Rh/Cu-catalyzed Ketone #-Functionalization via Merging Ketone Dehydrogenation and Carboxyl-directed C-H Alkylation

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Rh/Cu-catalyzed Ketone β-Functionalization via Merging Ketone Dehydrogenation and Carboxyl-directed C-H Alkylation

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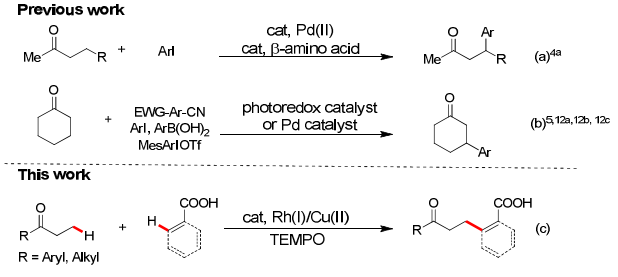
ABSTRACT: An efficient Rh/Cu-catalyzed method has been developed for the direct β-arylation or alkenylation of ketones using (hetero)aryl or alkenyl carboxylic acids as coupling partners. This direct ketone β-functionalization reaction proceeded via merging Cu-catalyzed ketone dehydrogenative desaturation and Rh-catalyzed carboxyl-directed C-H alkylation, exhibited a broad substrate scope for both coupling partners. TEMPO proved to be essential for both dehydrogenation process and generation of the active Rh-catalyst for C-H activation.

KEYWORDS: Dehydrogenation • Cascade reaction • Ketone • Carboxylic acid • Alkylation

β-arylated saturated ketones are the structural motifs that are embedded in many natural products and bioactive compounds.[1] Consequently, efficient methods for constructing such structures are always the goal sought after by chemists. Traditionally, β-arylated ketone architectures are constructed through the aldol condensation/hydrogenation two-step procedure,[2] or rhodium-catalyzed Michael addition of aryl organometallic reagents to enones.[3] These conventional methods either require harsh reaction conditions such as strong bases that limit substrate scope, or employ the reactants that are often prepared by way of multi-step synthetic sequences, which prompts chemists to invent the efficient methods that produce β-arylated ketones in atom- and step-economical manner staring from simple reactants. Recently, a breakthrough has been achieved in the development of the bidentate directing group-assisted β-C(sp3)-H activation reaction of carbonyl compounds.[4] In this context, Yu and co-workers [4a] have realized β-C(sp3)-H arylation reaction of ketones with aryl iodides as arylating reagents (Scheme 1a) by using amino acid as a transient directing group. MacMillan and co-workers have demonstrated that merging the organocatalysis and photoredox catalysis enabled β-C(sp3)-H arylation reaction of aliphatic ketones using dicyanobenzene as an arylating reagent (Scheme 1b).[5]

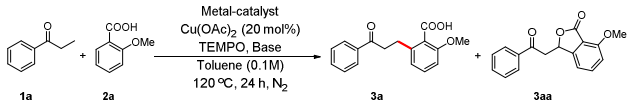
On the other hand, due to the importance of olefins in organic synthesis, transition metal-catalyzed dehydrogenative desaturation of various compounds to generate olefins has recently attracted considerable interest.[6-8] Moreover, efforts to achieve the tandem metal-catalyzed dehydrogenation/secondary olefin reaction sequence have led to the inventions of diverse interesting chemical transformations,[9-13] including Baudoin's Pd-catalyzed β-C-H arylation of α-substituted esters[10a, b, c] and *N*-Boc-piperidines with aryl halides,[10d] and Pihko's β-C-H indolation of β-keto esters.[11] As for the tandem sequence to access β-arylated ketone, Dong and Li have established the Pd-catalyzed β-arylation reaction of ketones with aryl iodides,[12a] diaryliodonium salts[12b] and arylboronic acids[12c] via ketone dehydrogenative desaturation respectively (Scheme 1b). Newhouse and co-workers have developed the cascade Pd-catalyzed ketone dehydrogenation/organocuprate conjugate addition process to realize β-functionalization or α,β-difunctionalization of cyclic ketones, including ketone β-arylation.[13] Very recently, our group has discovered a Cu-catalyzed radical-based ketone dehydrogenative desaturation process that could merge conjugate addition of nucleophiles to the newly formed enones to furnish β-functionalized saturated ketones.[14] Herein, we report a novel method for facile synthesis of β-arylated or β-alkenylated ketones via merging Cu(II)-catalyzed ketone dehydrogenation and Rh-catalyzed carboxyl-directed *ortho*-C-H alkylation of (hetero)aryl- or alkenyl carboxylic acids with enone (Scheme 1c). [15]

Scheme 1. The Metal-catalyzed Direct β-Csp³-H Arylation of Ketones



Actually, the implementation of the tandem dehydrogenative desaturation/C-H alkylation of arene with enone to construct β-aryl saturated ketone represents a challenge for the following reasons: 1) the compatibility between the dehydrogenative desaturation and the C-H fuctionalization is required; 2) the β-aryl ketone products compete with ketone starting materials for dehydrogenation to form the overoxidized side-product;[16] 3) the expected alkyl-M intermediate in the C-H alkylation catalysis tends to undergo β-H elimination to form overoxidized side-products. One of our strategies to address these problems is the identification of a suitable catalyst system responsible for C-H alkylation with olefin, which is compatible with the Cu-catalyzed dehydrogenative desaturation process.[14] We hypothesized that if the C(sp3)-M bond of the alkyl-M intermediate generated is enough polar, this intermediate would prefer protonolysis over β-elimination. Since increasing the concentration of ketone could accelerate Cu-catalyzed ketone dehydrogenation to enone, [14a] the use of excessive ketone starting material would suppress dehydrogenation of β-aryl ketone products.

Table1. The Selected Result of the Optimization Studies on the Ketone β-Arylation [a]

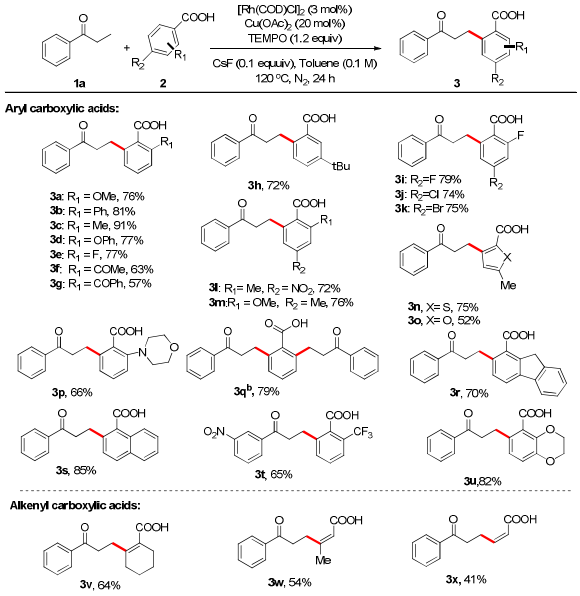


Entry	Cat.(mol%)	Base (mol%)	TEMPO (equiv.)	Yield (%)	
				3a[b]	**3aa**
1	$Pd(OAc)_2$ (5)	--	1.0	n.d	24
2	$[Ru(p\text{-}cym)Cl_2]_2$ (5)	--	1.0	n.d	23
3	$[Rh(Cp^*)Cl_2]_2$ (5)	--	1.0	n.d	35
4	$Rh(PPh_3)_3Cl$ (5)	--	1.0	n.d	12
5	$[Rh(COD)Cl]_2$ (5)	--	1.0	65	<5
6	$[Rh(COD)Cl]_2$ (3)	--	1.0	52	<5
7	$[Rh(COD)Cl]_2$ (3)	--	1.2	70	<5
8	$[Rh(COD)Cl]_2$ (3)	CsF (10)	1.2	82	<5

[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.2 mmol), [b] yield as determined by NMR.

With these considerations in mind, we chose the reaction of propiophenone (**1a**) with *ortho*-methoxy benzoic acid (**2a**) as a model system for the optimization of reaction conditions (Table 1). Benzoic acids were used as arylating reagents because benzoic acids are readily available, versatile arylating reagents via decarboxylative cross-coupling reactions [17] or carboxyl-directed *ortho*-C-H functionalization reactions. [18] Our targeted reaction aimed at the carboxyl-directed C-H alkylation to produce **3a** of which carboxyl group is able to undergo protodecarboxylation or various decarboxylative cross-coupling reaction, and therefore allow for the further elaboration of products. The undesired lactone by-product **3aa** came from overoxidation of **3a** via further dehydrogenation of **3a** and subsequent conjugate addition of carboxyl to enone. Initially, we screened a variety of metal catalysts in the presence of one equivalent of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and 20 mol% $Cu(OAc)_2$, and found that the metal catalysts, which are regularly used for C-H activation reactions, allowed for the reaction of **1a** with **2a** to occur but gave overoxidized product **3aa** (entries 1-4). Gratifyingly, we obtained the targeted product in 65% yield using $[Rh(COD)Cl]_2$ (5 mol%) [15b, 19] as a catalyst (entry 5). Reducing loading of $[Rh(COD)Cl]_2$ to 3 mol% led to a decrease in the yield of **3a** (entry 6). However, increasing the amount of TEMPO to 1.2 equivalents gave 70% yield with 3 mol% $[Rh(COD)Cl]_2$ catalyst (entry 7). Then, we checked the effect of bases on the reaction outcome. Although acetate and carbonate salts have a negative effect on the reaction (see Table S1 in the Supporting Information), 10 mol% CsF could increase the yield to 82% (entry 8).

Scheme 2. The Scope of Carboxylic Acid [a]



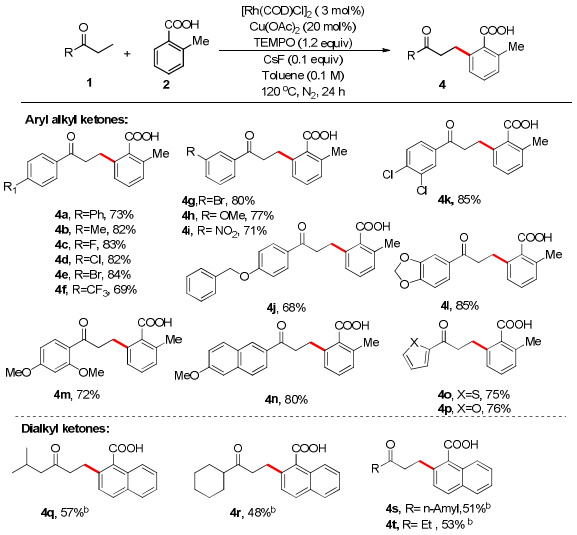
[a]Reaction conditions: **1a** (0.6 mmol), **2** (0.2 mmol), All isolated yields. [b]**1a** (0.8 mmol), TEMPO (2.4 equiv.).

With the optimized reaction conditions in hand, we evaluated the substrate scope of carboxylic acids (Scheme 2). Ortho-substituted benzoic acids gave good-to-excellent yields and variation of the ortho-substituents of these benzoic acids did not significantly affect the reaction outcomes (**3a-3g**, **3t**). Although nonsubstituted benzoic acids gave di-substituted product (**3q**), the reaction of 3-*t*-butyl benzoic acid occurred only on the less sterically hindered position (**3h**). A series of multi-substituted benzoic acids could be smoothly transformed into the corresponding products in good yields (**3i-3m**, **3r**, **3u**). Heteroaryl carboxylic acids were also suitable substrates as illustrated by **3n** and **3o**. Interestingly, this protocol was amenable to carboxyl-directed alkenylic C-H alkylation of alkenyl carboxylic acids (**3v-3x**), further highlighting the generality of this protocol.

Next, we explored the substrate scope of saturated ketones (Scheme 3). A variety of electronically diverse functionalities on 4-positions of phenyl rings in propiophenones were well tolerated to give the β-arylation ketones in excellent yields (**4a-4f** and **4j**). Changing the substitution position to meta-position of phenyl ring in propiophenones had no effect on the reaction yields (**4g-4i**). Propiophenones containing multi-substituted phenyl rings were also suitable for this transformation (**4k-4m**). Additionally, heteroaromatic ketones such as 2-propionylfuran and 2-propionylthiophene participated in the targeted β-arylation reaction without side reactions occurring at their reactive C-2 or C-3 positions of heteroaromatic rings (**4o** and **4p**). As exemplified in the cases of **4q**-**4t**, aliphatic

ketones also underwent β-arylation reaction which occurred exclusively on less sterically hindered ethyl moiety. This selective β-arylaton of aliphatic ketones circumvented the formidable synthesis of the alkyl vinyl ketones used in Ru-catalyzed hydroarylation of olefins, and provided a solution to the selectivity issue encountered in the synthesis of β-aryl ketone via aldol reaction of unsymmetrical ketone.

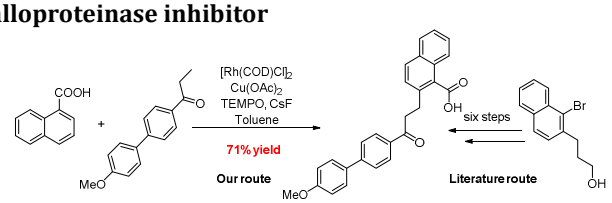
Scheme 3. The Scope of Saturated Ketones [a]



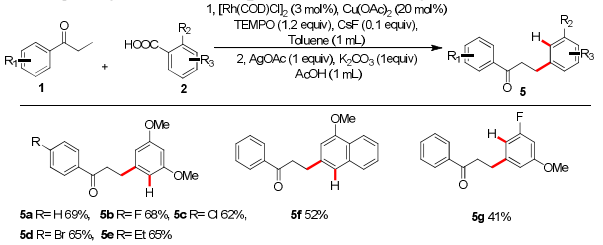
[a]Reaction conditions: **1** (0.6 mmol), **2** (0.2 mmol). All isolated yields. [b] $Cu(OAc)_2$ (40 mol%) was used.

Our Rh/Cu catalyzed method also enabled one-step gram-scale synthesis of a kind of matrix metalloproteinase inhibitor in 71% yield using commercially available starting materials. In sharp contrast, this matrix metalloproteinase inhibitor was previously synthesized by way of a six-step synthetic route starting from 3-(1-bromnaphthalen-2yl) propan-1-ol (Scheme 4). [20]

Scheme 4. One Step Synthesis of a kind of matrix metalloproteinase inhibitor



Scheme 5. One-pot procedure for Rh/Cu-catalyzed ketone β-arylation and protodecarboxylation[a]

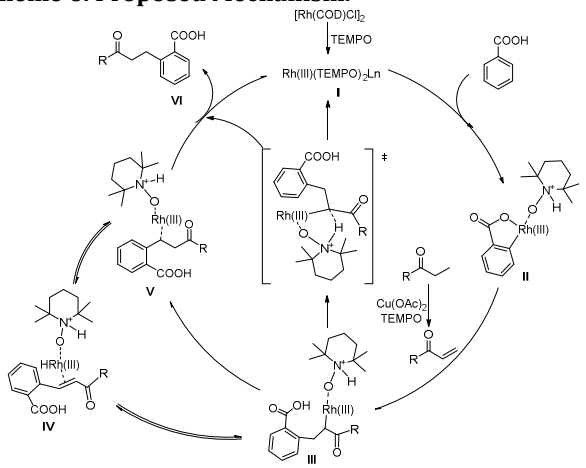


[a]Reaction conditions: **1** (0.6 mmol), **2** (0.2 mmol), 120 °C, 24 h, N_2. All isolated yields.

To test the feasibility of further transformation of these ketone β-arylation products, we investigated one-pot two-step procedure for Rh/Cu catalyzed carboxyl-directed C-H alkylation and subsequent protodecarboxylation. We are pleased to find that adding AgOAc (1 equiv.), K_2CO_3 (1 equiv.) and HOAc to the reaction system after Rh/Cu catalysis process allowed for protodecarboxylation of these β-arylation products to generate 1,3,5-trisubstituted benzenes as final products in synthetically useful yields (Scheme 5).

To gain an insight into the Rh/Cu catalyzed β-arylation of ketone, we conducted preliminary mechanism investigations (See Supporting Information for details). By means of a H/D exchange experiment, we initially explored the effect of TEMPO on $[Rh(COD)Cl]_2$-mediated carboxyl-directed *ortho* C-H activation. In the presence of D_2O (20 equiv.) and TEMPO (1.2 equiv.), 30% of C-H bond *ortho* to carboxyl group in 2-methoxy-benzoic acid was deuterated, indicating that the reversible C-H cyclorhodation occurred. Control experiments revealed that only negligible H/D exchanges occurred in the absence of TEMPO, suggesting that TEMPO played a key role in the $[Rh(COD)Cl]_2$-mediated C-H activation step. Moreover, TEMPO was essential for $[Rh(COD)Cl]_2$-catalyzed carboxyl-directed C-H alkylation of benzoic acids with enone, consistent with H/D exchange experiments. In light of these observations, we reasoned that TEMPO would promote the generation of the active Rh catalyst for C-H bond activation, likely by oxidation of Rh(I) to Rh(III) species as proposed by Studer and co-workers [21] for the Rh-catalyzed oxidative cross-coupling reactions with TEMPO as the only terminal oxidant. Moreover, we conducted the reaction of 1(3-methoxyphenyl)propan-1-one with [D5]benzoic acid under standard reaction conditions and found that 45% of deuterium on ortho-position of [D5]benzoic acid was incorporated to α-position of β-arylated ketone product, and 35% to β-position.

Scheme 6. Proposed Mechanism.



The identification of enone intermediate in the reaction system and the experiments described by Scheme *S1-S3* supported that the Rh/Cu-catalyzed ketone β-arylation occurred via the in-situ ketone dehydrogenation and C-H alkylation with the enone. Scheme 6 shows a proposed mechanism for the Rh-catalyzed carboxyl-directed *ortho* C-H alkylation with the enone. Initially, the catalytically active $Rh(III)(TEMPO)_2Ln$ **I** is generated via oxidation of $[Rh(COD)Cl]_2$ by TEMPO (2 equiv.). After carboxylate coordinates to Rh(III) catalyst **I**, *ortho* C-H metalation proceeds via a concerted metalation/deprotonation mechanism (CMD) to form aryl-Rh(III) species **II**, [22] in which TEMPO-

anion ligand accepts proton by its nitrogen atom to promote C-H metalation. Olefin insertion into aryl-Rh bond leads to formation of alkyl-Rh intermediate **III** that undergoes protonolysis via proton transfer from the nitrogen atom of coordinating TEMPO ligand to the carbon atom of C-Rh bond to release product **VI**. Meanwhile, Product **VI** is also produced through protonolysis of isomeric alkyl-Rh intermediate **V**, which is generated from intermediate **III** via β-H elimination and subsequent re-insertion process,[15b, 23] since deuterium atoms were incorporated to both α and β positions of β-arylated ketone product in the deuterium-labeling experiment. The fact that 80% of *ortho*-deuterium atoms of [D_5]benzoic acid were incorporated into the final product implicates that after accepting proton in the C-H metalation process, TEMPO still coordinates to Rh atom in the form of zwitterion, and therefore makes it easy to deliver proton to the proximal Rh-C bond of alkyl-Rh intermediate.

In summary, we have developed the Rh/Cu catalyzed direct β-arylation or alkenylation of ketones with aryl or alkenyl carboxylic acids as coupling partners via combination of Cu/TEMPO-promoted ketone dehydrogenation process with Rh-catalyzed carboxyl-directed C-H alkylation with enone. Both aryl alkyl ketones and dialkyl ketones underwent β-functionalization reactions with a broad range of aryl carboxylic acids as well as alkenyl carboxylic acids with good selectivity in good-to-excellent yields. The strategy to merge the dehydrogenative desaturation and the C-H activation reaction would bring about discoveries of various new transformations due to versatile reactivity of olefins and diversity of C-H activation reactions.

ASSOCIATED CONTENT

Supporting Information. Experiment procedures, characterization data, ^{1}H, ^{13}C and ^{19}F spectra for compounds, mechanism study. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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REFERENCES

1. (a) Mathiesen, L.; Malterud, E.; Sund, R. B. Antioxidant activity of fruit exudate and C-methylated dihydrochalcones from Myrica gale. *Planta. Med.* **1995**, *61*, 515-518. (b) Mathiesen, L.; Malterud, E.; Sund, R. B. Hydrogen Bond Formation as Basis For Radical Scavenging Activity: A Structure–Activity Study of C-Methylated Dihydrochalcones from *Myrica gale* and Structurally Related Acetophenones**.** *Free Radical Bio* & *Med.* **1997**, *22*, 307-311.

2. Thebtaranonth, C.; Thebtaranonth, Y. *The Chemistry of Enones.;* Patai, S.; Rappoport, Z. Eds*.;* John Wiley & Sons: New York, **1989.** Vol. 29, p 199.

3. (a) Sakai, M.; Hayashi, H.; Miyaura, N. Rhodium-Catalyzed Conjugate Addition of Aryl- or 1-Alkenylboronic Acids to Enones. *Organometallics.* **1997**, *16*, 4229-4231. (b) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. Catalytic Cycle of Rhodium-Catalyzed Asymmetric 1,4-Addition of Organoboronic Acids. Arylrhodium, Oxa-π-allylrhodium, and Hydroxorhodium Intermediates. *J. Am. Chem. Soc.* **2002**, *124*, 5052-5058. (c) Fagnou, K.; Lautens, M. Rhodium-Catalyzed Carbon–Carbon Bond Forming Reactions of Organometallic Compounds. *Chem. Rev.* **2003**, *103*, 169-196. (d) Hayashi, T.; Yamasaki, K. Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions. *Chem. Rev.* 2003, *103*, 2829-2844.

4. (a) Zhang, F.-L.; Hong, k.; Li, T.-J.; Park, H.; Yu, J.-Q. Functionalization of C(sp^3)–H bonds using a transient directing group. *Science.* **2016**, *351*, 252-256. (b) Zhu, R-Y.; Liu, R.-Y.; Park, H.S.; Hong, K.; Wu, Y.; Senanayake, H.; Yu, J.-Q. Versatile Alkylation of (Hetero)Aryl Iodides with Ketones via β-C(sp^3)–H Activation. *J. Am. Chem. Soc.* **2017**, *139*, 16080-16083. (c) Huang, Z.; Dong, G. Catalytic C-C bond forming transformations via direct β-C-H functionalization of carbonyl compounds. *Tetrahedron.* **2014**, *55*, 5869-5889. (d) He, G.; Wang, B.; Nack, W. A.; Chen, G. Syntheses and Transformations of α‑Amino Acids via Palladium-Catalyzed Auxiliary-Directed sp^3 C–H Functionalization. *Acc. Chem. Res.* **2016,** *49*, 635-645. (e) Yang, K.; Li, Q.; Liu, Y.; Li, G.; Ge, H. Catalytic C–H Arylation of Aliphatic Aldehydes Enabled by a Transient Ligand. *J. Am. Chem. Soc.* **2016,** *138*, 12775-12778.

5. (a) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. Photoredox Activation for the Direct β-Arylation of Ketones and Aldehydes. *Science.* **2013**, *339*, 1593-1596. (b) Petronijevic, F. R.; Nappi, M.; MacMillan, D. W. C. Direct β-Functionalization of Cyclic Ketones with Aryl Ketones via the Merger of Photoredox and Organocatalysis. *J. Am. Chem. Soc.* **2013**, *135*, 18323-18326.

6. (a) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. A New Method for the One-Step Synthesis of α,β-Unsaturated Carbonyl Systems from Saturated Alcohols and Carbonyl Compounds. *J. Am. Chem. Soc.* **2000,** *122*, 7596-7597. (b) Uyanik, M.; Akakura, M.; Ishihara, K. 2-Iodoxybenzenesulfonic Acid as an Extremely Active Catalyst for the Selective Oxidation of Alcohols to Aldehydes, Ketones, Carboxylic Acids, and Enones with Oxone. *J. Am. Chem. Soc.* **2009**, 131, 251-262.

7. (a) Diao, T.; Stahl, S. S. Synthesis of Cyclic Enones via Direct Palladium-Catalyzed Aerobic Dehydrogenation of Ketones. *J. Am. Chem. Soc.* **2011,** *133*, 14566-14569. (b) Diao, T.; Wadzinski, T. J.; Stahl, S. S. Direct aerobic α, β-dehydrogenation of aldehydes and ketones with a $Pd(TFA)_2$/4,5-diazafluorenone catalyst. *Chem. Sci*. **2012**, *3*, 887-891. (c) Bigi, M. A.; White, M. C. Terminal Olefins to Linear α, β-Unsaturated Ketones: Pd(II)/Hypervalent Iodine Co-catalyzed Wacker Oxidation–Dehydrogenation. *J. Am. Chem. Soc.* **2013,** *135*, 7831-7834. (d) Chen, M.; Dong, G. Direct Catalytic Desaturation of Lactams Enabled by Soft Enolization. *J. Am. Chem. Soc.* **2017**, *139*, 7757-7760. (e) Wang, Z.; He, Z.; Zhang, L.; Huang, Y. Iridium-Catalyzed Aerobic α, β-Dehydrogenation of γ, δ-Unsaturated Amides and Acids: Activation of Both α- and β-C–H bonds through an Allyl–Iridium Intermediate. *J. Am. Chem. Soc.* **2018**, *140,* 735-740.

8. (a) Yi, C. S.; Lee, D. W. Efficient Dehydrogenation of Amines and Carbonyl Compounds Catalyzed by a Tetranuclear Ruthenium-μ-oxo-μ-hydroxo-hydride Complex. *Organometallics*. **2009**, *28*, 947-949. (b) Kusumoto, S.; Akiyama, M.; Nozaki, K. Acceptorless Dehydrogenation of C–C Single Bonds Adjacent to Functional Groups by Metal–Ligand Cooperation. *J. Am. Chem. Soc.* **2013,** *135*, 18726-18729.

9. (a) Stang, E. M.; White, M. C. Molecular Complexity via C–H Activation: A Dehydrogenative Diels–Alder Reaction. *J. Am. Chem. Soc*. **2011**, *133*, 14892-14895. (b) Goldman, A. S.; Roy, A. H.; Huang, Z.; Ahuja, R.; Schinski, W.; Brookhart, M. Catalytic Alkane Metathesis by Tandem Alkane Dehydrogenation-Olefin Metathesis. *Science.* **2006**, *312*, 257-261. (c) Jia, X.; Huang, Z. Conversion of alkanes to linear alkylsilanes using an iridium–iron-catalysed tandem dehydrogenation–isomerization–hydrosilylation. *Nat. Chem.* **2016,** *8*, 157-161. (d) Wang, B.; Du, H.; Shi, Y. A Palladium-Catalyzed Dehydrogenative Diamination of Terminal Olefins. *Angew. Chem. Int. Ed.* **2008**, *47*, 8224-8227. (e) Li, C.-J. Cross-Dehydrogenative Coupling (CDC): Exploring C-C Bond Formations beyond Functional Group Transformations. *Acc. Chem. Res.* **2009**, 42, 335-344.

10. (a) Renaudat, A.; Jean-Gérard, L.; Jazzar, R.; Kefalidis, C. E.;Clot, E.; Baudoin, O. Palladium-Catalyzed β Arylation of Carboxylic Esters. *Angew. Chem. Int. Ed.* **2010**, *49*, 7261-7265. (b) Larini, P.; Kefalidis, C. E.; Jazzar, R.; Renaudat, A.; Clot, E.; Baudoin, O. On the Mechanism of the Palladium-Catalyzed β-Arylation of Ester Enolates. *Chem. Eur. J.* **2012**, 18, 1932-1944. (c) Aspin, S.; Goutierre, A.-S.; Larini,P.; Jazzar, R.; Baudoin, O. Synthesis of Aromatic α-Aminoesters: Palladium-Catalyzed Long-Range Arylation of Primary Csp^3-H Bonds. *Angew. Chem. Int. Ed.* **2012**, *51*, 10808-10811. (d) Millet, A.; Larini, P.; Clot, E.; Baudoin, O. Ligand-controlled β-selective C(sp^3)–H arylation of N-Boc-piperidines. *Chem. Sci.* **2013,** *4*, 2241-2247.

11. (a) Leskinen, M. V.; Yip, K.-T.; Valkonen, A.; Pihko, P. M. Palladium-Catalyzed Dehydrogenative β'-Functionalization of β-Keto Esters with Indoles at Room Temperature. *J. Am. Chem. Soc.* **2012**, *134*, 5750-5753. (b) Leskinen, M. V.; Madarász, Á.; Yip, K.-T.; Vuorinen, A.; Pápai, I.; Neuvonen, A. J.; Pihko, P. M. Cross-Dehydrogenative Couplings between Indoles and β‑Keto Esters: Ligand-Assisted Ligand Tautomerization and Dehydrogenation via a Proton-Assisted Electron Transfer to Pd(II). *J. Am. Chem. Soc.* **2014**, *136*, 6453-6462. (c) Nimje, R. Y.; Leskinen, M. V.; Pihko, P. M A. Three-Component Palladium-Catalyzed Oxidative C-C Coupling Reaction: A Domino Process in Two Dimensions. *Angew. Chem. Int. Ed.* **2013**, *52*, 4818-4822.

12. (a) Huang, Z.; Dong, G. Catalytic Direct β‑Arylation of Simple Ketones with Aryl Iodides. *J. Am. Chem. Soc.* **2013**, *135*, 17747-17750. (b) Huang, Z.; Sam, Q. P.; Dong, G. Palladium-catalyzed direct β-arylation of ketones with diaryliodonium salts: a stoichiometric heavy metal-free and user-friendly approach*. Chem. Sci.* **2015**, *6*, 5491-5498. (c) Hu, X.; Yang, X.; Dai, X.-J.; Li, C.-J. Palladium-Catalyzed Direct β-C-H Arylation of Ketones with Arylboronic Acids in Water. *Adv. Synth. Catal.* **2017**, *359*, 2402-2406.

13. (a) Chen, Y.; Romaire, J. P.; Newhouse, T. R. Palladium-Catalyzed α,β-Dehydrogenation of Esters and Nitriles. *J. Am. Chem. Soc.* **2015**. *137*, 5875-5878. (b) Chen, Y.; Turlik, A.; Newhouse, T. R. Amide α,β-Dehydrogenation Using Allyl-Palladium Catalysis and a Hindered Monodentate Anilide. *J. Am. Chem. Soc.* **2016**. *138*, 1166-1169. (c) Chen, Y.; Huang, D.; Zhao, Y.; Newhouse, T. R. Allyl-Palladium-Catalyzed Ketone Dehydrogenation Enables Telescoping with Enone α, β-Vicinal Difunctionalization. *Angew. Chem. Int. Ed.* **2017**. *56*, 8258-8262. (d) Zhao, Y.; Chen, Y.; Newhouse, T. R. Allyl-Palladium-Catalyzed α, β-Dehydrogenation of Carboxylic Acids via Enediolates. *Angew. Chem. Int. Ed.* **2017**. *56*, 13122-13125.

14. (a) Jie, X.; Shang, Y.; Zhang, X.; Su, W. Cu-Catalyzed Sequential Dehydrogenation–Conjugate Addition for β‑Functionalization of Saturated Ketones: Scope and Mechanism. *J. Am. Chem. Soc.* **2016**, *138*, 5623-5633. (b) Shang, Y.; Jie, X.; Jonnada, K.; Zafar, S. N.; Su, W. Dehydrogenative desaturation-relay via formation of multi-center-stabilized radical intermediates. *Nat. Commun.* **2017**, *8*, 2273-2280.

15. (a) Rouquet, G.; Chatani, N. Ruthenium-catalyzed ortho-C–H bond alkylation of aromatic amides with α, β-unsaturated ketones via bidentate-chelation assistance. *Chem. Sci.* **2013**, *4*, 2201-2208. (b) Ryu, J.; Cho, S. H.; Chang, S. A Versatile Rhodium(I) Catalyst System for the Addition of Heteroarenes to both Alkenes and Alkynes by a C-H Bond Activation. *Angew. Chem. Int. Ed.* **2012**, *51*, 3677-3681. (c) Yang, L.; Qian, B.; Huang, H. Brønsted Acid Enhanced Rhodium-Catalyzed Conjugate Addition of Aryl C-H Bonds to α, β-Unsaturated Ketones under Mild Conditions *Chem. Eur. J.* **2012**, *18*, 9511-9515. (d) Yang, L.; Correia, A. C.; Li, C.-J. Rhodium-catalyzed C–H activation and conjugate addition under mild conditions. *Org. Biomol. Chem.* **2011**, 9, 7176-7179.

16. (a) Izawa, Y.; Pun, D.; Stahl, S. S. Palladium-Catalyzed Aerobic Dehydrogenation of Substituted Cyclohexanones to Phenols. *Science.* **2011**, *333*, 209-213. (b) Pun, D.; Diao, T.; Stahl, S. S. Aerobic Dehydrogenation of Cyclohexanone to Phenol Catalyzed by $Pd(TFA)_2$/2-Dimethylaminopyridine: Evidence for the Role of Pd Nanoparticles. *J. Am. Chem. Soc.* **2013**, *135*, 8213-8221. (c) Ueno, S.; Shimizu, R.; Kuwano, R. Nickel-Catalyzed Formation of a Carbon–Nitrogen Bond at the β Position of Saturated Ketones. *Angew. Chem. Int. Ed.* **2009**, *48*, 4543-4545. (d) Moon, Y.; Kwon, D.; Hong, S. Palladium-Catalyzed Dehydrogenation/Oxidative Cross-Coupling Sequence of β-Heteroatom-Substituted Ketones. *Angew. Chem. Int. Ed.* **2012**, *51*, 11333-11336. (e) Shang, Y.; Jie, X.; Zhou, J.; Hu, P.; Huang, S.; Su, W. Pd-Catalyzed C–H Olefination of (Hetero)Arenes by Using Saturated Ketones as an Olefin Source. *Angew. Chem. Int. Ed.* **2013**, *52*, 1299-1303. (f) Gandeepan, P.; Rajamalli, P.; Cheng, C.-H. Palladium-Catalyzed Dehydrogenative β‑Arylation of Simple Saturated Carbonyls by Aryl Halides. *ACS. Catal.* **2014**, *4*, 4485-4489.

17. For reviews on decarboxylative cross-coupling reactions, see (a) Rodríguez, N.; Goossen, L. J. Decarboxylative coupling reactions: a modern strategy for C–C-bond formation. *Chem. Soc. Rev.* **2011,** *40*, 5030-5048. (b) Larrosa, I.; Cornella, J. Decarboxylative Carbon-Carbon Bond-Forming Transformations of (Hetero)aromatic Carboxylic Acids. *Synthesis* **2012,** *44*, 653-676. (c) Wei, Y.; Hu, P.; Zhang, M.; Su, W. Metal-Catalyzed Decarboxylative C–H Functionalization. *Chem. Rev.* **2017**, *117*, 8864-8907.

18. (a) Engle, M. k.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C-H Functionalization Reactions. *Acc. Chem. Res.* **2012,** *45*,788-802. (b) 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. (c) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. Synthesis of Stilbene and Distyrylbenzene Derivatives through Rhodium-Catalyzed Ortho-Olefination and Decarboxylation of Benzoic Acids. *Org. Lett*. **2010**, *12*, 5776-5779. (d) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. Rhodium-Catalyzed Regioselective Olefination Directed by a Carboxylic Group. *J. Org. Chem.* **2011**, *76*, 3024-3033.

19. (a) Fu, G. C. *Modern Rhodium-Catalyzed Organic Reactions.;* Evans, P. A., Eds.; Wiley-VCH: Weinheim, **2005**, Chapter *4*, p 79. (b) Colby, D.A.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed C-C Bond Formation via Heteroatom-Directed C-H Bond Activation. *Chem. Rev.* **2010**, *110*, 624-655. (c) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. Transition-Metal-Catalyzed C–H Alkylation Using Alkenes. *Chem. Rev.* **2017,** *117*, 9333-9403.

20. Hajduk, P. J.; Shuker, S. B.; Nettesheim, G. D.; Craig, R.; Augeri, D. J.; Betebenner, D.; Albert, D. H.; Guo, Y.; Meadows, R.P.; Xu, L.; Michaelides, M.; Davidsen, S. K.; Fesik, S. W. NMR-Based Modification of Matrix Metalloproteinase Inhibitors with Improved Bioavailability. *J. Med. Chem.* **2002**, *45*, 5628-5639.

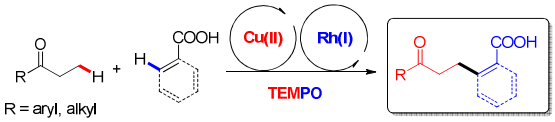
21. (a) Vogler, T.; Studer, A. Oxidative Coupling of Arylboronic Acids with Arenes via Rh-Catalyzed Direct C-H Arylation. *Org. Lett.* **2008**, *10*, 129-131. (b) Vogler, T.; Studer, A. Rhodium-Catalyzed Oxidative Homocoupling of Boronic Acids. *Adv. Synth. Catal.* **2008**, *350*, 1963-1967.

22. TEMPO assisted dehydrogenation via *N-H* bond formation, see: Ryland, B. L.; McCann, S. D.; Brunold, T.C.; Stahl, S.S. Mechanism of Alcohol Oxidation Mediated by Copper(II) and Nitroxyl Radicals. *J. Am. Chem. Soc.* **2014**, *136,* 12166-12173.

23. (a) Tsui, G.C.; Menard, F.; Lautens, M. Regioselective Rhodium(I)-Catalyzed Hydroarylation of Protected Allylic Amines with

Arylboronic Acids. *Org. Lett.* **2010**, 12, 2456-2459. (b) Tsui, G. C.; Lautens, M. Linear-Selective Rhodium(I)-Catalyzed Addition of Arylboronic Acids to Allyl Sulfones. *Angew. Chem. Int. Ed.* **2010,** *49*,8938-8941.

SYNOPSIS TOC



R = aryl, alkyl

- ***52*** *examples, up to* ***91****% yield*
- *Compatibility and cooperation between dehydrogenation and C-H alkylation*
- *Preferential dehydrogenation of staring materials to avoid overoxidation of products*