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Letter

Pd(II)-Catalyzed Annulation Reactions of Epoxides with Benzamides to Synthesize Isoquinolones

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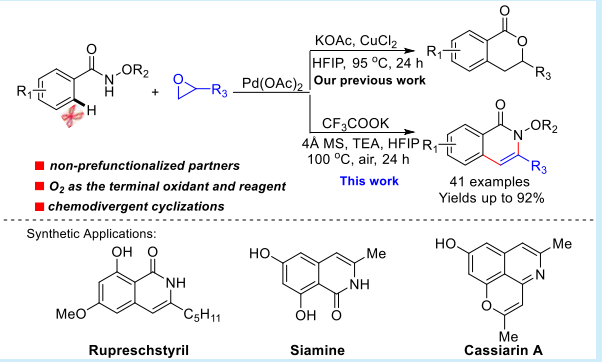
ABSTRACT: Epoxides as alkylating reagents are unprecedentedly applied in Pd(II)-catalyzed C−H alkylation and oxidative annulation of substituted benzamides to synthesize isoquinolones rather than isochromans, which is accomplished through alerting the previously reported reaction mechanism by the addition of oxidant and TEA. Under these conditions, various isoquinolones have been prepared with yields up to 92%. In addition, this methodology has been successfully employed in the total syntheses of rupreschstyril, siamine, and cassiarin A in an expedient fashion.

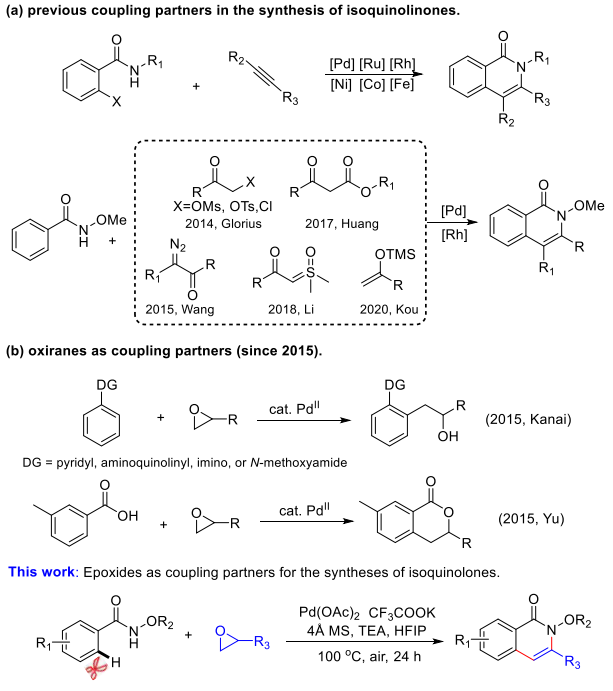


Isoquinolone is a widely existing class of skeletons usually possessing unique bioactivities.[1] Various methods for its synthesis have gradually been reported.[2] Among them, employing alkynes as coupling partners[3] and requiring transition metal catalysts[4−9] are the main features. Recently, various intrinsically unique coupling partners have been developed. In 2014, Glorius and co-workers employed α-MsO/TsO/Cl ketones as alkylating reagents accomplishing the syntheses of isoquinolones.[10] In 2017, Huang and co-workers developed β-keto esters as coupling partners to react with *N*-alkoxybenzamides via a cascade DCC/annulation reaction, resulting in isoquinolone derivatives.[11] Meanwhile, novel diazo compounds[12] and sulfoxonium ylides[13] as coupling/cyclization partners to synthesize *N*-methoxyisoquinolones have been gradually reported. More recently, Kou's group[14] reported Rh(III)-catalyzed oxidative coupling of *N*-methoxybenzamides with silyl enol ethers to render the *N*-methoxy-3-hydroxy dihydroisoquinolones in good yields (Scheme 1). These methodologies, however, suffer from some drawbacks, mainly the coupling partners are highly active, are difficult to prepare and store, and require prefunctionalization. Because of these challenges, development of more effective methods to prepare isoquinolones is still in demand.

As versatile coupling/cyclization partners, oxiranes have shown robustness in heterocycle synthesis involving C−H activation.[15] In 2015, Kanai's[16] and Yu's[17] groups respectively revealed the application of epoxides as the coupling partners for the first time in Pd-catalyzed C−H alkylation reactions, which provided a labor-saving alternative to construct isochromans.

Recently, our group employed oxiranes to construct the isochroman core of natural product berkelic acid.[18a] Together

Scheme 1. Coupling Partners for the Syntheses of Isoquinolones



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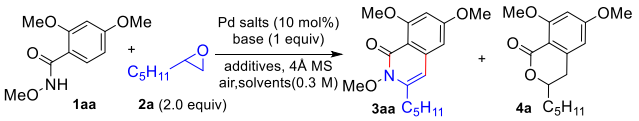
with our work, some other follow-up reports further revealed the robustness of this alkylation reagents by synthesizing useful phenethyl-substituted alcohols with high atom economy.[18b,g] However, to our knowledge, syntheses of isoquinolones using oxiranes as coupling partners has not been reported. The challenge is the Pd-alkoxide, which is generated from ring opening of epoxide, prefers to attack the carbonyl group of the amide group, leading to lactonization to generate isochromans,[17,18a] rather than conducted β-hydrogen elimination to form the ketone carbonyl followed byintramolecular lactamization/dehydration to afford isoquinolones. We proposed that the existence of appropriate base may promote the β-H elimination of Pd-alkoxide to afford isoquinolones (see the mechanism section). In order to identify the above-mentioned proposal and in continuation of our interest in heterocycle building,[19] we herein reveal an example of Pd(II)-catalyzed cascade reaction of *N*-alkoxylbenzamides with oxiranes derivatives for the synthesis of isoquinolones.

The initial experiment was performed with *N*-2,4-trimethoxybenzamide **1aa** and epoxide **2a** using $Pd(OAc)_2$ as the catalyst and KOAc as the additive (Table 1, entry 1). Indeed,

Table 1. Optimization of Reaction Conditions[a]



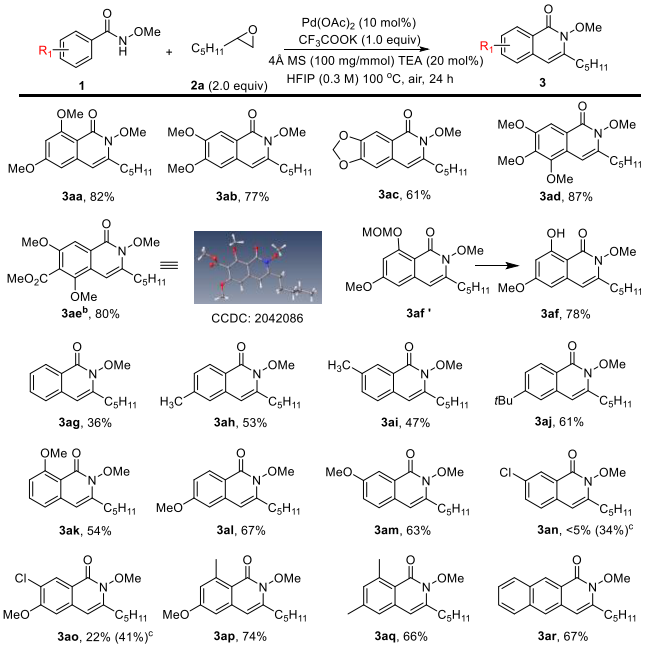
Entry	Catalyst system	Solvents	Additives	Yield (%) 3aa	Yield (%) 4a
1	$Pd(OAc)_2$/KOAc	Toluene		23%	13%
2	$Pd(OAc)_2$/KOAc	1,4-dioxane		12%	<5%
3	$Pd(OAc)_2$/KOAc	HFIP		34%	42%
4	$Pd(OAc)_2$/KOAc	*o*-Xylene		30%	21%
5	$Pd(OAc)_2$/CF_3CO_2K	HFIP		55%	23%
6	$Pd(OAc)_2$/CF_3CO_2Na	HFIP		46%	17%
7	$PdCl_2$/CF_3CO_2K	HFIP		47%	14%
8	$Pd(TFA)_2$/CF_3CO_2K	HFIP		38%	18%
9	$Pd(OAc)_2$/CF_3CO_2K	HFIP	AgOAc	59%	20%
10	$Pd(OAc)_2$/CF_3CO_2K	HFIP	Ag_2O	52%	22%
11	$Pd(OAc)_2$/CF_3CO_2K	HFIP	$CuCl_2$	<5%	45%
12	$Pd(OAc)_2$/CF_3CO_2K	HFIP	BQ	22%	14%
13	$Pd(OAc)_2$/CF_3CO_2K	HFIP	TEA	64%	20%
14	$Pd(OAc)_2$/CF_3CO_2K	HFIP	20 mol % TEA	82%	11%

[a]**1aa** (0.1 mmol), **2a** (0.2 mmol), Pd salts (10 mol %), additives (1.0 equiv), solvent (0.3 mL), 100 °C, 24 h, air, isolated yields. BQ = benzoquinone.

isoquinolone **3aa** as well as isochroman **4a** was generated respectively in 23% and 13% yields. Subsequently, we investigated the infulence of solvent (entries 1−4), and HFIP was proven to be the optimal one that produced **3aa** in 34% yield (entry 3). Significantly, changing KOAc to potassium trifluoroacetate (CF_3CO_2K) displayed some extent of selectivity toward isoquinolone, increasing the yield of **3aa** to 55%, but sodium trifluoroacetate (CF_3CO_2Na) gave a slightly lower yield of 46% (entries 5 and 6). Other Pd salts like $PdCl_2$ or $Pd(TFA)_2$ decreased the yields to 47% and 38%, respectively (entries 7 and 8). Further screening of oxidants revealed that AgOAc could afford a small improvement yield (59% entry 9) but the $CuCl_2$ reduced the yield drastically (entry 11); in addition, other oxidants like benzoquinone were not effective in this case (entry 12). To our delight, in the presence of TEA, the yield of **3aa** increased to 64%, while the yield of the byproduct isochroman **4a** was low (entry 13). When 20 mol % of TEA was added, a further improved yield of **3aa** (82%) was realized (entry 14). This result indicated that TEA may act as ligand that plays a crucial role in stabilizing the Pd catalyst and promoting reoxidation of Pd(0) by O_2.[20]

After determining the optimal reaction conditions, we studied reactivities of other *N*-methoxybenzamide derivatives (Scheme 2). To our delight, dimethoxy or trimethoxy

Scheme 2. Substrates Scope of *N*-Methoxybenzamides[a]



[a]Isolated yields. [b]Non-hydrogens atoms are shown as 30% ellipsoids. [c]Yields of corresponding isochromans.

substituted substrates all reacted well, affording isoquinolones (**3aa**−**3af**) in 61%−87% yields. Not surprisingly, *N*-methoxybenzamides bearing trimethoxy groups gave corresponding products with better yields than the dimethoxy substituted substrates. Particularly, substrate **1ae** with an electron-withdrawing methyl ester behaved well in this reaction, affording product **3ae** in a slightly lower yield of 80% compared with the methoxy-substituted substrate **1ad**. The MOM protected substrate **1af** gave the corresponding product smoothly; however, it was difficult to purify, which prompted us to deprotect MOM in the process of post-treatment, giving the product **3af** in a good yield of 78% in two steps. Subsequently, electron-donating groups (methyl, methoxy, and *tert*-butyl) substituted *N*-methoxybenzamides gave the desired products in 47−61% yields. In general, non/methyl substituents gave inferior yields compared with the methoxy substituents and the *ortho*-methoxy group gave a lower yield compared to the methoxy group in the *meta*/*para*-position. Unexpectedly, the presence of a *meta*-Cl substituent retarded the reactions

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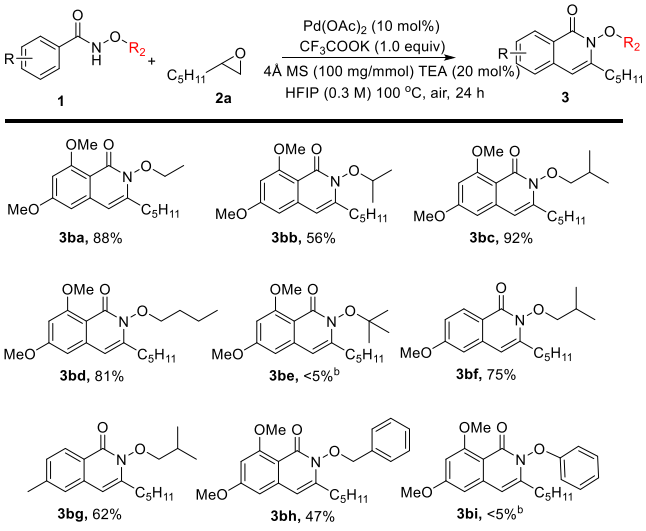
greatly, providing product **3an** in trace amount. The apparent electron effect of a substituent in the 3-position was also observed in substrate **1ao**, in which isoquinolones **3ao** was obtained in 22% yield. Moreover, 4-methoxy-2-methylbenzamide **1ap**, 2,4-dimethylbenzamide **1aq**, and 2-naphthamide **1ar** were compatible in this transformation, and moderate yields of corresponding products **3ap**, **3aq**, and **3ar** were obtained.

Beyond the *N*-methoxy group, a variety of *N*-protecting groups were investigated and electronic and steric effects were observed (Scheme 3). For example, substrate **1ba** containing

Scheme 3. Substrates Scope of *N*-Protecting Groups[a]



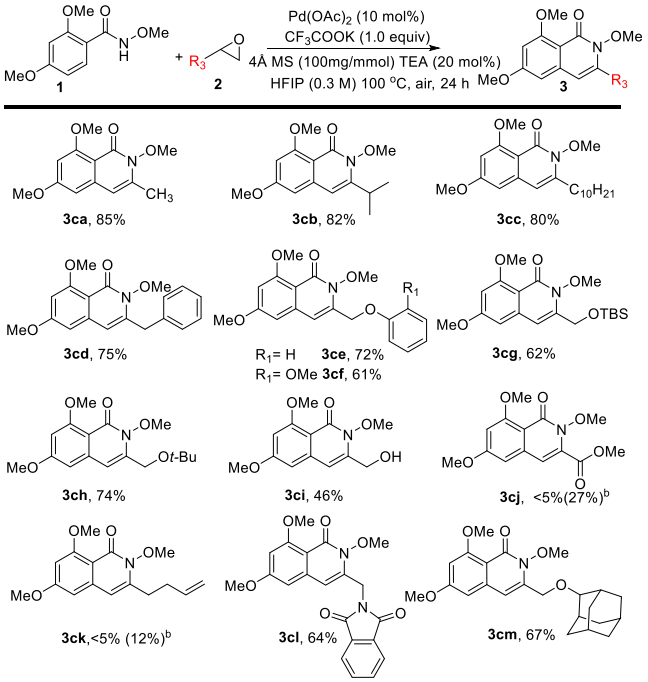
[a]Isolated yields. [b]Corresponding isochromans were not observed.

an *N*-ethoxy group afforded a better yield compared with the *N*-methoxy substituent by increasing the nucleophilicity of the nitrogen atom. The reaction of linear *N*-butoxy substrate **1bd** offered the desired isoquinolone in 81% yield, while substrate **1bb** bearing an isopropoxy gave **3bb** in 56% yield and *tert*-butoxy substituted substrate did not provide the desired product. It is pleasing that the reaction of *N*-isobutoxy substituted substrate **1bc** afforded **3bc** in 92% yield, and this *N*-protecting group was also employed in 4-methoxy/methyl benzamides **1bf** and **1bg**, and synthetically useful yields were obtained. When the *N*-protecting group was benzyloxy, isoquinolone **3bh** was obtained in 47% yield; however, *N*-phenoxy substrate **1bi** did not offer the desired product.

Finally, the scope of epoxides was extensively tested (Scheme 4). Alkylation with simple propylene oxide and other 2-alkyloxiranes gave *N*-methoxyisoquinolones **3ca**−**3cc** in 80−85% isolated yields. Actually, phenyl and protected hydroxyl groups (**3 cd**−**3ch**, **3cm**) gave inferior yields (61−75%) compared with 2-alkyloxiranes, presumably due to the additional coordinating oxygen atom or π-electrons of the phenyl of oxiranes might inhibit the β-hydrogen elimination process for coordinating to the palladium catalyst. Surprisingly, 2-ylmethanol oxirane was also tolerant in this reaction, affording **3ci** in 46% yield. Further exploration demonstrated that α-ester and vinyl moieties (**1cj**, **1ck**) were not compatible with this protocol. Besides, isoindoline-1,3-dione worked well in this transformation, and a moderate yield of corresponding product **3cl** was obtained.

Moreover, this methodology was successfully applied to the late stage modification of estrone, a compound possessing

Scheme 4. Substrates Scope of Epoxides[a]



[a]Isolated yields. [b]Yields of corresponding isochromans.

extensive pharmacological activities, leading to **3cn** in 58% yield.

The practicability of this protocol was also demonstrated by the total syntheses of rupreschstyril,[21] siamine,[22] and cassiarin A;[23] which, however, were previously synthesized in slightly lower overall yields and many steps. Removal of the methoxy group and subsequent deprotection of the MOM group in isoquinolin-1-one **3af′** provided rupreschstyril in 83% yield. Similarly, siamine (**2**), another alkaloid of *Cassia siamea*, was obtained in 76% yield from isoquinolin-1-one **3ca**. As for cassiarins A (**3**), treatment of **3ca** with sodium hydride at 120 °C removed the methoxy group, followed by treatment with *N*-phenyl-bis(trifluoromethanesulfonimide) providing triflate **4** in 73% yield in one pot, which subsequently coupled with the *in situ* generated propyne to provide alkyne **5** in 87% yield. Then, demethylation of **5** with BBr_3 and spontaneous 6-*endo*-*dig* cyclization gave cassiarin A (**3**) in a total of 4 steps and 37% overall yield from **1aa** (Scheme 5).

To gain insights into the mechanism, coupling of **1al** with **2a** in the absence of 4 Å molecular sieve and TEA has been conducted. As a result, isochroman **3as**, 3-hydroxy-3,4-dihydroisoquinolin-1-one **3at**, and isoquinolone **3al** were obtained in 24%, 13%, and 21% yields, respectively. Notably, **3at** could fully convert to isoquinolone **3al** in the presence of 4 Å molecular sieve at 100 °C in HFIP. When the reaction was performed under an O_2 or Ar atmosphere, **3al** was obtained respectively in 69% and 14% yields, indicating the critical role of oxygen in this reaction. According to our preliminarily mechanistic experiments and the literature precedent,[24] a plausible mechanism is proposed (Scheme 6). Cyclometalation of benzamide with palladium(II) generates a palladacyclic intermediate **A**,[25] which reacted with epoxide via an S_N2 nucleophilic ring-opening process generating Pd-alkoxide species **B**.[17] Intermediate **B** undergoes β-hydrogen elimination to form the ketone carbonyl product **D** and Pd-hydride species,[20a,26] followed by the nucleophilic addition of nitrogen

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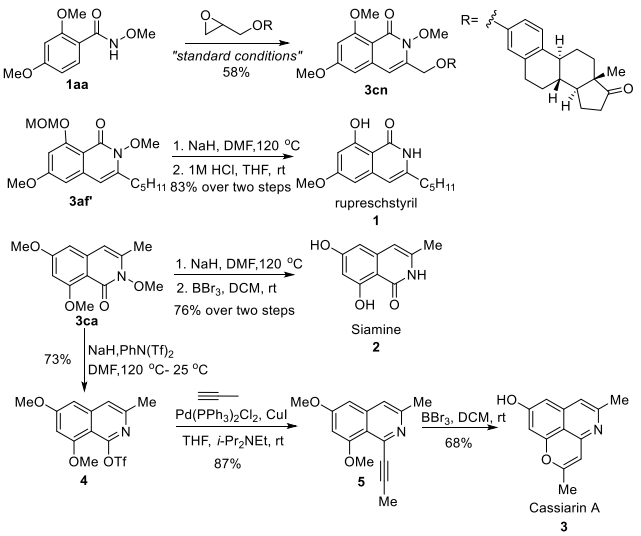
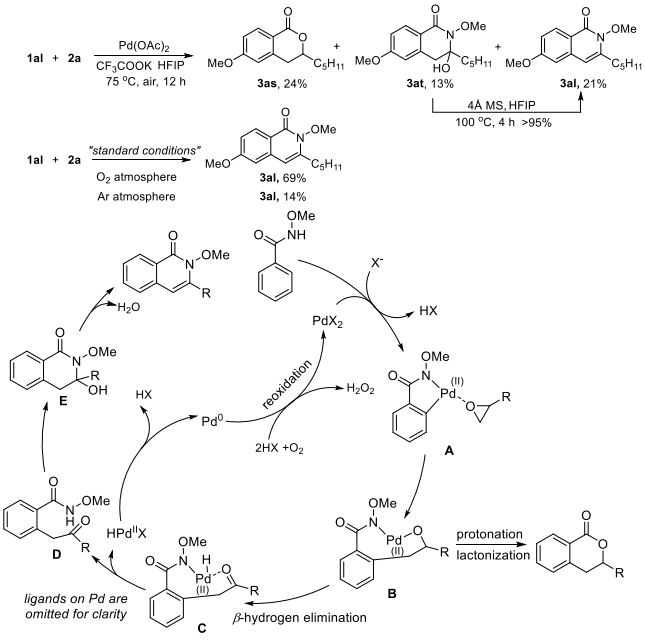
Scheme 5. Late-Stage Modification and Synthetic Applications



Scheme 6. Control Experiments and Proposed Reaction Mechanism



to the carbonyl group in **D** giving intermediate **E**, which then affords isoquinolone upon dehydration.[13] The Pd-hydride species is oxidized by O_2 to Pd(II),[20] which re-enters the catalytic cycle. In contrast, protonation and lactonization of species **B** would afford 3,4-dihydroisocoumarins as byproducts.

In conslusion, an example of palladium-catalyzed C−H alkylation and cascade annulation unprecedentedly using the easily prepared oxiranes as coupling partners to generate isoquinolones rather than isochromans is presented. Notably, the formation of isoquinolones or isochromans is controlled by the reaction conditions; that is, compared to conditions giving isochromans, the addition of potassium trifluoroacetate and TEA could promote the dehydration of Pd-alkoxide, resulting in the formation of isoquinolones rather than isochromans. The reaction works efficiently in various substrates, and natural products including supreschstyril, siamine, and cassiarin A have been synthesized in high efficiency by this new methodology. In addition, other novel transformations of epoxides are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04097.

Experimental procedures, spectroscopic data, and crystallographic data for **3ae** (CCDC 2042086) (PDF)

Accession Codes

CCDC 2042086 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

§H.W. and F.C. contributed equally.

Notes

The authors declare no competing financial interest.

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