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

Yang Liao,[†] Yi Zhou,[‡] Zhen Zhang,[‡] Junzhen Fan,[†] Feng Liu,*[,†,‡] and Zhangjie Shi *[,†,§]

[†]Department of Chemistry, Fudan University. Shanghai, 200438, China.

[‡]School of Perfume and Aroma Technology, Shanghai Institute of Technology. Shanghai, 201418, China.

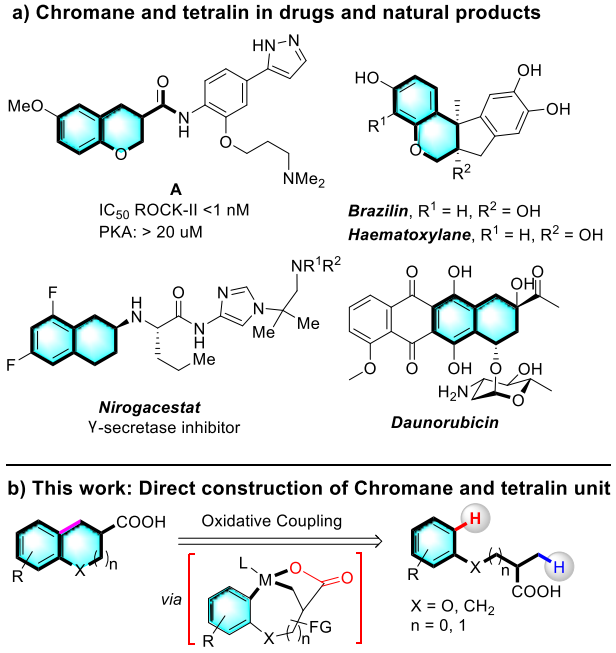
[§]State Key Laboratory of Organometallic Chemistry, SIOC, CAS. Shanghai, 200032, China.

ABSTRACT: Direct oxidative coupling of different inert C-H bonds is the most straightforward and environmentally benign method to construct C-C bonds. In this article, we developed a Pd-catalyzed intramolecular oxidative coupling between unactivated aliphatic and aryl C-H bonds. This chemistry showed great 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.

Chromane 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 the 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 tethered arenes.[8] Apparently, direct oxidative coupling between aliphatic and aromatic C-H bonds *via* transition-metal catalysis would be a straightforward, atomic and step-economic 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.

Indeed, oxidative coupling of two different C-H bonds showed its 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 have 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 few examples were reported.[12] In 2017, our group reported an example to construct dihydrobenzofurans from 3-alkyloxyl-benzoic acid, in which aromatic carboxylic acid was considered as a directing group, the intramolecular cross-coupling was manipulated by tuning the reactivity with a proper ligand.[12c] Another elegant example reported by Loh and coworkers 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 pallacycles as key intermediates. Although the directing-group-promoted unactivated aliphatic C-H bonds functionalization with different reaction partners were well explored,[13] the oxidative coupling of unactivated C(sp^3)-H with C(sp^2)-H bond has never been approached by initiating from aliphatic C-H activation.

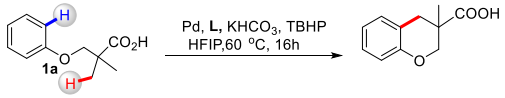
Scheme 1. The importance of Chromane/tetralin units and the straightforward strategy for synthesis.



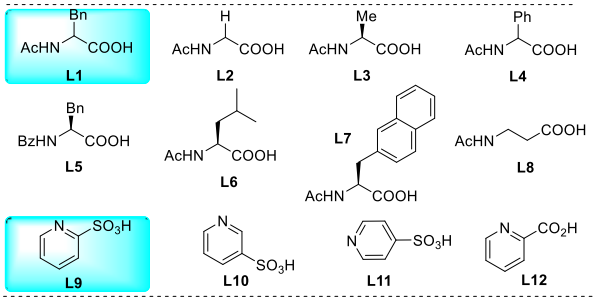
As known, aliphatic carboxylic acid is one kind of important organic compound. Direct C-H functionalization of aliphatic carboxylic acids can derive valuable compounds from readily available chemicals by using carboxylates as weakly coordinating directing groups. This chemistry has drawn much attention in the past decades, and many elegant progress has been made with efforts.[14] In those trans-

formations, 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 benzo-fused ring systems from linear aromatic substituted aliphatic carboxylates.

Table 1. Optimization of Reaction Conditions[a]



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	**L3L9**	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[d, e, f]	**L1**/**L9**	93	87
19[d, f, g]	**L1**/**L9**	>95	82
20[e, f, g]	**L1**/**L9**	>95	81
21[e, f, h, i]	**L1**/**L9**	>95	92 (88)[j]

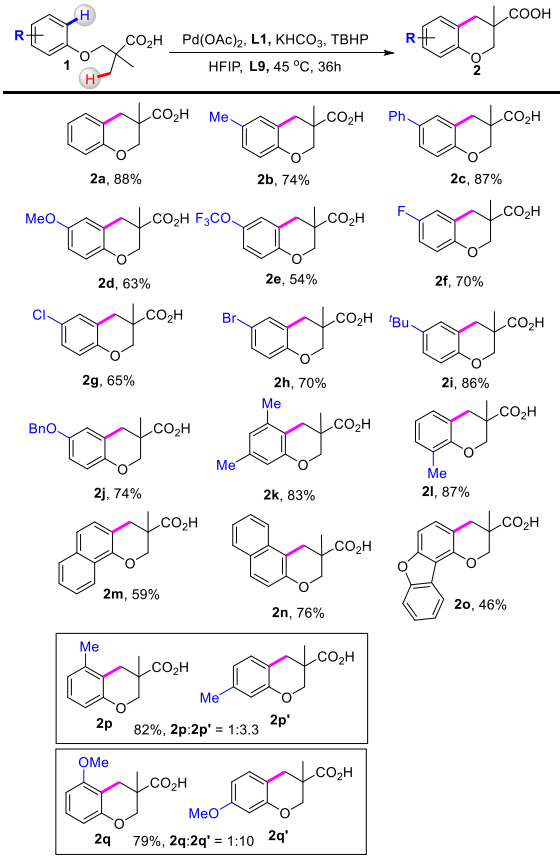


[a] Conditions: 1a (0.5 mmol, 1.0 eq.), $Pd(CH_3CN)_2Cl_2$ (5 mol%), amino acid ligands (10 mol%), pyridine ligands (10 mol%), $KHCO_3$ (0.75 mmol, 1.5 eq.), TBHP (1.0 mmol, 2.0 eq.), HFIP (4.0 mL), 60 °C, 16 hrs.
[b] Determined by ^1H NMR with 1,3,5-Trimethoxybenzene as an internal standard.
[c] 60 °C. [d] 24 hrs. [e] 45 °C. [f] $Pd(OAc)_2$ was used instead of $Pd(CH_3CN)_2Cl_2$. [g] 50 °C.
[h] 36 hrs. [i]TBHP (1.5 equiv) was used. [j]The data in the parentheses was isolated yield of **2a**.

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 essential in aliphatic C-H activations.[15] We first attempted to carry out the reaction with $Pd(CH_3CN)_2Cl_2$ as the catalyst, $KHCO_3$ as a base, and TBHP as an oxidant in HFIP at 60 °C, the desired product 3-methyl-chromane-3-carboxylic acid **2a** was obtained in a 21% NMR yield, by using 1,3,5-trimethoxy-benzene as an internal standard (entry **1**). In previous studies, ligands were proved to be important to accelerate the rate of C-H activation and hence promote the reaction efficiency.[12c,13,14,16] Therefore, various ligands were tested in the reaction. With 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 the existence of 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 utterly **1a** conversion and an 80% NMR yield of **2a** (entry **4**). After implementing the reaction with a broad scope of ligands/co-ligands, **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 taken. Finally, by treating the starting material **1a** with $Pd(OAc)_2$ (5 mol%), Ac-Phe-OH (10 mol%)/ Pyridine-2-sulfonic Acid (10 mol%), $KHCO_3$ (1.5 eq.), and *tert*-butyl hydrogen peroxide (TBHP, 1.5 eq., 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 %).

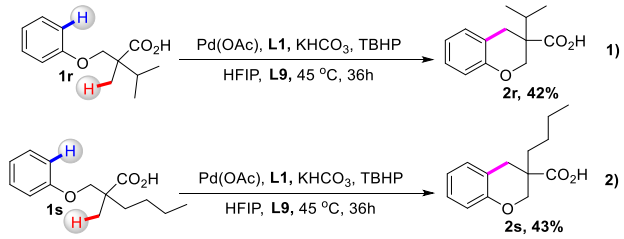
Subsequently, we explored the substrate scope of this oxidative coupling to synthesize the diverse chromane (Table **2**). A variety of *para*-substituted substrates on the phenyl group were examined. Both alkyl and aryl substituents, for example methyl, *tert*-butyl, and phenyl worked well, giving the desired products in good to excellent yields (**2b, 2c, and 2i**). *Para*-methoxy, trifluoromethoxy, benzyloxy 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-methyl phenol ether underwent this intramolecular oxidative coupling smoothly, forming the anticipated 5, 7-dimethylchromane-3-carboxylic acid **2k** (83 %) and 8-methylchromane-3-carboxylic acid **2l** (87 %), severally. 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 poly fused ring system **2o** 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*-sp^2 C-H bond functionalization product dominated the site selectivity (**2p**:**2p'** = 1:3.3, **2q**:**2q'** = 1:10).

Table 2. Substrate Scope [a,b]



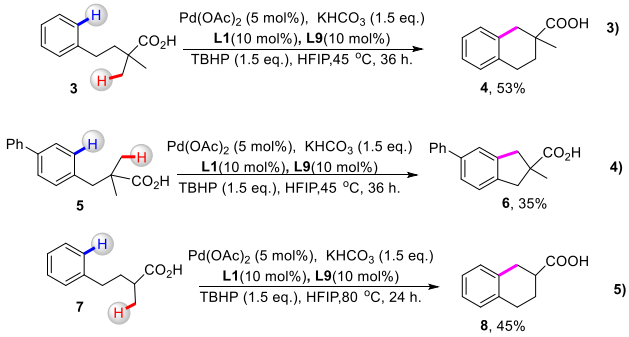
[a] Condition: **1** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), **L1** (10 mol%), **L9** (10 mol%), $KHCO_3$ (0.75 mmol, 1.5 equiv), TBHP (0.75 mmol, 1.5 equiv), HFIP (4.0 mL), 45 °C, 36 hours.
[b] Isolated yield.

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 *n*-Bu (eq **1**) and *i*-Pr (eq **2**) groups, showing an excellent selectivity among different types of C(sp^3)-H bonds.

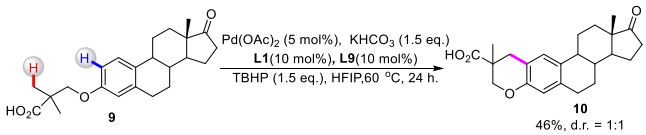


For further investigating this chemistry, the "O" linker was replaced by a "C" linker of substrate analogs, which could quickly produce the tetralin core structures (Scheme **2**). To our delight, tetralin-2-carboxylic acid **4** was formed with a good yield from **3** (eq **3**). 2,3-dihydro-1H-indene-2-carboxylic acid **6** could also be obtained with 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-3-phenoxypropanoic 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.

Scheme 2. Oxidative coupling of Phenyl alkyl substituted isobutyric acid



Scheme 3. Oxidative coupling of Estrone derivative



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.

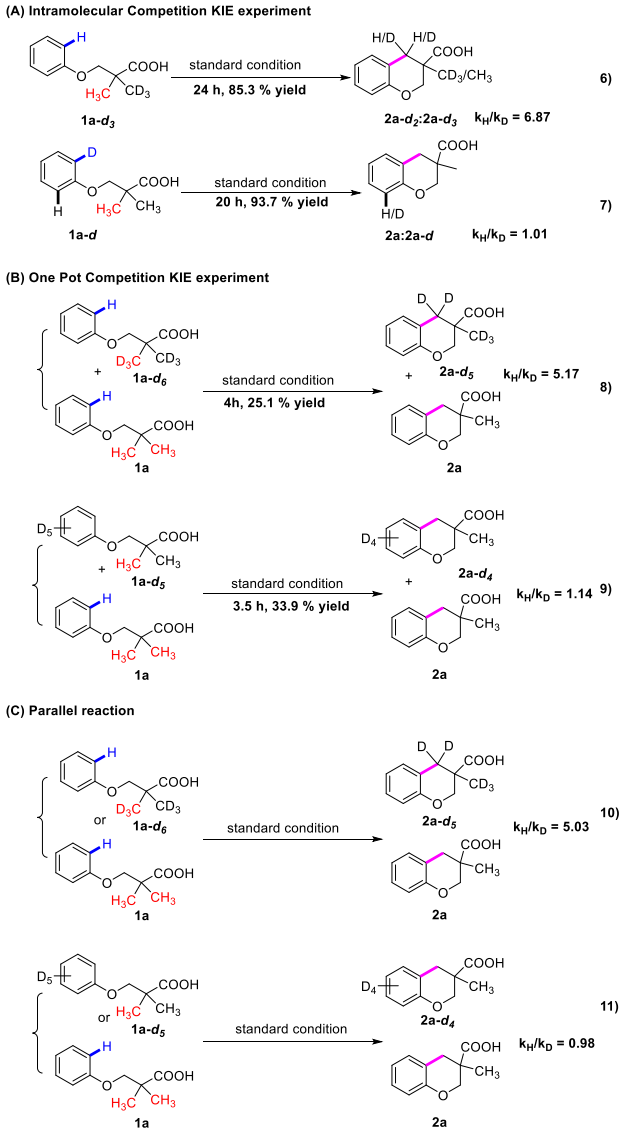
To gain mechanistic insight into the reaction, we conducted a series of experiments to measure kinetic isotope effects (KIEs) (Scheme **4**).[17] Firstly, intramolecular competition oxidative coupling of *mono* CD_3 substrate **1a**-d_3 (eq **6**) and mono-deuterated substrate **1a**-*d* (eq **7**) were 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**-d_6 + **1a** (eq **8**) and **1a**-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, the magnitude of these two KIEs (k_H/k_D = 5.03, eq **10**; k_H/k_D = 0.98, eq **11**) were very similar to the one pot competition KIEs (k_H/k_D = 5.17, eq **8**; k_H/k_D = 1.14, eq **9**). These experiments directly indicated that the unactivated C(sp^3)-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 Pd(II)/Pd(0) cycle likely took place in the present case.[19]

Based on previous reports and the above described experimental results, we proposed a plausible mechanism as shown in Figure **1**. Firstly, $Pd(OAc)_2$ combined with **L1** to

generate Pd-complex ***int a***; The β-C(sp^3)H of carboxylate was activated by Pd-complex ***int a*** through the weak coordination of carboxylate. After the oxidation by TBHP, Cyclic-Pd(IV) complex ***int b*** was formed. **L9** then binded with the Pd-center to form a zwitterionic species with the dissociation of carboxylic acid,[20] then to active the C(sp^2)-H bond and give a 7-membered cyclic species ***int c***. Reductive elimination of ***int c*** was expected to produce the desired product **2** and liberate ***int d***. By the association of HOAc, ***int a*** was regenerated to fulfill this catalytic cycle by releasing ^{t}BuOH and H_2O.

Scheme 4. Kinetic isotope effects experiments.



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 co-ligands, the β-C(sp^3)-H bond of carboxylate and the ortho-C(sp^2)-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 cleavge was involved at the RDS. Further studies to clearly understand the mechanism and to explore its synthetic application were underway.

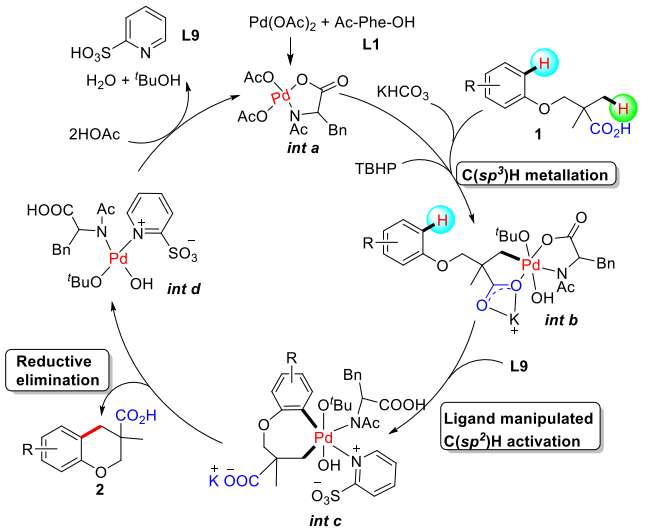


Figure 1. Plausible mechanism.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General procedural information, characterization of new compounds, details of ECD and DFT calculations, NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*zjshi@fudan.edu.cn

*liufeng@fudan.edu.cn

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Dedicated to P. H. Dixneuf for his outstanding contribution to organometallic chemistry and catalysis.

Dedicated to the 100th anniversary of Chemistry at Nankai Univerisity.

We thank the National Nature Science Foundation of China This work was supported by NSFC (21988101, 21761132027, 22071029), Science and Technology Commission of Shanghai Municipality (19XD1400800, 18JC1411300), Shanghai Municipal Education Commission (2017-01-07-00-07-E00058), Key-Area Research and Development Program of Guangdong Province (2020B010188001), and Shanghai Gaofeng & Gaoyuan Project for University Academic Program Development. We thank D. Zhai, K. Wang, C. Du, S. Xie, C. Wang, T. Liu, D. Chen, X. Lin, L. Zheng, X. Chen, H. Chen, H. Diao, W. Wang, Q. Xu, L. Ma, X. Luan, G. Yang, Z. Zhuang, H. Du, C. Bao, Y. Luo, J. Chen and Prof. B. Guan for their generous help on preparing this manuscript.

REFERENCES

(1) (a) Tipton, K. F. Enzymology of monoamine oxidase. *Cell Biochem. Funct.* **1986**, *4*, 79-87. (b) Chen, Y. T.; Bannister, T. D.; Weiser, A.; Griffin, E.; Lin, L.; Ruiz, C.; Cameron, M. D.; Schürer, S.; Duckett, D.; Schröter, T.; LoGrasso, P.; Feng, Y. Chroman-3-amides as potent Rho kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6406-6409. (c) Hoffner, B.; Elias, A. D.; Villalobos, V. M. Targeted Therapies in the Treatment of Sarcomas. *Target. Oncol.* **2018**, *13*, 557-565. (d) Elmehriki, A. A. H.; Gleason, J. L. A Spiroalkylation Method for the Stereoselective Construction of α-Quaternary Carbons and Its Application to the Total Synthesis of (R)-Puraquinonic Acid. *Org. Lett.* **2019**, *21*, 9729-9733. (e) Qiu, L.; Zhou, G.; Cao, S. Targeted inhibition of ULK1 enhances daunorubicin sensitivity in acute myeloid leukemia. *Life Sci.* **2020**, *243*, 117234.

(2) (a) Xiong, D.; Zhou, W.; Lu, Z.; Zeng, S.; Wang, J. J. A highly enantioselective access to chiral chromanones and thiochromanones via copper-catalyzed asymmetric conjugated reduction of chromones and thiochromones. *Chem. Commun.* **2017**, *53*, 6844-6847. (b) Ashley, E. R.; Sherer, E. C.; Pio, B.; Orr, R. K.; Ruck, R. T. Ruthenium-Catalyzed Dynamic Kinetic Resolution Asymmetric Transfer Hydrogenation of β-Chromanones by an Elimination-Induced Racemization Mechanism. *ACS Catal.* **2017**, *7*, 1446-1451.

(3) (a) Hodgetts, K. J. Inter- and intramolecular Mitsunobu reaction based approaches to 2-substituted chromans and chroman-4-ones. *Tetrahedron* **2005**, *61*, 6860-6870. (b) Wang, Y.; Franzen, R. Synthesis of 2-Aryl-Substituted Chromans by Intramolecular CO Bond Formation. *Synlett* **2012**, *23*, 925-929. (c) Zhang, X.; Li, Z.; Shi, Z. Palladium-catalyzed base-accelerated direct C–H bond alkenylation of phenols to synthesize coumarin derivatives. *Org. Chem. Front.* **2014**, *1*, 44-49.

(4) (a) Catellani, M.; Chiusoli, G. P.; Marzolini, G.; Rossi, E. Designing a catalytic synthesis of 4-methylcoumarin from ortho-iodophenyl 3-butenoate: Ring closure and isomerization control. *J. Organomet. Chem.* **1996**, *525*, 65-69. (b) Yamamoto, Y.; Kirai, N. Synthesis of 4-Arylcoumarins via Cu-Catalyzed Hydroarylation with Arylboronic Acids. *Org. Lett.* **2008**, *10*, 5513-5516. (c) Giguère, D.; Cloutier, P.; Roy, R. Domino Heck/Lactonization-Catalyzed Synthesis of 3-C-Linked Mannopyranosyl Coumarins. *J. Org. Chem. 2***009**, *74*, 8480-8483. (d) Valente, S.; Kirsch, G. Facile synthesis of 4-acetyl-coumarins, -thiocoumarin and -quinolin-2(1H)-one via very high α-regioselective Heck coupling on tosylates. *Tetrahedron Lett.* **2011**, *52*, 3429-3432. (e) Ferguson, J.; Zeng, F.; Alper, H. Synthesis of Coumarins via Pd-Catalyzed Oxidative Cyclocarbonylation of 2-Vinylphenols. *Org. Lett.* **2012**, *14*, 5602-5605. (f) Sasano, K.; Takaya, J.; Iwasawa, N. Palladium(II)-Catalyzed Direct Carboxylation of Alkenyl C–H Bonds with CO_2. *J. Am. Chem. Soc.* **2013**, *135*, 10954-10957.

(5) (a) Hong, L.; Wang, L.; Sun, W.; Wong, K.; Wang, R. Organocatalytic Asymmetric Friedel–Crafts Alkylation/Cyclization Cascade Reaction of 1-Naphthols and α,β-Unsaturated Aldehydes: An Enantioselective Synthesis of Chromanes and Dihydrobenzopyranes. *J. Org. Chem. 2***009**, *74*, 6881-6884. (b) Hao, X.; Lin, L.; Tan, F.; Ge, S.; Liu, X.; Feng, X. Asymmetric synthesis of chromans via the Friedel–Crafts alkylation–hemiketalization catalysed by an N,N′-dioxide scandium(iii) complex. *Org. Chem. Front.* **2017**, *4*, 1647-1650.

(6) Collin, G.; Höke, H.; Greim, H. Naphthalene and Hydronaphthalenes. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, 2003.

(7) (a) Bowman, W. R.; Storey, J. M. D. Synthesis using aromatic homolytic substitution-recent advances. *Chem. Soc. Rev.* **2007**, *36*, 1803-1822. (b) Allin, S. M.; Barton, W. R. S.; Russell Bowman, W.; Bridge Née Mann, E.; Elsegood, M. R. J.; McInally, T.; McKee, V. Bu_3SnH-mediated radical cyclisation onto azoles. *Tetrahedron* **2008**, *64*, 7745-7758. (c) Vaillard, S. E.; Schulte, B.; Studer, A. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009, pp 475-511.(d) Hayashi, R.; Cook, G. R. In *In Handbook of Cyclization Reactions,*; Ma, S., Ed.; Wiley-VCH: Weinheim, 2010, pp 1025-1054.(e) Wang, L.; Wu, F.; Chen, J.; Nicewicz, D. A.; Huang, Y. Visible-Light-Mediated [4+2] Cycloaddition of Styrenes: Synthesis of Tetralin Derivatives. *Angew. Chem., Int. Ed.* **2017**, *56*, 6896-6900.

(8) (a) Hennessy, E. J.; Buchwald, S. L. Synthesis of Substituted Oxindoles from α-Chloroacetanilides via Palladium-Catalyzed C–H Functionalization. *J. Am. Chem. Soc.* **2003**, *125*, 12084-12085. (b) Lapointe, D.; Fagnou, K. Palladium-Catalyzed Benzylation of Heterocyclic Aromatic Compounds. *Org. Lett.* **2009**, *11*, 4160-4163. (c) Beaulieu, L. B.; Roman, D. S.; Vallée, F.; Charette, A. B. Nickel(0)/NaHMDS adduct-mediated intramolecular alkylation of unactivated arenes via a homolytic aromatic substitution mechanism. *Chem. Commun.* **2012**, *48*, 8249-8251. (d) Liu, C.; Liu, D.; Zhang, W.; Zhou, L.; Lei, A. Nickel-Catalyzed Aromatic C–H Alkylation with Secondary or Tertiary Alkyl–Bromine Bonds for the Construction of Indolones. *Org. Lett.* **2013**, *15*, 6166-6169. (e) Venning, A. R. O.; Bohan, P. T.; Alexanian, E. J. Palladium-Catalyzed, Ring-Forming Aromatic C–H Alkylations with Unactivated Alkyl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 3731-3734.

(9) (a) Li, C. Cross-Dehydrogenative Coupling (CDC): Exploring C–C Bond Formations beyond Functional Group Transformations. *Acc. Chem. Res.* **2009**, *42*, 335-344. (b) Li, Y.; Li, B.; Lu, X.; Lin, S.; Shi, Z. Cross Dehydrogenative Arylation (CDA) of a Benzylic C-H Bond with Arenes by Iron Catalysis. *Angew. Chem., Int. Ed.* **2009**, *48*, 3817-3820. (c) Neufeldt, S. R.; Sanford, M. S. Controlling Site Selectivity in Palladium-Catalyzed C-H Bond Functionalization. *Acc. Chem. Res.* **2012**, *45*, 936-946. (d) Fier, P. S.; Hartwig, J. F. Selective C-H Fluorination of Pyridines and Diazines Inspired by a Classic Amination Reaction. *Science* **2013**, *342*, 956. (e) Girard, S. A.; Knauber, T.; Li, C. The Cross-Dehydrogenative Coupling of C-H Bonds: A Versatile Strategy for C-C Bond Formations. *Angew. Chem., Int. Ed.* **2014**, *53*, 74-100. (f) Mo, F.; Dong, G. Regioselective ketone α-alkylation with simple olefins via dual activation. *Science* **2014**, *345*, 68. (g) Varun, B. V.; Dhineshkumar, J.; Bettadapur, K. R.; Siddaraju, Y.; Alagiri, K.; Prabhu, K. R. Recent advancements in dehydrogenative cross coupling reactions for CC bond formation. *Tetrahedron Lett.* **2017**, *58*, 803-824. (h) Huang, C.; Kang, H.; Li, J.; Li, C. En Route to Intermolecular Cross-Dehydrogenative Coupling Reactions. *J. Org. Chem. 2***019**, *84*, 12705-12721.

(10) Correia, C. A.; Li, C. Copper-Catalyzed Cross-Dehydrogenative Coupling (CDC) of Alkynes and Benzylic C-H Bonds. *Adv. Synth. Catal.* **2010**, *352*, 1446-1450.

(11) (a) Kovacic, P.; Jones, M. B. Dehydro coupling of aromatic nuclei by catalyst-oxidant systems: poly(p-phenylene). *Chem. Rev.* **1987**, *87*, 357-379. (b) Mukhopadhyay, S.; Rothenberg, G.; Lando, G.; Agbaria, K.; Kazanci, M.; Sasson, Y. Air Oxidation of Benzene to Biphenyl – A Dual Catalytic Approach. *Adv. Synth. Catal.* **2001**, *343*, 455-459. (c) Li, R.; Jiang, L.; Lu, W. Intermolecular Cross-Coupling of Simple Arenes via C-H Activation by Tuning Concentrations of Arenes and TFA. *Organometallics* **2006**, *25*, 5973-5975. (d) Stuart, D.; Fagnou, K. The Catalytic Cross-Coupling of Unactivated Arenes. *Science (New York, N.Y.)* **2007**, *316*, 1172-1175. (e) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. C–C Bond Formation via Double C–H Functionalization: Aerobic Oxidative Coupling as a Method for Synthesizing Heterocoupled Biaryls. *Org. Lett.* **2007**, *9*, 3137-3139. (f) Stuart, D. R.; Fagnou, K. The Catalytic Cross-Coupling of Unactivated Arenes. *Science* **2007**, *316*, 1172. (g) Li, B.; Tian, S.; Fang, Z.; Shi, Z. Multiple C H Activations To Construct Biologically Active Molecules in a Process Completely Free of Organohalogen and Organometallic Components. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115-1118. (h) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. Metal-Free Oxidative Cross-Coupling of Unfunctionalized Aromatic Compounds. *J. Am. Chem. Soc.* **2009**, *131*, 1668-1669.

(12) (a) Liégault, B.; Fagnou, K. Palladium-Catalyzed Intramolecular Coupling of Arenes and Unactivated Alkanes in Air. *Organometallics* **2008**, *27*, 4841-4843. (b) Wu, X.; Zhao, Y.; Ge, H. Pyridine-enabled copper-promoted cross dehydrogenative coupling of C(sp2)–H and unactivated C(sp3)–H bonds. *Chem. Sci.* **2015**, *6*,

5978-5983. (c) Shi, J.; Wang, D.; Zhang, X.; Li, X.; Chen, Y.; Li, Y.; Shi, Z. Oxidative coupling of sp2 and sp3 carbon–hydrogen bonds to construct dihydrobenzofurans. *Nat. Commun.* **2017**, *8*, 238. (d) Tan, G.; You, J. Rhodium(III)-Catalyzed Oxidative Cross-Coupling of Unreactive C(sp3)-H Bonds with C(sp2)–H Bonds. *Org. Lett.* **2017**, *19*, 4782-4785. (e) Jiang, Y.; Deng, G.; Zhang, S.; Loh, T. Directing Group Participated Benzylic C(sp3)-H/C(sp2)-H Cross-Dehydrogenative Coupling (CDC): Synthesis of Azapolycycles. *Org. Lett.* **2018**, *20*, 652-655.

(13) (a) Yu, J.; Shi, Z. *C-H activation*; Springer, 2010; Vol. 292. (b) Baudoin, O. Transition metal-catalyzed arylation of unactivated C(sp3)-H bonds. *Chem. Soc. Rev.* **2011**, *40*, 4902-4911. (c) Li, H.; Li, B.; Shi, Z. Challenge and progress: palladium-catalyzed sp3 C-H activation. *Catal. Sci. Technol.* **2011**, *1*, 191-206. (d) Rouquet, G.; Chatani, N. Catalytic Functionalization of C(sp2)-H and C(sp3)-H Bonds by Using Bidentate Directing Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726-11743. (e) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon–Hydrogen Bonds. *Acc. Chem. Res.* **2015**, *48*, 1053-1064. (f) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. Transition metal-catalyzed C-H bond functionalizations by the use of diverse directing groups. *Org. Chem. Front.* **2015**, *2*, 1107-1295. (g) He, G.; Wang, B.; Nack, W. A.; Chen, G. Syntheses and Transformations of α-Amino Acids via Palladium-Catalyzed Auxiliary-Directed sp3 C-H Functionalization. *Acc. Chem. Res.* **2016**, *49*, 635-645. (h) Hartwig, J. F. Evolution of C–H Bond Functionalization from Methane to Methodology. *J. Am. Chem. Soc.* **2016**, *138*, 2-24. (i) Parasram, M.; Gevorgyan, V. Silicon-Tethered Strategies for C–H Functionalization Reactions. *Acc. Chem. Res.* **2017**, *50*, 2038-2053. (j) Labinger, J. A. Platinum-Catalyzed C–H Functionalization. *Chem. Rev.* **2017**, *117*, 8483-8496. (k) Baudoin, O. Ring Construction by Palladium(0)-Catalyzed C(sp3)-H Activation. *Acc. Chem. Res.* **2017**, *50*, 1114-1123. (l) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J. Palladium-Catalyzed Transformations of Alkyl C–H Bonds. *Chem. Rev.* **2017**, *117*, 8754-8786. (m) He, C.; Gaunt, M. J. Ligand-assisted palladium-catalyzed C–H alkenylation of aliphatic amines for the synthesis of functionalized pyrrolidines. *Chem. Sci.* **2017**, *8*, 3586-3592. (n) Chu, J. C. K.; Rovis, T. Complementary Strategies for Directed C(sp3)-H Functionalization: A Comparison of Transition-Metal-Catalyzed Activation, Hydrogen Atom Transfer, and Carbene/Nitrene Transfer. *Angew. Chem., Int. Ed.* **2018**, *57*, 62-101. (o) Wang, W.; Lorion, M. M.; Shah, J.; Kapdi, A. R.; Ackermann, L. Late-Stage Peptide Diversification by Position-Selective C–H Activation. *Angew. Chem., Int. Ed.* **2018**, *57*, 14700-14717. (p) Xu, Y.; Dong, G. sp3 C-H activation via exo-type directing groups. *Chem. Sci.* **2018**, *9*, 1424-1432. (q) Rej, S.; Chatani, N. Rhodium-Catalyzed C(sp2)- or C(sp3)-H Bond Functionalization Assisted by Removable Directing Groups. *Angew. Chem., Int. Ed.* **2019**, *58*, 8304-8329. (r) Chen, Z.; Rong, M.; Nie, J.; Zhu, X.; Shi, B.; Ma, J. Catalytic alkylation of unactivated C(sp3)-H bonds for C(sp3)-C(sp3) bond formation. *Chem. Soc. Rev.* **2019**, *48*, 4921-4942. (s) Roy, P.; Bour, J. R.; Kampf, J. W.; Sanford, M. S. Catalytically Relevant Intermediates in the Ni-Catalyzed C(sp2)-H and C(sp3)-H Functionalization of Aminoquinoline Substrates. *J. Am. Chem. Soc.* **2019**, *141*, 17382-17387. (t) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. Efficient catalytic addition of aromatic carbon-hydrogen bonds to olefins. *Nature* **1993**, *366*, 529-531. (u) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. A Ruthenium-Catalyzed Reaction of Aromatic Ketones with Arylboronates: A New Method for the Arylation of Aromatic Compounds via C-H Bond Cleavage. *J. Am. Chem. Soc.* **2003**, *125*, 1698-1699. (v) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. Recent advances in the transition metal-catalyzed twofold oxidative C–H bond activation strategy for C–C and C-N bond formation. *Chem. Soc. Rev.* **2011**, *40*, 5068-5083. (w) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. Towards mild metal-catalyzed C–H bond activation. *Chem. Soc. Rev.* **2011**, *40*, 4740-4761. (x) Furukawa, T.; Tobisu, M.; Chatani, N. C–H Functionalization at Sterically Congested Positions by the Platinum-Catalyzed Borylation of Arenes. *J. Am. Chem. Soc.* **2015**, *137*, 12211-12214. (y) Yamaguchi, A. D.; Chepiga, K. M.; Yamaguchi, J.; Itami, K.; Davies, H. M. L. Concise Syntheses of Dictyodendrins A and F by a Sequential C–H Functionalization Strategy. *J. Am. Chem. Soc.* **2015**, *137*, 644-647.

(14) (a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. Oxidative Cross-Coupling of N-(2'-Phenylphenyl)benzene- sulfonamides or Benzoic and Naphthoic Acids with Alkenes Using a Palladium−Copper Catalyst System under Air. *J. Org. Chem.* **1998**, *63*, 5211-5215. (b) Zhang, F.; Hong, K.; Li, T.; Park, H.; Yu, J. Functionalization of C (sp3)–H bonds using a transient directing group. *Science* **2016**, *351*, 252-256. (c) Liu, L.; Liu, Y.; Shi, B. Synthesis of amino acids and peptides with bulky side chains via ligand-enabled carboxylate-directed γ-C(sp3)-H arylation. *Chem. Sci.* **2020**, *11*, 290-294. (d) Zhuang, Z.; Yu, J. Lactonization as a general route to β-C(sp3)–H functionalization. *Nature* **2020**, *577*, 656-659. (e) Das, J.; Dolui, P.; Ali, W.; Biswas, J. P.; Chandrashekar, H. B.; Prakash, G.; Maiti, D. A direct route to six and seven membered lactones via γ-C(sp3)-H activation: a simple protocol to build molecular complexity. *Chem. Sci.* **2020**, *11*, 9697-9702.

(15) (a) Luh, T.; Hu, Z. Thorpe–Ingold effect in organosilicon chemistry. *Dalton T.* **2010**, *39*, 9185-9192. (b) O'Neill, M. J.; Riesebeck, T.; Cornella, J. Thorpe–Ingold Effect in Branch-Selective Alkylation of Unactivated Aryl Fluorides. *Angew. Chem., Int. Ed.* **2018**, *57*, 9103-9107.

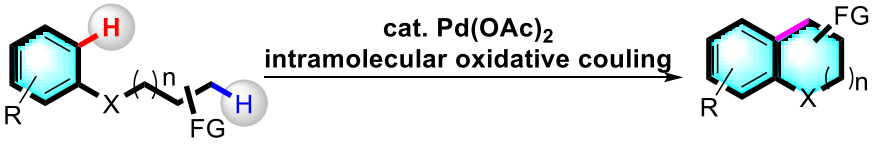
(16) (a) Muñiz, K. High-Oxidation-State Palladium Catalysis: New Reactivity for Organic Synthesis. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412-9423. (b) Wang, D.; Engle, K. M.; Shi, B.; Yu, J. Ligand-Enabled Reactivity and Selectivity in a Synthetically Versatile Aryl C-H Olefination. *Science* **2010**, *327*, 315. (c) Novák, P.; Correa, A.; Gallardo-Donaire, J.; Martin, R. Synergistic Palladium-Catalyzed C(sp3)-H Activation/C(sp3)-O Bond Formation: A Direct, Step-Economical Route to Benzolactones. *Angew. Chem., Int. Ed.* **2011**, *50*, 12236-12239. (d) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J. Ligand-enabled cross-coupling of C(sp3)–H bonds with arylboron reagents via Pd(II)/Pd(0) catalysis. *Nat. Chem.* **2014**, *6*, 146-150. (e) Chen, G.; Gong, W.; Zhuang, Z.; Andrä, M. S.; Chen, Y.; Hong, X.; Yang, Y.; Liu, T.; Houk, K. N.; Yu, J. Ligand-accelerated enantioselective methylene C(sp3)–H bond activation. *Science* **2016**, *353*, 1023. (f) Zhu, Y.; Chen, X.; Yuan, C.; Li, G.; Zhang, J.; Zhao, Y. Pd-catalysed ligand-enabled carboxylate-directed highly regioselective arylation of aliphatic acids. *Nat. Commun.* **2017**, *8*, 14904. (g) Tong, H.; Zheng, S.; Li, X.; Deng, Z.; Wang, H.; He, G.; Peng, Q.; Chen, G. Pd(0)-Catalyzed Bidentate Auxiliary Directed Enantioselective Benzylic C-H Arylation of 3-Arylpropanamides Using the BINOL Phosphoramidite Ligand. *ACS Catal.* **2018**, *8*, 11502-11512. (h) Dolui, P.; Das, J.; Chandrashekar, H. B.; Anjana, S. S.; Maiti, D. Ligand-Enabled Pd(II)-Catalyzed Iterative γ-C(sp3)-H Arylation of Free Aliphatic Acid. *Angew. Chem., Int. Ed.* **2019**, *58*, 13773-13777.

(17) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C-H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066-3072.

(18) **1a** was treated with $Pd(OAc)_2$ (1.0 eq.), Ac-Phe-OH (2.0 eq.)/ Pyridine-2-sulfonic Acid (1.0 eq.), $KHCO_3$ (1.5 eq.), in HFIP at 45 ^oC for 20 h , no desired product **2a** was observed.

(19) Wei, Y.; Yoshikai, N. Oxidative Cyclization of 2-Arylphenols to Dibenzofurans under Pd(II)/Peroxybenzoate Catalysis. *Org. Lett.* **2011**, *13*, 5504-5507.

(20) (a) Zhang, Y.; Shi, B.; Yu, J. Pd(II)-Catalyzed Olefination of Electron-Deficient Arenes Using 2,6-Dialkylpyridine Ligands. *J. Am. Chem. Soc.* **2009**, *131*, 5072-5074. (b) Chen, F.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.; Shi, B. Pd(II)-catalyzed alkoxylation of unactivated C(sp3)-H and C(sp2)-H bonds using a removable directing group: efficient synthesis of alkyl ethers. *Chem. Sci.* **2013**, *4*, 4187-4192. (c) Park, H.; Chekshin, N.; Shen, P.; Yu, J. Ligand-Enabled, Palladium-Catalyzed β-C(sp3)-H Arylation of Weinreb Amides. *ACS Catal.* **2018**, *8*, 9292-9297.



FG = Functional Group
X = O, CH_2
n = 0, 1