1.** Pd-catalyzed cross-coupling reaction based on aryl iodide.

In view of the widespread application of C–C bond formation transformations based on Catellani reaction,[11–14] we hypothesized that a similar mechanism might also operate in a designed Pd-catalyzed cascade C–N bond formation process (Scheme 2). The five-membered palladacycle **B** would be produced first through oxidative addition of aryl iodide **1** with $Pd^0$, *syn*-carbopalladation with norbornene, and intramolecular C–H activation/deprotonation reaction. Oxidative addition of the electrophilic amination agent ($R_2N$–X) **2** to the $Pd^{II}$ center of **B** would generate a $Pd^{IV}$ species **C**,[16] which undergoes reductive elimination to give an amination complex **D**. Alternatively, the direct electrophilic amination of $R_2N$–X with palladacycle **B** facilitated by the concomitant N–O cleavage to form amination complex **D** is conceivable.[6] Next, expulsion of norbornene moiety followed by Mizoroki–Heck coupling between the aminated ArPdX species **E** and alkene **3** would give the desired C–H amination/C–X alkenylation product **4**. Although the sequential *ortho* C–C formation reactions using alkyl or aryl electrophiles (R–Br) in Catellani reaction have been extensively studied,[11–14] however, to our surprise, using nitrogen electro-

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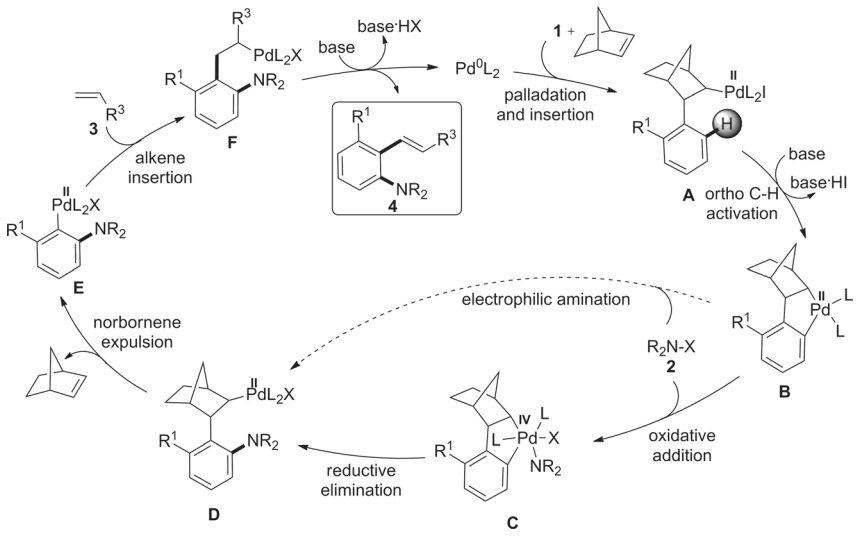
*Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201400084.*



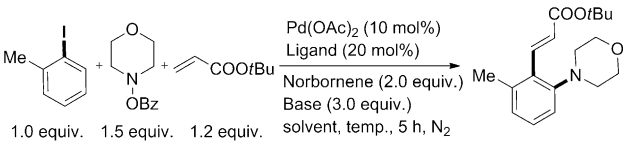

**Scheme 2.** Possible mechanism.

philes ($R_2N^+$) as an alternative in the palladium catalyzed reaction conditions has rarely been documented till now,[6a,17] The use of nitrogen as an electrophile in the Catellani reaction was recently reported by Dong and prompts us to report our studies which provide further support for the feasibility of this approach.[17b] Therefore, this Pd/norbornene-mediated domino reaction should provide an opportunity of *ortho*-selective C–N bond and *ipso* C–C bond formation processes in a one-pot procedure, thus would represent a useful extension to the known Catellani-type C–H amination reactions.

Our study commenced with the $Pd(OAc)_2$-catalyzed norbornene-mediated reaction of 1-iodo-2-methylbenzene (**1a**) with a secondary cyclic electrophilic amination agent ($R_2NX$) **2** and *tert*-butyl acrylate (**3a**). After a survey of the reaction conditions by varying the $R_2NX$ agents (**2**), ligands, bases, as well as the effect of different additives, we were pleased to find that when morpholino benzoate (**2a**) was employed[18] as a substrate, the corresponding product **4a** could be isolated in 34% yield with excellent *E* configuration double bond in the presence of $Cs_2CO_3$ (3.0 equiv) in $CH_3CN$ at 80 °C (Table 1, entry 1). In the absence of $Ph_3P$, a complex mixture of products was observed (entry 2). A reduced yield of **4a** was obtained (24% yield) while with 1.0 equivalent of norbornene (entry 3).[19] The product **4a** could be isolated in 32% yield when $Pd_2(dba)_3$ (10 mol%) was used as a catalyst instead of $Pd(OAc)_2$ (entry 4). The reaction with 4-chloromorpholine as an electrophilic amination agent led to reduced yield, presumably due to the high reactivity and instability of this reagent under the reaction condition (entry 5).[20]

As the investigation proceeded, we became aware that the choice of phosphine ligand is crucial for the success of the reaction. While tri-2-furylphosphine, $PtBu_3{\cdot}HBF_4$, and $(4\text{-}CF_3C_6H_4)_3P$ gave low yields, a good result was obtained when an electronically rich but sterically neutral ligand, $(4\text{-}MeOC_6H_4)_3P$, was employed, affording 83% yield of **4a**. Remarkably, the other electronically rich but sterically hindrance ligands, such as SPhos and XantPhos, resulted in rather sluggish performances (Table 1, entries 6–12). The base effect showed marginal influence on the transformation, since $K_2CO_3$ gave only trace yield of product **4a**, and none of the other bases was superior to $Cs_2CO_3$ (Table 1, entries 13–15). Among the solvents examined, toluene gave a reasonable yield of 71% of **4a**, while inferior conversion was obtained in 1,4-dioxane, and polar solvents such as DMF, DMSO, and DMA usually led to faster conversion but lower yields (Table 1, entries 16–20). Attempts to improve the yield of **4a** by varying the temperature and concentration of the reaction were unsuccessful as well (Table 1, entries 21–23).

**Table 1.** Optimization of the reaction conditions.[a]

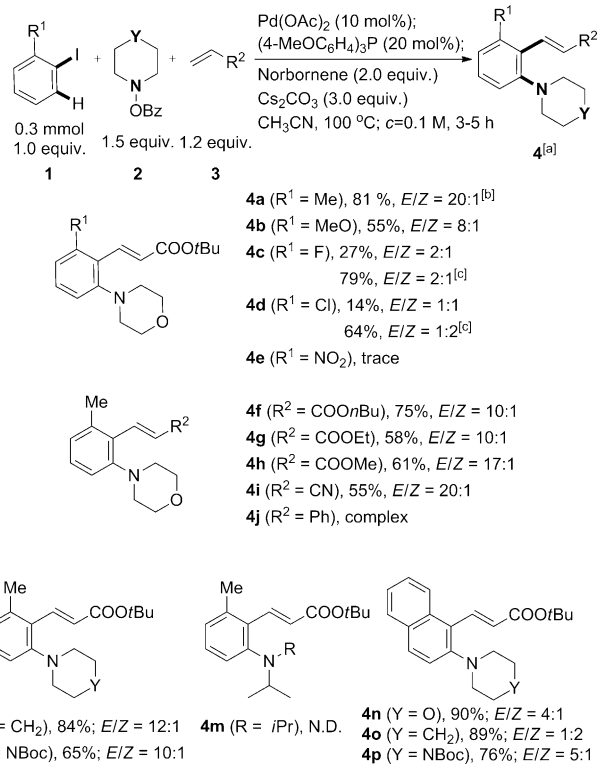



1.0 equiv. **1a** 1.5 equiv. **2a** 1.2 equiv. **3a** **4a**

| | Ligand | Base | Solvent | *T* [°C] | Yield [%] |
|---|---|---|---|---|---|
| 1 | $Ph_3P$ | $Cs_2CO_3$ | $CH_3CN$ | 80 | 34 |
| 2 | – | $Cs_2CO_3$ | $CH_3CN$ | 80 | 27 |
| 3 | $Ph_3P$ | $Cs_2CO_3$ | $CH_3CN$ | 100 | 24[b] |
| 4 | $Ph_3P$ | $Cs_2CO_3$ | $CH_3CN$ | 100 | 32[c] |
| 5 | $Ph_3P$ | $Cs_2CO_3$ | $CH_3CN$ | 80 | complex[d] |
| 6 | $(2\text{-furyl})_3P$ | $Cs_2CO_3$ | $CH_3CN$ | 100 | 34 |
| 7 | $PtBu_3{\cdot}HBF_4$ | $Cs_2CO_3$ | $CH_3CN$ | 100 | 12 |
| **8** | **$(4\text{-}MeOC_6H_4)_3P$** | **$Cs_2CO_3$** | **$CH_3CN$** | **100** | **83** |
| 9 | $(4\text{-}CF_3C_6H_4)_3P$ | $Cs_2CO_3$ | $CH_3CN$ | 100 | 18 |
| 10 | $(4\text{-}MeC_6H_4)_3P$ | $Cs_2CO_3$ | $CH_3CN$ | 100 | 37 |
| 11 | SPhos | $Cs_2CO_3$ | $CH_3CN$ | 80 | 33 |
| 12 | XantPhos | $Cs_2CO_3$ | $CH_3CN$ | 80 | 4 |
| 13 | $(4\text{-}MeOC_6H_4)_3P$ | $K_2CO_3$ | $CH_3CN$ | 100 | 5 |
| 14 | $(4\text{-}MeOC_6H_4)_3P$ | KO*t*Bu | $CH_3CN$ | 100 | 20 |
| 15 | $(4\text{-}MeOC_6H_4)_3P$ | DBU | $CH_3CN$ | 100 | 20 |
| 16 | $(4\text{-}MeOC_6H_4)_3P$ | $Cs_2CO_3$ | 1,4-dioxane | 100 | 38 |
| 17 | $(4\text{-}MeOC_6H_4)_3P$ | $Cs_2CO_3$ | toluene | 100 | 71 |
| 18 | $(4\text{-}MeOC_6H_4)_3P$ | $Cs_2CO_3$ | DMF | 100 | 42 |
| 19 | $(4\text{-}MeOC_6H_4)_3P$ | $Cs_2CO_3$ | DMA | 100 | 45 |
| 20 | $(4\text{-}MeOC_6H_4)_3P$ | $Cs_2CO_3$ | DMSO | 100 | 51 |
| 21 | $(4\text{-}MeOC_6H_4)_3P$ | $Cs_2CO_3$ | $CH_3CN$ | 80 | 52 |
| 22 | $(4\text{-}MeOC_6H_4)_3P$ | $Cs_2CO_3$ | $CH_3CN$ | 100 | 70[e] |
| 23 | $(4\text{-}MeOC_6H_4)_3P$ | $Cs_2CO_3$ | $CH_3CN$ | 100 | 69[f] |

[a] Reaction conditions: **1a** (0.30 mmol, 1.0 equiv), **2a** (0.45 mmol, 1.5 equiv), **3a** (0.36 mmol, 1.2 equiv), $Pd(OAc)_2$ (0.03 mmol, 10 mol%), $Ph_3P$ (0.06 mmol, 20 mol%), norbornene (0.6 mmol, 2.0 equiv), $Cs_2CO_3$ (0.9 mmol, 3.0 equiv), $CH_3CN$ (3.0 mL, 0.10 M), 80 °C, $N_2$; isolated yields based on **1a**; [b] with norbornene (1.0 equiv); [c] $Pd_2(dba)_3$ (10 mol%) instead of $Pd(OAc)_2$; [d] 4-chloromorpholine (1.5 equiv) instead of **2a**; [e] $CH_3CN$ (1.0 mL, 0.30 M); [f] $CH_3CN$ (2.0 mL, 0.15 M).

With the optimized reaction conditions in hand [$Pd(OAc)_2$ (10 mol%), (4-$MeOC_6H_4)_3P$ (20 mol%), norbornene (2.0 equiv), $Cs_2CO_3$ (3.0 equiv), $CH_3CN$ (3.0 mL, 0.10 M), 100 °C, $N_2$], the scope and limitation of this transformation was next explored by using various iodoarenes **1**, *N*,*N*-dialkyl *O*-acyl hydroxylamines **2**, and terminal alkenes **3**. A wide range of alkenyl aromatic tertiary amines **4** could be readily obtained by following the established procedure (Scheme 3). The reaction can be




**Scheme 3.** Synthesis of alkenyl aromatic tertiary amine **4** by domino reaction of aryl iodide **1**, secondary cyclic $R_2N$–OBz **2** and activated terminal alkene **3**. [a] Isolated yield based on **1**. *E*/*Z* ratio was determined by $^1H$ NMR spectroscopy. [b] Reaction was carried out in 5 mmol scale (1.23 g of **4a** was obtained). [c] (2-Furyl)$_3$P (0.06 mmol, 20 mol%) and toluene (2 mL) instead of (4-$MeOC_6H_4)_3P$ and $CH_3CN$.

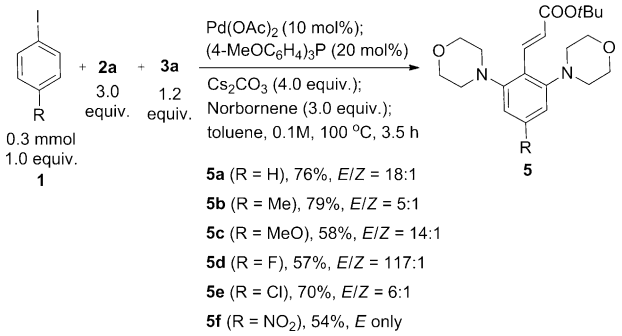
scaled up without difficulty to preparative gram scale of 5 mmol, affording 1.23 g of product **4a** (81% yield) with an *E*/*Z* isomer ratio of 20:1. Iodoarenes **1** with electron-donating substituents at the *ortho* position of C–I bond participated in the amination/alkenylation domino reaction smoothly (**4a** and **b**).

However, the transformation of *ortho*-halogen (F and Cl) substituted iodoarenes **1** with **2a** and **3a** were rather sluggish, affording the desired products **4c** and **d** in poor yields under the standard conditions, due to the formation of undesired Mizoroki–Heck-type cross-coupling byproducts as the main outcomes. To our delight, good yields of products **4c** and **d** were obtained when (2-furyl)$_3$P was employed as a ligand and toluene as the reaction medium.[21] Notably, the *E*/*Z* isomers were almost equal and inseparable in **4c** and **d**, and the *Z* isomer of **4d** was likely to be the major product as determined by $^1H$ NMR analysis. The unusual low *E*/*Z* selectivities herein (as compared to typical Mizoroki–Heck coupling reactions) were still uncertain at the present stage, presumablely the choice of ligand should take into account in the case of **4c** and **d**. Besides, the inherent steric and electronic nature of the substrates might play importance to some extent, since compounds **4k** and **o** (vide infra) were obtained in a sharp contrast of *E*/*Z* selectivities under the same catalytic conditions. When compound 1-iodo-2-nitrobenzene was employed in the reaction, trace amount of compound **4e** can be detected, and the Mizoroki–Heck type byproduct (*E*)-*tert*-butyl 3-(2-nitrophenyl)-acrylate was isolated in 43% yield under the standard conditions. Switching to the use of 1-bromo-2-nitrobenzene in this reaction resulted in less than 10% yield of **4e** as estimated by crude $^1H$ NMR spectroscopy.

For the reaction of various alkenes with *o*-iodotoluene **1a** and morpholino benzoate **2a**, terminal alkenes such as *n*-butyl acrylate (**4f**), ethyl acrylate (**4g**), methyl acrylate (**4h**) and acrylonitrile (**4i**) efficiently participate to produce the corresponding amination/alkenylation products in good yields ranging from 55–75% (Scheme 3). However, the alkenylation teminal-step was completely inhibited and a complex mixture of **4j** was observed when unactivated styrene was used as a substrate, presumably due to low reactivity of the olefin, and the formation of various byproducts aroused from the competitive reactions. Finally, the scope of the *O*-benzoyl hydroxylamines **2** in the present reaction was evaluated. It was found that the reaction proceeds smoothly for secondary cyclic *O*-benzoyl hydroxylamines, since the piperidin-1-yl (**4k**) and Boc-protected piperazin-1-yl (**4l**) were isolated in good to excellent yields under the standard conditions. For the reaction of acyclic *O*-benzoyl-*N*,*N*-diisopropylhydroxylamine participated reactions, the desired product **4m** was not isolated, suggesting that the reaction may inherently suffered from steric demand limitation. The reaction worked well in the reaction of 1-iodonaphthalene with secondary cyclic *O*-benzoyl hydroxylamines **2** and *tert*-butyl acrylates **3a**, as the corresponding products which bearing a naphthalene substituent (**4n**–**p**) can be accessed in high yields using this methodology.

In the case of aryl iodides **1** bearing no *ortho*-substituent reacted with morpholino benzoate **2a** and *tert*-butyl acrylate **3a**, the 1,3-diaminated cinnamates **5** can be obtained. Reasonable yields of products **5a**–**f** could be produced when 3.0 equivalents of norbornene was employed in the reaction in anhydrous toluene at 100 °C (Scheme 4). It is noteworthy that the common reactive functional groups, such as fluoro, chloro, nitro, alkene, and ester group, were compatible in the present catalytic reaction, implying that further incorporation of such molecules into larger systems by employing the reactive functionalities as synthetic handles can be easily manipulated.

In summary, we have disclosed a novel palladium-catalyzed norbornene-mediated domino reaction of aryl halides, secondary cyclic electrophilic amination agent ($R_2N$–OBz) and activated terminal olefins, selectively affording a series of *ortho*-alkenyl aromatic amines in moderate to excellent yields. The success of the present reaction demonstrates a useful extension of *ortho*-selective C–H amination processes to existing $Pd^{II}$/nor-




**Scheme 4.** Synthesis of alkenyl aromatic bis-tertiary amines **5**.

bornene-mediated Catellani-type cascade reaction, and benefits the design of new synthetic methodologies to valuable arylamine derivatives. Efforts on expanding the substrate scope as well as application of the current method to the synthesis of useful N-containing heterocyclic compounds are currently underway.

## Experimental Section

### Typical procedure for the preparation of compound 4a

To a 25 mL of Schlenk tube equipped with a Teflon-coated magnetic stir bar was charged with 1-iodo-2-methylbenzene **1a** (65.4 mg, 0.30 mmol), morpholino benzoate **2a** (93.2 mg, 0.45 mmol), *tert*-butyl acrylate **3a** (48.6 mg, 0.36 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $(4\text{-}MeOC_6H_4)_3P$ (21.1 mg, 0.06 mmol), $Cs_2CO_3$ (293.4 mg, 0.9 mmol), norbornene (57.6 mg, 0.6 mmol), and $CH_3CN$ (3.0 mL). The brown suspension was stirred at room temperature for 10 min under $N_2$, and then heated to 100 °C for 5 h. The reaction was monitored by TLC. After being cooled to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL), transferred to a 50 mL of separation funnel and washed with water (15 mL), extracted with ethyl acetate (3×10 mL). The organic phase was collected, washed with brine, dried over $Na_2SO_4$, and concentrated. The crude residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (10:1, *v/v*) as eluent to give the corresponding pure product **4a**.

## *Acknowledgements*

Financial support from National Natural Science Foundation of China (21202065), the Specialized Research Fund for the Doctoral Program of Higher Education (20123604120003), and a Sponsored Program for Cultivating Youths of Outstanding Ability from Jiangxi Normal University are gratefully acknowledged.

**Keywords:** alkenylation · C–H amination · norbornene · palladium · tandem reaction

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Received: January 8, 2014
Published online on March 12, 2014