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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Practical Pd(II)-Catalyzed C−H Alkylation with Epoxides: One-Step Syntheses of 3,4-Dihydroisocoumarins

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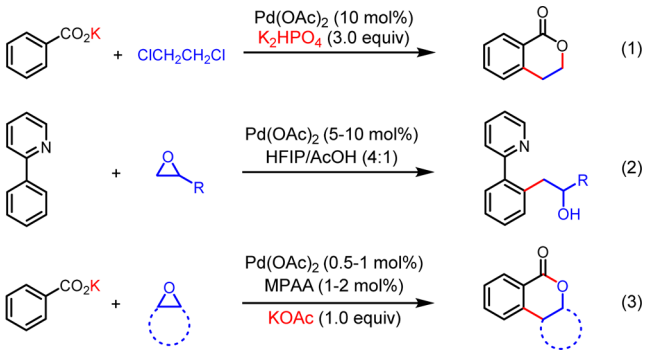
Supporting Information

ABSTRACT: Pd(II)-catalyzed *ortho*-alkylation of benzoic acids with both terminal and internal epoxides affords 3,4-dihydroisocoumarins in one step. The presence of potassium countercations is crucial for this reaction. Monoprotected amino acid ligands significantly promote this reaction, enabling the development of a practical C−H alkylation reaction using 0.5 mol % Pd catalyst. The inversion of stereochemistry in the C−H alkylation step is consistent with a redox-neutral S_N2 nucleophilic ring-opening process as opposed to a Pd(II)/Pd(IV) pathway.

Transition-metal-catalyzed alkylation of arenes[1] has emerged as an attractive alternative method to the traditional Friedel−Crafts alkylation reactions.[2] While Pd(II)-catalyzed C(sp^2)−H coupling with alkylborons has been demonstrated with limited scope,[3] alkylation of arenes with alkyl halides using directing groups has been extensively reported using Pd,[4,5] Ni,[6,7] Ru,[8] Co,[9] and Fe[10] catalysts.[11] The Co- and Fe-catalyzed alkylation reactions pioneered by Nakamura typically use RMgX/RX as the alkylating reagents. In contrast, Pd catalysts are mainly compatible with alkyl iodides/bromides using Ag(I) to promote the Pd(II)/Pd(IV) redox pathway.[4c,d,f,5] We have previously documented a rare example of Pd-catalyzed *ortho*-alkylation with alkyl chlorides leading to 3,4-dihydroisocoumarins (eq 1).[4b] The lack of precedent for oxidation of Pd(II) to



Pd(IV) by alkyl chlorides renders a Pd(II)/Pd(IV) reaction pathway unlikely. Instead, a simple electrophilic cleavage or S_N2 nucleophilic attack of the weakly coordinating arylpalladium intermediate with the alkyl chloride electrophile was proposed. Pd(II)-catalyzed *ortho*-deuteration of benzoic acids with DOAc provides further evidence that these weakly coordinated palladacycles can react with less oxidizing electrophiles such as proton[12] and alkyl chloride[4b] via Pd(II)/Pd(II) redox-neutral chemistry.

While Pd catalysts have shown promise in accommodating simple substrates in C−H alkylation,[4,5] the scope of substrates and alkyl halide coupling partners and the turnover numbers still must be substantially improved prior to synthetic applications. Difficulties are largely due to the undesired β-hydride elimination pathway of the alkylmetal species as documented in the cross-coupling reactions.[13] Recently, Kanai's group reported an important finding that 2-phenylpyridines undergo *ortho*-alkylation with terminal epoxides (eq 2), thus providing an alternative alkylation method.[14] One example of an *N*-methoxybenzamide substrate was also shown to be compatible in this work. Carefully designed mechanistic experiments support the proposed involvement of Pd(II)/Pd(IV) redox catalysis, demonstrating the first example of Pd(IV) catalysis with epoxide as the oxidant. Herein we report a highly efficient *ortho*-alkylation of benzoic acids with a wide range of terminal as well as internal epoxides to afford 3,4-dihydroisocoumarins[15] in a cascade reaction (eq 3). A remarkable enhancement by the potassium cation is essential for this reaction. The use of internal epoxides also allows us to establish the stereochemical course of the alkylation step as an inversion.

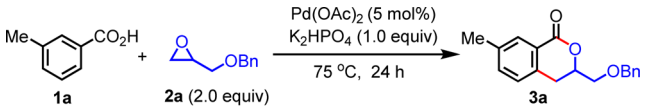
The use of countercations (Na^+, K^+, R_4N^+)[16] and mono-*N*-protected amino acid (MPAA) ligands[17] to promote carboxyl-directed C−H activation has significantly improved the efficiency and scope of *o*- or β-C−H functionalization reactions. However, C−H alkylation of carboxylic acid substrates without installation of a directing group remains a significant challenge. First, facile alkylation of the carboxyl group with alkyl chlorides except for 1,2-dichloroethane halts the reaction at low conversion. Second, alkylation with secondary alkyl halides has not been achieved, partly because of the undesired β-hydride elimination pathway. We therefore set out to test whether *ortho*-alkylation of benzoic acids with epoxides as alternative alkylating reagents could overcome these limitations. First, epoxides do not readily alkylate the carboxyl group. Second, if nucleophilic ring opening by the arylpalladium species is operative, an alkoxypalladium (instead of an alkylpalladium) intermediate will be formed, thereby preventing β-hydride elimination. Encouragingly, reaction of *m*-methylbenzoic acid (**1a**) with 2-((benzyloxy)methyl)oxirane (**2a**) using 5 mol % Pd under the conditions previously reported for the alkylation with 1,2-dichloroethane afforded the alkylation/lactonization product **3a** in 8−12% yield using *tert*-butyl methyl ether (TBME), dioxane, or toluene as the solvent

Received: July 18, 2015
Published: August 14, 2015

DOI: 10.1021/jacs.5b07507
J. Am. Chem. Soc. 2015, 137, 10950−10953

(Scheme 1). The presence of K_2HPO_4 is essential for this reactivity. Further solvent screening identified hexafluoroisopropanol (HFIP) as the most suitable solvent, affording **3a** in 90% yield. In contrast to Kanai's finding that HOAc is essential for alkylation to proceed in HFIP, addition of HOAc to our reaction significantly decreased the yield to 50%.

Scheme 1. Solvent Screening of the C(sp^2)–H Alkylation[a,b]

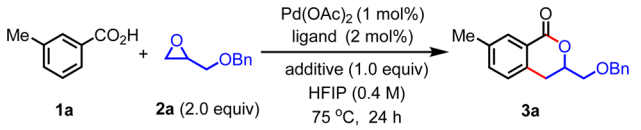


solvent	yield of **3a**
TBME	8%
1,4-dioxane	12%
toluene	10%
HFIP	90%

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv), $Pd(OAc)_2$ (5 mol %), K_2HPO_4 (1.0 equiv), solvent (0.25 mL), 75 °C, 24 h. [b]The yields were determined by ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard.

Considering that our previous alkylation reaction typically requires a high Pd catalyst loading (10 mol %), we attempted to further reduce the catalyst loading for this alkylation reaction (Table 1). Encouragingly, the use of 1 mol % $Pd(OAc)_2$ afforded **3a** in moderate yield (65%) (entry 1). Replacing K_2HPO_4 with K_3PO_4 or KH_2PO_4 decreased the yield to 38% or 5%, respectively (entries 2 and 3). The use of KOAc in place of K_2HPO_4 afforded a small improvement, affording 75% yield (entry 4). A remarkable countercation effect was observed using CsOAc, NaOAc, or LiOAc as the additive, which reduced the yield drastically (entries 5–7). Guided by previous findings of ligand acceleration,[17] we tested a wide range of MPAA ligands. We found that either Ac-leucine or Ac-*tert*-leucine improved the yield to 99% (entries 12 and 14). Under these conditions, the catalyst loading could be further reduced to 0.5 mol %, although this led to a slightly lower yield (84%; entry 14).

Table 1. Impacts of Countercations and Ligands[a]

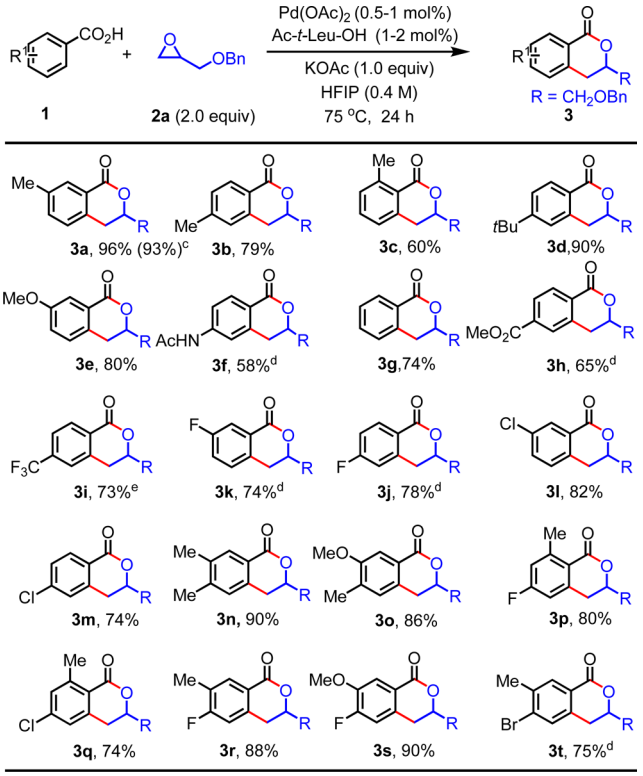


entry	additive	ligand	yield (%)[b]
1	K_2HPO_4	–	65
2	K_3PO_4	–	38
3	KH_2PO_4	–	5
4	KOAc	–	75
5	CsOAc	–	56
6	NaOAc	–	5
7	LiOAc	–	trace
8	–	–	trace
9	KOAc	Ao-Gly-OH	85
10	KOAc	Ac-Ala-OH	85
11	KOAc	Ac-Val-OH	94
12	KOAc	Ac-Leu-OH	99 (74)[c]
13	KOAc	Ac-Ile-OH	94
14	KOAc	Ac-*t*-eu-OH	99 (84)[c]

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv), $Pd(OAc)_2$ (1 mol %), ligand (2 mol %), additive (1.0 equiv), HFIP (0.25 mL), 75 °C, 24 h. [b]Determined by ^1H NMR analysis of the crude products using CH_2Br_2 as an internal standard. [c]$Pd(OAc)_2$ (0.5 mol %), ligand (1 mol %).

With the optimized conditions in hand, we examined the scope of benzoic acids using **2a** as the alkylating electrophile (Table 2).

Table 2. Benzoic Acid Substrate Scope[a,b]



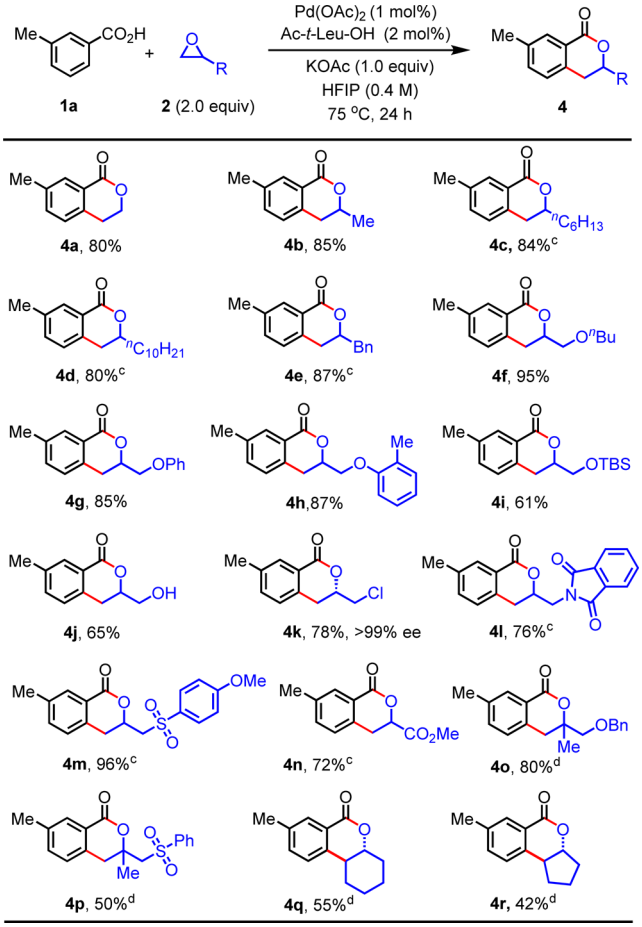
[a]Reaction conditions: **1** (0.1 mmol), **2a** (2.0 equiv), $Pd(OAc)_2$ (1 mol %), Ac-*t*-Leu-OH (2 mol %), KOAc (1.0 equiv), HFIP (0.25 mL), 75 °C, 24 h. [b]Isolated yields based on **1** are shown. [c]**1a** (1.36 g, 10 mmol), $Pd(OAc)_2$ (0.5 mol %), Ac-*t*-Leu-OH (1 mol %). [d]$Pd(OAc)_2$ (2.5 mol %), Ac-*t*-Leu-OH (5 mol %). [e]$Pd(OAc)_2$ (5 mol %), Ac-*t*-Leu-OH (10 mol %).

Electron-donating groups on the aryl ring are well-tolerated in general (**3a–f**). The gram-scale reaction of **1a** gives **3a** in comparable yield. However, the *o*-methyl group gives a lower yield (**3c**, 60%). Interestingly, the acetamide directing group does not prevent the carboxyl-directed C–H activation but does give a lower yield (**3f**, 58%). Nonsubstituted benzoic acid affords the desired product in 74% yield (**3g**). Various electron-withdrawing groups, including ester, trifluoromethyl, fluoro, and chloro, are also compatible with this reaction (**3h–m**). Disubstituted benzoic acids also afford the desired alkylation products in good yields (**3n–t**). A substrate containing a bromo substituent requires the use of 2.5 mol % Pd to obtain synthetically useful yield (**3t**).

Considering the limited scope of the alkyl chloride coupling partners in our previous reaction,[4b] we extensively tested the scope of epoxides as the alkylating reagent (Table 3). Alkylation with simple ethylene oxide, propylene oxide, and other 2-alkyloxiranes give the desired 3,4-dihydroisocoumarins **4a–e** in 80–87% isolated yield. Importantly, the coupling partners in this alkylation reaction are not limited to epoxides containing an adjacent coordinating group, presumably because of the high

DOI: 10.1021/jacs.5b07507
J. Am. Chem. Soc. 2015, 137, 10950–10953

Table 3. Epoxide Substrate Scope[a,b]

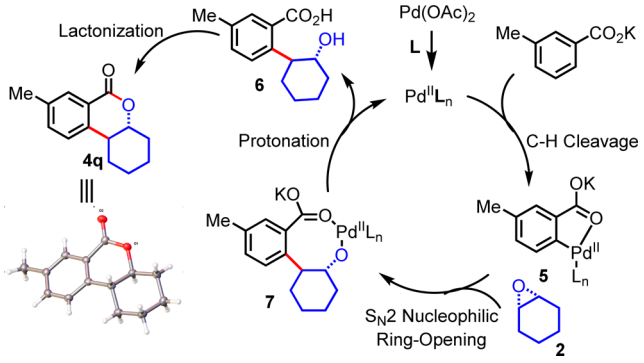


[a]Reaction conditions: **1a** (0.1 mmol), **2** (2.0 equiv), $Pd(OAc)_2$ (1 mol %), Ac-*t*-Leu-OH (2 mol %), KOAc (1.0 equiv), HFIP (0.25 mL), 75 °C, 24 h. [b]Isolated yields based on **1** are shown. [c]$Pd(OAc)_2$ (2.5 mol %), Ac-*t*-Leu-OH (5 mol %). [d]$Pd(OAc)_2$ (10 mol %), Ac-*t*-Leu-OH (20 mol %).

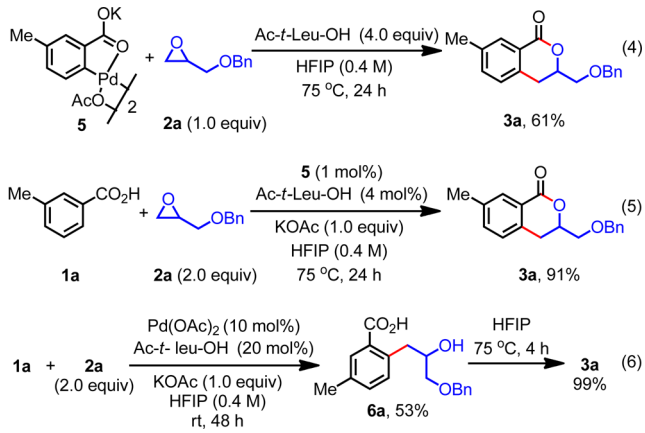
reactivity of the weakly coordinated arylpalladium intermediates. Epoxides containing a phenyl or variously protected hydroxyl group give excellent yields (**4f**–**h**), except that *tert*-butyldimethylsilyl (TBS) protection lowers the yield to 61% (**4i**). Surprisingly, a free *β*-hydroxyl group is tolerated, affording a versatile synthon **4j** in 65% yield. Further exploration demonstrated that *β*-chloro, protected amino, and sulfonyl groups as well as an *α*-ester group are all compatible with this alkylation protocol (**4k**–**n**). When chiral (*S*)-(+)-epichlorohydrin is used as a coupling partner, the product **4k** is obtained with >99% ee. 1,1-Disubstituted oxiranes are also reactive coupling partners, affording the desired products **4o** and **4p** in isolated yields of 80 and 50%, respectively. Finally, we were able to alkylate **1a** with 1,2-disubstituted oxiranes to give the trans products **4q** and **4r** in moderate yields using 10 mol % Pd catalyst (both structures were characterized by X-ray analysis).

The previously observed lack of reactivity between the arylpalladium(II) intermediates and epoxides led to the proposal of several plausible reaction pathways involving Pd(IV) intermediates.[13] While Pd(II) species coordinated with pyridine could be oxidized to Pd(IV) by the oxirane C–O bond, we hypothesize that our weakly coordinated arylpalladium intermediate reacts with the epoxide via a redox-neutral S_N2 nucleophilic ring-opening process (Scheme 2).[18,19] Subsequent

Scheme 2. Proposed Mechanism



lactonization of the free hydroxyl group affords the 3,4-dihydroisocoumarin. Our experimental data are consistent with the proposed reaction pathway. First, inversion of the stereochemistry is observed with **4q** and **4r**. Although inversion in the oxidation of Pd(II) to Pd(IV) by primary alkyl iodides is possible via S_N2 attack of the Pd(II) at the carbon center, retention in alkylation with secondary *cis*-cyclohexyl iodide via Pd(IV) has been unambiguously elucidated in an elegant study by Chen's group.[4f] Second, the isolated arylpalladium(II) intermediates are reactive not only stoichiometrically but also catalytically (eqs 4 and 5). Third, the free alcohol intermediate **6a** was also isolated



by running this reaction at room temperature. Subsequent lactonization of **6a** occurred under the reaction conditions to give the desired product in 99% yield (eq 6).

In summary, we have developed an efficient Pd-catalyzed ortho-alkylation with both terminal and internal epoxides. The inversion of stereochemistry in the ring-opening step supports a redox-neutral S_N2 nucleophilic ring-opening reaction pathway, mimicking the Grignard reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07507.

Experimental procedures and spectral data for all new compounds (PDF)

Crystallographic data for **4q** (CIF)

Crystallographic data for **4r** (CIF)

DOI: 10.1021/jacs.5b07507
J. Am. Chem. Soc. 2015, 137, 10950–10953

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge support from The Scripps Research Institute and NSF under the CCI Center for Selective C−H Functionalization (CHE-1205646).

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