Intramolecular Oxidative Coupling between Unactivated Aliphatic C-H and Aryl C-H Bonds

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potential to build up fused cyclic scaffolds from linear substrates through oxidative couplings. Privileged chromane and tetralin scaffolds were constructed from readily available linear starting materials in the absence of any organohalides and organometallic partners.

hromane and tetralin are vital structural units in natural products and pharmaceutical molecules (Scheme 1a).¹ In general, chromanes are synthesized through the reduction of chromanones,² intramolecular C-O formations,³ cross-coupling of organohalides with different partners,⁴ as well as Friedel-Crafts alkylations,⁵ while tetralins are constructed through hydrogenation of naphthalenes,⁶ Friedel-Crafts cyclization of aryl derivatives,⁷ or C-H alkylation of alkene

vated aliphatic and aryl C-H bonds. This chemistry showed great

Scheme 1. Importance of Chromane/Tetralin Units and a Straightforward Strategy for Synthesis



b) This work: Direct construction of Chromane and tetralin unit



tethered arenes.⁸ Apparently, the direct oxidative coupling between aliphatic and aromatic C-H bonds via transitionmetal catalysis would be a straightforward, atomic- and stepeconomic method to construct such benzo-fused cyclic structural units from linear starting materials equipped with phenyl substituents, providing an efficient strategy to approach the fused ring systems.

n = 0 1

Indeed, oxidative coupling of two different C-H bonds showed great advantages in constructing C-C bonds.⁹ In the past decades, relatively active aliphatic C-H bonds, such as benzylic/allylic C-H bonds and C-H bonds adjacent to heteroatoms in the substrates, have been broadly applied to oxidative coupling as partners, which were well-featured as cross-dehydrogenative coupling reactions (CDC).9,10 Biaryl construction through oxidative couplings from two arenes has also been well investigated.¹¹ In comparison, the investigation of oxidative coupling between both unactivated aliphatic and aromatic C-H bonds is far behind, and only a few examples were reported.¹² In 2017, our group reported an example to construct dihydrobenzofurans from 3-alkyloxybenzoic acid, in which aromatic carboxylic acid was considered as a directing group, and the intramolecular cross-coupling was manipulated by tuning the reactivity with a proper ligand.^{12c} Another elegant example reported by Loh and co-workers provided an efficient method to construct dihydroquinolinones through oxidative couplings.^{12e} In both cases, the oxidative coupling was initiated from aromatic C-H bond activation by directing strategy with palladacycles as key intermediates. Although

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directing-group-promoted unactivated aliphatic C–H bond functionalization with different reaction partners was well explored,¹³ the oxidative coupling of unactivated $C(sp^3)$ –H with a $C(sp^2)$ –H bond by initiation from aliphatic C–H activation has rarely been reported.^{12f–h}

As known, aliphatic carboxylic acid is one kind of important organic compound. Direct C-H functionalization of aliphatic carboxylic acids can derive valuable compounds from readily available chemicals by using carboxylates as weakly coordinating directing groups. This chemistry has drawn much attention in the past decades, and significant progress has been made with efforts.¹⁴ An elegant aliphatic acid directed β -C(sp³)-H functionalization example was published by Yu group.^{14d} In those transformations, either $Pd(0)/Pd(II)^{14a-c}$ or Pd(II)/Pd(IV)^{14d} catalytic cycles were proposed, and the ligands showed their uniqueness in catalysis. We envisioned that, if equipping an aryl group at the proper position of the carboxylic acids, a coordinating pattern of palladacycles which was formed through carboxylates directed aliphatic C-H activation may facilitate the intramolecular oxidative coupling (Scheme 1b). This approach might open a new channel to synthesize benzofused ring systems from linear aromatic substituted aliphatic carboxylates.

Based on this hypothesis, we set out to investigate the intramolecular oxidative coupling between both unactivated aliphatic and aromatic C-H bonds. 2,2-Dimethyl-3-phenoxypropanoic acid 1a was initially selected as a candidate since the Thorpe–Ingold effect of geminal dimethyl substituents was found to be essential in aliphatic C-H activations.¹⁵ We first attempted to carry out the reaction with Pd(CH₂CN)₂Cl₂ as the catalyst, KHCO3 as a base, and TBHP as an oxidant in HFIP at 60 °C, and the desired product 3-methylchromane-3carboxylic acid 2a was obtained in a 21% NMR yield by using 1,3,5-trimethoxybenzene as an internal standard (entry 1). In previous studies, ligands were shown to be important to accelerate C-H bond activation and hence promote the reaction efficiency.^{12c,13,14,16} Therefore, various ligands were tested in the reaction. In previous efforts from Yu's group, protected amino acids showed their "magic" effect in aliphatic C-H functionalization.^{16b,d,e} As expected, with the addition of ligand L1 (Ac-Phe-OH), the yield of the desired product (2a) was somewhat improved, revealing that amino acid ligands exhibited a potentially positive effect on this intramolecular oxidative coupling reaction as observed in Table 1, entry 2. On the contrary, pyridine-2-sulfonic acid L9 inhibited the reactivity (entry 3). To our delight, a 10%:10% combination of L1 and L9 dramatically promoted this reaction, giving an complete 1a conversion and an 80% NMR yield of 2a (entry 4).¹⁶ⁱ After the reaction was implemented with a broad scope of ligands/coligands, L1/L9 was found as the most feasible combination (Table S1, S2; Table 1, entry 5-14). These results revealed intriguingly synergistic coordination of the L1/ L9 combo. Then further investigations of some other parameters, like Pd salts, temperature, reaction time, and oxidants (see the Supporting Information for details) were undertaken. Finally, by treating the starting material 1a with Pd(OAc)₂ (5 mol %), Ac-Phe-OH (10 mol %)/pyridine-2sulfonic acid (10 mol %), KHCO₃ (1.5 equiv), and tert-butyl hydrogen peroxide (TBHP, 1.5 equiv, both 70% solution in water or 5.5 M in decane gave the same result) in HFIP at 45 °C for 36 h, the desired product 2a was obtained with the highest isolated yield (entry 21, 88%).

Table 1. Optimization of Reaction Conditions^a

H H 1a	^{CO₂H} -	Pd, L, KHCO ₃ , TBHP HFIP, 60 °C, 16 h	CO ₂ H
entry	ligands	conv of $1a^{b}$ (%)	yield of $2a^b$ (%)
1	-/-	23	21
2	L1/-	35	25
3	-/L9	10	7
4	L1/L9	>95	80
5	L1/L10	20	20
6	L1/L11	20	17
7	L1/L12	<5	0
8	L2/L9	71	51
9	L3/L9	85	68
10	L4/L9	38	36
11	L5/L9	<5	0
12	L6/L9	73	58
13	L7/L9	90	74
14	L8/L9	42	34
15 ^c	L1/L9	70	68
16 ^{c,d}	L1/L9	78	74
17 ^{d,e}	L1/L9	83	78
18 ^{<i>d</i>,<i>e</i>,<i>f</i>}	L1/L9	93	87
19 ^{d,f,g}	L1/L9	>95	82
$20^{e_{i}f_{i}g}$	L1/L9	>95	81
$21^{e,f,h,i}$	L1/L9	>95	92 (88) ^j

^{*a*}Reaction Conditions: **1a** (0.5 mmol, 1.0 equiv), $Pd(CH_3CN)_2Cl_2$ (5 mol %), amino acid ligands (10 mol %), pyridine ligands (10 mol %), KHCO₃ (0.75 mmol, 1.5 equiv), TBHP (1.0 mmol, 2.0 equiv), HFIP (4.0 mL), 60 °C, 16 h. ^{*b*}Determined by ¹H NMR with 1,3,5-trimethoxybenzene as an internal standard. ^{*c*}60 °C. ^{*d*}24 h. ^{*e*}45 °C. ^{*f*}Pd(OAc)₂ was used instead of Pd(CH₃CN)₂Cl₂. ^{*g*}50 °C. ^{*h*}36 h. ^{*i*}TBHP (1.5 equiv) was used. ^{*j*}The data in parentheses is the isolated yield of **2a**.



Subsequently, we explored the substrate scope of this oxidative coupling to synthesize the diverse chromane (Table 2). A variety of para-substituted substrates on the phenyl group were examined. Both alkyl and aryl substituents, for example, methyl, tert-butyl, and phenyl, worked well, giving the desired products in good to excellent yields (2b, 2c, and 2i). p-Methoxy-, trifluoromethoxy-, benzyloxy-, and phenyl-derived ethers were suitable substrates, affording the corresponding chromane-3-carboxylic acids 2d, 2e, and 2j in 63%, 54%, and 74% yields, respectively. The halide substituents also furnished the products in good yields (2f-2h). The reactive halide substituents provided another possibility for further functionalization through orthogonal cross-coupling reactions. 3,5-Dimethyl- and 2-methylphenol ether underwent this intramolecular oxidative coupling smoothly, forming the anticipated 5, 7-dimethylchromane-3-carboxylic acid 2k (83%) and 8-



Table 2. Substrate Scope^{*a,b*}

^aReaction conditions: 1 (0.5 mmol), Pd(OAc)₂ (5 mol %), L1 (10 mol %), L9 (10 mol %), KHCO3 (0.75 mmol, 1.5 equiv), TBHP (0.75 mmol, 1.5 equiv), HFIP (4.0 mL), 45 °C, 36 h. ^bIsolated yield. ^c2.0 mmol scale.

methylchromane-3-carboxylic acid 2l (87%). The naphthol ethers were then tested, and the coupling products were obtained in good yield (2m and 2n), no matter whether 1- or 2- naphthyl derivatives were delivered, while the latter reaction showed a unique α -regioselectivity. While the dibenzo [b,d]furan unit was introduced to the reaction system, the anticipated coupling proceeded to give a polyfused ring system 20 in a moderate yield. This result also demonstrated that the heterocycles survived well. Meta-substituted phenyl ether substrates were examined, excellent reactivity and acceptable regioselectivity were obtained, and the less steric hindered para-sp² C-H bond functionalization product dominated the site selectivity (2p/2p' = 1:3.3, 2q/2q' = 1:10).

To extend the substrate scope and examine the chemoselectivity between primary and secondary or tertiary C-H bonds, we introduced other alkyl groups to replace one of the methyl group at the α -position of the carboxylate. This intramolecular oxidative coupling reaction took place at the methyl group beyond both 'Pr (eq 1) and "Bu (eq 2) groups, showing an excellent selectivity among different types of $C(sp^3)$ –H bonds.

For further investigating this chemistry, the "O" linker was replaced by a "C" linker of substrate analogues, which could



quickly produce the tetralin core structures (Scheme 2). To our delight, tetralin-2-carboxylic acid 4 was formed in good





yield from 3 (eq 3). 2,3-Dihydro-1H-indene-2-carboxylic acid 6 could also be obtained with a 35% yield, showing great potential to synthesize indane derivatives (eq 4). We were happy to find that the oxidative coupling product 8 was also produced in a moderate yield by treating 2-methyl-3phenoxypropanoic acid 7 under standard reaction conditions (eq 5). This result indicated that the Thorpe–Ingold effect is not that essential in our system, thus providing broader application of this chemistry.

We next conducted the oxidative coupling with natural product scaffold to further explore the application of this chemistry. Estrone derivative 9 was tested in this system, yielding 46% yield of the desired compound 10 (Scheme 3). This method efficiently builds up the complexity of natural and existing molecules for material chemistry and drug discovery.

Scheme 3. Oxidative Coupling of Estrone Derivative



To gain mechanistic insight into the reaction, we conducted a series of experiments to measure kinetic isotope effects (KIEs) (Scheme 4).¹⁷ First, intramolecular competition oxidative coupling of mono CD_3 substrate $1a - d_3$ (eq 6) and monodeuterated substrate 1a-d (eq 7) were carried out under standard conditions, respectively.

We observed a large primary KIE (6.87, eq 6) of the methyl $C(sp^3)$ -H bond, while the aryl $C(sp^2)$ -H bond KIE was 1.01 (eq 7), among the magnitude range of the typical secondary KIE. Next, intermolecular one-pot competition reactions using an equimolar mixture of $1a \cdot d_6 + 1a$ (eq 8) and $1a \cdot d_5 + 1a$ (eq



9) resulted the KIE magnitude of 5.17 and 1.14, correspondingly. Finally, we ran two pairs of intermolecular parallel experiments, and the magnitudes of these two KIEs $(k_{\rm H}/k_{\rm D} = 5.03, {\rm eq}\ 10; {\rm k}_{\rm H}/{\rm k}_{\rm D} = 0.98, {\rm eq}\ 11)$ were very similar to the one-pot competition KIEs $(k_{\rm H}/k_{\rm D} = 5.17, {\rm eq}\ 8; k_{\rm H}/k_{\rm D} = 1.14, {\rm eq}\ 9)$. These experiments directly indicated that the unactivated C(sp³)-H bond cleavage occurred during the rate-determining step (RDS) of this intramolecular oxidative coupling reaction. In addition, the control experiment of **1a** with the stoichiometric Pd(OAc)₂ in the absence of TBHP did not afford any **2a** at all,¹⁸ indicating that the Pd(II)/Pd(IV) cycle, instead of the Pd(II)/Pd(0) cycle, likely took place in the present case.¹⁹

Based on previous reports and the above-described experimental results,^{14b,20} we proposed a plausible mechanism as shown in Figure 1. First, Pd(OAc)₂ combined with L1 and L9 to generate a Pd-complex *int a*; the β -C(sp³)H of carboxylate was activated by Pd complex *int a* through the weak coordination of carboxylate, producing the cyclic-Pd (II) complex *int b*. After oxidation by TBHP,^{20d} cyclic-Pd (IV) complex *int c* was formed, and then the the C(sp²)–H bond was activated to give a 7-membered cyclic species *int d*. By the



association of two AcOH, reductive elimination of *int d* was expected to produce the desired product 2, releasing ^tBuOH and H_2O .

In conclusion, we have developed a $Pd(OAc)_2$ -catalyzed, carboxylate-directed intramolecular oxidative coupling of α methyl- β -arenoxy(benzyl)propanoic acid. By synergism employing Ac-Phe-OH (L1) and pyridine-2-sulfonic acid (L9) as coligands, the β -C(sp³)-H bond of carboxylate and the *ortho*-C(sp²)-H bond on aromatic ring was activated and coupled to form chromane-3-carboxylic acid or tetralin derivatives under mild conditions. Kinetic studies indicated that the aliphatic C-H cleavage was involved in the RDS. Further studies to clearly understand the mechanism and to explore its synthetic application are underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04239.

Representative experimental procedures, the details of KIE experiments, necessary characterization data for all new compounds, and NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to P. H. Dixneuf (Université de Rennes 1) for his outstanding contribution to organometallic chemistry and catalysis. Dedicated to the 100th anniversary of Chemistry at Nankai University.

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