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Merging C−H Activation and Strain−Release in Ruthenium-Catalyzed Isoindolinone Synthesis

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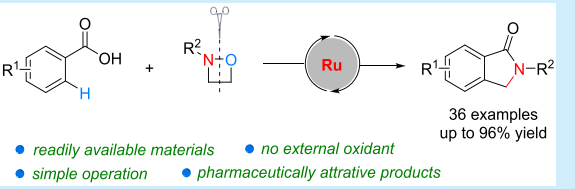
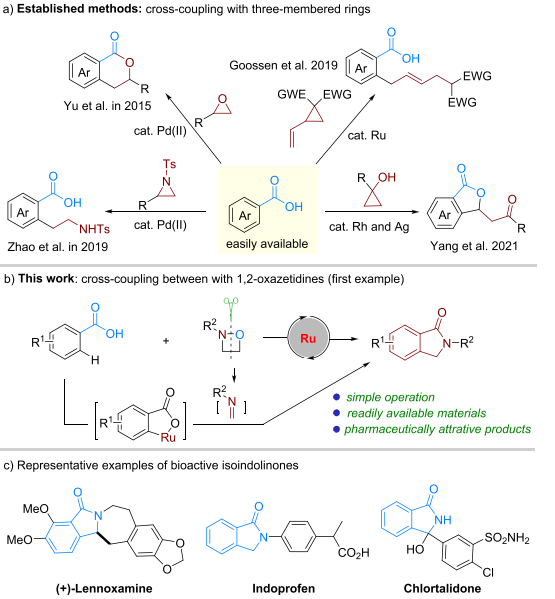
ABSTRACT: The merger of strain−release of 1,2-oxazetidines with carboxylic acid directed C−H activation in catalytic synthesis of isoindolinones is reported for the first time. This reaction opens a new and sustainable avenue to prepare a range of structurally diverse isoindolinone skeletons from readily available benzoic acids. The success of late-stage functionalization of some bioactive acids, and concise synthesis of biologically important skeletons demonstrated its great synthetic potential in drug discovery. Mechanistic studies indicated a plausible C−H activation/β-carbon elimination/intramolecular cyclization cascade pathway.



Small (typically three- and four-membered) ring systems are important and versatile building blocks for rapidly accessing complex molecular architectures in organic chemistry.[1] The strain energies of cyclopropane and cyclobutane are 27.5 and 26.5 kcal/mol, respectively, which are much larger than those of cyclohexane (0.0 kcal/mol) and cyclopentane (7.4 kcal/mol).[2] The selective strain−release of small rings offers a unique opportunity and thermodynamic driving force for the transformation of these reactive feedstocks into value-added chemicals and functional materials.[3] In this context, the synergistic combination of transition-metal-catalyzed C(sp^2)−H activation and strained ring cleavage has been widely exploited for the reconstruction of small rings over the past decades.[2b,4] While these reactions can be efficient and useful, their applications are often hampered by the inevitable requirement of strong N-directing groups, expensive metal catalyst (Rh, Pd, etc.), or high loading of Ag or Cu additives.[2b,5] Therefore, the practicality and cost issues in this field have spurred ongoing efforts to explore novel catalytic technologies that rely upon readily available substrates, an inexpensive metal catalyst, and simple operation.

Benzoic acids are among the most widely occurring and easily available feedstock chemicals in metal-catalyzed cross-coupling reactions.[6] In recent years, the merger of benzoic acids with ring opening of strained rings has emerged as an attractive strategy to invent valuable cross-coupling reactions, which are currently elusive with the use of other strong N-directing groups. In 2015, Yu et al. reported the first example of Pd(II)-catalyzed C−H alkylation of benzoic acids with epoxides, delivering a range of dihydroisocoumarins in high efficiency (Scheme 1a).[7] By employing aliphatic aziridines as efficient coupling partners, the group of Zhao achieved a Pd-catalyzed carboxylic acid directed C(sp^2)−H alkylation of benzoic acids for the synthesis of β-arylethylamine skeletons.[8] Very recently, Yang and Huang et al. disclosed a novel C−H activation/cyclization cascade of carboxylic acids with cyclopropanols enabled by a cooperative $[Cp^*RhCl_2]_2$/AgOAc catalytic system.[9] Moreover, Goossen and we demonstrated a

Scheme 1. Cross-Coupling Reactions between Benzoic Acids and Small Ring Systems



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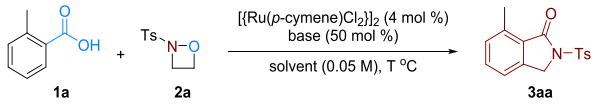
Ru-catalyzed C−H allylation of benzoic acids with vinylcyclopropanes.[10] Despite the success in benzoic acid-mediated ring-opening reactions of three-membered rings, there is still no example of strain-enabled cross-coupling reaction between benzoic acids and four-membered rings to date.

1,2-Oxazetidines are highly strained four-membered rings, which perform a higher ring strain energy even than oxaziridines (calcd 25.2 kcal/mol vs 22.9 kcal/mol).[11] The first synthesis of 1,2-oxazetidines date back to 1970, but the development of catalytic systems for their transformation is a recent achievement.[12] To the best of our knowledge, only four examples have been reported to date. Orentas[13] and Hu[14] et al. independently employed 1,2-oxazetidines as an efficient source of electrophilic oxygen to react with nucleophilic organometallic agents and β-keto esters. The groups of Loh[15] and Hu[16] applied 1,2-oxazetidines in Co- and Ru-catalyzed C−H aminomethylation of heteroarenes and enamides, respectively. Among these protocols, the addition of expensive silver salts is inevitably required. Based on the insight gained from these important works, we recently questioned if the strain−release of 1,2-oxazetidines and carboxylic acid directed C−H activation can be successfully combined to create a convenient access to bioactive isoindolinone skeletons (Scheme 1b). The proposed reaction is quite challenging due to the weakly coordinated carboxylate group for C−H activation step. Moreover, the carboxylate group is a strong nucleophile, which may directly attack 1,2-oxazetidine to deliver the undesired ring-opening byproducts. According to our ongoing efforts in catalytic transformation of benzoic acids and heterocycle synthesis,[17] we believe that the rational combination of metal catalyst and solvent may provide a solution to the aforementioned problems. In should be noted that isoindolinones are widely found in natural products and bioactive molecules (Scheme 1c).[18] The established methods mainly rely on the use of stoichiometric oxidants, high temperatures (>200 °C), and specialized *N*-directing groups.[19] The success of this reaction opens a new and sustainable avenue to prepare isoindolinones.

To test the possibility of proposed reaction, we commence the study with the reaction of 2-methylbenzoic acid **1a** and *N*-tosyl-1,2-oxazetidine **2a**. To our delight, the desired isoindolinone product **3aa** can be obtained in 17% yield by employing $[\{Ru(p\text{-cymene})Cl_2\}]_2$ as the catalyst and K_2CO_3 as the base in toluene at 110 °C (Table 1, entry 1). The screening of solvents demonstrated that toluene was the optimal solvent, while other solvents such as CH_3CN and dioxane were ineffective. To further improve the reaction efficiency, the effect of bases has been systematically investigated. By using Na_2CO_3 and K_3PO_4, the yields of **3aa** can be slightly increased to 20% and 24% yields, respectively (entries 5 and 6). KOPiv significantly improved the reaction efficiency to give **3aa** in 30% yield. Other commonly used metal catalysts such as $[RhCp^*Cl_2]_2$ and $[IrCp^*Cl_2]_2$ delivered inferior results (entries 9 and 10). It was found that this reaction was sensitive to the amount of **2a** and reaction temperature. Increasing the loading of **2a** and reaction temperature (120 °C) dramatically improved the outcome of **3aa** (entry 11, 55% yield). Fortunately, the yield of **3aa** can be further improved to 88% (entry 13), when the reaction was conducted at 140 °C.

With the optimal conditions in hand, we next explored the generality of this cascade reaction. As shown in Scheme 2, this reaction exhibited a broad scope with good functional group

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	solvent	base	T (°C)	yield (%)[b]
1	toluene	K_2CO_3	110	17
2	CH_3CN	K_2CO_3	110	trace
3	dioxane	K_2CO_3	110	trace
4	mesitylene	K_2CO_3	110	15
5	toluene	Na_2CO_3	110	20
6	toluene	K_3PO_4	110	24
7	toluene	Cs_2CO_3	110	15
8	toluene	KOPiv	110	30
9[c]	toluene	KOPiv	110	26
10[d]	toluene	KOPiv	110	0
11[e]	toluene	KOPiv	120	55
12[e]	toluene	KOPiv	130	62
13[e]	toluene	KOPiv	140	88

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), $[\{Ru(p\text{-cymene})Cl_2\}]_2$ (4 mol %), base (50 mol %), solvent (2.0 mL) at 110 °C for 16 h. [b]Isolated yields. [c]$[RhCp^*Cl_2]_2$ (4 mol %) was used. [d]$[IrCp^*Cl_2]_2$ (4 mol %) was used. [e]**2a** (0.25 mmol) was used.

tolerance, furnishing the expected isoindolinone products in useful to good yields (38−96% yield). Aromatic acids bearing different alkyl groups such as methyl, ethyl, benzyl, and phenylethyl smoothly reacted with **2a**. Leaving groups such as Cl (**3fa**, **3ja**, **3na**, **3ra**, and **3va**), Br (**3ia** and **3ma**), and I (**3oa** and **3pa**) were well-tolerated in this catalytic system. It should be mentioned that benzoic acid bearing a 3-Br or 3-Cl at the aromatic ring resulted in a mixture of C2- and C6-functionalized products with moderate regioselectivity. Importantly, sensitive groups such as ester (**3sa**), nitro (**3ta**), and *N*,*N*-dimethyl groups (**3ha**) were retained after the reaction, which are ineffective in our previous protocol.[17d] In addition, simple benzoic acid was also compatible in this reaction (**3wa**). Both tetrahedro-1-naphthoic acid and 2-naphthoic acid were successfully coupled with *N*-tosyl-1,2-oxazetidine **2a**, affording structurally complex isoindolinones **3ya** and **3za** in 87% and 96% yields, respectively. Moreover, this catalytic system can be further applied to the late-stage modification of some bioactive benzoic acids such as adapalene (**4aa**), probenecid (**4ba**), flufenamic acid (**4ca**), and bexarotene (**4da**), which strongly demonstrated its synthetic potential in medicinal chemistry. However, heteroaromatic carboxylic acids such as thiophene-2-carboxylic acid and 1*H*-indole-3-carboxylic acid were not suitable for this reaction at the current stage (see SI for more information). Of note, this reaction can be successfully scaled up to 1 mmol without the loss of efficiency (**3aa**, 86% yield).

Furthermore, the effect of the N-protecting group of 1,2-oxazetidine **2** has also been investigated. As outlined in Scheme 2b, aromatic rings of 1,2-oxazetidines bearing electron-donating groups (methoxyl and trimethyl) and electron-withdrawing groups (CF_3, Br, Cl, and F) were well-tolerated in this catalytic system, delivering the desired isoindolinone products (**3ab**−**3ag**) in generally good yields (40−95% yield). However, the substituents on the oxazetidine ring were not compatible in this catalytic system (see SI for more information).

To further demonstrate the synthetic utility of this methodology, we first removed the Ts protecting group from isoindolinone product **3wa** under the Na/naphthalene

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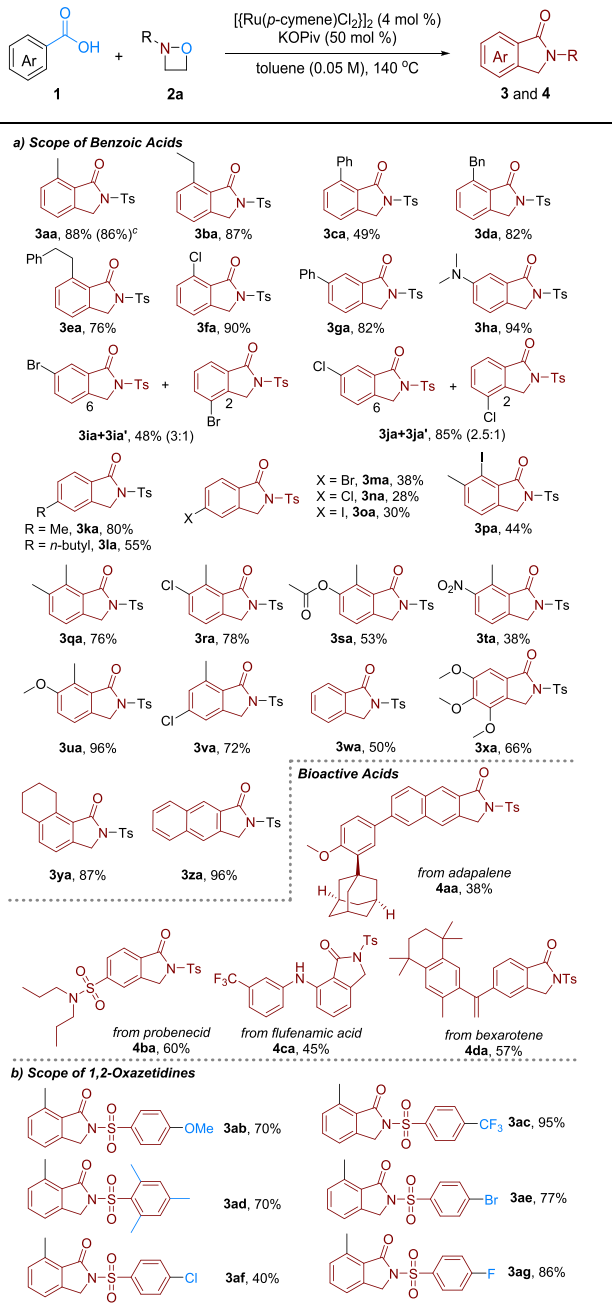
Scheme 2. Scope of Benzoic Acids and 1,2-Oxazetidines[a,b]

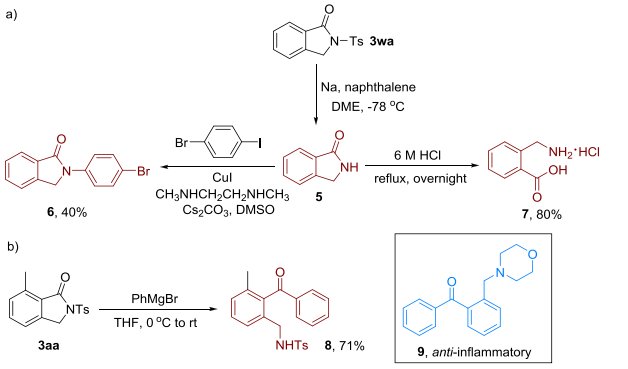


[a]Conditions: **1** (0.1 mmol), **2a** (0.25 mmol), [{Ru(*p*-cymene)Cl_2}]$_2$ (4 mol %), KOPiv (0.05 mmol), toluene (2.0 mL), 140 °C, 10 h. [b]Isolated yields after flash chromatography. [c]1 mmol scale.

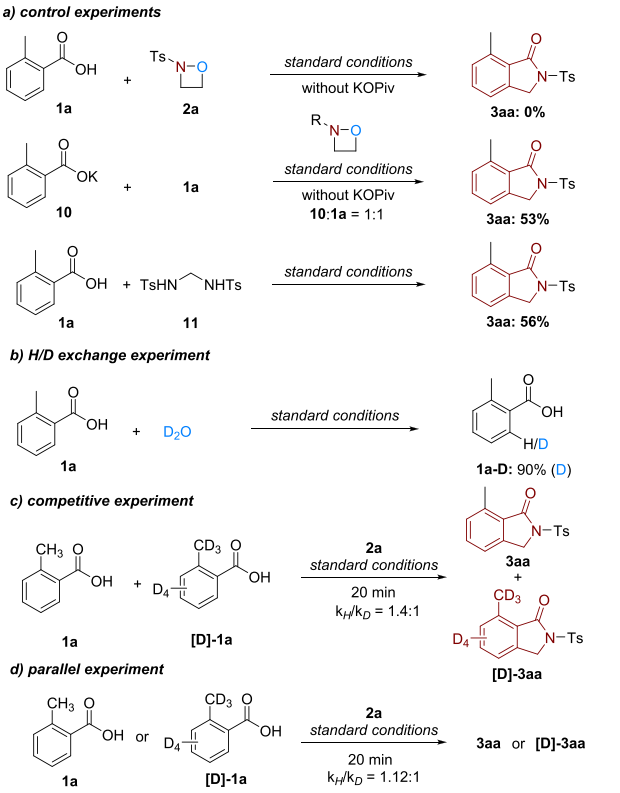
reductive system at −78 °C. In the presence of CuI catalyst, the resulting N-free isoindolinone **5** smoothly coupled with 4-bromoiodobenzene to give product **6** in a useful yield, which shows good antiviral activity (Scheme 3a, left).[20] Moreover, exposure of product **5** to 6 M HCl easily offers the ring-opening product **7** in 80% yield (Scheme 3a, right). Significantly, the reaction of **3aa** with PhMgBr efficiently gives rise to aminomethylbenzophenone **8**. It should be mentioned that product **8** is the core skeleton of a important *anti*-inflammatory compound **9** (Scheme 3b).[21]

To investigate the reaction mechanism, first, a series of control experiments were conducted. As shown in Scheme 4a,

Scheme 3. Synthetic Application of This Methodology



Scheme 4. Mechanistic Study



the reaction did not occur in the absence of KOPiv. In addition, the mixture of potassium 2-methylbenzoate **10** and **1a** delivered the desired product **3aa** in 53% yield. These two reactions demonstrated the importance of base, which may promote the initial generation of potassium 2-methylbenzoate from benzoic acid. Bis(tosylamido)methane **11** is a precursor of the reactive formaldimine compound.[22] The reaction of **1a** with **11** proceeded well under the standard conditions, suggesting the intermediacy of a formaldimine species in this transformation. In the absence of **2a**, 90% deuterium of **1a** was observed when 10 equiv of D_2O were added to the reaction system. This result confirmed that the formation of the five-membered ruthenacycle was a reversible step (Scheme 4b). Moreover, no significant kinetic isotope effects (KIEs) were observed in competitive (k_H/k_D = 1.40:1) and parallel (k_H/k_D = 1.12:1) experiments at the early stage of this reaction (20 min), which indicated the C−H bond activation might not be the rate-determining step for this reaction (Scheme 4c and 4d).

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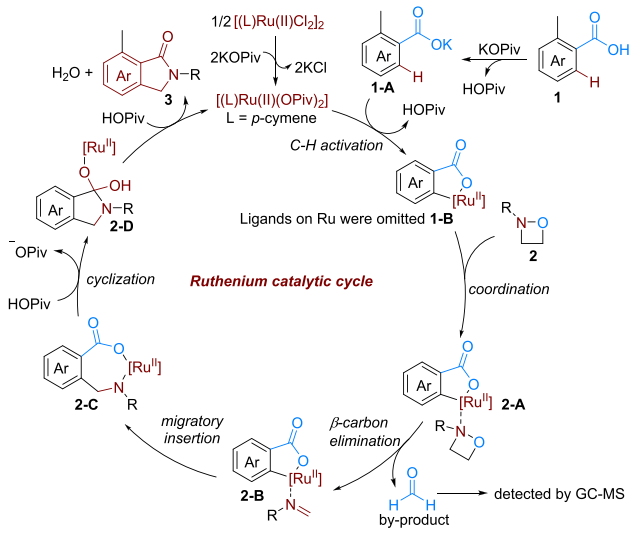
Based on these observations and literature precedents,[15,16] a plausible Ru-catalyzed C−H activation/β-carbon elimination/intramolecular cyclization cascade mechanism was proposed in Scheme 5. In the presence of KOPiv, the rapidly deprotonation

Scheme 5. Plausible Catalytic Cycle



of benzoic acid offers potassium 2-methylbenzoate **1-A**, following by a Ru-catalyzed C−H activation to form a five-membered ruthenacycle intermediate **1-B**. Then, the coordination of 1,2-oxazetidine **2** to **1-B** generates intermediate **2-A**, which performs a β-carbon elimination to afford Ru-imine complex **2-B** along with the formation of formaldehyde as the byproduct. The formaldehyde byproduct can be detected by GC-MS (see SI for more information). Subsequently, the migratory insertion of **2-B** results in a Ru-complex **2-C**, which then proceeds in an intramolecular cyclization to give intermediate **2-D**. The resulting **2-D** delivers the final isoindolinone product by release of H_2O with the regeneration of the Ru catalyst for the next catalytic cycle.

In summary, we successfully combined the strain−release of 1,2-oxazetidines with carboxylic acid directed C−H activation in Ru-mediated isoindolinone synthesis for the first time, furnishing a range of structurally diverse isoindolinone skeletons. The attractive advantages of this reaction include simple operation, broad scope, and highly functional group tolerance, which obviates the use of external oxidants. Importantly, this methodology can be successfully applied to the late-stage modification of some bioactive acids and concise synthesis of biologically important skeletons, demonstrating its great synthetic potential in drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02131.

Detailed experimental procedures and NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Pirenne, V.; Muriel, B.; Waser, J. Catalytic Enantioselective Ring-Opening Reactions of Cyclopropanes. *Chem. Rev.* **2021**, *121*, 227−263. (b) Biletskyi, B.; Colonna, P.; Masson, K.; Parrain, J. L.; Commeiras, L.; Chouraqui, G. Small Rings in the Bigger Picture: Ring Expansion of Three- and Four-membered Rings to Access Larger All-carbon Cyclic Systems. *Chem. Soc. Rev.* **2021**, *50*, 7513. (c) Li, D.; Zang, W.; Bird, M. J.; Hyland, C. J. T.; Shi, M. Gold-Catalyzed Conversion of Highly Strained Compounds. *Chem. Rev.* **2021**, *121*, 8685. Please see SI ref 5 for more related references.

(2) (a) Magers, D.; Davis, S. Ring Strain in the Oxazetidines. *J. Mol. Struct.: THEOCHEM* **1999**, *487*, 205−210. (b) Wang, F.; Yu, S.; Li, X. Transition Metal-catalysed Couplings between Arenes and Strained or Reactive Rings: Combination of C−H Activation and Ring Scission. *Chem. Soc. Rev.* **2016**, *45*, 6462−6477.

(3) Murakami, M.; Ishida, N. Cleavage of Carbon−Carbon σ-Bonds of Four-Membered Rings. *Chem. Rev.* **2021**, *121*, 264−299.

(4) (a) Deng, L.; Dong, G. Carbon−Carbon Bond Activation of Ketones. *Trends in Chemistry* **2020**, *2*, 183−198. (b) Bai, D.; Yu, Y.; Guo, H.; Chang, J.; Li, X. Nickel(0)-Catalyzed Enantioselective [3 + 2] Annulation of Cyclopropenones and α,β-Unsaturated Ketones/Imines. *Angew. Chem., Int. Ed.* **2020**, *59*, 2740−2744. (c) Shi, P.; Tu, Y.; Wang, C.; Kong, D.; Ma, D.; Bolm, C. Synthesis of Benzothiadiazine-1-oxides by Rhodium-Catalyzed C−H Amidation/

https://doi.org/10.1021/acs.orglett.1c02131
Org. Lett. XXXX, XXX, XXX−XXX

Cyclization. *Org. Lett.* **2020**, *22*, 8842−8845. (d) Xu, S.; Takamatsu, K.; Hirano, K.; Miura, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 11797−11801. (e) Xu, S.; Takamatsu, K.; Hirano, K.; Miura, M. Synthesis of Seven-Membered Benzolactones by Nickel-Catalyzed C−H Coupling of Benzamides with Oxetanes. *Chem. - Eur. J.* **2019**, *25*, 9400−9404. Please see SI ref 6 for more related references.

(5) (a) Yu, S.; Li, X. Mild Synthesis of Chalcones via Rhodium(III)-Catalyzed C−C Coupling of Arenes and Cyclopropenones. *Org. Lett.* **2014**, *16*, 1220−1223. (b) Zhou, X.; Yu, S.; Kong, L.; Li, X. Rhodium(III)-Catalyzed Coupling of Arenes with Cyclopropanols via C−H Activation and Ring Opening. *ACS Catal.* **2016**, *6*, 647−651.

(6) (a) Hu, X.-Q.; Liu, Z. K.; Hou, Y. X.; Gao, Y. Single Electron Activation of Aryl Carboxylic Acids. *iScience* **2020**, *23*, 101266. (b) Zeng, Z.; Feceu, A.; Sivendran, N.; Gooßen, L. J. Decarboxylation-Initiated Intermolecular Carbon-Heteroatom Bond Formation. *Adv. Synth. Catal.* **2021**, *363*, 2678−2722. (c) Das, J.; Mal, D. K.; Maji, S.; Maiti, D. Recent Advances in External-Directing-Group-Free C−H Functionalization of Carboxylic Acids Without Decarboxylation. *ACS Catal.* **2021**, *11*, 4205−4229. (d) Wei, Y.; Hu, P.; Zhang, M.; Su, W. Metal-Catalyzed Decarboxylative C−H Functionalization. *Chem. Rev.* **2017**, *117*, 8864−8907. (e) Font, M.; Quibell, J. M.; Perry, G. J. P.; Larrosa, I. The Use of Carboxylic Acids as Traceless Directing Groups for Regioselective C−H Bond Functionalisation. *Chem. Commun.* **2017**, *53*, 5584−5597. Please see SI ref 7 for more related references.

(7) Cheng, G.; Li, T. J.; Yu, J. Q. Practical Pd(II)-Catalyzed C−H Alkylation with Epoxides: One-Step Syntheses of 3,4-Dihydroisocoumarins. *J. Am. Chem. Soc.* **2015**, *137*, 10950−10953.

(8) Zhou, K.; Zhu, Y.; Fan, W.; Chen, Y.; Xu, X.; Zhang, J.; Zhao, Y. Late-Stage Functionalization of Aromatic Acids with Aliphatic Aziridines: Direct Approach to Form B-Branched Arylethylamine Backbones. *ACS Catal.* **2019**, *9*, 6738−6743.

(9) Wang, S.; Miao, E.; Wang, H.; Song, B.; Huang, W.; Yang, W. Rh-Catalyzed Cascade C−H Activation/C−C Cleavage/cyclization of Carboxylic Acids with Cyclopropanols. *Chem. Commun.* **2021**, *57*, 5929−5932.

(10) Hu, Z.; Hu, X.-Q.; Zhang, G.; Gooßen, L. J. Ring-Opening Ortho-C−H Allylation of Benzoic Acids with Vinylcyclopropanes: Merging Catalytic C−H and C−C Activation Concepts. *Org. Lett.* **2019**, *21*, 6770−6773.

(11) (a) Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRS Press: Boca Raton, FL, 2002. (b) Alcamí, M.; Mó, O.; Yáñez, M. G2 Ab Initio Calculations on Three-Membered Rings: Role of Hydrogen Atoms. *J. Comput. Chem.* **1998**, *19*, 1072−1086.

(12) (a) Barker, M. W.; Gill, J. T. Heterocycles from Ketenimines. IV. 3-Iminosubstituted-1,2Oxazetidines. *J. Heterocycl. Chem.* **1970**, *7*, 1203−1204. (b) Baldwin, J. E.; Bhatnagar, A. K.; Choi, S. C.; Shortridge, T. J. Rearrangement of Strained Dipolar Species, Aziridine N-Oxides II. *J. Am. Chem. Soc.* **1971**, *93*, 4082−4083.

(13) Javorskis, T.; Sriubaitė, S.; Bagdžiūnas, G.; Orentas, E. N-Protected 1,2-Oxazetidines as a Source of Electrophilic Oxygen: Straightforward Access to Benzomorpholines and Related Heterocycles by Using a Reactive Tether. *Chem. - Eur. J.* **2015**, *21*, 9157−9164.

(14) (a) Wu, B.; Yang, J.; Gao, M.; Hu, L. Ring-Strain-Enabled Catalytic Asymmetric Umpolung C−O Bond-Forming Reactions of 1,2-Oxazetidines for the Synthesis of Functionalized Chiral Ethers. *Org. Lett.* **2020**, *22*, 5561−5566. (b) Wu, B.; Chen, H.; Gao, M.; Gong, X.; Hu, L. Synthesis of 1,3-Aminoalcohols and Spirocyclic Azetidines via Tandem Hydroxymethylation and Aminomethylation Reaction of B-Keto Phosphonates with N-Nosyl-O-(2-bromoethyl)-hydroxylamine. *Org. Lett.* **2021**, *23*, 4152−4157.

(15) Li, S.; Shi, P.; Liu, R. H.; Hu, X. H.; Loh, T. P. Cobalt-Catalyzed N−O and C−C Bond Cleavage in 1,2-Oxazetidines: Solvent-Controlled C−H Aminomethylation and Hydroxymethylation of Heteroarenes. *Org. Lett.* **2019**, *21*, 1602−1606.

(16) Li, S.; Shan, Q. C.; Hu, L. M.; Ma, X. Q.; Hu, X. H. Merging Alkenyl C−H Activation with the Ring-opening of 1,2-oxazetidines: Ruthenium-catalyzed Aminomethylation of Enamides. *Chem. Commun.* **2020**, *56*, 7969−7972.

(17) (a) 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. (b) Hu, X.-Q.; Liu, Z. K.; Hou, Y. X.; Zhang, G.; Gao, Y. Ru-catalysed $C(sp^2)$−H Vinylation/annulation of Benzoic Acids and Alkynes: Rapid Access to Medium-sized Lactones. *Chem. Commun.* **2021**, *57*, 1113−1116. (c) Gao, Y.; Nie, J.; Li, Y.; Li, X.; Chen, Q.; Huo, Y.; Hu, X.-Q. Rh-Catalyzed C−H Amination/Annulation of Acrylic Acids and Anthranils by Using − COOH as a Deciduous Directing Group: An Access to Diverse Quinolines. *Org. Lett.* **2020**, *22*, 2600−2605. (d) Hu, X.-Q.; Hou, Y. X.; Liu, Z. K.; Gao, Y. Ruthenium-catalysed C−H/C−N Bond Activation: Facile Access to Isoindolinones. *Org. Chem. Front.* **2021**, *8*, 915−921. (e) 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. (f) Gao, Y.; Yang, S.; Huo, Y.; Chen, Q.; Li, X.; Hu, X.-Q. NiH-Catalyzed Hydroamination/Cyclization Cascade: Rapid Access to Quinolines. *ACS Catal.* **2021**, *11*, 7772−7779.

(18) (a) Speck, K.; Magauer, T. The chemistry of isoindole natural products. *Beilstein J. Org. Chem.* **2013**, *9*, 2048−2078. (b) Csende, F.; Miklós, F.; Porkoláb, A. Design and synthesis of some isoindoline derivatives as analogues of the active anti-inflammatory Indoprofen. *ARKIVOC* **2013**, *2013*, 378−388.

(19) (a) Murahashi, S. Synthesis of Phthalimidines from Schiff bases and carbon monoxide. *J. Am. Chem. Soc.* **1955**, *77*, 6403−6404. (b) Rosenthal, A.; Astbury, R. F.; Hubscher, A. Reaction of aromatic ketoximes with carbon monoxide and hydrogen1. *J. Org. Chem.* **1958**, *23*, 1037−1039. (c) Hernando, E.; Villalva, J.; Martínez, Á. M.; Alonso, I.; Rodríguez, N.; Gómez Arrayás, R.; Carretero, J. C. Palladium-Catalyzed Carbonylative Cyclization of Amines via γ-$C(sp^3)$−H Activation: Late-Stage Diversification of Amino Acids and Peptides. *ACS Catal.* **2016**, *6*, 6868−6882. Please see SI ref 8 for more related references.

(20) Wang, Y.; Wang, H.; Jiang, X.; Jiang, Z.; Guo, T.; Ji, X.; Li, Y.; Li, Y.; Li, Z. Synthesis and Broad Antiviral Activity of Novel 2-aryl-isoindolin-1-ones Towards Diverse Enterovirus A71 Clinical Isolates. *Molecules* **2019**, *24*, 985.

(21) Coombs, R.; Houlihan, W. J.; Nadelson, J.; Takesue, E. I. Synthesis and Antiinflammatory Activity of tert-aminomethylbenzophenones. *J. Med. Chem.* **1971**, *14*, 1072−1074.

(22) Li, Z. Y.; Chaminda Lakmal, H. H.; Cui, X. Enabling Catalytic Arene C−H Amidomethylation via Bis(tosylamido)methane as a Sustainable Formaldimine Releaser. *Org. Lett.* **2019**, *21*, 3735−3740.

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