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Scalable Synthesis of Oxazolones from Propargylic Alcohols through Multistep Palladium(II) Catalysis: β-Selective Oxidative Heck Coupling of Cyclic Sulfonyl Enamides and Aryl Boroxines**

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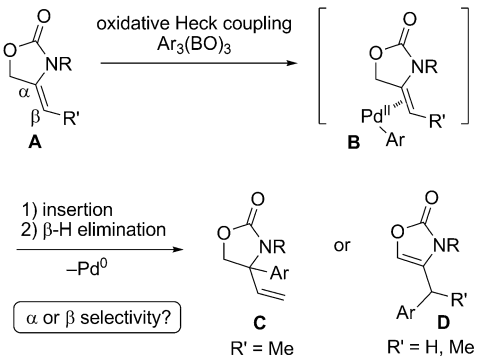
Palladium-catalyzed cross-coupling reactions are among the most widely used and versatile reactions for carbon–carbon bond formation in organic synthesis.[1] Of particular importance is the palladium(0)-catalyzed Mizoroki–Heck reaction, discovered in the 1970s,[2] which has since then been developed successfully. The outcome of the Mizoroki–Heck reaction is the rapid formation of new carbon–carbon bonds between alkenes and aryl halides or pseudohalides (e.g. Ar–OTf, Tf = trifluoromethanesulfonyl). Interestingly, prior to the reaction of aryl halides, Heck disclosed a catalytic reaction yielding the same type of products that proceeded in an oxidative manifold and relied on $PdCl_2$ and $CuCl_2$ in combination with an aryl mercury species and an olefin.[3] A modified variant in which a vinylboronic acid was used instead of the mercury reagent as the coupling partner was reported by Dieck and Heck in 1975.[4] However, in the latter reaction, $Pd(OAc)_2$ was used in stoichiometric amounts. To circumvent the use of stoichiometric quantities of a Pd^{II} catalyst, Cho and Uemura reported a catalytic version of the oxidative Heck coupling of arylboronic acids in 1994.[5] The oxidative Heck coupling has since been studied in detail by several research groups, including those of Larhed,[6] Mori,[7] and Jung.[8] Heck-type coupling reactions are often limited to a narrow range of alkene coupling partners, thus hampering the use of this methodology in complex organic synthesis. The latter issue has recently been addressed (in part), and much effort has been devoted to broadening the synthetic utility of this transformation as well as gaining a more detailed understanding of its mechanism.[9]

Heck-type coupling reactions have been investigated extensively with various transmetalation partners, including arylbismuth reagents,[10] arylantimony reagents,[11] arylsilanes,[12] arylstannanes,[8a] and arylphosphonic acids;[13] however, arylboronic acids remain the most widely used coupling partners owing primarily to their relatively nontoxic nature and overall stability together with their commercial availability.

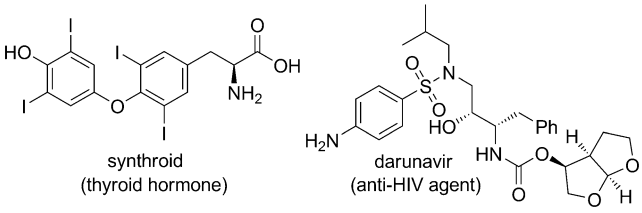
Our long-standing interest in palladium(II)-catalyzed oxidative carbon–carbon bond-forming reactions,[14] and more recently in the oxidative Heck reaction,[15] has led us to search for robust synthetic procedures that enable smooth carbon–carbon bond formation under oxidative conditions. We have been particularly interested in broadening the scope of the oxidative Heck reaction with respect to the alkene component to enable the synthesis of more complex molecules. Herein we disclose a novel and selective palladium(II)-catalyzed oxidative coupling between cyclic enamides **A** and aryl boroxines that provides access to useful aryl-substituted amino acid precursors **C** and/or **D** (Scheme 1). The target β-



Scheme 1. Envisioned palladium(II)-catalyzed oxidative Heck arylation of cyclic enamides.

arylated cyclic carbamate **D** contains a prevalent structural backbone suitable for the synthesis of a wide range of natural products, chiral ligands, and pharmaceuticals[16] (Scheme 2).

Inspired by the studies of Larhed and co-workers on the oxidative Heck arylation of acyclic enamides,[6g] we aimed to



Scheme 2. Examples of pharmaceuticals with structural elements of the products obtained in this study.

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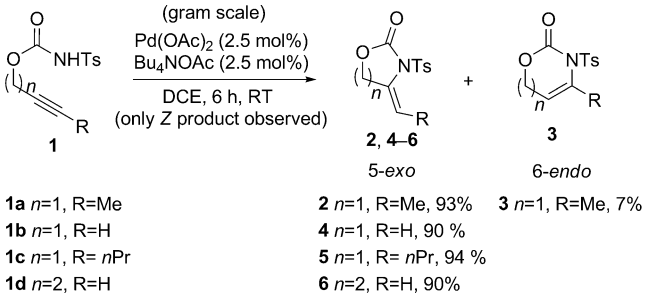
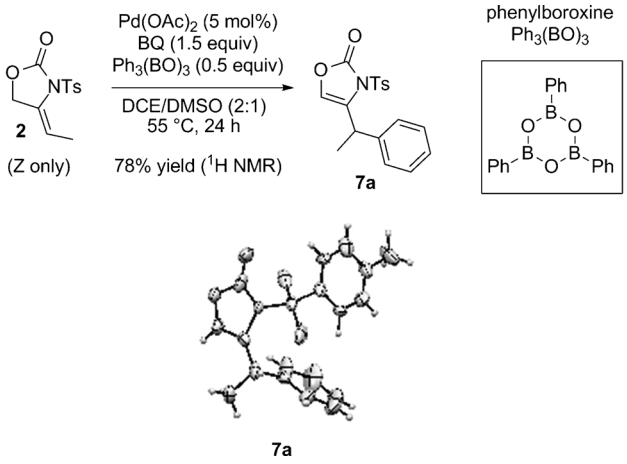
develop a catalytic multistep protocol that could provide access to arylated cyclic carbamates from propargylic alcohols and isocyanates through palladium(II)-mediated hydroamination. Subsequent palladium(II)-catalyzed oxidative coupling of the cyclic carbamate with an appropriate transmetalation partner would then produce the desired oxazolone.

The desired propargylic carbamates were obtained by the condensation of a propargylic alcohol with an equimolar amount of tosylisocyanate (TsNCO) in 1,2-dichloroethane (DCE). The subsequent cyclization, which formally constitutes a hydroamination of tosylcarbamates **1**, was then investigated.[17,18] The best conditions for this transformation were found to be treatment with $Pd(OAc)_2$ (2.5 mol%) along with Bu_4NOAc (2.5 mol%) in DCE at room temperature. Under these reaction conditions, the desired tosyl-protected enamides **2** and **4–6** resulting from a 5-*exo* cyclization were obtained with *Z* selectivity in excellent yields (Scheme 3).



Scheme 3. Palladium(II)-catalyzed cycloisomerization (hydroamination) of propargylic tosylcarbamates. Ts = *p*-toluenesulfonyl.

Having found efficient catalytic conditions for the palladium(II)-catalyzed cycloisomerization, we turned our attention toward the oxidative arylation. Treatment of the cyclic enamide **2** with $Pd(OAc)_2$ (5 mol%), commercially available $PhB(OH)_2$ (1 equiv), and 1,4-benzoquinone (BQ; 1.5 equiv) in a mixture of DCE and DMSO provided **7a** as a single regioisomer.[19] We were surprised to find that the oxidative arylation occurred exclusively at the β carbon atom and with selective β-hydride elimination to give oxazolone **7a**. This finding clearly demonstrates that cyclic enamides show completely different reactivity toward palladium(II)-catalyzed oxidative arylation than the acyclic enamides studied by Larhed and co-workers, when arylation preferentially occurred at the α carbon atom.[6g] Furthermore, the most efficient source of aryl groups proved to be triarylboroxines[20] ($Ar_3(BO)_3$); all other related reagents, such as arylboronic acids ($ArB(OH)_2$), *N*-methyliminodiacetic acid (MIDA) boronates, potassium aryltrifluoroborates, and arylboronic esters, provided the desired oxazolones in only moderate yields. For complete consumption of the starting material, an excess of both $Ar_3(BO)_3$ (0.50–0.67 equiv, which corresponds to 1.5–2.0 equiv of the "aryl group") and BQ (1.5 equiv) was required (Scheme 4). A closer inspection of the crude reaction mixture revealed that the homocoupled product (Ar–Ar) was formed in varying amounts; this side reaction



Scheme 4. Initial conditions for the oxidative Heck arylation of **2** and X-ray crystal structure of the product **7a** (right). DMSO = dimethyl sulfoxide.

consumed both the aryl boroxine and the oxidant. The choice of catalyst turned out to be less crucial: at a catalyst loading of 5 mol%, $Pd(OAc)_2$, $Pd(OCOCF_3)_2$, $Pd(OPiv)_2$, and $Pd(acac)_2$ (acac = acetylacetonate, Piv = pivaloyl) all catalyzed the reaction at 55 °C to some extent, albeit with some minor variations.

During our initial studies of this reaction, it quickly became apparent that the addition of a cosolvent in the form of dry DMSO is required. In a 2:1 mixture of a chosen solvent and DMSO, the reaction proved effective at 55 °C with many common solvents, such as THF, DCE, EtOAc, toluene, and acetone. We finally chose DCE, as both carbamate formation and the palladium(II)-catalyzed cycloisomerization (Scheme 3) proceeded well in this solvent. The ratio of DCE to DMSO was also investigated. It was found that the amount of DMSO is crucial; when too much DMSO was used, it had a strong inhibitory effect (Figure 1). The best results were obtained with a 70:30 mixture of DCE and DMSO, which corresponds to approximately 15 equivalents of DMSO relative to the starting enamide **2**. With this set of reaction conditions, we were able obtain **7a** in 84% yield (as based on

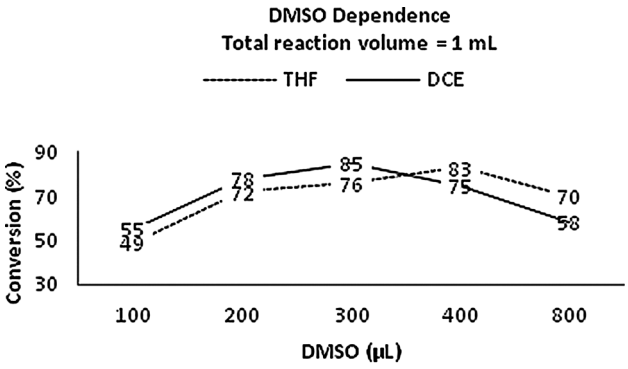
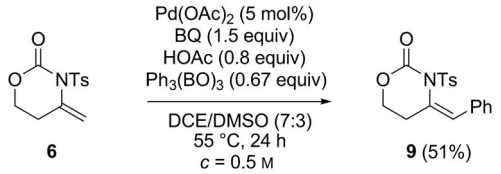


Figure 1. Conversion observed in the oxidative Heck arylation of cyclic enamide **2** with varying amounts of DMSO. The yield was determined by ^1H NMR spectroscopy ($CDCl_3$) with methyl methoxyacetate (1 equiv) as the internal standard.

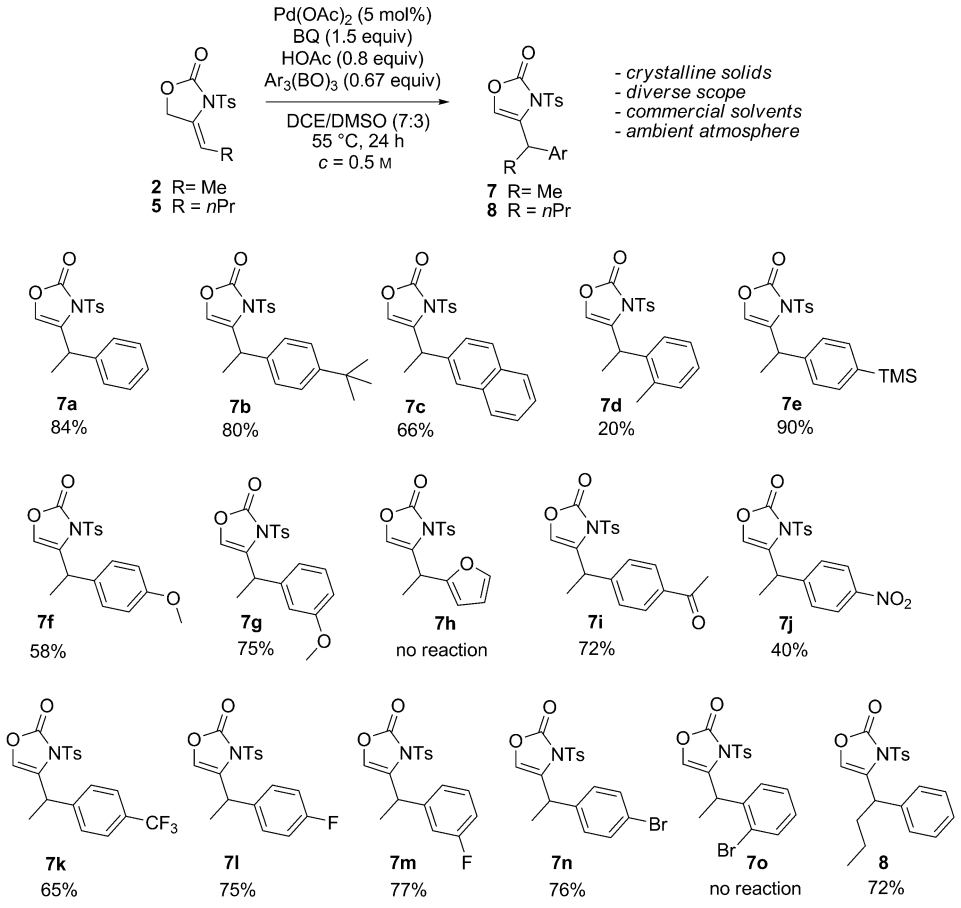
^{1}H NMR spectroscopic measurements with an internal standard). We reinvestigated the use of THF as a solvent with DMSO as a cosolvent and found that THF performed similarly to DCE as a solvent, with the difference that the optimum amount of DMSO in the solvent mixture was 40% (Figure 1).

After some further alterations of the reaction parameters, which mainly involved the introduction of HOAc (0.8 equiv) and some further tweaking of the stoichiometry between $Ar_3(BO)_3$ and BQ, we were confident that we had a working reaction protocol. Under these conditions, we investigated the scope of the transformation with a range of $Ar_3(BO)_3$ and the two structurally different cyclic enamides **2** and **5** (Scheme 5). Gratifyingly the reaction proceeded consistently well with a range of electronically different $Ar_3(BO)_3$, including those with alkyl, Cl, Br, F, NO_2, TMS, keto, CF_3, and MeO substituents. Electron-rich $Ar_3(BO)_3$ produced the desired products **7a–c** and **7e–g** in good to excellent yield. However, as the electron density of the C–B bond increases, the yield drops, as indicated by the quite modest yield of 58% observed with *p*-methoxyphenylboroxine (product **7f**) as opposed to 75% for *m*-methoxyphenylboroxine (product **7g**). Surprisingly, 2-furylboroxine completely failed to produce the desired arylated product **7h**. Electron-deficient aryl boroxines underwent the oxidative Heck reaction to give **7i–m** in around 75% yield in most cases. We were positively surprised to see that the reaction is compatible with *p*-trifluoromethyl groups (product **7k**, 65%) as well as simple *p*- and *m*-fluoro substituents (products **7l**, 75% and **7m**, 77%). However, one electron-deficient boroxine, namely, *p*-nitrophenylboroxine, displayed considerably lower activity, and product **7j** was formed in lower yield.

Two structurally different cyclic enamides, **2** and **5**, were investigated in this oxidative Heck reaction. When the size of the substituent on the cyclic enamide was increased from a methyl to a propyl group, the reaction performed well with the phenyl-substituted boroxine to give the expected product **8**, which was isolated in 72% yield (Scheme 5). With the six-membered cyclic enamide **6**, the yield dropped to 51% for the Heck coupling product **9** (Scheme 6).



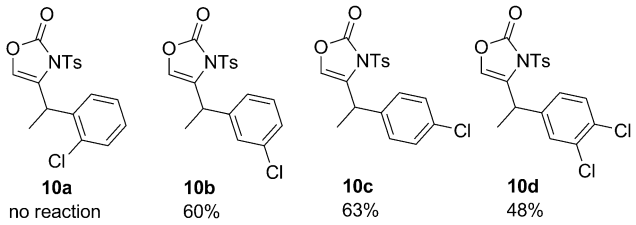
Scheme 6. Palladium(II)-catalyzed oxidative Heck reaction between the six-membered cyclic enamide **6** and phenylboroxine.



Scheme 5. Palladium(II)-catalyzed oxidative Heck reaction between cyclic enamides and aryl boroxines. The reactions were carried out at 55 °C in a 70:30 mixture of DCE and DMSO. The yields given are for the isolated product after flash chromatography. TMS = trimethylsilyl.

As this study progressed, one major limitation became evident. Aryl boroxines with an *ortho* substituent were inefficient as coupling partners (products **7d** and **7o**, Scheme 5). This behavior was surprising, and the rationale behind it is still not known. Our current explanation is that transmetalation becomes more difficult as a result of steric factors, especially if the aryl boroxine is the actual transmetalation species (Scheme 10).

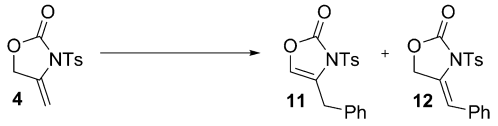
Finally, we used an array of chlorinated aryl boroxines in the oxidative coupling to determine the effect of differently substituted chlorides. The boroxine with an *ortho*-chloro substituent was incompatible with the reaction (product **10a**), whereas the *meta*- and *para*-substituted counterparts behaved similarly to nonchlorinated substrates (products **10b**, 60% and **10c**,



Scheme 7. Trends observed in the oxidative Heck arylation of cyclic enamides with chloro-substituted aryl boroxines.

63%; Scheme 7). The introduction of two chloro substituents (3,4-dichlorophenylboroxine) resulted in an approximate 15% loss in yield (product **10d**).

The oxidative Heck coupling of substrate **4**, the simplest cyclic enamide formed in the cycloisomerization, was not included in Scheme 5. This case requires additional comment, and our attempts to arylate **4** are summarized in Scheme 8.



Catalyst (5 mol%)	Ratio (**11**/**12**)
$Pd(OAc)_2$	80 : 20
$[Pd(IMes)(OAc)_2]$	38 : 62

Scheme 8. Product distribution observed when the simplest cyclic enamide, **4**, was used in the oxidative Heck coupling.

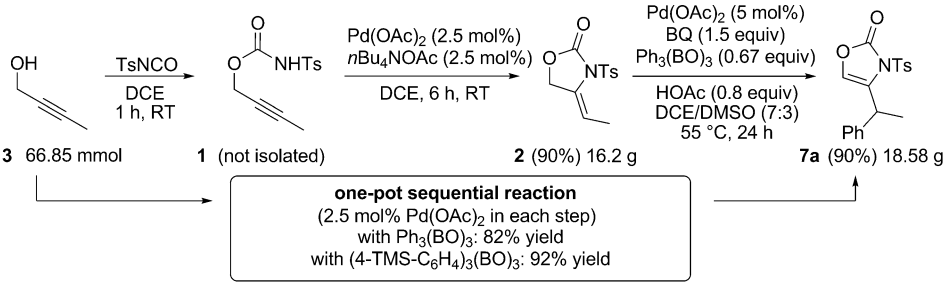
Interestingly, the oxidative Heck arylation of **4** afforded two products, both of which are derived from arylation of the β carbon atom: the *endo* alkene **11** and the *exo* alkene **12**. The latter was formed exclusively with the *Z* configuration. The ratio between these two products depends on the palladium catalyst used. When $[Pd(IMes)(OAc)_2]$ (IMes = bisimidazol-2-ylidene) was employed as the catalyst, the ratio of **11** to **12** was 38:62. The highest selectivity for **11** was observed with $Pd(OAc)_2$, which afforded **11** and **12** in a ratio of 80:20. We have not yet found conditions that show complete selectivity for **11** or **12**. These two isomers originate from the same organopalladium intermediate, which undergoes β-hydride elimination through two different pathways. In the selectivity-determining step, it seems that the electronic nature and perhaps structural factors of the catalyst play a role in the selectivity of the β-hydride elimination. It was shown that **11** does not isomerize to **12** under the reaction conditions; thus, any variation in distribution based on a subsequent isomerization can be ruled out.

Our ultimate goal throughout this study was to develop a robust and scalable procedure that provides access to useful building blocks (oxazolones) for the synthesis of biologically active compounds. The reaction was therefore tested on a scale of more than 60 mmol. The treatment of alcohol **13** with an equimolar amount of TsNCO provided the propargylic carbamate **1** in quantitative yield (Scheme 9). Carbamate **1** was then subjected to the palladium(II)-catalyzed cycloisomerization to provide the cyclic enamide **2** (16.2 g, 90% yield as based on **13**). This quantity of **2** was subjected to the palladium(II)-catalyzed oxidative Heck reaction with phenylboroxine to provide 18.6 g (90%) of the desired phenylated oxazolone **7a**.

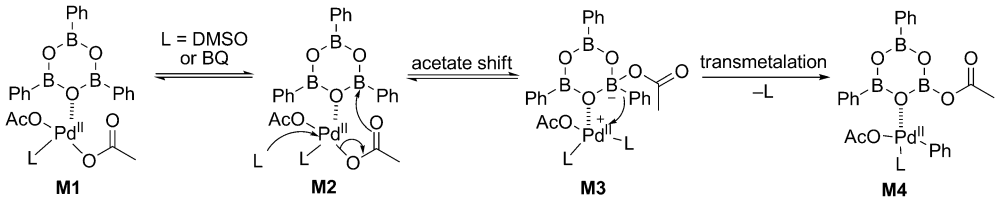
Having proved that this reaction was scalable, we embarked on our ultimate goal: to perform this reaction in a one-pot sequential fashion. The stage was set, as we had already spent considerable time finding reaction conditions that (possibly) would be compatible with each individual step (solvent, base, and catalyst). To our delight, we could use almost the same conditions as described in Scheme 5 to directly conduct this reaction in a one-pot sequential manner (1 mmol scale). The only modification that we made was to lower the catalytic loading in both palladium(II)-catalyzed reactions from 5 to 2.5 mol% of $Pd(OAc)_2$. With this approach, only one extraction and purification step was required, thus making this reaction attractive from a preparative perspective. The yield of **7a** obtained by the one-pot procedure on a small scale (82%) was comparable to the overall yield of the three-step reaction on a large scale (81%).

The mechanism of the oxidative Heck reaction has been studied both experimentally and computationally in quite some detail.[21] From these studies it is clear that the reaction relies on initial transmetalation of some form of $[L_mPd(OAc)_n]$ species to give an arylpalladium species, which undergoes insertion of a π-coordinated alkene with subsequent β-hydride elimination. One interesting aspect of the present study is that arylboronic acids ($ArB(OH)_2$) perform poorly; it therefore seems unlikely that $ArB(OH)_2$ is the actual transmetalation species in the reaction described herein.

We speculate that the aryl boroxine is transmetalated directly with the palladium acetate catalyst through a pseudo-intramolecular migration of the acetate anion (**M2**) to give a tetrahedral borate intermediate (**M3**; Scheme 10). On the basis of the effect of DMSO on the reaction, we suggest that



Scheme 9. Scale-up and one-pot sequential oxidative Heck reaction starting from the propargylic alcohol **13**.



Scheme 10. Schematic description of one possible DMSO-aided transmetalation pathway.

the process is facilitated by DMSO or possibly by BQ (as the ligand L). We have no direct experimental evidence for this mechanism, but similar mechanisms have been suggested previously, for example, in the "boron-to-zinc" transmetalation between Et_2Zn and aryl boroxines.[22] Another plausible pathway is that the small amount of water present slowly releases small quantities of $ArB(OH)_2$ through hydrolysis of the boroxine, and the $ArB(OH)_2$ in turn undergoes transmetalation with the Pd catalyst in a more conventional fashion. The latter process seems less likely simply on account of the observation that the addition of a large excess of the "free arylboronic acid" inhibits the reaction.

In summary, we have developed a catalytic procedure for the formation of cyclic tosylenamides that relies on a simple catalyst ($Pd(OAc)_2$), a simple base (Bu_4NOAc), and cheap and commercially available substrates (propargylic alcohols and tosylisocyanate). The main feature of this method is the β-selective Pd-catalyzed oxidative Heck reaction, which enables selective arylation of the cyclic enamide to give valuable oxazolones with high efficiency. In this process, β-hydride elimination occurs selectively at the position adjacent to the carbamate oxygen atom to provide the oxazolone with one new tertiary stereogenic center in good to excellent yield. The oxidative Heck reaction requires a cheap catalyst ($Pd(OAc)_2$) and oxidant (BQ) together with commercially available aryl sources (aryl boroxines). The showcased protocol is very robust and proved readily scalable to >66 mmol. Finally, and most importantly, the three-step reaction was successfully conducted in a one-pot sequential fashion, thus minimizing the work needed for workup and purification. We are confident that the oxazolones will be useful in the synthesis of ligands, pharmaceuticals, and other biologically active substances. Further studies on the reaction scope with more structurally diverse enamides and propagylic alcohols/amines are under way. We also intend to study the chemistry of the acquired oxazolones to determine what reactivity this moiety displays in classical reactions, such as hydrogenation, hydrolysis, and transition-metal-catalyzed reactions.

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[18] Further details regarding this transformation will be disclosed elsewhere. Additional details regarding the depicted reaction can be found in the Supporting Information.

[19] At this point of the investigation, we used commercially available phenylboronic acid as the source of the aryl group. However, we quickly realized that most of the boronic acids that we acquired from commercial suppliers contained the cyclic aryl boroxine and in fact very small amounts of the $ArB(OH)_2$.

[20] The aryl boroxines were prepared by the removal of water with a Dean–Stark apparatus. See the Supporting Information for more details.

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