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Palladium-Catalyzed Enantioselective Alkenylation of Enelactams Using a Relay Heck Strategy

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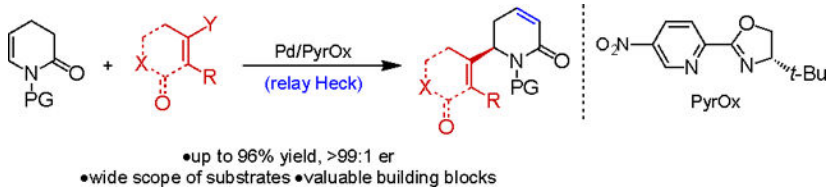
Abstract

In this report, we describe a palladium-catalyzed redox relay Heck process to access optically active alkenylated α,β-unsaturated lactams. Under mild reaction conditions, electron-deficient alkenyl triflates and electron-rich alkenyl iodonium salts undergo enantioselective and site-selective coupling with enelactams to deliver the products in high yields and excellent enantioselectivities. Furthermore, the products allow facile access to natural products such as (+)-Calvine and (+)-2-Epicalvine in addition to the bioactive molecule aza-Goniothalamin.

Graphical Abstract

Two types of alkenes were installed via palladium-catalyzed enantioselective alkenylation of enelactams using a relay Heck strategy. Under the mild reaction conditions, both electron-deficient and electron-rich alkenyl electrophiles work well for the reaction delivering 6-alkenyl substituted α,β-unsaturated δ-lactams.



Keywords

palladium; enantioselectivity; alkenylation; relay Heck; lactam

Many biologically active compounds and natural products contain the lactam structural motif, which has therefore been used as a privileged structural subunit for the design of several pharmaceutical agents.[1,2] In addition, highly functionalized δ-lactams also serve as valuable building blocks for the synthesis of complex molecules due to their latent reactivity and the range of highly selective transformations they can undergo.[3] As a specific subclass of these building blocks, alkenyl substituted δ-lactams and piperidines are important intermediates in organic synthesis due to the presence of the alkenyl moiety in many δ-lactams of interest (Scheme 1a).[4,5] Many methods have been developed for installing alkenyl units enantioselectively using transition metal catalysis[6,7,8,9,10] and

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organocatalysis.[11] However, many of these methods are not capable of installing a wide variety of different types of alkenyl groups using a singular strategy on a heterocyclic ring structure.[12] Herein we report a palladium-catalyzed enantioselective relay Heck alkenylation of enelactams with both electron-rich and electron-deficient alkenyl electrophiles to deliver 6-alkenyl substituted α,β-unsaturated δ-lactams that are amenable for further functionalization.

Recently, our group developed an enantioselective arylation reaction of enelactams to produce α,β-unsaturated δ-lactams (Scheme 1b); however, alkenyl transfer was not possible under these conditions and the derivatization of the aryl group is limited. [13] We wanted to solve the inability to alkenylate the enelactam by employing a similar strategy[14] as the resulting lactam products would be of greater interest due to the two distinct alkenes present in the product (Scheme 1c). Our previously reported Heck alkenylations are limited to acyclic substrates,[15] and electron-rich alkenyl electrophiles are only suitable for trisubstituted alkenols due to unselective β-hydride elimination (which is avoided through the formation of a quaternary stereocenter).[15b] These limitations should be circumvented through the use of a cyclic substrate as has been previously reported[12] as β-hydride elimination requires a hydrogen *syn* to palladium and therefore can only occur away from the newly formed stereocenter in the proposed process (**A**, Scheme 1d). Additionally, following β-hydride elimination, the resultant Pd-hydride could dissociate from intermediate **B** to deliver β,γ-unsaturated δ-lactam **C** or reinsert to ultimately lead to the desired α,β-unsaturated δ-lactam (**3**).[13]

After optimizing the reaction conditions (Table 1, entry 1, see the supporting information for the detailed information) the effect of the nitrogen substituent of the enelactam was then evaluated. Enelactam substrates bearing benzyl, 1-naphthylmethyl, PMB (4-methoxybenzyl) and DMPM (2,4-dimethoxybenzyl) groups all gave the corresponding products (**3a**–**3d**) in excellent yields and enantioselectivities. Use of a methyl-protected enelactam furnished product **3e** with slightly lower yield (81%) and enantioselectivity (95:5 er). In addition, an unprotected enelactam (**2f**) successfully formed product **3f**, albeit in a modest yield, while Boc-protected enelactam (**2g**) delivered product **3g** in 77% yield. Products were accessed in uniformly high enantioselectivity.

Next, a number of electron-deficient alkenyl triflates were examined under the reaction conditions with benzyl-protected enelactam **2a**. A tetrasubstituted cyclohexenone triflate bearing a bromide generated the corresponding product (**3h**) in 62% yield and 95.5:4.5 er. Cyclic five- and six-membered-ring alkenyl triflates delivered products **3i** and **3j** in good yields and high enantiomeric ratios. Additionally, exo-cyclic alkenyl triflate **1k** furnished product **3k** in 92% yield with a 94:6 enantiomeric ratio. A dihydrobenzofuran-derived alkenyl triflate delivered product **3l** in 72% yield and 96:4 enantiomeric ratio. Lastly, acyclic electron-deficient alkenyl triflates with methyl, benzyl, and remote phthalimide substitution generated the corresponding products **3m**–**3o** in excellent yields and high enantiomeric ratios. It should be noted that no β,γ-unsaturated δ-lactams were observed in the reaction mixtures suggesting that the Pd-hydride does not dissociate from the alkene (Scheme 1). Additionally, the absolute configuration of product **3b** was determined to be (*R*) using X-ray

single crystal diffraction,[16] which is in agreement with our previously reported Heck arylation of enelactams.[13] All other products were assigned by analogy to product **3b**.

The efficient derivatization of medium-sized rings in an enantioselective fashion is an important and challenging task in organic synthesis.[17] To expand the scope of this relay Heck alkenylation, seven-membered enelactam **4** was also evaluated, resulting in 7-alkenyl substituted α,β-unsaturated ε-lactams **5** (Table 2). Compared with the six-membered-ring enelactams, diminished reactivity was observed with the larger ring size. As a consequence, the catalyst loading was increased to 10 mol % and five equivalents of enelactam **4** were necessary. Importantly, unreacted enelactam could be recovered. Under the modified reaction conditions, triflate **1a** and benzyl-protected enelactam **4a** furnished product **5a** in 46% yield and >99:1 er. Modification of the benzyl protecting group to a PMB group resulted in a similar yield and enantioselectivity (**5b**). Lastly, an exo-cyclic alkenyl triflate delivered the corresponding product (**5c**) in 54% yield and >99:1 er.

To further expand the diversity of products that can be accessed using this methodology, electron-rich alkenyl electrophiles were also tested under the reaction conditions. As discussed in the introduction, the use of electron-rich alkenyl electrophiles in relay Heck reactions has traditionally been challenging. An alkenyl boronic acid was first tested in the reaction with enelactam **2a**. Use of ligands **L1** and **L2** again resulted in similar yields and enantiomeric ratios (Table 3, entries 1 and 2). An alkenyl triflate delivered the desired product in 60% yield with 75:25 er (entry 3). An alkenyl iodonium salt was also tested in the reaction, and after evaluating a variety of palladium sources the product was obtained in moderate yields and enantiomeric ratios (entries 4 and 5). Switching to a Boc-protected enelactam (**2g**) led to higher enantiomeric ratios (entries 6 and 7). Selecting a BF_4 iodonium salt and adjusting the equivalents of enelactam and the iodonium salt resulted in a slight boost in yield and selectivity (entries 8 and 9). Finally, changing the solvent to MeCN resulted in a 64% yield and 93:7 er (entry 10).

The scope of the alkenyl electrophiles was evaluated using the optimal iodonium salt and the Boc-protected enelactam (Table 4). A variety of substituted styrenyl iodonium tetrafluoroborate salts were examined. Electrophiles with an unsubstituted arene (**7a**) as well as a *para*-methyl group on the arene (**7b**) gave the desired product in moderate yield and enantioselectivity, whereas the *para*-fluoro variant (**7c**) produced the product in 52% yield and 80:20 er. Simple alkyl-substituted alkenyl iodonium salts could furnish the desired product with good enantioselectivity under the optimized reaction conditions, however with concomitant deprotection of the Boc group as a major by-product. To solve this problem, a mixed solvent system (DMF + MeCN) was introduced and the precatalyst was altered to $Pd(MeCN)_2(OTs)_2$ resulting in desired product **7d** in 54% yield with 94:6 er with no undesired deprotection. Larger alkyl-substituted substrates such as β-*tert*-butyl and β-cyclohexyl substituted alkenyl iodonium salt delivered the corresponding products **7e** and **7f** in 51% and 63% yield, respectively, and improved enantioselectivity. The β-benzyl substituted reagent produced product **7g** in 59% yield and 90:10 enantiomeric ratio. Alkenyl iodonium salts bearing a remotely positioned chloride or a longer alkyl-substituted substrate gave products **7h** and **7i** in moderate yields and good enantiomeric ratios. It is important to

note that alkenyl triflates are proposed to react through a Pd(0)/Pd(II) catalytic cycle, while a Pd(II)/Pd(IV) catalytic cycle could not be excluded for the alkenyl iodonium salts.[14i,18]

These 6-alkenyl substituted α,β-unsaturated δ-lactams are amenable to several selective functional group transformations as demonstrated in Scheme 2. For example, product **3j** was selectively reduced to deliver lactam **8** in near quantitative yield with no erosion of enantioselectivity (Scheme 2a). Ester **3j** can also be reduced to alcohol **9** using DIBAL-H. Furthermore, product **7d** was easily transformed to unprotected lactam **10** via hydrogenation followed by acid mediated Boc-deprotection (Scheme 2b). Lactam **10** can then be used for the synthesis of natural products (+)-Calvine and (+)-2-Epicalvine following known procedures.[19] The bioactive molecule aza-Goniothalamin was synthesized using this methodology followed by deprotection of **7a** (Scheme 2c). Diastereoselective conjugate addition followed by a Boc-deprotection/$LiAlH_4$ reduction sequence can be implemented to access 2,4-disubstituted piperidines (**13**) in excellent diastereomeric ratio (Scheme 2d).

In summary, we have reported a new method to synthesize enantiomerically enriched 6-alkenyl substituted α,β-unsaturated δ-lactams via a palladium-catalyzed relay Heck reaction. Both electron-deficient and electron-rich alkenyl electrophiles are successfully applied in the reaction, electron-deficient alkenyl triflates delivering the corresponding products in excellent yields and enantiomeric ratios, and electron-rich alkenyl iodonium salts giving the corresponding products in moderate yields and good enantiomeric ratios. These products can easily be transformed into key intermediates for the synthesis of several natural products as exemplified by the routes to (+)-Calvine and (+)-2-Epicalvine and bioactive molecule aza-Goniothalamin.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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[16]. The absolute configuration of 3b was established by the X-ray diffraction analysis (CCDC 1891433).

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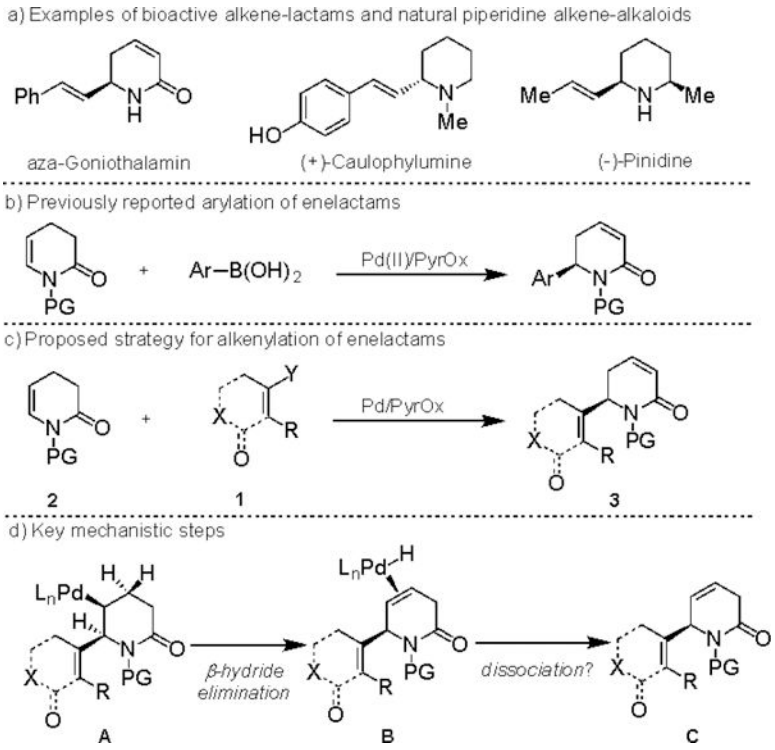
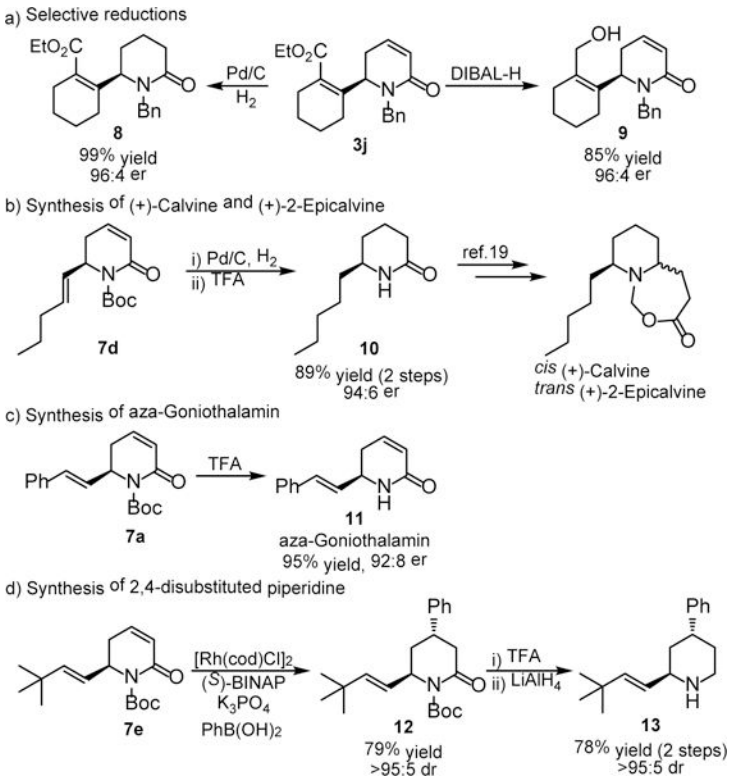


Scheme 1.

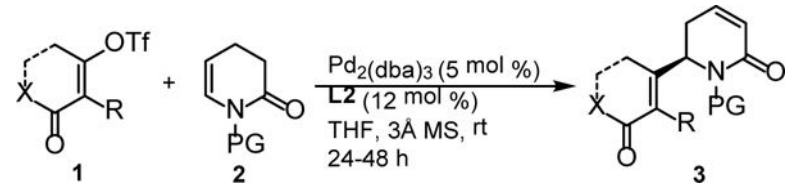
[a] Examples of bioactive molecules and natural products. [b] Previously reported arylation of enelactams. [c] Proposed strategy for alkenylation of enelactams. [d] Key mechanistic steps.

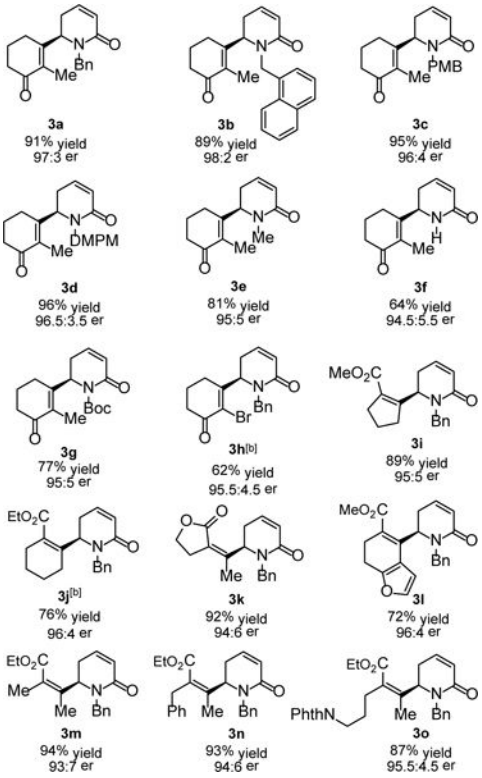


Scheme 2.
Product derivatization.

Table 1.

Scope of Enelactams with Various Protecting Group and Alkenyl Triflates [a]



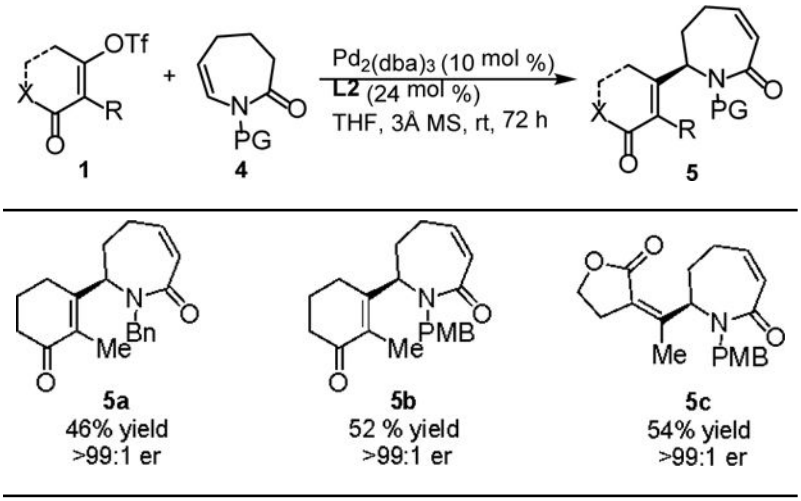


[a]The reaction was conducted with **1** (0.2 mmol), **2** (0.3 mmol) in the presence of $Pd_2(dba)_3$ (5 mol %), ligand (12 mol %) in THF (1.0 mL). Isolated yield. The er values were determined by SFC equipped with a chiral column.

[b]**1** (0.2 mmol) and **2a** (0.4 mmol) were used in the presence of $Pd_2(dba)_3$ (10 mol %) and ligand (24 mol %). PMB = 4-methoxybenzyl. DMPM = 2,4-dimethoxybenzyl. Boc = *tert*-butyloxy carbonyl.

Table 2.

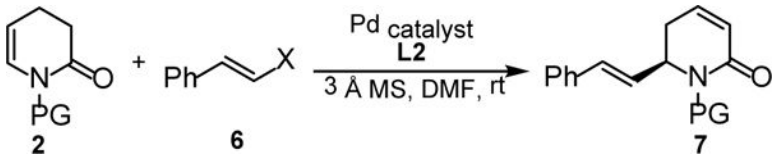
Substrate Scope of Seven-Membered Enelactams [a]

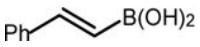
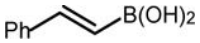
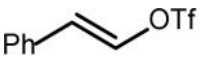
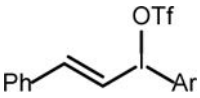
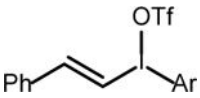
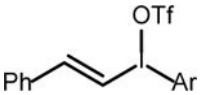
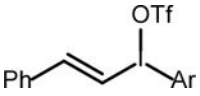
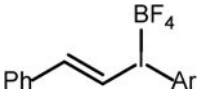
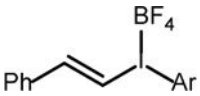
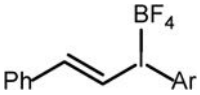


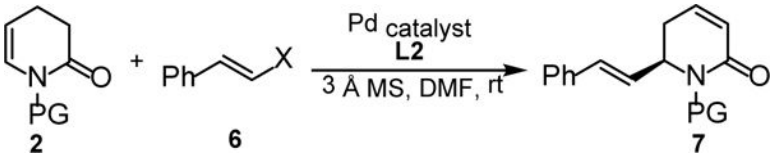
[a]The reaction was conducted with **1** (0.2 mmol), **4** (1.0 mmol) in the presence Pd2(dba)3 (10 mol %), ligand (24 mol %) in THF (1.0 mL). Isolated yield. The er values were determined by SFC.

Table 3.

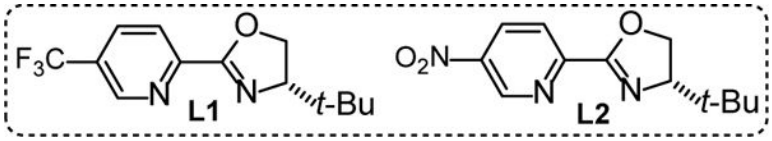
Reaction Optimization for Electron-rich Alkenyl Electrophiles[a]



Entry	Alkenyl source	Palladium salt	Yield[g]	Er[h]
1[b, c]		$Pd(CH_3CN)_2(OTs)_2$	26	72:28
2[c]		$Pd(CH_3CN)_2(OTs)_2$	20	75:25
3[d]		$Pd_2dba_3{\cdot}CHCl_3$	60	75:25
4[d]		$Pd_2dba_3{\cdot}CHCl_3$	77	79:21
5[d]		$Pd(CH_3CN)_2(OTs)_2$	55	80:20
6[d, e]		$Pd(CH_3CN)_2(OTs)_2$	49	85:15
7[d, e]		$Pd(TFA)_2$	47	88:12
8[d, e]		$Pd(TFA)_2$	41	90:10
9[e, f]		$Pd(TFA)_2$	53	90:10
10[e, f, g]		$Pd(TFA)_2$	64	93:7



Entry	Alkenyl source	Palladium salt	Yield[g]	Er[h]



[a] The reaction was conducted on a 0.1 mmol scale (**2a**) in the presence of Pd (10 mol %), ligand (12 mol %) in DMF at room temperature.

[b] **L1** was used as the ligand.

[c] 1:3 of enelactam and boronic acid under an oxygen atmosphere.

[d] 2:1 of enelactam and **6**.

[e] **2g** was used.

[f] 5:1 of enelactam and **6**.

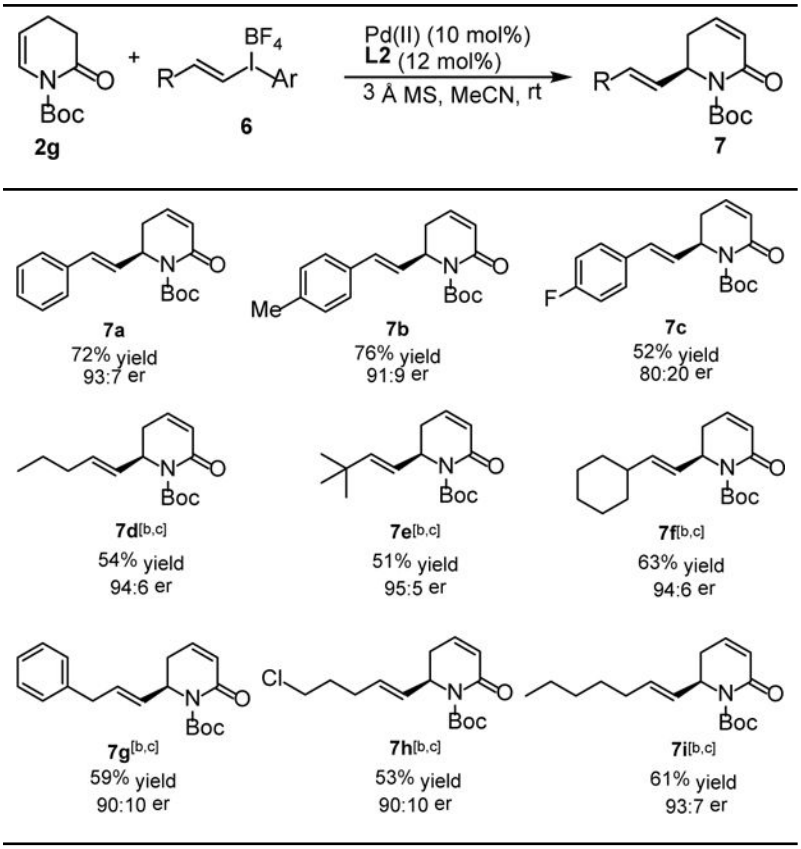
[g] MeCN was used as the solvent.

[h] Isolated yield.

[i] The er values were determined by SFC equipped with a chiral column.

Table 4.

Substrate Scope of Alkenyl Iodonium Salts [a]



[a]Reaction conditions: $Pd(TFA)_2$ (10 mol %), **L2** (12 mol %), **2g** (1.0 mmol), **6** (0.2 mmol), 3Å MS (300 mg/mmol) in 0.5 mL of MeCN, at room temperature, 72 – 120 h.

[b]The solvent was a mixture of DMF and MeCN (0.2 mL + 0.2 mL).

[c]$Pd(MeCN)_2(OTs)_2$ was used. Ar = 2-MePh.