Pd-Catalyzed Cross-Coupling of Highly Sterically Congested Enol Carbamates with Grignard Reagents *via* C-O Bond Activation

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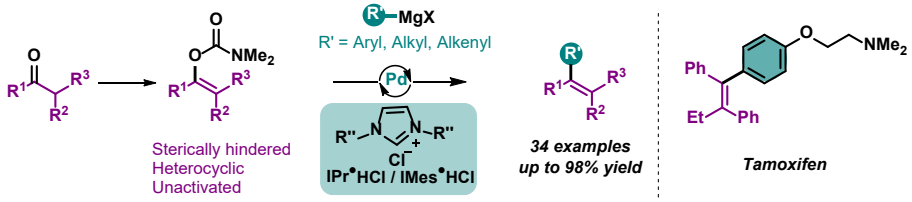
Supporting Information Placeholder



ABSTRACT: The palladium-catalyzed cross-coupling reaction of enol carbamates to construct highly sterically congested alkenyl compounds is presented for the first time. This protocol demonstrates the potential of using thermal stable and highly atom-economic enol electrophiles as building blocks in bulky alkene synthesis. This reaction accommodates a broad substrate scope with excellent *Z*/*E* isomer ratios, which also provides a new synthetic pathway for accessing Tamoxifen.

Alkenes are important structures constituting valuable materials[1] and bioactive agents[2]. The Wittig olefination[3] represents a classical approach to prepare alkene. However, the disadvantages are obvious due to the multiple synthetic steps and wasted stoichiometric phosphorus oxide side-products.

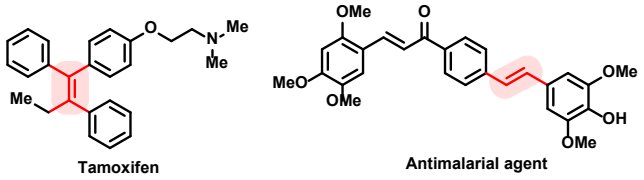


Figure 1. Bioactive agents containing alkene motifs.

The past few decades have seen the dramatic development of transition metal-catalyzed cross-coupling in organic synthesis.[4] Developed reactions involving diverse mechanisms have provided alternative routes to desired alkenyl compounds.[5] Pd-catalyzed cross-coupling reactions using alkenyl halides have proven successful, affording corresponding products in intra/inter molecular manners.[6] However, multi-substituted alkenyl halides are not broadly available, which limits their utility in cross-coupling reactions. Thus, exploring alternative electrophiles remains a valuable pursuit.

In the past few decades, O-based electrophiles from phenols have risen to become powerful alternatives to aryl halides.[7] Indeed, enol electrophiles are also a highly attractive complement to alkenyl halides: 1) they can be prepared easily from carbonyl compounds, one of the most abundant feedstocks from nature or the chemical industry; and 2) they can provide easy access for various substitution patterns of carbonyl compounds electrophiles with respect to alkenyl halides (Figure 2). Recent advancements demonstrate the practical application of enol sulfonates in cross-coupling reactions[8] and other transformations.[9] Enol phosphates[10] also have emerged as applicable alkenyl precursors. Nevertheless, sporadic reports focusing on enol carboxylates[11] as well as enol carbamates[12] show relatively higher atom-efficiency in cross-coupling reactions.

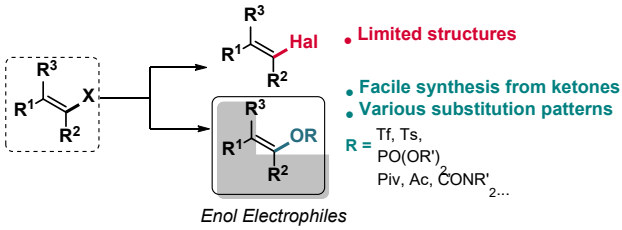


Figure 2. Features of enol electrophiles.

Among diverse transformations, transition metal-catalyzed cross-coupling reactions for C-C bond construction remain indispensable tools.[13] With regard to nucleophiles, Grignard reagents remain common carbon synthons due to their high reactivity and variety (Figure 3). Shi and co-workers[14] reported on a representative iron-catalyzed cross-coupling reaction of

alkenyl pivalates with Grignard reagents; however, the study only included alkylation examples, and the attempt to couple unactivated electrophiles was unsuccessful. In another study, Jacobi von Wangelin and co-workers[15] investigated the iron-catalyzed cross-coupling of alkenyl acetates with Grignard reagents. Although the scope of alkenyl electrophiles is advanced, the sensitivity of this Fe-catalyzed system to steric bulk is a recognized deficiency. Frantz and co-workers[16] developed an Fe-catalyzed cross-coupling reaction between stereo-defined enol carbamates and Grignard reagents for stereoselective acrylates synthesis. However, the literature seldom reports on examples other than alkylation. Recently, Knochel and co-workers[17] demonstrated successful arylation and alkenylation of alkenyl acetates under Co-catalyzed conditions. Nevertheless, these electrophiles were limited to activated substrates.

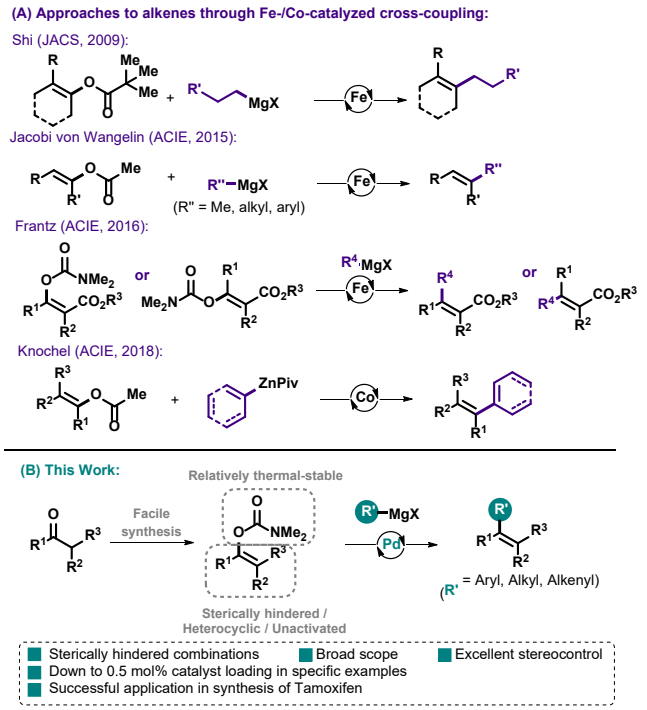
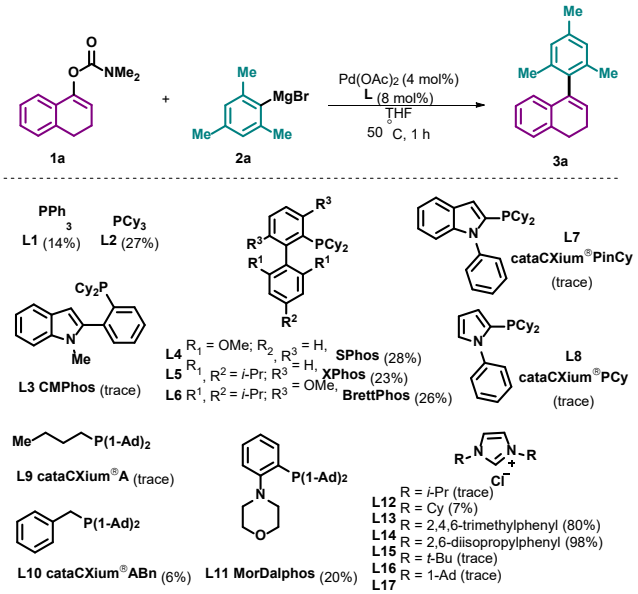


Figure 3. Transition metal-catalyzed cross-coupling reactions of enol carboxylates and carbamates using organometallics.

Palladium catalytic systems have exhibited effectiveness in synthesizing multi-substituted alkenes with alkenyl tosylates, yet the formation of extremely sterically congested alkene remains challenging.[18] On the other hand, enol carbamates are highly attractive electrophiles for several reasons: 1) they possess higher atom-economy compared to their sulfonate and phosphate counterparts; 2) they have excellent tolerance to thermal decomposition with respect to corresponding alkenyl pivalates and alkenyl tosylates, which benefit to its shelf life;[19] and 3) they can be prepared easily from carbonyl compounds. However, the activation of inert enol carbamate C-O via the less nucleophilic and oxophilic palladium system remains challenging. Herein, we report the first Pd-catalyzed sterically congested cross-coupling reaction between enol carbamates and Grignard reagents (Figure 3).

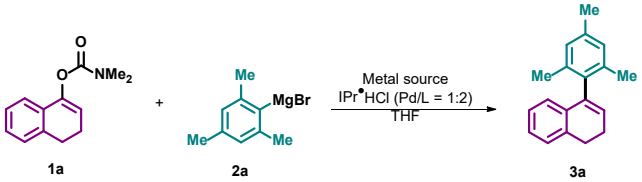
The ligand effect to this reaction was firstly investigated. 3,4-Dihydronaphthalen-1-yl dimethylcarbamate **1a** and mesitylmagnesium bromide **2a** was selected as model substrate for the screening (Scheme 1). Classical phosphine ligands, PPh_3 and PCy_3, gave low yields. Ligands previously used in the activation of alkenyl tosylates, such as CMPhos,[20] were found to be inactive. Screened Buchwald-type ligands (SPhos, XPhos and BrettPhos) led to relatively low yields, while ligands from Beller's group (Scheme 1, L8-L10) did not promote this reaction. MorDalphos was successfully employed in the activation of relatively challenging C-O bonds in our previous reports,[21] but it was not effective in this transformation. Fortunately, *N*-heterocyclic carbenes (NHCs) afforded promising yields (Scheme 1, L14, L15). IPr•HCl was superior to other derivatives. We speculated that the electron-donating properties as well as steric effects of NHCs facilitated the coupling process.[22] According to the screening results, the steric bulk of the *N*-substitutions greatly impacted the outcome.[23]

Scheme 1. Evaluation of Ligands[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), THF (total around 1 mL), $Pd(OAc)_2$ (4 mol%), ligand (8 mol%), under N_2 at 50 °C for 1 h; calibrated GC−FID yields are reported using dodecane as the internal standard.

Table 1. Optimization of Reaction Conditions[a]



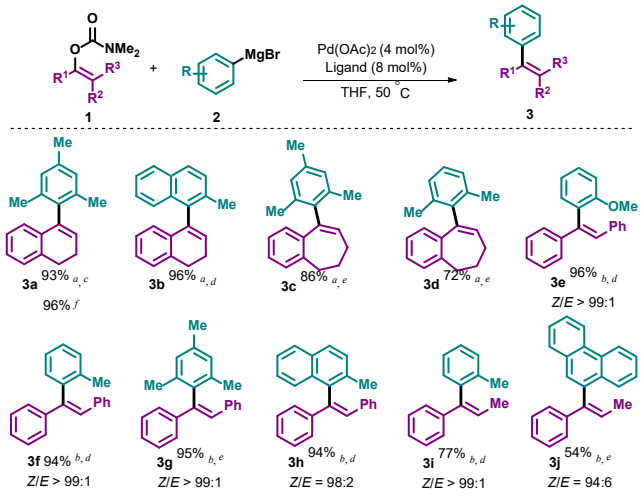
entry	catalyst (mol%)	condition [°C/h]	**3a** [%]
1	$Pd(OAc)_2$ (4)	50 / 1	98%, 93%[b]
2	$NiCl_2$ (4)	50 / 1	56%
3	$Pd(OAc)_2$ (4)	25 / 8	95%, 91%[b]
4	$Pd(OAc)_2$ (2)	50 / 1	93%
5	$Pd(OAc)_2$ (2)	25 / 1	64%
6	$Pd(OAc)_2$ (1)	50 / 1	66%

7	$Pd(OAc)_2$ (1)	50 / 3	90%
8	$Pd(OAc)_2$ (1)	25 / 8	44%

[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.4 mmol), THF (total around 1 mL); under N_2, temperatures and reaction time are indicated; calibrated GC−FID yields are reported using dodecane as the internal standard. [b]Isolated yields.

Encouraged by the screening results, we selected IPr•HCl to evaluate other condition parameters (Table 1). The condition without alteration afforded excellent yield by GC detection as well as isolation (Table 1, entry 1). The use of $NiCl_2$ as metal source only afforded moderate product yield for this reaction (Table 1, entry 2). This Pd-catalyzed reaction proceeded smoothly at room temperature without diminishing the yield (Table 1, entry 3). Lowering the catalyst loading by 2 mol% of Pd, good yields were still obtained under the condition of elevated temperature (Table 1, entry 4 and entry 5). Elevation of temperature and extended reaction time enabled a further decrease in the catalyst loading with good yields (Table 1, entry 6-8).

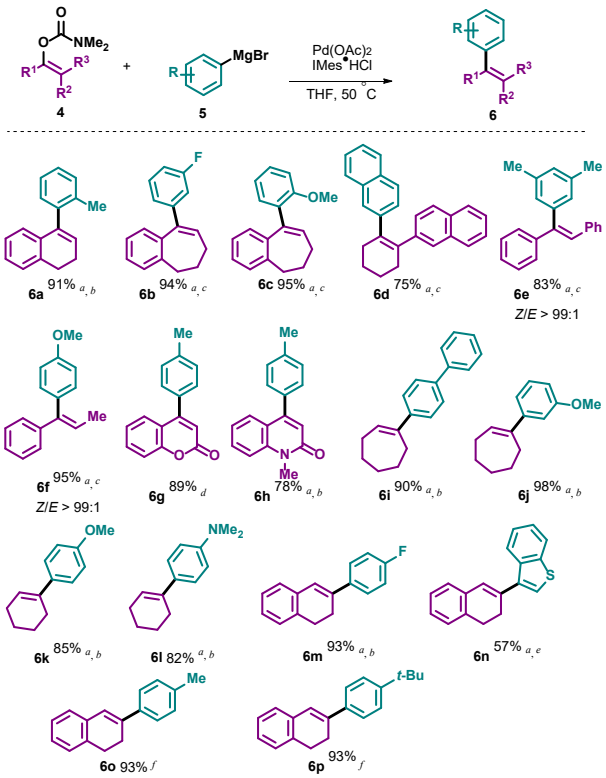
Scheme 2. Pd/NHC-Catalyzed Sterically Hindered Cross-Coupling between Enol Carbamates and Grignard Reagents.



[a]Reaction condition: $Pd(OAc)_2$ (4 mol%), ligand: IPr•HCl (8 mol%), ArMgBr (0.4 mmol), 50 °C, under N_2; isolated yields are reported. [b]Reaction condition: $Pd(OAc)_2$ (4 mol%), ligand: IMes•HCl (8 mol%), ArMgBr (0.4 mmol), 50 °C, under N_2; isolated yields are reported; *Z*/*E* ratios were determined by GCMS analysis of the crude reaction mixture. [c]Reaction time: 1 h. [d]Reaction time: 3 h. [e]Reaction time: 12 h. [f]The reaction was conducted on 1 mmol scale at 50 °C for 4 h under N_2.

Following condition optimization, we first examined the scope of sterically hindered cross-coupling between enol carbamates and Grignard reagents (Scheme 2). According to the condition screening, the attempt to reduce the catalyst loading may be influenced by the reaction temperature. In view of the bulky coupling partners that could participate in the scope, we decided to perform the reaction at 50 °C. The Pd/NHC catalytic system efficiently promoted the cross-coupling reaction of α-naphthalenlyl carbamates with sterically hindered arylmagnesium bromides, affording corresponding products with quantitative yields (Scheme 2, **3a** and **3b**). Excellent yield maintained when the reaction was scaled up (Scheme 2, **3a**). Carbamate with a larger seven-membered ring also smoothly coupled with highly hindered 2,6-substituted aryl Grignard reagents (Scheme 2, **3c** and **3d**). Acyclic enol carbamates constituted the second part of the scope (Scheme 2, **3e-3j**). Compared to the cyclic electrophiles, cross-coupling of carbamates with congested α-substitutions could be more demanding. However, by adjusting the size of the NHC ligand, we found that the reaction proceeded well in the presence of sterically hindered arylmagnesium bromides, obtaining diverse triaryl ethylene compounds (Scheme 2, **3e-3h**) in good yields. We further tested deactivated substrates (Scheme 2, **3i** and **3j**), and though a prolonged reaction time was needed, we obtained coupling products with good-to-moderate yields. High stereoselectivity is critical in alkene synthesis.

Scheme 3. Cross-Coupling of Less Sterically Hindered/Unactivated Enol Carbamates.



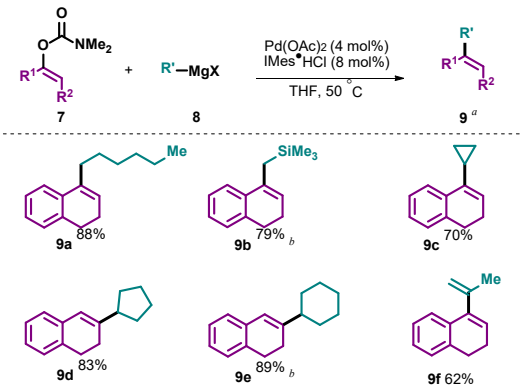
[a]Reaction condition: $Pd(OAc)_2$ (4 mol%), IMes•HCl (8 mol%), ArMgBr (0.4 mmol), 50 °C, under N_2; isolated yields are reported. *Z*/*E* ratios were determined by GCMS analysis of the crude reaction mixture. [b]Reaction time: 3 h. [c]Reaction time: 12 h. [d]Reaction condition: $Pd(OAc)_2$ (4 mol%), IMes•HCl (8 mol%), NaO*t*Bu (16 mol%), ArZnCl (0.4 mmol), r.t., 12 h, under N_2; isolated yield. [e]Reaction time: 14 h. [f]Reaction condition: $Pd(OAc)_2$ (0.5 mol%), IMes•HCl (1 mol%), ArMgBr (0.4 mmol), r.t., 1 h, under N_2; isolated yields.

In this reaction, the configuration retention of alkenyl skeletons was achieved, affording multi-substituted products with excellent *Z*/*E* isomer ratios (Scheme 2, **3e-3j**). It is worth noting that extremely sterically congested alkene can also be synthesized in excellent yield (Scheme 2, **3g-3j**).We have also attempted to investigate the reactivity of (*E*)-1,2-diphenylvinyl

dimethylcarbamate. However, the preparation of the corresponding (*E*)-enol carbamate was unsuccessful.

Next, we turned our attention to the reactivity of this Pd/NHC system, studying the cross-coupling reactions of less sterically hindered and/or unactivated enol carbamates (Scheme 3). In general, substrates participating in the sterically hindered cross-coupling reaction also successfully coupled with less hindered Grignard reagents (Scheme 3, **6a-6c**, **6e** and **6f**). Unactivated substrate bearing a bulky group at α-position was also converted into the symmetrical alkenyl product (Scheme 3, **6d**). The transformation of heterocyclic carbamates was also applicable (Scheme 3, **6h**), and we found aryl zinc reagent to be a feasible nucleophile for the base sensitive lactone (Scheme 3, **6g**). Cycloalkanone-derived deactivated enol carbamates also reacted under this condition, affording good-to-excellent yields (Scheme 3, **6i-6m**). Enol pivalate (3,4-dihydronaphthalen-2-yl pivalate) was also successfully employed as electrophile with (4-fluorophenyl)magnesium bromide to obtain the corresponding product **6m** with 92% product yield. Heterocyclic nucleophile was also transformed into the desired product (Scheme 3, **6n**). It is worth noting that this system showed high efficacy in the activation of unactivated substrates at a low catalyst loading. Reducing the catalyst loading to 0.5 mol% of Pd still led to the desired products in excellent yields (Scheme 3, **6o** and **6p**). These results exemplify the feasibility of significantly minimizing the metal residual in products, compared to related methods involving other transition metals (Fe, Co, etc.).[14-17]

Scheme 4. Pd/NHC-Catalyzed Alkylation/Alkenylation of Enol Carbamates.

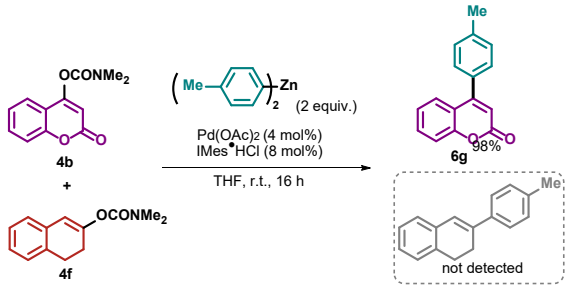


[a]Reaction condition: $Pd(OAc)_2$ (4 mol%), IMes•HCl (8 mol%), R'MgBr (0.4 mmol), 50 °C, 3 h; isolated yields are reported. [b]R'MgCl (0.4 mmol) was used.

Palladium-catalyzed alkylation and alkenylation via coupling reaction are known to be challenging due to the potential rapid β-hydride elimination and isomerization.[24] To investigate the generality of the scope, we further examined other types of C-C bond formations with this catalytic system. To our delight, successful transformations were achieved in the presence of primary/secondary alkyl nucleophiles (Scheme 4, **9a-9e**). Alkenylation of enol carbamate was also applicable, affording the conjugated alkene in a moderate yield (Scheme 4, **9f**).

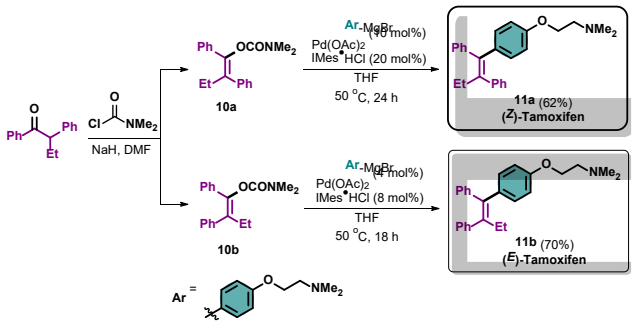
In light of the applicable arylation of coumarin carbamate (Scheme 3, **6g**) using organozinc reagent, we attempted a selective cross-coupling investigation (Scheme 5). When aryl zinc reagent was employed, only the coumarin product **6g** was selectively formed.[25] This result indicates that selective functionalization of a more complex substrate with multiple C-O bonds could be realized using a weaker nucleophile.

Scheme 5. Selective Coupling of Activated Enol Carbamate with Organozinc Reagent.



Tamoxifen, one of the most-prescribed anti-cancer drug,[26] was selected as a representative standard for evaluating the practicability of this cross-coupling strategy (Scheme 6). Carbamate precursors **10a** and **10b** were prepared as single isomers from commercially available 1,2-diphenylbutan-1-one. Subsequent cross-coupling afforded Tamoxifen **11a** and its (*E*)-isomer **11b** separately without deterioration of stereoselectivity. To access this important compound, various cross-coupling methods have been developed involving the use of corresponding alkenyl halide or alkenyl boronate as the counterpart, which requires tedious synthetic procedures.[27] To the best of our knowledge, there exist no reports on using easily accessible enol as a coupling counterpart to prepare Tamoxifen. This protocol distinguishes itself from other methods, representing an alternative approach for synthesizing Tamoxifen and its derivatives with good atom-efficiency.

Scheme 6. Synthesis of Tamoxifen.



In conclusion, we have developed a Pd-catalyzed highly sterically congested cross-coupling reaction between enol carbamates and Grignard reagents. A range of alkenes bearing bulky substitutions were synthesized with high *Z*/*E* isomer ratios. The scope was further extended to alkylation and alkenylation. This catalytic system exhibited high reactivity towards less-hindered substrates under the condition of low catalyst loading. Selective C-O bond activation towards different substrates was demonstrated. Furthermore, this cross-coupling reaction provided a new and practical synthetic route to Tamoxifen and (*E*)-Tamoxifen. We believe that this strategy could contribute to the synthesis of challenging multi-substituted alkenes by utilizing the skeletons from carbonyl compounds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Procedure details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to Professor Chak-Po Lau on the occasion of his 70th birthday.

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