Letter

Ruthenium(II) Catalysis/Noncovalent Interaction Synergy for Cross-Dehydrogenative Coupling of Arene Carboxylic Acids

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Ruthenium(II) Catalysis/Noncovalent Interaction Synergy for Cross-Dehydrogenative Coupling of Arene Carboxylic Acids

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ABSTRACT: *A ruthenium catalyzed cross-dehydrogenative coupling is developed with the aid of weakly coordinating carboxylic acid group towards the dimerization of arene carboxylic acids. The protocol is operationally simple and suitable to fabricate diverse homo- as well as cross-dimerized products in high yields. Computational insights have also been unveiled to comprehend the plausible reaction mechanism. The critical innovation of the synthetic strategy hinges on the soluble basic additive DBU, which constitutes a synergy of Ru(II)-catalysis with noncovalent interaction and thus, stabilizes pivotal intermediates to promote the challenging dimerization process.*

KEYWORDS: C–H activation, Ru(II)-catalysis, noncovalent interaction, weak coordination, cross–dehydrogenative coupling, diphenic acids, DFT computation.

Demystifying powerful and efficient synthetic arsenals for practical accessibility to natural products and versatile synthetic building blocks from structurally simplified progenitors is a continuous enterprise in contemporary organic synthesis. On this ground, owing to their diverse display in organic synthesis, 2,2′-biaryl acid motifs, both in symmetrical and unsymmetrical substitution patterns, have always remained in the focus of general interest.[1,2] They are the key precursors for the synthesis of numerous

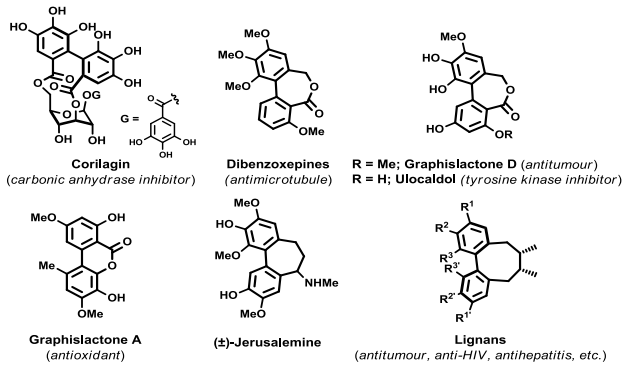
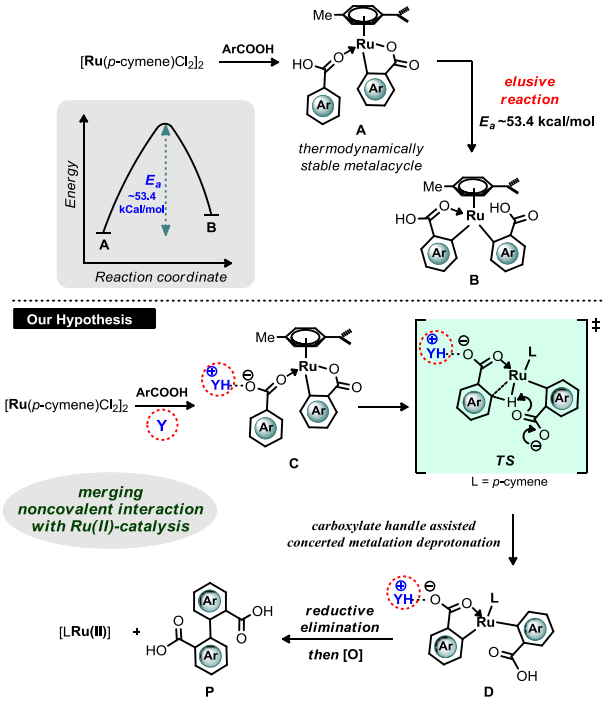


Figure 1. Representative biologically active molecules with 2,2′-biaryl acid scaffold and derivatives thereof

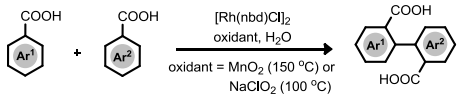
natural products and drug molecules,[2-4] high performance polymers,[5] diverse C_2-symmetric chiral ligands or auxiliaries,[6] and their sugar analogues are naturally occurring biologically active molecules that exhibit therapeutic properties (Figure 1). Despite the immense importance of this multi-faceted class of biaryl analogues, modular synthetic routes towards these scaffolds are limited. Traditionally, they have been synthesized using transition-metal promoted Ullmann-coupling strategy,[7,8] Suzuki cross-coupling method,[9] or oxidation of phenanthrene derivatives.[10,11] However, all these processes require prefunctionalized precursors and offer limited access to these molecules. Thus, a strategic development of direct synthetic route to streamline the construction of these molecular architectures would greatly enrich the synthetic chemist's repertoire. Ideally, a C–H/C–H cross-coupling of commercially available, cheap, and bench-stable benzoic acids would be the most appropriate disconnection, which can reduce the synthetic overhead for the rapid production of diverse diphenic acids. To address the aforementioned goal, we envisaged to devise a Ru(II)-catalyzed direct C–H/C–H cross-dehydrogenative coupling (CDC) of benzoic acids (Scheme 1).



Scheme 1. Hypothesis for Cross-dehydrogenative Dimerization of Benzoic Acids

Notably, in last two decades, transition-metal catalyzed cross-dehydrogenative coupling reactions of otherwise inert C–H bonds have been realized as a powerful and straightforward transformative tool for the regioselective functionalization of organic molecules since it can evade

tedious prefunctionalization processes, widen the substrate accessibility, and render easy late-stage functionalization.[12] However, major breakthroughs came, particularly in the arena of weakly coordinating common organic functional group assisted CDC reactions, under expensive iridium, rhodium, and palladium catalysis, and solution for the use of inexpensive and bench-stable ruthenium(II) catalysts is largely unanswered and mostly restricted to Heck-type olefination processes.[12-14] In fact, even after the tremendous advancement of carboxylate directed ruthenium(II) catalysis for annulation,[15a-d] olefination,[15e-i] alkylation,[15j-k] alkynylation,[15l] arylation,[16] allylation,[17] and heteroatom functionalization[18] of arenes, carboxylate directed cross-dehydrogenative coupling reaction between two arenes is still unknown under ruthenium catalysis. To the best of our knowledge, till date, the cross-dehydrogenative dimerization of benzoic acids was accomplished only under Rh-catalysis (Scheme 2).[13l-n]

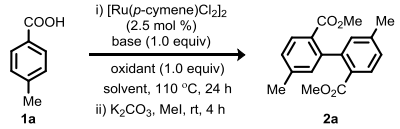


Scheme 2. Previous Reports on Rh-Catalyzed Cross-dehydrogenative Dimerization of Benzoic Acids

Considering this synthetic space, we first evaluated the mechanistic feasibility of this approach by calculating the activation energy (E_a) for the formation of alleged intermediate **B** from the ruthenacycle **A**, which necessitates a second C–H metalation step (Scheme 1). At this scenario, ruthenacycle **A** has to mislay its stable 5-membered chelation with high kinetic barrier i.e. E_a ~ 53.4 kcal/mol. Recent trends in organic chemistry have rigorously harnessed various noncovalent interactions such as ion-pair, hydrogen-bonding etc., to steer diverse organic transformations including C–H activation.[19] Thus, we hypothesized that this kinetically constrained process could be circumvented through beneficial noncovalent interactions in the transition-state (Scheme 1). It has been shown that protonated organic bases alluringly stabilize the carboxylate intermediates in several organocatalytic processes.[20] We were optimistic that a judicial choice of an organic base (**Y**) would stabilize the **TS**, illustrated in Scheme 1, favoring the transformation from **C** to **D**, which later on reductive elimination would lead to the product diphenic acid **P**.

Guided by this considerations on the merger of noncovalent interaction with Ru(II) catalysis, at the outset, we examined the oxidative dimerization of 4-toluic acid (**1a**) as a model substrate under aerial atmosphere (Table 1). Gratifyingly, the treatment of **1a** with $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), *i*Pr_2NEt base in dioxane solvent at 110 °C dispensed the desired product **2a** in 15% yield after the esterification (entry 1). Other organic bases such as DMAP, DABCO, and *N*-methyl morpholine were unable to promote this transformation (entries 2–4). The hindered amidine base DBU was documented to stabilize the proline derived enamine carboxylate intermediate with prolinate–$DBUH^+$ ion pair formation.[19a,b] Thus, we next performed the reaction using DBU as the base. To our delight, the transformation occurred smoothly with increased yield (54%, entry 5). Other organic solvents were screened, but they were found less effective than dioxane (entries 6–8). When molecular oxygen was used in lieu of air, yield was improved slightly and further examinations of different oxidants provided CuO as the best choice, delivering **2a** in 72% isolated yield (entries 9–13). The lowering of reaction temperature to 100 °C had a detrimental effect on the reaction outcome (entry 14). As anticipated, common inorganic bases such as K_2CO_3 and NaOAc remained unproductive (entries 15–16). Interestingly, in line with our hypothesis, the use of DBU congener DBN supplied 51% yield of **2a**, signifying the important role of amidine bases to promote this CDC reaction (entry 17).

Table 1. Optimization of Ru(II)-Catalyzed Dimerization of Aromatic Acids[a]

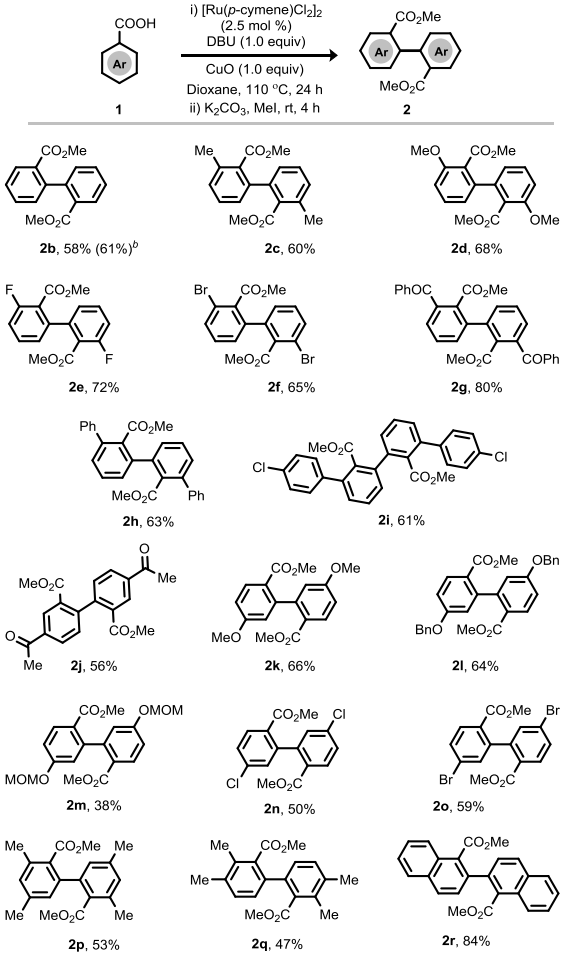


Entry	Base	Oxidant	Solvent	Yield (%)
1	*i*Pr_2NEt	air	Dioxane	15
2	DMAP	air	Dioxane	NR
3	DABCO	air	Dioxane	NR
4	*N*-methyl morpholine	air	Dioxane	NR
5	DBU	air	Dioxane	54
6	DBU	air	DMF	12
7	DBU	air	Toluene	40
8	DBU	air	$MeNO_2$	NR
9	DBU	O_2	Dioxane	59
10	**DBU**	**CuO**	**Dioxane**	**72**
11	DBU	MnO_2	Dioxane	56
12	DBU	Ag_2O	Dioxane	30
13	DBU	$Cu(OAc)_2.H_2O$	Dioxane	NR
14	DBU	CuO	Dioxane	49[b]
15	K_2CO_3	CuO	Dioxane	NR
16	NaOAc	CuO	Dioxane	NR
17	DBN	CuO	Dioxane	51

[a]Unless otherwise noted, all reactions were conducted on a 0.3 mmol scale with oxidant (1.0 equiv), base (1.0 equiv), solvent (0.4 mL) at 110 °C. Yields are those of isolated products. [b]Reaction was performed at 100 °C. DMAP: 4-dimethylaminopyridine; DABCO: 1,4-diazabicyclo[2.2.2]octane; DBU: 1,8-diazabicyclo[5.4.0] undec-7ene; DBN: 1,5-diazabicyclo[4.3.0]non-5-ene.

Having acquired the optimal conditions, we next sought to explore the scope of the reaction (Table 2). The present catalytic conditions were quite general to diverse carboxylic acids. Aromatic carboxylic acids having functional groups such as methyl, methoxy, halides, and benzoyl at the *ortho*-position were tolerated under the

Table 2. Scope of Ru(II)-Catalyzed Homo-dimerization of Benzoic Acids[a]

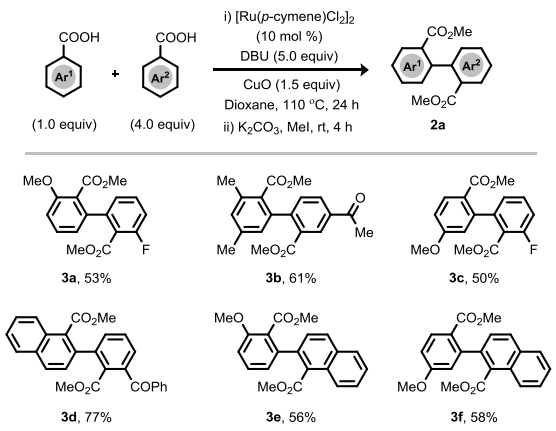


[a]All reactions were conducted on a 0.4 mmol scale with CuO (1.0 equiv), DBU (1.0 equiv), dioxane (0.4 mL) at 110 °C; esterification was performed using MeI (3.0 equiv) and K_2CO_3 (3.0 equiv). Yields of isolated ester products were provided. [b]Reaction was conducted on 1.0 mmol scale with CuO (1.0 equiv), DBU (1.0 equiv), dioxane (1.0 mL) at 110 °C, 36 h; esterification was performed using MeI (3.0 equiv) and K_2CO_3 (3.0 equiv).

reaction conditions to deliver high yields of the desired products **2b**-**g**. Biphenyl carboxylic acids were also effectively participated in this transformation to give **2h**-**i** with extended π-system. Benzoic acid bearing strongly electron withdrawing acetyl functionality in the *meta*-position was endured under the current reaction conditions to provide 56% yield of **2j**. Electron donating methoxy substituent at the *para*-position offered 66% yield of the anticipated product **2k**. Benzoic acids with common protecting groups like benzyl (Bn) and methoxymethyl (MOM) were viable substrates for this strategy (**2l**-**m**). Importantly, the catalytic conditions were able to accommodate sensitive halogen functionalities at the *para*-position, rendering good yields of the desired products (**2n**-**o**). Dimerizations of hindered dimethylbenzoic acids and 1-naphthoic acid were also achieved to prepare **2p**, **2q**, and **2r** in 53%, 47%, and 84% yields, respectively.

To adorn the synthetic versatility of the protocol further, we attempted the more challenging cross-dimerization of benzoic acids (Table 3). Employment of electron donating group substituted benzoic acids in combination with electron withdrawing group substituted benzoic acids under the optimal conditions with a change in molar ratio of the reaction partners provided synthetically useful yields of the desired cross-dimerized products (**3a**–**c**). Exposure of 1-naphthoic acid to substituted benzoic acids was also fruitful to give desired products **3d**–**f** in good yields (56-77%). It is worth noting that a suitable choice of benzoic acids is important in the cross-dimerization reaction as electronic bias plays a decisive role in product formation. It has been observed that a combination of two electron-rich benzoic acids failed to provide the cross-dimerized product under the standard reaction conditions and mostly homo-dimerized products were observed as major products.

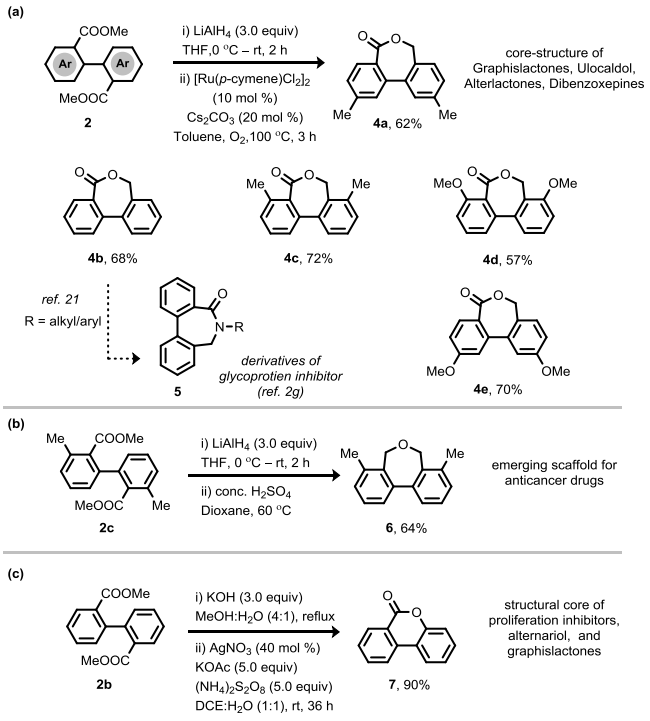
Table 3. Scope of Ru(II)-Catalyzed Cross-dimerization of Benzoic Acids[a]



[a]All reactions were conducted on a 0.2 mmol scale with CuO (1.5 equiv), DBU (5.0 equiv), dioxane (0.5 mL) at 110 °C; esterification were performed using MeI (8.0) and K_2CO_3 (4.0 equiv). Yields of isolated ester products were provided.

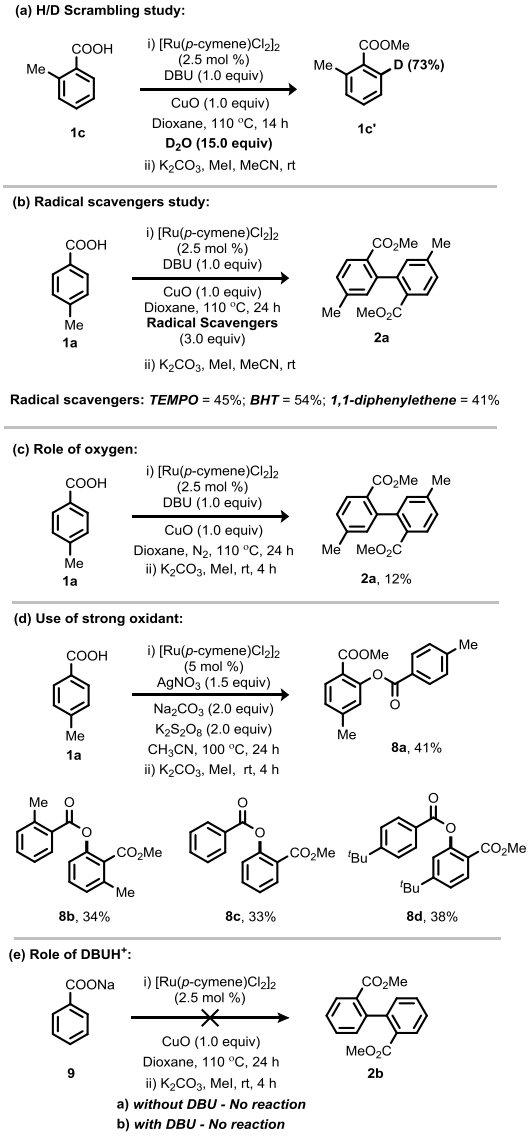
To demonstrate the synthetic potential, products were utilized in the synthesis of various biologically important biphenyl-tethered heterocycles (Scheme 3). The dimerized products **2a**-**d** and **2k** were separately reduced using $LiAlH_4$ and individual crude products were then treated with $[RuCl_2(p\text{-cymene})]_2$ catalyst under oxygen atmosphere to construct 7-membered cyclic lactones (**4a**-**e**), an abundant core found in various natural products such as isokotanin, ulocladol, and graphislactones (Scheme 3a).[2d-e,i-o] Lactone **4e** can be easily manipulated to its amide congeners following literature procedure.[21] Reduction followed by the treatment of concentrated H_2SO_4 on **2c**

generated the 7-membered cyclic ether **6** in 64% yield and such molecular frameworks are potential pharmaceutical target for anticancer drugs (Scheme 3b).[2i] Notably, in all these transformations, the compounds were purified only in the final steps. Further, we were also successful to achieve a silver(I)-mediated decarboxylative cyclization to construct biologically potent benzo[c]chromen-6-one **7** in 90% yield (Scheme 3c).[2p-s]



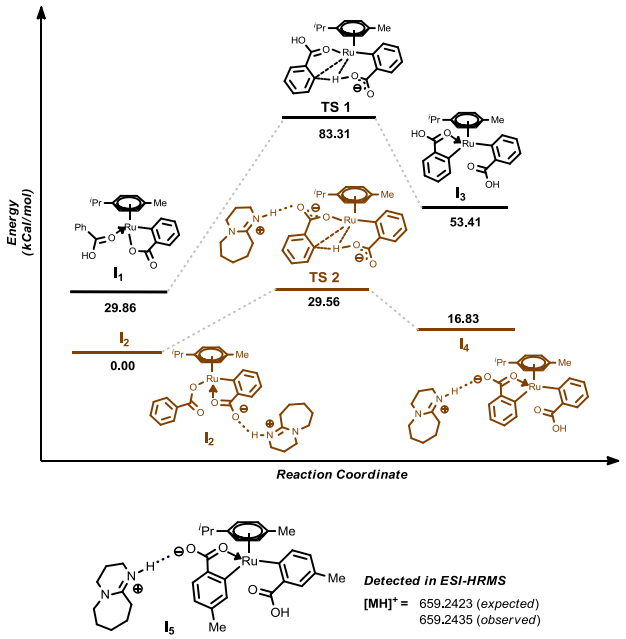
Scheme 3. Synthetic Applications of Cross-dehydrogenative Dimerization Products

To comprehend the plausible reaction mechanism, we performed the deuterium scrambling study, which revealed the reversible nature of C–H metalation (Scheme 4a). Also, significant amount of product **2a** was formed in the presence of excess amounts of radical scavengers such as TEMPO, BHT, and 1,1-diphenylethene, refuting the involvement of radical pathway in the reaction mechanism (Scheme 4b). The use of oxygen (air) was also crucial as the yield dropped significantly when the reaction was executed in inert atmosphere (Scheme 4c). To gain insights on the possibility of Ru(IV)/Ru(II)-mechanistic route, we used strong oxidants in the absence of DBU. Astonishingly, we did not observe any C–C dimerized product, while C–O dimerized product **8a-d** were formed when stoichiometric amount of $AgNO_3$ was used as oxidant along with potassium persulfate (Scheme 4d). The use of sodium benzoate (**9**) instead of benzoic acid was ineffective to construct the C–C dimerized product even in the presence of DBU (Scheme 4e). These experiments bolstered the unique role of DBU in this transformation and hint of the possible involvement of $DBUH^+$ ion.



Scheme 4. Mechanistic Studies of the Cross-dehydrogenative Dimerization of Benzoic Acids

With the objective of verifying the decisive role of DBU in this transformation, a computational study using density functional theory (DFT) has been performed to compare the energies of key intermediates and transition-states of the second C–H metalation process. As depicted in Scheme 5, we observed a stabilizing electrostatic interaction between $DBUH^+$ and intermediate ruthenium-carboxylate complexes which effectually decrease the activation energy for carbometallation by ~23.84 kCal/mol (Scheme 5).[22] The inner-sphere coordination of DBU was ruled out considering the rapid protonation in presence of equimolar benzoic acid. Further, the intermediate $\mathbf{I_5}$ was detected in ESI-HRMS analysis of the crude reaction mixture of **1a**, corroborating the computational findings and our working hypothesis (Scheme 5).



Scheme 5. Computation Insights to the Role of DBU and Detection of a Key Intermediate with ESI-HRMS Analysis of the Dimerization Reaction of 1a

In conclusion, we have developed a weak coordination assisted Ru(II)-catalyzed cross-dehydrogenative coupling of aromatic carboxylic acids. The protocol tolerated various common organic functional groups to produce good yields of the desired 2,2′-biaryl acid scaffolds. The cross-dimerization of benzoic acids has also been achieved through judicious modification of the reaction conditions. The synthetic applicability of this protocol has been showcased through the formation of biologically potent biphenyl tethered lactones, ether, and benzocoumarine. Computational studies disclosed that the basic additive DBU plays a pivotal role to promote this transformation through an electrostatic interaction with Ru(II)-carboxylate intermediates. Further applications of this Ru(II)-DBU synergy for carboxylate assisted C–H bond functionalization reaction is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

Synthetic procedures, characterization data for all compounds, copies of ^{1}H and ^{13}C NMR spectra, and computational details (PDF)

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REFERENCES

(1) (a) Nelson, T. D.; Crouch, R. D. Cu, Ni, and Pd Mediated Homocoupling Reactions in Biaryl Syntheses: The Ullmann Reaction. *Org. React.* **2004**, 265–555. (b) Salem, M. A.; Helel, M. H.; Ammar, Y. A.; El-Gaby, M. S. A.; Thabet, H. K.; Gouda, M. A. Diphenic Acid Derivatives: Synthesis, Reactions, and Applications. *Synth. Commun.* **2017**, *47*, 935-960.

(2) (a) Nelson, T. D.; Meyers, A. I. A Rapid Total Synthesis of an Ellagitannin. *J. Org. Chem.* **1994**, *59*, 2577–2580. (b) Quideau, S.; Feldman, K. S. Ellagitannin Chemistry. *Chem. Rev.* **1996**, *96*, 475–504. (c) Bringmann, G.; Hinrichs, J.; Pabst, T.; Henschel, P.; Peters, K.; Peters, E.-M. From Dynamic to Non-Dynamic Kinetic Resolution of Lactone-Bridged Biaryls: Synthesis of Mastigophorene B. *Synthesis* **2001**, *2001*, 155–167. (d) Bringmann, G.; Hinrichs, J.; Henschel, P.; Kraus, J.; Peters, K.; Peters, E.-M. Atropo-Enantioselective Synthesis of the Natural Bicoumarin (+)-Isokotanin A via a Configurationally Stable Biaryl Lactone. *European J. Org. Chem.* **2002**, 1096–1106. (e) Wu, G.; Guo, H. F.; Gao, K.; Liu, Y. N.; Bastow, K. F.; Morris-Natschke, S. L.; Lee, K. H.; Xie, L. Synthesis of Unsymmetrical Biphenyls as Potent Cytotoxic Agents. *Bioorganic Med. Chem. Lett.* **2008**, *18*, 5272–5276. (f) Song, C.; Zhao, P.; Hu, Z.; Shi, S.; Cui, Y.; Chang, J. An Improved Method for the Synthesis of γ-DDB. *Bioorganic Med. Chem. Lett.* **2010**, *20*, 2297–2298. (g) Gu, X.; Ren, Z.; Tang, X.; Peng, H.; Zhao, Q.; Lai, Y.; Peng, S.; Zhang, Y. Synthesis and Biological Evaluation of Novel Bifendate Derivatives Bearing 6,7-Dihydro-dibenzo[*c*,*e*]azepine Scaffold as Potent P-Glycoprotein Inhibitors. *Eur. J. Med. Chem.* **2012**, *51*, 137–144. (h) Gu, X.; Ren, Z.; Tang, X.; Peng, H.; Ma, Y.; Lai, Y.; Peng, S.; Zhang, Y. Synthesis and Biological Evaluation of Bifendate–Chalcone Hybrids as a New Class of Potential P-Glycoprotein Inhibitors. *Bioorganic Med. Chem.* **2012**, *20*, 2540–2548. i) Joncour, A.; Liu, J. M.; Décor, A.; Thoret, S.; Wdzieczak-Bakala, J.; Bignon, J.; Baudoin, O. Synthesis of Anti-Microtubule Biaryls and Preliminary Evaluation as Vascular-Disrupting Agents. *ChemMedChem* **2008**, *3*, 1731–1739. j) Abe, H.; Nishioka, K.; Takeda, S.; Arai, M.; Takeuchi, Y.; Harayama, T. Synthesis of Graphislactones A-D through a Palladium-Mediated Biaryl Coupling Reaction of Phenyl Benzoate Derivatives. *Tetrahedron Lett.* **2005**, *46*, 3197 – 3200. k) Altemçller, M.; Gehring, T.; Cudaj, J.; Podlech, J.; Goesmann, H.; Feldmann, C.; Rothenberger, A. Total Synthesis of Graphislactones A, C, D, and H, of Ulocladol, and of the Originally Proposed and Revised Structures of Graphislactones E and F. *Eur. J. Org. Chem.* **2009**, 2130 – 2140. l) Aly, A. H.; Edrada-Ebel, R.; Indriani, I. D.; Wray, V.; Mueller, W. E. G.; Totzke, F.; Zirrgiebel, U.; Schaechtele, C.; Kubbutat, M. H. G.; Lin, W. H.; Proksch, P.; Ebel, R. Cytotoxic Metabolites from the Fungal Endophyte Alternaria sp. and Their Subsequent Detection in Its Host Plant Polygonum Senegalense. *J. Nat. Prod.* **2008**, *71*, 972 – 980. m) Höller, U.; König, G.; Wright, A. D. A New Tyrosine Kinase Inhibitor from a Marine Isolate of Ulocladium Botrytis and New Metabolites from the Marine Fungi Asteromyces Cruciatus and Varicosporina Ramulosa. *Eur. J. Org. Chem.* **1999**, 2949 – 2955. n) Tanahashi, T.; Takenaka, Y.; Nagakura, N.; Hamada, N. 6H-Dibenzo[b,d]pyran-6-one Derivatives from the Cultured Lichen Mycobionts of Graphis spp. and Their Biosynthetic Origin. *Phytochemistry* **2003**, *62*, 71 – 75. o) Koch, K.; Podlech, J.; Pfeiffer, E.; Metzler, M. Total Synthesis of Alternariol. *J. Org. Chem.* **2005**, *70*, 3275–3276. p) Schmidt, J. M.; Tremblay, G. B.; Pagé, M.; Mer-

cure, J.; Feher, M.; Dunn-Dufault, R.; Peter, M. G.; Redden, P. R. Synthesis and Evaluation of a Novel Nonsteroidal-Specific Endothelial Cell Proliferation Inhibitor. *J. Med. Chem.* **2003**, *46*, 1289–1292. q) Demuner, A. J.; Barbosa, L. C. A.; Miranda, A. C. M.; Geraldo, G. C.; Da Silva, C. M.; Giberti, S.; Bertazzini, M.; Forlani, G. The Fungal Phytotoxin Alternariol 9-Methyl Ether and Some of Its Synthetic Analogues Inhibit the Photosynthetic Electron Transport Chain. *J. Nat. Prod.* **2013**, *76*, 2234–2245.

(3) a) Jurd, L. Plant Polyphenols. III. The Isolation of a New Ellagitannin from the Pellicle of the Walnut. *J. Am. Chem. Soc*. **1958**, *80*, 2249–2252. b) Nelson, T. D.; Meyers, A. I. A Rapid Total Synthesis of an Ellagitannin. *J. Org. Chem*. **1994**, *59*, 2577–2580. c) Chen, D.-F.; Zhang, S.-X.; Xie, L.; Xie, J.-X.; Chen, K.; Kashiwada, Y.; Zhou, B.- N.; Wang, P.; Cosentino, L. M.; Lee, K.-H. Anti-aids Agents—XXVI. Structure-activity Correlations of Gomisin-G-Related Anti-HIV Lignans from *Kadsura Interior* and of Related Synthetic Analogues. *Bioorg. Med. Chem.* **1997**, *5*, 1715–1723.

(4) a) Liu, Y.; Zhang, D.; Zou, D.; Wang, Y.; Duan, C.; Jia, L.; Xie, P.; Feng, F.; Wang, F.; Zhang, X. X.; Zhang, Q. Development and In Vitro Characterizations of Bifendate Nanosuspensions. *J. Biomed. Nanotechnol.* **2011**, *7*, 621–631. b) Jin, J.; Sun, H.; Wei, H.; Liu, G. The Anti-hepatitis Drug DDB Chemosensitizes Multidrug Resistant Cancer Cells *in vitro* and *in vivo* by Inhibiting P-gp and Enhancing Apoptosis. *Invest. New Drugs* **2007**, *25*, 95–105.

(5) a) Ghosh, M. K.; Mittal, K. L. In *Polyimides Fundamentals and Applications*, Marcel Dekker, New York, 1996. b) Sakayori, K.; Shibasaki, Y.; Ueda, M. Synthesis and Properties of Poly(amic acid)s and Polyimides Based on 2,2′,6,6′-Biphenyltetracarboxylic Dianhydride. *J. Polym. Sci. Part A* **2006**, *44*, 6385 – 6393.

(6) a) Andrus, M. B.; Asgari, D.; Sclafani, J. A. Efficient Synthesis of 1,1'-Binaphthyl and 2,2'-Bi-*o*-tolyl-2,2'-bis(oxazoline)s and Preliminary Use for the Catalytic Asymmetric Allylic Oxidation of Cyclohexene. *J. Am. Chem. Soc.* **1997**, *62*, 9365–9368. b) Uozumi, Y.; Kato, K.; Hayashi, T. Catalytic Asymmetric Wacker-Type Cyclization. *J. Am. Chem. Soc.* **1997**, *119*, 5063–5064. c) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.- W.; Zheng, J.-H.; Cheung, K.-K. Design and Synthesis of Chiral Ketones for Catalytic Asymmetric Epoxidation of Unfunctionalized Olefins. *J. Am. Chem. Soc.* **1998**, *120*, 5943–5952.

(7) a) Ranu, B. C.; Dutta, P.; Sarkar, A. Indium Promoted Reductive Homocoupling of Alkyl and Aryl Halides. *Tetrahedron Lett*. **1998**, *39*, 9557 – 9558. b) Lin, G.-Q.; Hong, R. A New Reagent System for Modified Ullmann-Type Coupling Reactions: $NiCl_2(PPh_3)_2/PPh_3$/Zn/NaH/Toluene. *J. Org. Chem.* **2001**, *66*, 2877 – 2880. c) Saphier, M.; Masarwa, A.; Cohen, H.; Meyerstein, D. Copper(I) as a Homogeneous Catalyst for the Ullmann Reaction in Aqueous Solutions – The Transformation of 2-Bromobenzoate into Salicylate. *Eur. J. Inorg. Chem*. **2002**, 1226 – 1234. d) Rusonik, I.; Cohe, H.; Meyerstein, D. Cu(I)(2,5,8,11-Tetramethyl-2,5,8,11-tetraazadodecane)$^+$ as a Catalyst for Ullmann's Reaction. *Dalton Trans.* **2003**, 2024–2028. e) Chang, J.; Guo, X.; Cheng, S.; Guo, R.; Chen, R.; Zhao, K. Efficient Synthesis of γ-DDB. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 2131 – 2136. f) Chang, Y. M.; Lee, S. H.; Cho, M. Y.; Yoo, B. W.; Rhee, H. J.; Lee, S. H. Homocoupling of Aryl Iodides and Bromides Using a Palladium/Indium Bimetallic System. *Synth. Commun*. **2005**, *35*, 1851–1857.

(8) a) Montoya-Pelaez, P. J.; Uh, Y.-S.; Lata, C.; Thompson, M. P.; Lemieux, R. P.; Crudden, C. M. The Synthesis and Resolution of 2,2′-, 4,4′-, and 6,6′-Substituted Chiral Biphenyl Derivatives for Application in the Preparation of Chiral Materials. *J. Org. Chem*. **2006**, *71*, 5921 – 5929. b) Vonlanthen, D.; Rotzler, J.; Neuburger, M.; Mayor, M. Synthesis of Rotationally Restricted and Modular Biphenyl Building Blocks. *Eur. J. Org. Chem*. **2010**, 120 – 133.

(9) Tao, B.; Goel, S. C.; Singh, J.; Boykin, D. W. A Practical Preparation of 2-Carboxyphenylboronic Acid and Its Application for the Preparation of Biaryl-2-carboxylic Acids using Suzuki Coupling Reactions. *Synthesis* **2002**, 1043 – 1046.

(10) a) Adam, W.; Herrmann, W. A.; Lin, J.; Saha-Moller, C. R.; Fischer, R. W.; Correia, J. D. G. Homogeneous Catalytic Oxidation of Arenes and a New Synthesis of Vitamin K_3. *Angew. Chem. Int. Ed.* **1994**, *33*, 2475–2477. b) Samanta, S.; Adak, L.; Jana, R.; Mostafa, G.; Tuononen, H. M.; Ranu, B. C.; Goswami, S. Oxidative ortho-C-N Fusion of Aniline by OsO_4. Isolation, Characterization of Oxo-Amido Osmium(VI) Complexes, and Their Catalytic Activities for Oxidative C–C Bond Cleavage of Unsaturated Hydrocarbons. *Inorg. Chem*. **2008**, *47*, 11062–11070.

(11) a) Bischoff, F.; Adkins, H. The Condensation of Diphenic Anhydride with Resorcinol. *J. Am. Chem. Soc.* **1923**, *45*, 1030–1033. b) ten Brink, G.-J.; Vis, J.-M.; Arends, I. W. C. E.; Sheldon, R. A. Selenium-Catalyzed Oxidations with Aqueous Hydrogen Peroxide. 2. Baeyer–Villiger Reactions in Homogeneous Solution. *J. Org. Chem*. **2001**, *66*, 2429 – 2433. c) Kang, S.; Lee, S.; Jeon, M.; Kim, S. M.; Kim, Y. S.; Han, H.; Yang, J. W. In situ Generation of Hydroperoxide by Oxidation of Benzhydrols to Benzophenones Using Sodium Hydride under Oxygen Atmosphere: Use for the Oxidative Cleavage of Cyclic 1,2-Diketones to Dicarboxylic Acids. *Tetrahedron Lett*. **2013**, *54*, 373–376. d) Zhang, D.-L.; Zhou, L.-Y.; Quan, J.-M.; Zhang, W.; Gu, L.-Q.; Huang, Z.-S.; An, L.-K. Oxygen Insertion of *o*-Quinone under Catalytic Hydrogenation Conditions. *Org. Lett.* **2013**, *15*, 1162–1165.

(12) Selective reviews on cross-dehydrogenative coupling- a) Li, C. J. Cross-Dehydrogenative Coupling (CDC): Exploring C–C Bond Formations beyond Functional Group Transformations. *Acc. Chem. Res.* **2009**, *42*, 335–344. b) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon–Carbon Bonds by Oxidizing Two Carbon–Hydrogen Bonds. *Chem. Rev.* **2011**, *111*, 1215–1292. c) Yang, Y.; Lan, J.; You, J. Oxidative C–H/C–H Coupling Reactions between Two (Hetero)arenes. *Chem. Rev.* **2017**, *117*, 8787–8863. For reviews on weak coordination assisted C-H activation- d) Drapeau, M. P.; Gooßen, L. J. Carboxylic Acids as Directing Groups for C–H Bond Functionalization. *Chem. Eur. J.* **2016**, *22*, 18654–18677. e) Ackermann, L. Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C–H/Het–H Bond Functionalizations. *Acc. Chem. Res.* **2014**, *47*, 281–295. f) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. Weakly Coordinating Directing Groups for Ruthenium(II)-Catalyzed C–H Activation. *Adv. Synth. Catal.* **2014**, *356*, 1461–1479.

(13) Selected publications on Ir-Catalyzed CDC- a) Itoh, M.; Hirano, K.; Satoh, T.; Shibata, Y.; Tanaka, K.; Miura, M. Rhodium- and Iridium-Catalyzed Dehydrogenative Cyclization through Double C–H Bond Cleavages to Produce Fluorene Derivatives. *J. Org. Chem.* **2013**, *78*, 1365–1370. b) Suzuki, C.; Hirano, K.; Satoh, T.; Miura, M. Direct Synthesis of N–H Carbazoles via Iridium(III)-Catalyzed Intramolecular C–H Amination. *Org. Lett.* **2015**, *17*, 1597–1600. c) Tan, G.; You, Q.; Lan, J.; You, J. Iridium-Catalyzed Annulation Reactions of Thiophenes with Carboxylic Acids: Direct Evidence for a Heck-type Pathway. *Angew. Chem. Int. Ed.* **2018**, *57*, 6309–6313. Selected publications on Rh-Catalyzed CDC- d) Kuhl, N.; Hopkinson, M. N.; Glorius, F. Selective Rhodium(III)-Catalyzed Cross-Dehydrogenative Coupling of Furan and Thiophene Derivatives. *Angew. Chem. Int. Ed.* **2012**, *51*, 8230–8234. f) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. [$Rh^{III}Cp^*$]-Catalyzed Dehydrogenative Aryl-Aryl Bond Formation. *Angew. Chem. Int. Ed.* **2012**, *51*, 2247–2251. g) Qin, X.; Liu, H.; Qin, D.; Wu, Q.; You, J.; Zhao, D.; Guo, Q.; Huang, X.; Lan, J. Chelation-Assisted Rh(III)-Catalyzed C2-Selective Oxidative C–H/C–H Cross-Coupling of Indoles/Pyrroles with Heteroarenes. *Chem. Sci.* **2013**, *4*, 1964–1969. h) Deng, H.; Li, H.; Wang, L. ortho-Heteroarylation of Azobenzenes by Rh-Catalyzed Cross-Dehydrogenative Coupling: An Approach to Conjugated Biaryls. *Org. Lett.* **2016**, *18*, 3110–3113. i) He, S.; Tan, G.; Luo, A.; You, J. Rhodium-Catalyzed Oxidative C–H/C–H Cross-Coupling of Aniline with Heteroarene: N-Nitroso Group Enabled Mild Conditions. *Chem. Commun.* **2018**, *2*, 7794–7797. j) Shi, Y.; Zhang, L.; Lan, J.; Zhang, M.; Zhou, F.; Wei, W.; You, J. Oxidative C–H/C–H Cross-Coupling Reactions between N-Acylanilines and Benzamides Enabled by a Cp*-Free $RhCl_3$/TFACatalytic System. *Angew. Chem. Int. Ed.* **2018**, *57*, 9108–

9112. k) Zhang, X. S.; Zhang, Y. F.; Li, Z. W.; Luo, F. X.; Shi, Z. J. Synthesis of Dibenzo[c,e]oxepin-5(7H)-ones from Benzyl Thioethers and Carboxylic Acids: Rhodium-Catalyzed Double C–H Activation Controlled by Different Directing Groups. *Angew. Chem. Int. Ed.* **2015**, *54*, 5478–5482. l) Gong, H.; Zeng, H.; Zhou, F.; Li, C. J. Rhodium(I)-Catalyzed Regiospecific Dimerization of Aromatic Acids: Two Direct C–H Bond Activations in Water. *Angew. Chem. Int. Ed.* **2015**, *54*, 5718–5721. m) Zhang, H.; Deng, G. J.; Li, S.; Li, C. J.; Gong, H. Non-symmetrical Diarylcarboxylic Acids via Rhodium(I)-Catalyzed Regiospecific Cross- Dehydrogenation Coupling of Aromatic Acids: Twofold Direct C–H Bond Activations in Water. *RSC Adv.* **2016**, *6*, 91617–91620. n) Liu, Y.; Zhu, Y.; Li, C. J. Mild and Highly Regioselective Synthesis of Biaryl Acids via Rh (I)-Catalyzed Cross-Dehydrogenative Coupling of Benzoic Acids Using Sodium Chlorite as Oxidant. *Front. Chem. Sci. Eng.* **2018**, *12*, 3–8. Selected publications on Pd-Catalyzed CDC- o) Malakar, C. C.; Schmidt, D.; Conrad, J.; Beifuss, U. Double C-H Activation: The Palladium-Catalyzed Direct C-Arylation of Xanthines with Arenes. *Org. Lett.* **2011**, *13*, 1378–1381. p) Gong, X.; Song, G.; Zhang, H.; Li, X. Palladium-Catalyzed Oxidative Cross-Coupling between Pyridine N-Oxides and Indoles. *Org. Lett.* **2011**, *13*, 1766–1769. q) Li, H.; Liu, J.; Sun, C. L.; Li, B. J.; Shi, Z. J. Palladium-Catalyzed Cross-Coupling of Polyfluoroarenes with Simple Arenes. *Org. Lett.* **2011**, *13*, 276–279. r) He, C. Y.; Min, Q. Q.; Zhang, X. Palladium-Catalyzed Aerobic Dehydrogenative Cross-Coupling of Polyfluoroarenes with Thiophenes: Facile Access to Polyfluoroarene–Thiophene Structure. *Organometallics* **2012**, *31*, 1335–1340. s) Jiao, L. Y.; Smirnov, P.; Oestreich, M. Exceptionally Mild Palladium(II)-Catalyzed Dehydrogenative C–H/C–H Arylation of Indolines at the C-7 Position under Air. *Org. Lett.* **2014**, *16*, 6020–6023. t) Yamada, S.; Murakami, K.; Itami, K. Regiodivergent Cross-Dehydrogenative Coupling of Pyridines and Benzoxazoles: Discovery of Organic Halides as Regio-Switching Oxidants. *Org. Lett.* **2016**, *18*, 2415–2418. u) Pu, F.; Zhang, L.-Y.; Liu, Z.-W.; Shi, X.-Y. Palladium (II)-Catalyzed Decarboxylative Cross-Dehydrogenative Coupling: Direct Synthesis of meta-Substituted Biaryls from Aromatic Acids. *Adv. Synth. Catal.* **2018**, *360*, 1–7. v) Pintori, D. G.; Greaney, M. F. Oxidative C–H Homodimerization of Phenylacetamides *Org. Lett.* **2011**, *13*, 5713–5715.

(14) Publications on Ru-catalyzed CDC- a) Deng, G.; Zhao, L.; Li, C. J. Ruthenium-Catalyzed Oxidative Cross-Coupling of Chelating Arenes and Cycloalkanes. *Angew. Chem. Int. Ed.* **2008**, *47*, 6278–6282. b) Guo, X.; Deng, G.; Li, C. J. Ruthenium-Catalyzed Oxidative Homo-Coupling of 2-Arylpyridines. *Adv. Synth. Catal.* **2009**, *351*, 2071–2074. c) Zhang, L.; Zhu, L.; Zhang, Y.; Yang, Y.; Wu, Y.; Ma, W.; Lan, Y.; You, J. Experimental and Theoretical Studies on Ru(II)-Catalyzed Oxidative C–H/C–H Coupling of Phenols with Aromatic Amides Using Air as Oxidant: Scope, Synthetic Applications and Mechanistic Insights. *ACS Catal.* **2018**, *8*, 8324 – 8335.

(15) Selected publications on Ru-catalyzed functionalization of benzoic acid- annulation- a) Ackermann, L.; Pospech, J. Ruthenium-Catalyzed Oxidative C–H Bond Alkenylations in Water: Expedient Synthesis of Annulated Lactones. *Org. Lett.* **2011**, *13*, 4153–4155. b) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. Versatile Synthesis of Isocoumarins and α-Pyrones by Ruthenium-Catalyzed Oxidative C–H/O–H Bond Cleavages. *Org. Lett.* **2012**, *14*, 930–933. c) Mandal, A.; Dana, S.; Chowdhury, D.; Baidya, M. Ru^{II}-Catalyzed Annulative Coupling of Benzoic Acids with Vinyl Sulfone via Weak Carboxylate-Assisted C–H Bond Activation. *Asian J. Org. Chem.* **2018**, *7*, 1302–1306. d) Miura, H.; Terajima, S.; Shishido, T. Carboxylate-Directed Addition of Aromatic C–H Bond to Aromatic Aldehydes under Ruthenium Catalysis. *ACS Catal.* **2018**, *8*, 6246–6254. olefination- e) Zhang, J.; Shrestha, R.; Hartwig, J. F.; Zhao, P. A Decarboxylative Approach for Regioselective Hydroarylation of Alkynes. *Nat. Chem.* **2016**, *8*, 2–9. f) Huang, L.; Biafora, A.; Zhang, G.; Bragoni, V.; Gooßen, L. J. Regioselective C–H Hydroarylation of Internal Alkynes with Arenecarboxylates: Carboxylates as Deciduous Directing Groups. *Angew. Chem. Int. Ed.* **2016**, *55*, 6933–6937. g) Biafora, A.; Khan, B. A.; Bahri, J.; Hewer, J. M.; Goossen, L. J. Doubly Regioselective C–H Hydroarylation of Unsymmetrical Alkynes Using Carboxylates as Deciduous Directing Groups. *Org. Lett.* **2017**, *19*, 1232–1235. h) Kumar, N. Y. P.; Bechtoldt, A.; Raghuvanshi, K.; Ackermann, L. Ruthenium(II)-Catalyzed Decarboxylative C–H Activation: Versatile Routes to *meta*-Alkenylated Arenes. *Angew. Chem. Int. Ed.* **2016**, *55*, 6929–6932. i) Dana, S.; Mandal, A.; Sahoo, H.; Mallik, S.; Grandhi, G. S.; Baidya, M. Ru(II)-Catalyzed Oxidative Heck-Type Olefination of Aromatic Carboxylic Acids with Styrenes through Carboxylate-Assisted C–H Bond Activation. *Org. Lett.* **2018**, *20*, 716–719. alkylation- j) Mandal, A.; Sahoo, H.; Dana, S.; Baidya, M. Ruthenium(II)-Catalyzed Hydroarylation of Maleimides Using Carboxylic Acids as a Traceless Directing Group. *Org. Lett.* **2017**, *19*, 4138–4141. k) Kumar, N. Y. P.; Rogge, T.; Yetra, S. R.; Bechtoldt, A.; Clot, E.; Ackermann, L. Mild Decarboxylative C–H Alkylation: Computational Insights for Solvent-Robust Ruthenium(II) Domino Manifold. *Chem. - A Eur. J.* **2017**, *23*, 17449–17453. alkynylation- l) Mei, R.; Zhang, S. K.; Ackermann, L. Ruthenium(II)-Catalyzed C–H Alkynylation of Weakly Coordinating Benzoic Acids. *Org. Lett.* **2017**, *19*, 3171–3174.

(16) For carboxylate directed ruthenium catalysed arylation- a) Mei, R.; Zhu, C.; Ackermann, L. Ruthenium(II)-Catalyzed C–H Functionalizations on Benzoic Acids with Aryl, Alkenyl, and Alkynyl Halides by Weak-O-Coordination. *Chem. Commun.* **2016**, *52*, 13171–13174. b) Biafora, A.; Krause, T.; Hackenberger, D.; Belitz, F.; Goossen, L. J. ortho-C–H Arylation of Benzoic Acids with Aryl Bromides and Chlorides Catalyzed by Ruthenium. *Angew. Chem. Int. Ed.* **2016**, *55*, 14752–14755. c) Huang, L.; Weix, D. J. Ruthenium-Catalyzed C–H Arylation of Diverse Aryl Carboxylic Acids with Aryl and Heteroaryl Halides. *Org. Lett.* **2016**, *18*, 5432–5435. d) Simonetti, M.; Cannas, D. M.; Panigrahi, A.; Kujawa, S.; Kryjewski, M.; Xie, P.; Larrosa, I. Ruthenium-Catalyzed C–H Arylation of Benzoic Acids and Indole Carboxylic Acids with Aryl Halides. *Chem. - A Eur. J.* **2017**, *23*, 549–553. e) Simonetti, M.; Cannas, D. M.; Just-Baringo, X.; Vitorica-Yrezabal, I. J.; Larrosa, I. Cyclometallated Ruthenium Catalyst Enables Late-Stage Directed Arylation of Pharmaceuticals. *Nat. Chem.* **2018**, *10*, 724–731.

(17) For carboxylate directed ruthenium catalysed allylation- a) Trita, A. S.; Biafora, A.; Drapeau, M. P.; Weber, P.; Gooßen, L. J. Regiospecific ortho-C–H Allylation of Benzoic Acids. *Angew. Chem. Int. Ed.* **2018**, 1–6. b) Hu, X.-Q.; Hu, Z.; Trita, A. S.; Zhang, G.; Gooßen, L. J. Carboxylate-Directed C–H Allylation with Allyl Alcohols or Ethers. *Chem. Sci.* **2018**, *9*, 5289–5294. c) Hu, X.-Q.; Hu, Z.; Zhang, G.; Sivendran, N.; Gooßen, L. J. Catalytic C–N and C–H Bond Activation: ortho-Allylation of Benzoic Acids with Allyl Amines, *Org. Lett.* **2018**, *20*, 4337–4340.

(18) For carboxylate directed ruthenium catalysed heteroatom functionalization- Mandal, A.; Dana, S.; Sahoo, H.; Grandhi, G. S.; Baidya, M. Ruthenium(II)-Catalyzed ortho-C–H Chalcogenation of Benzoic Acids via Weak O-Coordination: Synthesis of Chalcogenoxanthones. *Org. Lett.* **2017**, *19*, 2430–2433.

(19) a) Breslow, R.; Zhang, X.; Huang, Y. Selective Catalytic Hydroxylation of a Steroid by an Artificial Cytochrome P-450 Enzyme. *J. Am. Chem. Soc.* **1997**, *119*, 4535–4536. b) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. Molecular Recognition in the Selective Oxygenation of Saturated C–H Bonds by a Dimanganese Catalyst. *Science* **2006**, *312*, 1941–1943. c) Leung, D. H.; Bergman, R. G.; Raymond, K. N. Scope and Mechanism of the C–H Bond Activation Reactivity within a Supramolecular Host by an Iridium Guest: A Stepwise Ion Pair Guest Dissociation Mechanism. *J. Am. Chem. Soc.* **2006**, *128*, 9781–9797. d) Das, S.; Brudvig, G. W.; Crabtree, R. H. High Turnover Remote Catalytic Oxygenation of Alkyl Groups: How Steric Exclusion of Unbound Substrate Contributes to High Molecular Recognition Selectivity. *J. Am. Chem. Soc.* **2008**, *130*, 1628–1637. e) Roosen, P. C.; Kallepalli, V. A.; Chattopadhyay, B.; Singleton, D. A.; Maleczka, R. E.; Smith, M. R. Outer-Sphere Direction in Iridium C–H Borylation. *J. Am. Chem. Soc.* **2012**, *134*, 11350–11353. f) Preshlock, S. M.; Plattner, D. L.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E.; Smith, M. R. A Trace-

less Directing Group for C–H Borylation. *Angew. Chem. Int. Ed.* **2013**, *52*, 12915–12919. g) Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. A meta-Selective C–H Borylation Directed by a Secondary Interaction between Ligand and Substrate. *Nat. Chem.* **2015**, *7*, 712–717. h) Davis, H. J.; Mihai, M. T.; Phipps, R. J. Ion Pair-Directed Regiocontrol in Transition-Metal Catalysis: A Meta-Selective C-H Borylation of Aromatic Quaternary Ammonium Salts. *J. Am. Chem. Soc.* **2016**, *138*, 12759–12762. i) Davis, H. J.; Genov, G. R.; Phipps, R. J. meta-Selective C–H Borylation of Benzylamine-, Phenethylamine-, and Phenylpropylamine-Derived Amides Enabled by a Single Anionic Ligand. *Angew. Chem. Int. Ed.* **2017**, *56*, 13351–13355. j) Chattopadhyay, B.; Dannatt, J. E.; Andujar-De Sanctis, I. L.; Gore, K. A.; Maleczka, R. E.; Singleton, D. A.; Smith, M. R. Ir-Catalyzed ortho-Borylation of Phenols Directed by Substrate-Ligand Electrostatic Interactions: A Combined Experimental/in Silico Strategy for Optimizing Weak Interactions. *J. Am. Chem. Soc.* **2017**, *139*, 7864–7871.

(20) a) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. Stabilization of Proline Enamine Carboxylates by Amine Bases. *Chem. - A Eur. J.* **2012**, *18*, 3362–3370. b) Tian, C. K.; Fu, A. P.; Zhao, C. Y.; Tian, F. H.; Duan, Y. B.; Wang, Z. H. Theoretical Investigation on the Role of Amine Bases in Stabilizing the Key Intermediate of Proline Enamine Carboxylate in Proline-Catalyzed Asymmetric Reactions. *Adv. Mater. Res.* **2014**, *998–999*, 124–127. c) Kennedy, C. R.; Guidera, J. A.; Jacobsen, E. N. Synergistic Ion-Binding Catalysis Demonstrated via an Enantioselective, Catalytic [2,3]-Wittig Rearrangement. *ACS Cent. Sci.* **2016**, *2*, 416–423.

(21) Roehrkasten, R.; Kreher, R. P. N-Heterocycles with a 2-Azaallyl System. 5. 7-Methoxy- and 7-Alkylthio-5H-dibenz[c,e]azepinium Salts: 7-Membered N-Heterocycles with an Integrated 2-Azaallyl System. Chem.-Ztg. **1991**, *115*, 193-201.

(22) Calculation has been performed using density functional M06 level of theory. The difference between activation energies = $E_a(1)$- $E_a(2)$ = [(83.31-29.86) – 29.56] = 23.84 kcal/mol.

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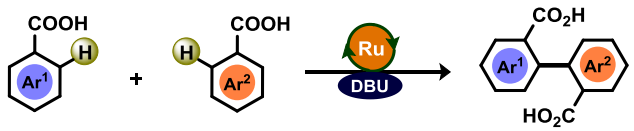

✓*Ru-DBU synergy* ✓*noncovalent interaction*
✓*bioactive motifs* ✓*DFT study and mechanistic insights*