UPDATES

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Advanced Synthesis & Catalysis

Synthesis of 2-(1-Alkoxyvinyl)anilines by Palladium/Norbornene-Catalyzed Amination Followed by Termination with Vinyl Ethers

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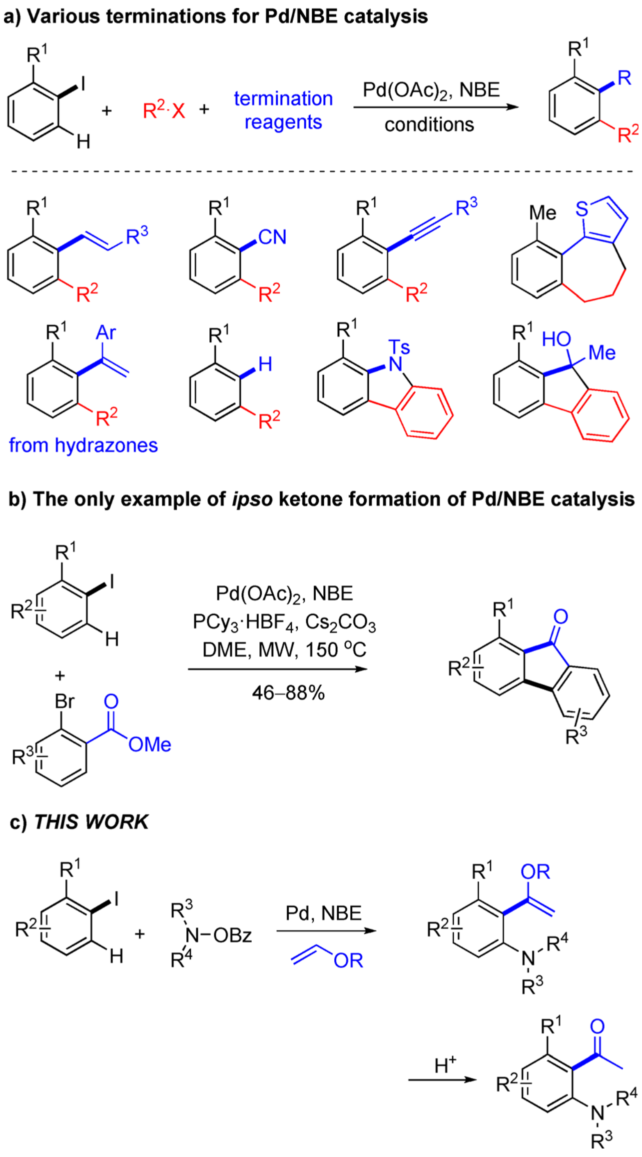
Abstract: A palladium/norbornene-catalyzed *ortho*-amination and *ipso* vinyl ether termination reaction of iodoarenes is reported. The benzyl vinyl ether serves as an efficient alternative carbonyl source in palladium/norbornene catalysis for the final *ipso* termination reaction to give [1-(benzyloxy)vinyl]arenes, which readily undergo hydrolysis to deliver methyl ketones under aqueous acidic conditions. The final Heck termination reaction with vinyl ethers has high branched/linear selectivity. This reaction tolerates a range of iodoarene and *O*-benzoylhydroxylamine substrates, and it provides a convenient way to prepare *o*-acetylanilines. The synthetic utility of [1-(benzyloxy)vinyl]arenes and the corresponding ketones is briefly investigated.

Keywords: carbonyl compounds; Heck reaction; norbornene; palladium; vinyl ethers

Palladium-catalyzed carbonylation is a powerful method for synthesizing carbonyl compounds.[1] These reactions are usually mild, efficient and tolerant of different functional groups; they occasionally allow multiple bonds to be formed in a step-economical manner. Palladium/norbornene (NBE)-catalyzed transformations, first reported by Catellani and co-workers in 1997,[2] are unique reactions which not only furnish the classic cross-couplings, Heck reaction or carbonylations etc., but also introduce functionality at the *ortho*-position *via* the norbornene-containing palladacycle intermediate. Such transformations have become a popular method for constructing polysubstituted arenes, particularly 1,2,3-trisubstituted ones. Simply by altering the termination reagents, which can include alkenes, cyano anion, alkynes, electron-rich arenes, hydrazones, amides and ketones, many diversely substituted arenes,[3,4] as well as natural products[5] were synthesized efficiently by many groups, notably those of Catellani, Lautens and their co-workers (Scheme 1a).

Ketones are an important type of functional group and intermediates in organic synthesis, and various biologically active molecules containing ketone moieties were discovered.[6] Recently the groups of Liang and Dong as well as our own group independently reported Pd/NBE-catalyzed *ortho*-acylation reactions by the use of acid chlorides or (mixed) anhydrides.[7] In contrast, we are aware of only one report using Pd/NBE catalysis to introduce ketone functionality at the *ipso*-position of iodoarenes.[8] Furthermore, this protocol was limited to the synthesis of 9*H*-fluoren-9-ones by the use of 2-bromobenzoates (Scheme 1b). Given the importance of aryl ketones, we report here a Pd/NBE-catalyzed synthesis of acetophenones by *ipso*-Heck termination with vinyl ethers (Scheme 1c).[9,10]

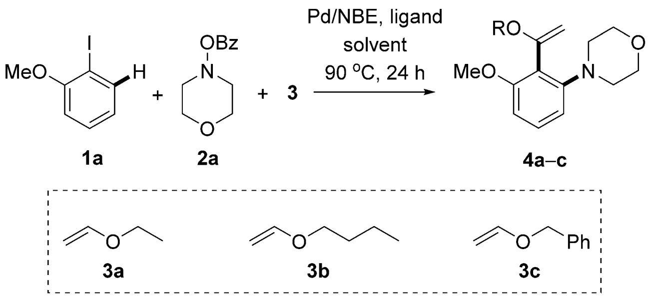
In our early work, we failed to synthesize ketones under standard Pd/NBE catalysis conditions when we used carbon monoxide as the carbonyl source, instead obtaining a complicated mixture.[11] This failure may reflect the fact that several intermediates in the catalytic cycle, such as ArPdX and intermediates **I** and **III** (Scheme 4), may react with carbon monoxide to give side products. Therefore, in order to introduce the ketone functionality, in the present work we opted for a Heck reaction by the use of vinyl ethers. The present work also built on the seminal work of Dong and co-workers in 2013, who reported a Pd/NBE-catalyzed *ortho*-amination reaction in which *O*-benzoylhydroxylamines served as the amination reagents.[4i] To our delight, in the presence of $Pd(OAc)_2$/NBE, DavePhos and Cs_2CO_3, the reaction of 2-iodoanisole **1a**, morpholine benzoate **2a** and ethyl vinyl ether **3a** gave the expected terminal vinyl ether **4a** in moderate yield (Table 1, entry 1). Compound **4a** was stable enough for regular column chromatographic purification on silica gel. Palladium chloride showed comparable efficiency as $Pd(OAc)_2$, while the reaction with



Scheme 1. Pd/NBE-catalyzed domino reactions.

$Pd_2(dba)_3$ gave only 15% yield of **4a** (entries 2 and 3). MeCN gave satisfactory results, while toluene and DMF proved to be unsuitable solvents for this transformation (entries 4–6). Ligand screening showed that both tris(2-furyl)phosphine (TFP) and PPh_3 gave similar results (entries 7 and 8). Meanwhile, $Pd(PPh_3)_4$ gave marginally lower yield than the $PdCl_2/PPh_3$ system (entry 9). Vinyl ethers with higher boiling points, such as *n*-butyl vinyl ether **3b** and benzyl vinyl ether **3c** led to higher isolated yields of the corresponding products (entries 10 and 11). Thus, benzyl vinyl ether **3c** was used in subsequent studies of substrate scope. During optimization of reaction conditions, dry and fresh distilled 1,4-dioxane was found to be critical for the reaction. Decreasing the loading of palladium catalyst to 2 mol% led to a significantly lower yield (entry 12).

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



Entry	Pd	Ligand	Solvent	3	4, Yield
1	$Pd(OAc)_2$	DavePhos	dioxane	**3a**	**4a**, 45%
2	$PdCl_2$	DavePhos	dioxane	**3a**	**4a**, 46%
3	$Pd_2(dba)_3$	DavePhos	dioxane	**3a**	**4a**, 15%
4	$PdCl_2$	DavePhos	PhMe	**3a**	**4a**, 27%
5	$PdCl_2$	DavePhos	MeCN	**3a**	**4a**, 44%
6	$PdCl_2$	DavePhos	DMF	**3a**	**4a**, 32%
7	$PdCl_2$	TFP	dioxane	**3a**	**4a**, 47%
8	$PdCl_2$	PPh_3	dioxane	**3a**	**4a**, 45%
9	$Pd(PPh_3)_4$	–	dioxane	**3a**	**4a**, 42%
10	$PdCl_2$	PPh_3	dioxane	**3b**	**4b**, 67%
11	$PdCl_2$	PPh_3	dioxane	**3c**	**4c**, 84%[b]
12	$PdCl_2$[c]	PPh_3	dioxane	**3c**	**4c**, 24%

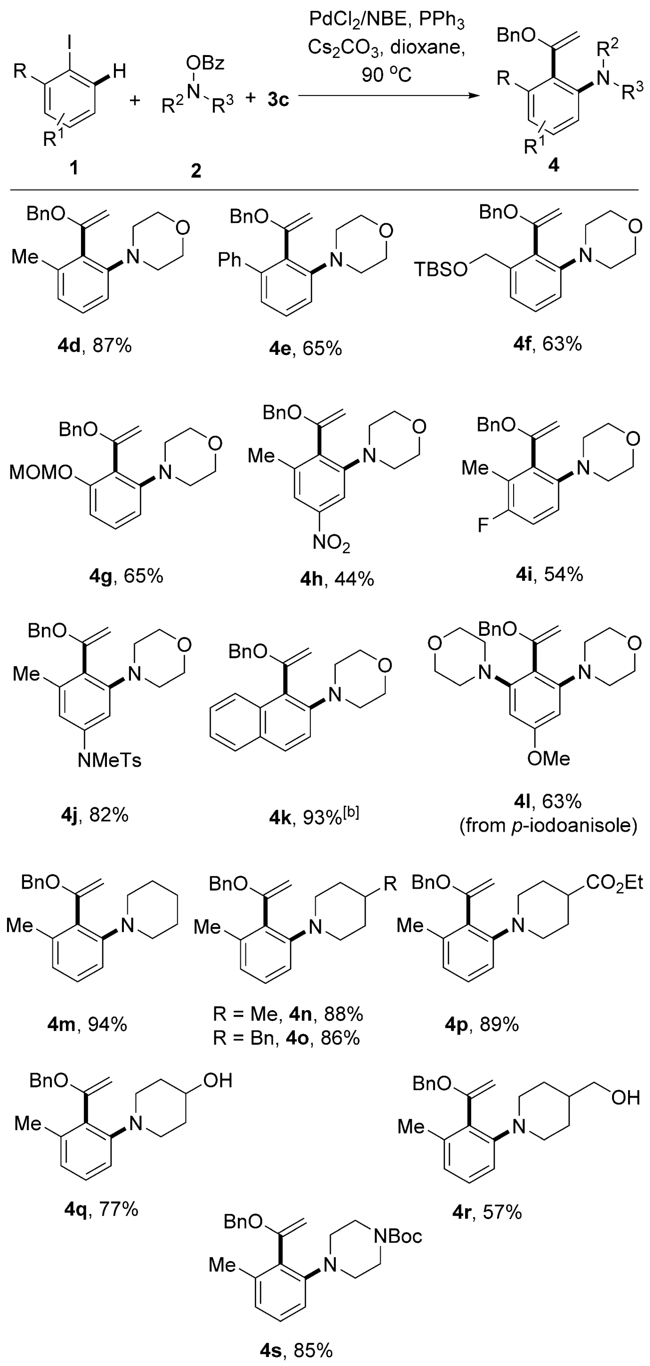
[a] The reaction was conducted with 0.20 mmol of **1a**, 0.30 mmol of **2a**, 0.60 mmol of **3**, 0.60 mmol of norbornene, 0.60 mmol of Cs_2CO_3, 5 mol% of $PdCl_2$, and 10 mol% of phosphine in the indicated solvent (2.0 mL, 0.10 mol/L).

[b] The regioisomer for the vinyl ether (linear product) was detected. Branched:linear product ~20:1.

[c] 2 mol% of $PdCl_2$ and 5 mol % of PPh_3 were used.

With the optimum reaction conditions in hand, we investigated the substrate scope of this reaction regarding various iodoarenes and *O*-benzoylhydroxylamines (Table 2). Besides **1a**, various *ortho*-substituents on the iodoarenes were tolerated in the reaction, including methyl, phenyl, O-TBS, hydroxymethyl and methoxymethoxy groups; the corresponding products **4d–g** were isolated in moderate to excellent yields. Both electron-withdrawing and electron-donating groups were tolerated on 2-iodotoluene, although substrates with electron-withdrawing groups led to relatively lower yields (**4h–j**). Using 1-iodonaphthalene in the reaction gave **4k** in 93% yield. *p*-Iodoanisole was smoothly converted to the diamino product **4l** in 63% yield. Evaluation of *O*-benzoylhydroxylamines showed that piperidine and its derivatives containing *p*-methyl, *p*-benzyl or 4-ethoxycarbonyl groups could be efficiently introduced at the *ortho*-position with excellent yields (**4m–p**). Both primary and secondary free alcohols were well tolerated (**4q** and **4r**), and the piperazine derivative **4s** was synthesized in a highly efficient manner.

Table 2. Substrate scope.[a]



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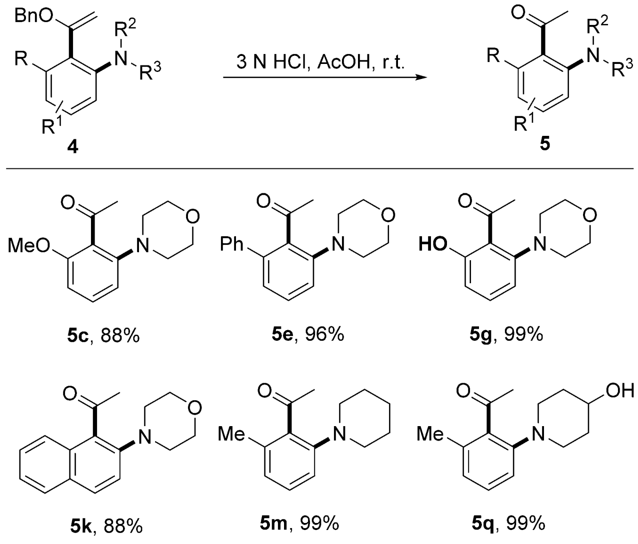
[a] The reaction was conducted with 0.20 mmol of **1**, 0.30 mmol of **2**, 0.60 mmol of **3c**, 0.60 mmol of norbornene, 0.60 mmol of Cs_2CO_3, 5 mol% of $PdCl_2$, and 10 mol% of PPh_3 in dioxane (2.0 mL, 0.10 mol/L).

[b] 10 mol% of $PdCl_2$ was used. TFP was the ligand and 4.0 mL of dioxane was used.

As expected, methyl aryl ketones were readily obtained from the [1-(benzyloxy)vinyl]arenes *via* acidic hydrolysis, and the corresponding products were obtained in yields of 88–99% (Table 3). Hydrolysis of **4g** resulted in cleavage of both vinyl ether and the MOM protective groups, giving **5g** in quantitative yield.

Table 3. Hydrolysis to methyl ketones.

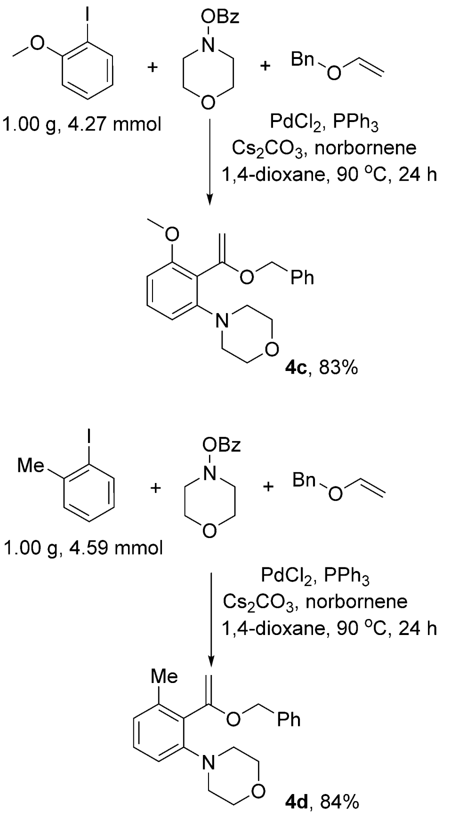


The reaction was scaled up uneventfully by using 1.0 gram of 1-iodo-2-methoxybenzene (4.27 mmol) or 1-iodo-2-methylbenzene (4.59 mmol) under standard reaction conditions. Good yields were obtained in both cases (Scheme 2).

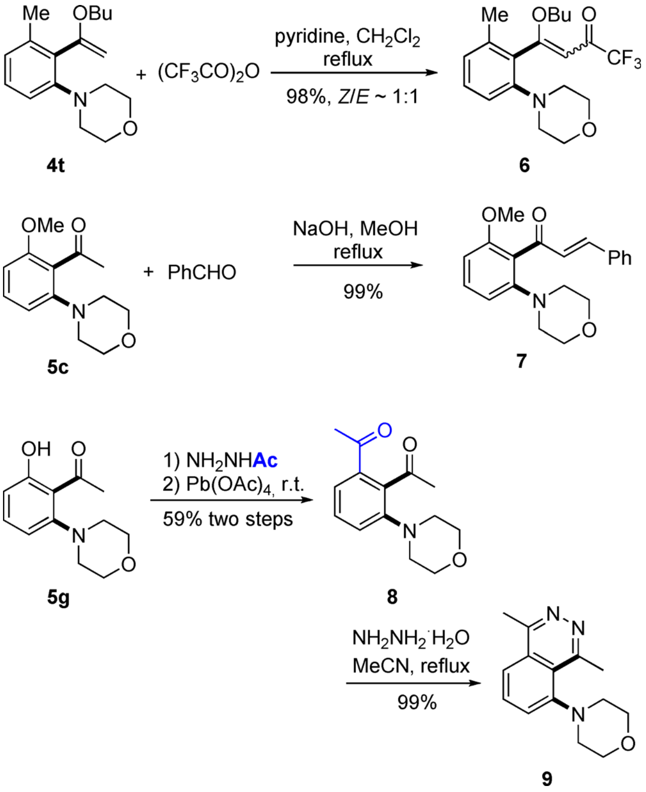
The synthetic utility of compounds **4** and **5** was briefly investigated (Scheme 3). Vinyl ether **4t** was efficiently acylated with trifluoroacetic anhydride, forming **6** in 98% yield with a *Z/E* ratio near 1:1 and retention of the vinyl ether moiety. The acetyl group was further functionalized *via* classic aldol condensation with benzaldehyde to give chalcone analogue **7**. Compound **5g** was converted to *o*-diacylbenzene derivative **8** *via* hydrazone formation followed by $Pb(OAc)_4$-mediated oxidative rearrangement.[12] The diketone **8** was readily transformed into phthalazine **9** in virtually quantitative yield.

A plausible catalytic cycle for our reaction is proposed in Scheme 4 using 2-iodotoluene, **2a** and **3c** as representative substrates. In the proposed mechanism, oxidative addition of 2-iodotoluene with Pd(0) gives an aryl-Pd(II) species, which generates a five-membered palladacycle **I** *via* NBE insertion and followed by C−H palladation. Oxidative addition of **I** with **2a** forms Pd(IV) complex **II**, which creates a C−N bond *via* reductive elimination.[13] Norbornene extrusion of **III** gives *ortho*-aminated Pd(II) species **IV**, which undergoes a classic Heck reaction with the benzyl vinyl ether **3c** to deliver the final product **4d**. Polarization of the C=C double bond in the vinyl ether may explain the observed high regioselectivity of the reaction.

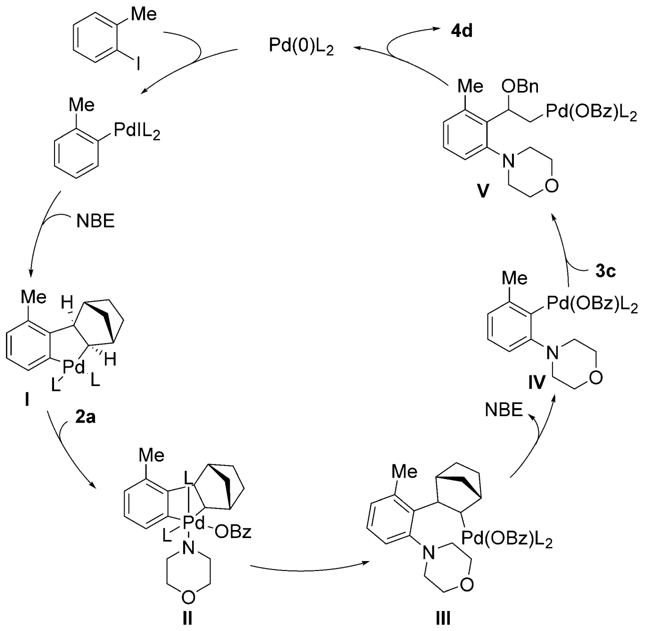
In conclusion, we have described a reaction involving Pd/NBE-catalyzed *ortho*-amination and *ipso* vinyl ether termination. Vinyl ethers are convenient and ef-



Scheme 2. Gram-scale reactions.



Scheme 3. Synthetic applications.



Scheme 4. Plausible catalytic cycle.

ficient alternatives to carbon monoxide for introducing *ipso* ketone moieties during the Pd/NBE-catalyzed process. Compounds **4** and **5** may be synthetically useful and can be transformed into vinyl ether **6**, chalcone derivatives and *o*-diacylanilines.

Experimental Section

Typical Procedure for the Palladium/Norbornene-Catalyzed *ortho*-Amination and *ipso* Heck Termination with Vinyl Ethers

A dried Schlenk tube was charged with 2-methoxyliodobenzene **1a** (46.8 mg, 0.20 mmol, 1.0 equiv.), *N*-benzoyloxymorpholine **2a** (62.0 mg, 0.30 mmol, 1.5 equiv.), benzyl vinyl ether **3c** (80.5 mg, 0.60 mmol, 3.0 equiv.), $PdCl_2$ (1.8 mg, 0.01 mmol, 5 mol%), PPh_3 (5.3 mg, 0.02 mmol, 10 mol%), norbornene (56.5 mg, 0.60 mmol, 3.0 equiv.) and Cs_2CO_3 (196.0 mg, 0.60 mmol, 3.0 equiv.) in 1,4-dioxane (2.0 mL). After stirring at 90 °C under an atmosphere of dry nitrogen for 24 h, the reaction mixture was cooled to room temperature and filtered through a pad of celite with EtOAc as the eluent. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give compound **4c**; yield: 54.4 mg (84%) ($b/l = 20:1$).

Acknowledgements

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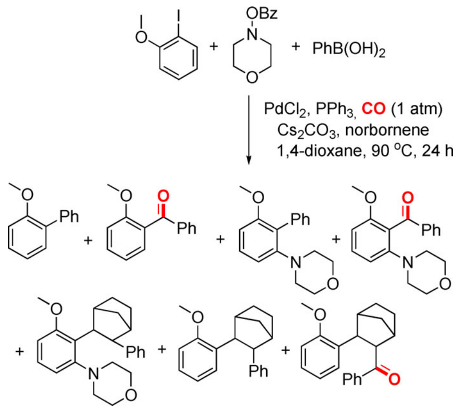
[11] The reaction **1a**, **2a** and phenylboronic acid in the presence of palladium chloride and norbornene under 1 atm of CO gave a complicated mixture, which tentatively was assigned as the following compounds by the analysis of crude ^{1}H NMR and GC-MS:



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