Cascade C-H Activation | Hot Paper

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# Ligand-Enabled Triple C–H Activation Reactions: One-Pot Synthesis of Diverse 4-Aryl-2-quinolinones from Propionamides**

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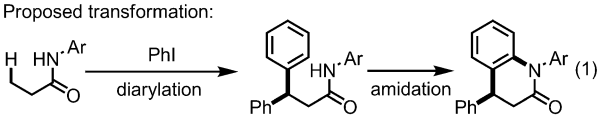
*Dedicated to Professor Björn Åkermark on the occasion of his 80th birthday*

***Abstract:*** *Diverse 4-aryl-2-quinolinones are prepared from propionamides in one pot by ligand-promoted triple sequential C–H activation reactions and a stereospecific Heck reaction. In these cascade reactions, three new C–C bonds and one C–N bond are formed to rapidly build molecular complexity from propionic acid.*

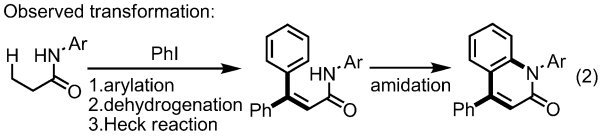
Ligand-controlled or ligand-accelerated C($sp^3$)–H activation with $Pd^{II}$ catalysts has recently emerged as a promising strategy for developing new catalytic transformations.[1–3] Notable examples include the cross-coupling of γ-C($sp^3$)–H bonds of protected amines with arylboron reagents enabled by mono-protected amino acid ligands[1] as well as β-arylation of primary and secondary C($sp^3$)–H bonds promoted by pyridine and quinoline ligands.[2] The compatibility of these ligands with C($sp^3$)–H activation and subsequent functionalization steps offers unprecedented opportunities to discover new catalytic reaction pathways by influencing the reactivity of various potential organopalladium intermediates. In particular, if a common ligand can be identified to promote cascade C–H activation reactions, molecular complexity and diversity can be readily generated from simple starting materials by sequential and diverse C–H functionalizations.[4] Indeed cascade reactions involving a Heck reaction and a subsequent C–H activation step provide an elegant route for the synthesis of spirodihydroquinolin-2-ones.[4f] However, cascade C–H activation reactions of simple aliphatic substrates leading to complexity have not been demonstrated.

Inspired by our studies of ligand-controlled β-arylation reactions of primary and secondary C($sp^3$)–H bonds,[2] we envisioned that sequential arylation of the β-C($sp^3$)–H bonds of propionamide followed by seven-membered cyclopalladation/amidation would result in a one-pot procedure for the preparation of 4-aryl-3,4-dihydro-2-quinolinones [Eq. (1)]. Herein we report the unexpected discovery of a novel procedure that combines three sequential C–H activation reactions of propionamide and a stereospecific Heck reaction in one pot to afford a diverse range of 4-aryl-2-quinolinones [Eq. (2)].

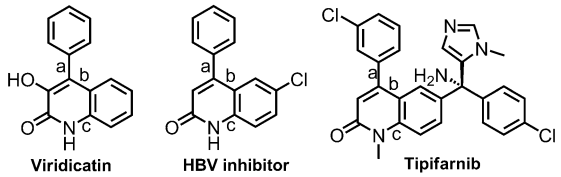
Proposed transformation:




Observed transformation:




4-Aryl-2-quinolinone derivatives constitute a valuable class of biologically active compounds, including natural products[5] and medicinal compounds[6] (Scheme 1). Moreover, they may serve as valuable synthetic intermediates to 2-(pseudo)haloquinolines as well as 2-alkoxyquinolines for use as ligands in C–H activation reactions.[2] Considering the broad interest in 4-aryl-2-quinolinones,[7] this newly developed one-pot procedure could prove useful in synthetic and medicinal chemistry.




***Scheme 1.*** Biologically active 4-aryl-2-quinolinones.

Our initial efforts were largely prompted by the prospect that simple and abundant starting materials (e.g. propionic acid) can be potentially transformed into complex molecules by multiple C–H functionalizations. Thus, amide **1a**, derived from propionic acid, was subjected to various arylation conditions previously developed in our laboratory in order to achieve diarylation and subsequent ligand promoted C–H lactamization [Eq. (1)]. We found, through extensive screening of palladium catalysts and solvents, that a combination of $PdCl_2$ and 2-alkoxylquinoline ligand **L1**[2b] in *t*-AmylOH catalyzed the sequential C–H activations/oxidative carbon–carbon bond forming reaction of **1a** to afford the unexpected 4-phenyl-2-quinolinone **3a** in 58% yield, along with a 17% yield of β-phenylated propionamide product **2a** (Table 1, for detailed screening, see the Supporting Information). The control experiment in the absence of ligand showed that **2a**

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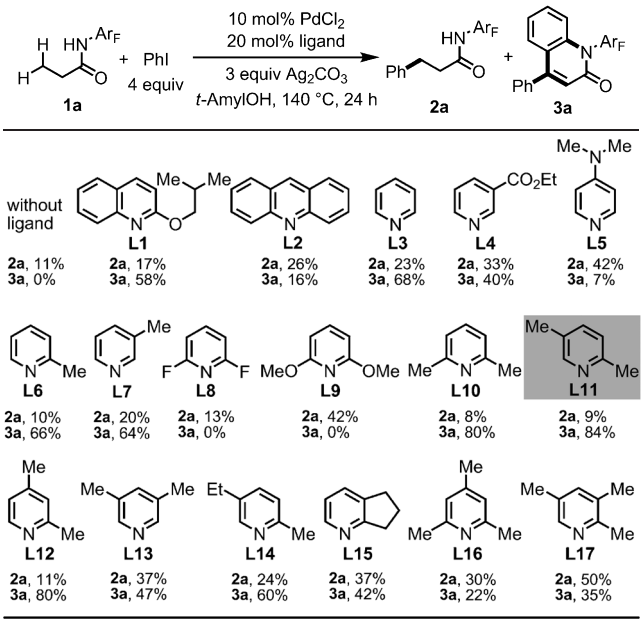
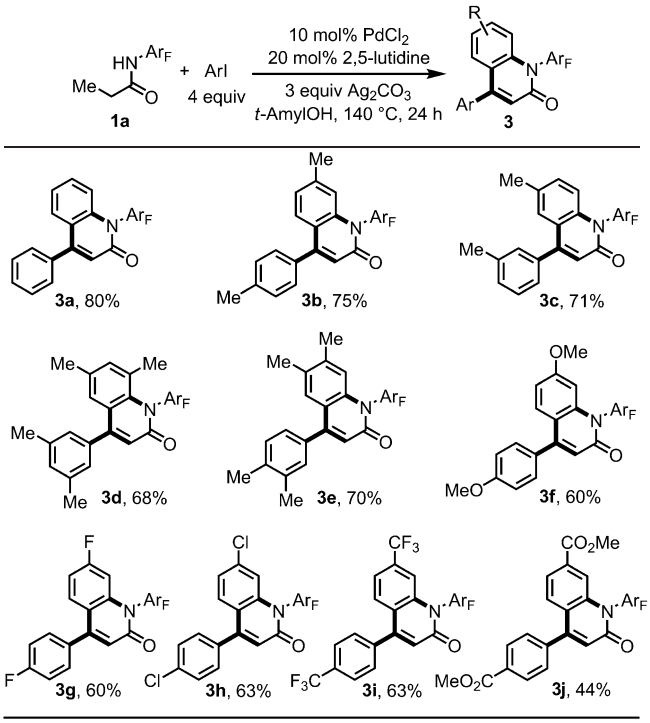
**Table 1:** Reaction discovery and ligand screening.[a,b,c]




[a] $Ar_F = (4\text{-}CF_3)C_6F_4$. [b] **1a** (0.2 mmol), $PdCl_2$ (0.02 mmol), $Ag_2CO_3$ (0.6 mmol), PhI (0.8 mmol), ligand (0.04 mmol), *t*-AmylOH (0.5 mL), 140 °C, 24 h. [c] Yield determined by NMR spectroscopy with $CH_2Br_2$ as the internal standard.

**Table 2:** Scope of aryl iodides.[a,b,c]




[a] $Ar_F = (4\text{-}CF_3)C_6F_4$. [b] **1a** (0.2 mmol), $PdCl_2$ (0.02 mmol), $Ag_2CO_3$ (0.6 mmol), ArI (0.8 mmol), 2,5-lutidine (0.04 mmol), *t*-AmylOH (0.5 mL), 140 °C, 24 h. [c] Yields of isolated products.

was formed in 11% yield as the only product. The observed dramatic impact of ligand **L1** on this reaction prompted us to further test a variety of pyridine- or quinoline-based ligands. Surprisingly, the use of simple pyridine **L3** as the ligand provided **3a** in 68% yield and **2a** in 23% yield. 2-Picoline (**L6**) and 3-picoline (**L7**) also gave comparable yields. 2,6-Dimethoxypyridine (**L9**) is highly selective for monoarylation, albeit in a relatively low yield (42% yield). Further investigation reveals that lutidines **L10**, **L11**, and **L12** are more effective than other pyridine ligands, affording the cyclized product **3a** in 80–84% yields.

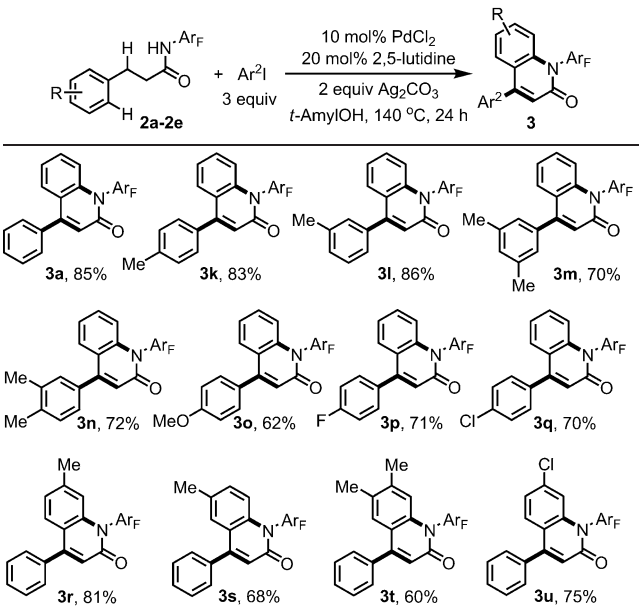
With these conditions in hand, we examined the scope of aryl iodides with **1a** to test the feasibility of preparing a variety of 4-aryl-2-quinolinones **3** (Table 2). Reactions with mono- or dimethyl substituted phenyl iodides yield 4-aryl-2-quinolinones **3b**–**3e** in 68–75% yields, with intramolecular amidation occurring at the less hindered position of the aryl group. *para*-Methoxyphenyl iodide was also reactive, affording the desired product **3f** in 60% yield. Electron-withdrawing fluoro, chloro and trifluoromethyl groups are also well tolerated (**3g**–**3i**), while the presence of a *para*-ester group decreased the yield to 44% (**3j**).

While one-pot synthesis of 4-aryl-2-quinolinones from a simple propionamide demonstrates excellent step economy, the incorporation of two identical aryl groups into the products results in limited structural diversity. In order to address this issue, we envisioned the installation of two distinct arenes through the mono-selective arylation of **1a** to yield various hydrocinnamic acid derivatives, followed by subsequent secondary arylation with a different aryl iodide to furnish heterodiaryl 2-quinolinones. Thus, we established moderately effective ligandless conditions for mono-arylation of **1a** and prepared hydrocinnamic acid amides **2a**–**2e** on gram scale (see Supporting Information). Hydrocinnamide **2a** was then further reacted with different aryl iodides ($Ar^2I$) under ligand-mediated conditions to afford a set of diverse 4-aryl-2-quinolinones **3k**–**3q** in 62–86% yield, with the $Ar^2$ group introduced regioselectively at the 4-position of the 2-quinolinone moiety (Table 3). While the use of other less hindered ligands **L3** and **L7** afforded the same regioselectivity, the yields decreased significantly (see Supporting Information). Hydrocinnamides **2b**–**2e** were also reacted with PhI under the standard conditions to afford various 4-aryl-2-quinolinones **3r**–**3u** in 60–81% yield. Notably, previous syntheses of 4-aryl-2-quinolinones by sequential Heck reaction/C–H lactamization use acrylamide as the starting material and proceed through three distinct steps catalyzed by three different catalysts.[7c] In addition, this method gave a mixture of regioisomers when two different aryls are incorporated into the products.

Considering that various 4-aryl-2-quinolinones contain different aryl groups (Ar) on the nitrogen, we made efforts to broaden the reaction scope by using differentially substituted propionamide substrates **1**, prepared from different anilines and propionyl chloride (Table 4). Thus, cascade products **3v**–**3z** were prepared in 62–75% yield with 2,6-difluoro or dichloro substitutions on the aryl ring (Ar). Further studies show that the 2,6-disubstitutions are required for sufficient reactivity. The amides derived from simple anilines also proceeded to afford $\mathbf{3a_1}$–$\mathbf{3i_1}$ in 40–54% yield. Methoxy ($\mathbf{3e_1}$), OTs ($\mathbf{3f_1}$), chloro ($\mathbf{3h_1}$), and bromo ($\mathbf{3i_1}$) groups on the aryl ring are also amenable to further synthetic elaborations.

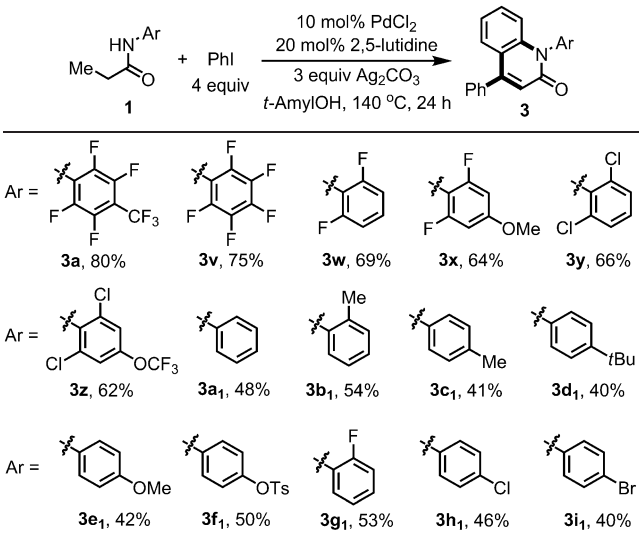
  

***Table 3:*** Incorporation of two different aryl groups.[a,b,c]




[a] $Ar_F = (4\text{-}CF_3)C_6F_4$. [b] **2** (0.2 mmol), $PdCl_2$ (0.02 mmol), $Ag_2CO_3$ (0.4 mmol), $Ar^2I$ (0.6 mmol), 2,5-lutidine (0.04 mmol), *t*-AmylOH (0.5 mL), 140 °C, 24 h. [c] Yields of isolated products.

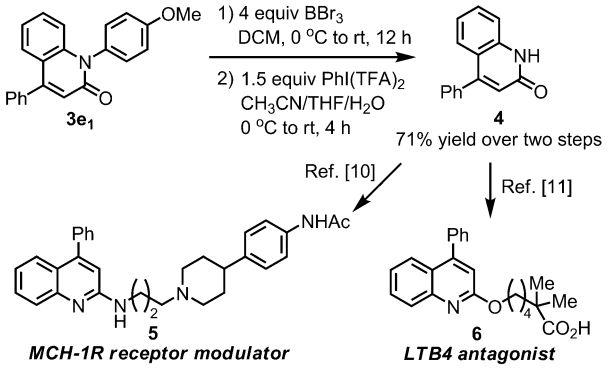
***Table 4:*** The scope of the *N*-aryl group.[a,b]




[a] **1** (0.2 mmol), $PdCl_2$ (0.02 mmol), $Ag_2CO_3$ (0.6 mmol), PhI (0.8 mmol), 2,5-lutidine (0.04 mmol), *t*-AmylOH (0.5 mL), 140 °C, 24 h. [b] Yields of isolated products.

Although the yields remain to be improved, this one-pot procedure utilizing inexpensive propionic acid as the starting material could prove broadly useful for medicinal chemistry.

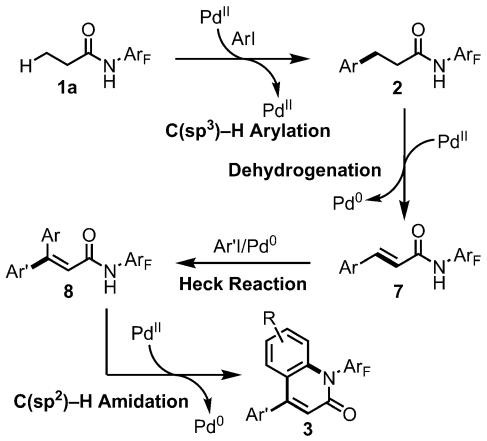
The use of *para*-methoxyaniline[8] also allowed us to establish a new route for the deprotection of N-substituted lactams.[9] Thus, 4-phenyl-2-quinolinone $\mathbf{3e_1}$ (prepared using our newly developed one-pot procedure) was deprotected to yield lactam **4**, which is a known precursor for the synthesis of drug molecules such as **5**[10] and **6**[11] (Scheme 2).




***Scheme 2.*** Synthetic applications.

Initially, it appeared plausible that the reaction pathway involves sequential β-arylations followed by dehydrogenation via Pd insertion, and finally intramolecular $C(sp^2)$–H amidation [Eq. (2)]. However, as illustrated in Table 3, incorporation of the second aryl is exclusively selective for the 4-position of the 2-quinolinone ring. This result reveals that the second aryl is consistently in a *trans* relationship with the amide directing group prior to the C–H lactamization. These observed results are inconsistent with a mechanism involving consecutive β-arylations followed by Pd-mediated dehydrogenation. In order to account for this selectivity, we instead propose participation of a stereospecific Heck reaction of a cinnamide intermediate with the second aryl iodide coupling partner.[12]

As such, we present the following mechanism: β-arylation of the primary $C(sp^3)$–H bond affords hydrocinnamide **2**. Pd-insertion into the secondary $C(sp^3)$–H bond followed by β-hydride elimination would then yield cinnamide intermediate **7**,[13] which allows for subsequent Heck coupling with a second aryl iodide. Intramolecular C–H amidation[14] would then provide the 4-aryl-2-quinolinone product **3** (Scheme 3). The reaction of independently prepared **7** with ArI also gave the desired quinolinones, thus verifying the viability of **7** as an intermediate (see Supporting Information).




***Scheme 3.*** Proposed catalytic pathway.

In conclusion, we have developed an unprecedented pyridine ligand-promoted cascade C–H activation of propionamides under oxidative palladium catalysis, which provides a one-pot procedure for the preparation of diverse 4-aryl-2-quinolinones from propionic acid. This cascade reaction involves the cleavage of five C–H bonds, two C–I bonds, and one N–H bond, and the formation of three C–C bonds and one C–N bond via four different types of palladium catalytic cycles. Further studies on the scope, mechanism, and synthetic application of this reaction are underway in our laboratory.

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