Letter

Iridium-Catalyzed Synthesis of Substituted Indanones from Aromatic Carboxylates and Unsaturated Ketones

Guodong Zhang, Zhiyong Hu, Giulia Bertoli, and Lukas J. Gooßen

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.9b02536 • Publication Date (Web): 02 Aug 2019

Iridium-Catalyzed Synthesis of Substituted Indanones from Aromatic Carboxylates and Unsaturated Ketones

Guodong Zhang, Zhiyong Hu, Giulia Bertoli, and Lukas J. Gooßen*

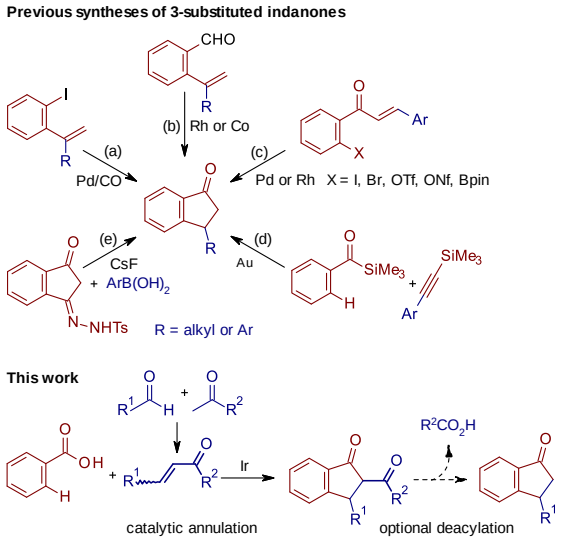
Fakultät für Chemie und Biochemie; Ruhr-Universität Bochum; Universitätsstr. 150, 44801 Bochum (Germany)

ABSTRACT: A catalytic annulation is presented that provides straightforward, modular synthetic access to 3-substituted indanones from benzoic acids and α,β-unsaturated ketones. It is catalyzed by a bimetallic Ir/In system and proceeds via hydroarylation followed by Claisen condensation and optional retro-Claisen deacylation. The annulation may be combined into a one-pot procedure with the synthesis of the unsaturated ketone substrates from aldehydes and acetone. Two complementary reaction protocols are provided that are applicable to diversely functionalized electron-rich and electron-poor substrates.

KEYWORDS: *iridium; C–H activation; benzoic acids; substituted indanones; diketo compounds*

Substituted indanones have distinct biological activity,[1] and are thus common substructures in pharmaceuticals.[2] Moreover, they are valuable synthetic intermediates.[3] Traditional synthetic entries to substituted indanones, such as inter- or intramolecular Friedel-Crafts reactions of cinnamic acid derivatives,[4] suffer from rather harsh, acidic conditions and/or low regioselectivities.

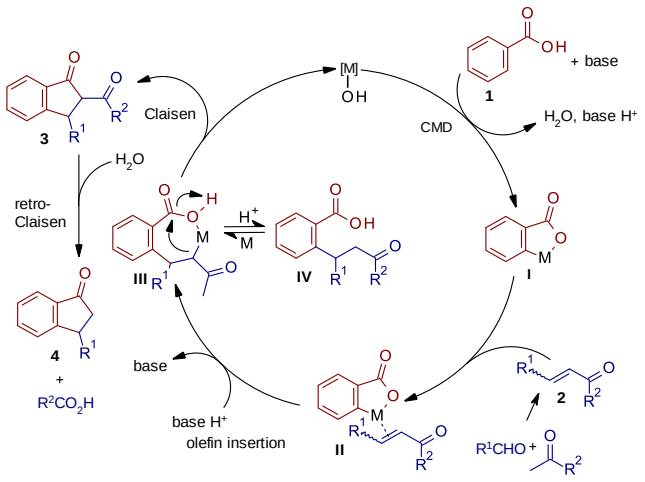
Scheme 1. Strategies for the synthesis of 3-substituted indanones.



Transition metal-catalyzed reactions aiming at the regioselective construction of substituted indanones (Scheme 1),[5] including Pd-catalyzed carbonylative cyclisations of iodo-substituted 1,1-diaryl alkenes (a)[6] and Rh- or Co-catalyzed hydroacylations (b) have opened up regioselective entries to this substrate class,[7] but depend on the availability of elaborate substrates. The same limitation applies to the reductive cyclisation of 2-substitued chalcones (c)[8] and Au-catalyzed C–H coupling of acylsilanes with TMS-arylacetylenes (d).[9] The CsF-promoted reductive cross-coupling of 1,3-indanedione monotosylhydrazone with an arylboronic acid exemplifies a synthetic strategy in which an organic residue is introduced selectively in the 3-position of a pre-formed indanone ring (e).[10]

As an advantageous alternative to these methods, we herein disclose a modular iridium-catalysed synthesis of indanones from widely available benzoic acid, aldehyde, and methyl ketone building blocks.[11]

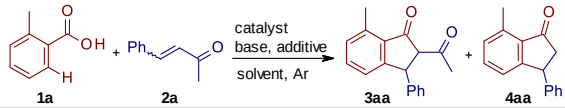
Scheme 2. Mechanistic blueprint of the targeted annelation.



In continuation of research performed in the groups of Yu,[12] Li,[13] Daugulis,[14] Larrosa,[15] Ackermann,[16] Su,[17] our group,[18] and others[19] on carboxylic acids as directing groups in C–H functionalizations, we recently discovered a new reaction mode of benzoic acids with α,β-unsaturated ketones (Scheme 2).[20] In the presence of a Rh catalyst, the benzoic acid **1** undergoes *ortho*-metalation to intermediate

I,[21] which in turn carbometalates the α,β-unsaturated ketone **2** to give **III**. Rather than continuing along known Heck-type or decarboxylative hydroarylation pathways,[22] the Rh enolate then substitutes the unprotected carboxylate OH group to give the Claisen product **3**. Under Lewis-acidic reaction conditions, this step is inevitably followed by a retro-Claisen deacylation,[23] furnishing the indanone **4**. The new reaction concept promised to open up a window of opportunities for the synthesis of indanones, but unfortunately, the scope of the prototypical Rh/In catalyst was rather limited. Best results were obtained with cyclic ketone substrates, whereas the yields were only moderate for simple alkenyl methyl ketones, and all test reactions had failed for 3-aryl alkenones. Moreover, it was not possible to stop the reaction at the acyl intermediate **III**. With Ru, similar substrates were reported to enter complex reaction cascades with double incorporation of the enone substrate into 2-substituted indanones and spirocyclic derivatives.[24]

Table 1. Optimization of the reaction conditions[a]



	catalyst	base, additive	solvent	**3aa** (%)	**4aa** (%)
1	$[RhCp^*Cl_2]_2$	K_2CO_3, $In(OTf)_3$	^{t}AmOH	N.D	35
2	$[RhCp^*Cl_2]_2$	K_2CO_3	-	20	2
3	$[Ru(cy)Cl_2]_2$	K_2CO_3	-	N.D	N.D
4	$[IrCODCl]_2$	K_2CO_3	-	N.D	N.D
5	$[IrCp^*Cl_2]_2$	K_2CO_3	-	39	25
7	$[IrCp^*Cl_2]_2$	K_3PO_4	-	35	8
8	$[IrCp^*Cl_2]_2$	Na_2CO_3	-	37	21
6	$[IrCp^*Cl_2]_2$	NaOAc	-	49	N.D
9	$[IrCp^*Cl_2]_2$	KOAc	-	55	N.D
10	$[IrCp^*Cl_2]_2$	KOAc[b]	-	63	3
11[c]	$[IrCp^*Cl_2]_2$	KOAc[b]	-	72	3
12	$[IrCp^*Cl_2]_2$	K_2CO_3	dioxane	28	20
13	$[IrCp^*Cl_2]_2$	K_2CO_3	NMP	N.D	21
14	$[IrCp^*Cl_2]_2$	K_2CO_3	^{t}AmOH	24	44
15	$[IrCp^*Cl_2]_2$	K_2CO_3,$Fe(OTf)_3$	^{t}AmOH	N.D	60
16	$[IrCp^*Cl_2]_2$	K_2CO_3, $Zn(OTf)_2$	^{t}AmOH	N.D	71
17	$[IrCp^*Cl_2]_2$	K_2CO_3, $Sc(OTf)_3$	^{t}AmOH	N.D	80
18	$[IrCp^*Cl_2]_2$	K_2CO_3, $In(OTf)_3$	^{t}AmOH	N.D	84

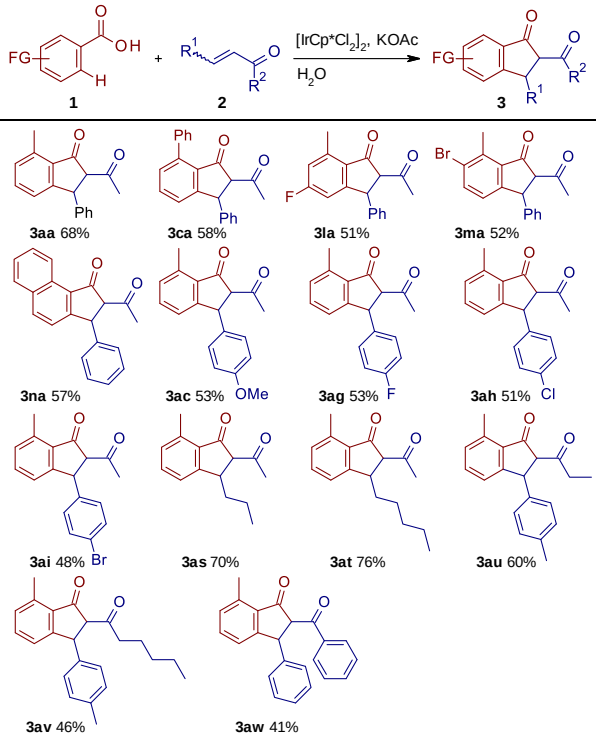
[a]Conditions: 0.5 mmol of **1a**, 0.8 mmol of **2a**, 3 mol% of catalyst, 7.5 mol% of additive, 0.4 equiv. of base, 0.2 mL of H2O or of 3/1 solvent/H2O, 140 °C, 16 h. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b]1.0 equiv. [c]150 °C. ^{t}AmOH = *tert*-amyl alcohol, cy = *p*-cymene.

We started our search for an effective and tuneable catalyst using the reaction of 2-methylbenzoic acid (**1a**) and β-phenyl vinyl ketone (**2a**) as a model (Table 1). As expected, unsatisfactory conversion mostly to the deacylated product **4aa** was observed in the presence of the Rh/In system (entry 1). In order to slow down deacylation, the Lewis acid InOTf was left out, and the reaction mixture was buffered with aqueous K_2CO_3. Under these conditions, neither ruthenium nor rhodium systems gave satisfactory conversion (entries 2-3).

In an extensive screening of various catalyst metals, solely $[IrCp^*Cl_2]_2$ gave significant amounts of the desired product **3aa**, along with the deacylation product **4aa** (entry 4-5).[25] Further investigations revealed that the base has a decisive influence on the ratio between these products (entries 6-9). Only with KOAc or NaOAc, **3aa** was obtained selectively, all other bases tested led to deacylation. After further adjustments (entries 10-11), the highest yield of **3aa** was obtained with 3 mol% $[IrCp^*Cl_2]_2$ as the catalyst in the presence of 2.5 M aqueous KOAc (1.0 equiv.) and 1.6 equiv. of the alkenone at 150 °C without solvent (Protocol A).

In the presence of K_2CO_3, the deacylated indanone **4aa** was formed in significant amounts (entry 5). Its fraction increased in aqueous polar organic solvents, particularly in ^{t}AmylOH/H_2O, where it was the major product (entries 12-14). Adding catalytic amounts of Lewis acids further promoted the deacylation step, and best results were obtained with $In(OTf)_3$ (entries 15–18).[23f] The highest selectivity for **4aa** was obtained when stirring **1a** with 1.6 equiv. of the alkenone in the presence of 3 mol% $[IrCp^*Cl_2]_2$ and 7.5% $In(OTf)_3$ with 0.4 equiv. of a 1 M solution of K_2CO_3 in a 3:1 ^{t}AmylOH/water mixture at 140 °C (Protocol B).

Table 2. Substrate scope of 2-acyl-3-arylindanones[a]

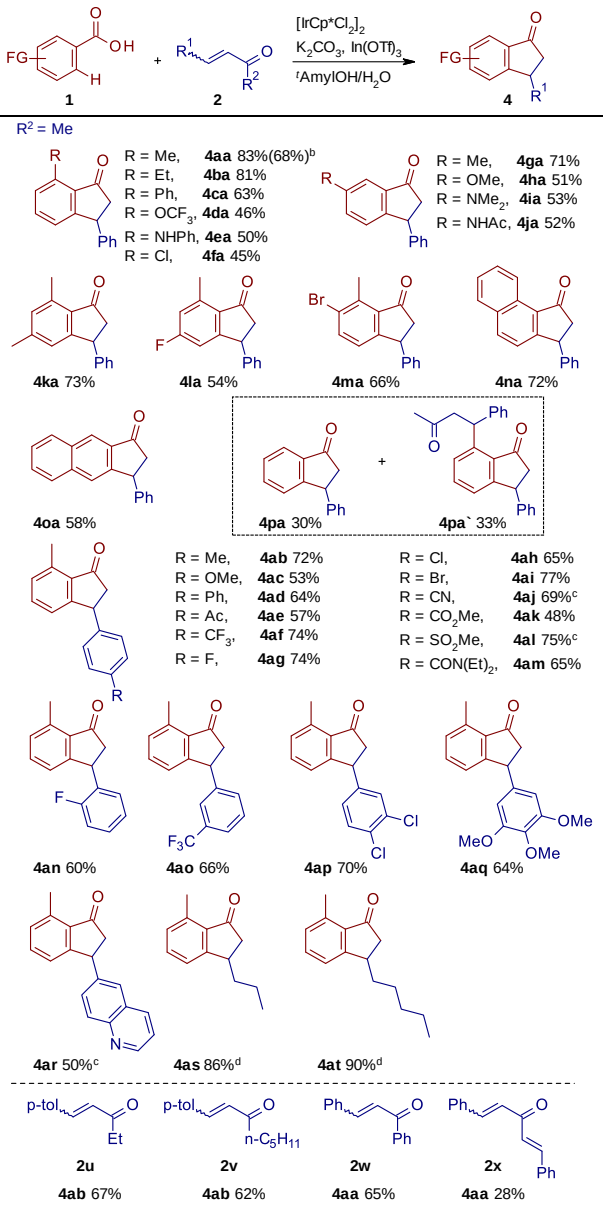


[a]Conditions: 0.5 mmol of **1**, 0.8 mmol of **2**, 3 mol% of [IrCp*Cl2]2, 0.5 mmol of KOAc, 0.2 mL H2O, 150 °C, 16 h.

Having thus found two complementary protocols for the non-deacylative (A) and deacylative annulation of benzoic

acids (B), we next investigated their preparative applicability to the synthesis of indanones. The scope of the non-deacylative protocol (A) was investigated by coupling representative aromatic carboxylic acids with several unsaturated ketones. As shown in Table 2, aliphatic as well as aromatic substituents bearing electron-donating or electron-withdrawing groups are smoothly converted (**3aa**-**3at**). Both aliphatic and aromatic acyl groups can be introduced in the 2-position (**3au**-**3aw**).

Table 3. Substrate scope of 3-arylindanones[a]



[a]Reaction conditions: 0.5 mmol of **1**, 0.8 mmol of **2**, 3 mol% of [IrCp*Cl2]2, 7.5 mol% of In(OTf)3, 0.2 mmol of K2CO3, 0.2 mL of tAmOH/H2O (3:1), 140 °C, 16 h. [b]10 mmol scale. [c]using 5 mol% of [IrCp*Cl2]2. [d]using 0.6 mmol of **2**.

The functional group tolerance was not tested for this protocol separately, since it is safe to assume that all compounds that were successfully converted in the deacylative reaction cascade (protocol B) will also survive this one-step process. The scope of the deacylative reaction variant (B) with regard to the aromatic carboxylic acid was tested using β-phenyl vinyl ketone (**2a**) as the coupling partner (Table 3). Benzoic acids bearing electron-donating or electron-withdrawing groups were smoothly coupled to give moderate to good product yields. For *meta*-substituted benzoic acids, C–H activation occurred selectively at the less hindered *ortho*-position (**4ga**-**4ja**). Multisubstituted benzoic and naphthyl carboxylic acids also gave high yields (**4ka**-**4oa**). When starting with unsubstituted benzoic acid (**1p**), the double hydroarylation product **4pa'** was obtained. Since the carbonyl group of indanones has been shown not to be an effective directing group for C–H activation,[26] the second hydroarylation must have occurred while the carboxylate group was still intact. Thus, one can conclude that the Ir enolate formation must be reversible (see Scheme 2, **III** ⇌ **IV**) and the hydroarylation step is faster than Claisen condensation. After double hydroarylation of **1p**, only one of the ketone side chains can undergo the subsequent Claisen steps leading to **4pa'**.

The scope with regard to the α,β-unsaturated ketones was explored using *o*-toluic acid as coupling partner. β-Arylated ketones bearing electron-rich and electron-poor substituents in their *o*-, *m*-, or *p*-position reacted similarly well, and various functional groups, including CF_3, halo, CN, keto, ester, amide, pyridyl, and sulfonyl moieties were tolerated. The new catalyst system gives higher yields for most substrates that can also be converted with the Rh-based catalyst, but interestingly, cyclic alkenones, which are optimal for the Rh protocol,[20] give unsatisfactory results (**4as**-**4at**).

The deacylative reaction variant (B) is not limited to methyl ketones but can be conducted with various long-chain alkyl, aryl, and even divinyl ketones. At this stage, other types of electron-deficient alkenes, including acid derivatives or aldehydes, did not give the desired product in either protocol (Scheme S6). The reaction was successfully scaled up to 10 mmol for the example of β-phenyl vinyl ketone (**4aa**). The key advantage of this synthetic entry to indanones is that the α,β-unsaturated ketones are easily accessible by aldol condensation of methyl ketones with aldehydes. This condensation step can even be performed in situ, which was demonstrated for the example of indanone **4aa** (Scheme 3).

Scheme 3. One-pot process from benzaldehyde and acetone.

The reaction mechanism was elucidated in a series of experiments (Scheme S1). In the presence of $[IrCp^*Cl_2]_2$, *o*-toluic acid was swiftly deuterated in *ortho*-position, indicating rapid and reversible C–H bond cleavage. Deuterium-labelling experiments revealed that the 3-arylindanone α-hydrogen originates from the solvent (Scheme S2).

Scheme 4. Mechanistic investigations.

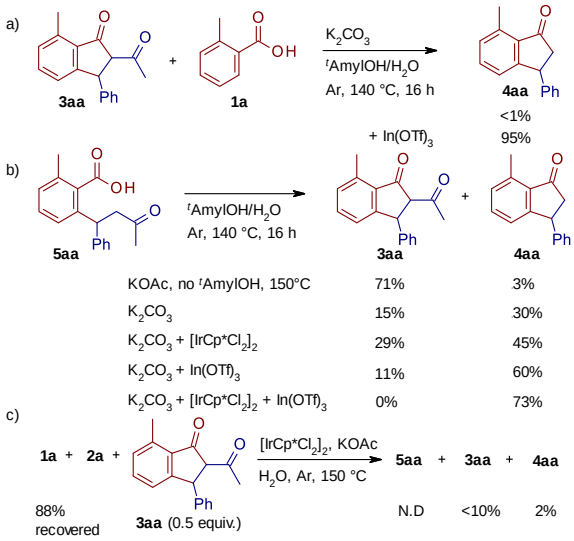
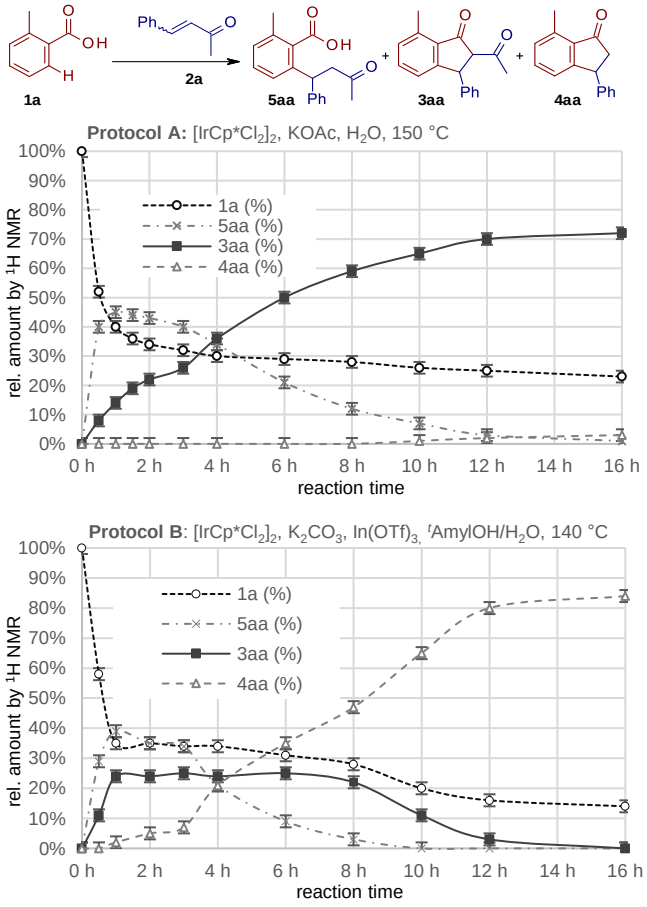


Chart 1. Yield-time plots for A) acylindanone protocol; B) deacylative protocol.



No deacylation of pre-formed **3aa** takes place without In(OTf)$_3$ (Scheme 4a). However, starting from the hydroarylation product **5aa**, Claisen reaction with partial deacylation is promoted even by K_2CO_3, which explains why strong bases must be avoided when aiming to form product **4aa**. [IrCp*Cl$_2$]$_2$ and In(OTf)$_3$ both facilitate this step (Scheme 4b). A control reaction, in which excess **3aa** was added, proceeded much more slowly, indicating that **3aa** interferes with the first reaction step, possibly by its chelating coordination to the iridium catalyst (Scheme 4c).

These experiments suggest the presence of two competing pathways for the deacylative process, one proceeding via intermediate **5aa** directly to product **4aa**, the other via formation of **3aa**. The conversion vs time plots in Chart 1 illustrate how the intermediates **5aa** (protocol A) or **3aa** and **4aa** (protocol B) temporarily build up in the non-deacylative and the deacylative reaction protocols, respectively. All findings are in excellent agreement with the proposed mechanism (Scheme 2).

In conclusion, a newly developed Ir-based catalyst system enables the modular construction of 3-substituted indanone moieties from simple benzoic acids, aldehydes, and alkyl ketones. It fulfills the high expectations raised by the prototype Rh-based catalyst generation and leads the hydroarylation/ Claisen approach to synthetic maturity. Two complementary reaction protocols provide selective entries to either 2-acyl indanones or their deacylated derivatives.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
General methods, detailed mechanistic studies, experimental procedures, synthesis and characterization of products, and NMR spectra (PDF).

AUTHOR INFORMATION

Corresponding Author

*E-mail: lukas.goossen@rub.de

ORCID

Lukas J. Gooßen: 0000-0002-2547-3037

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy – EXC-2033 – Projektnummer 390677874, SFB-TRR 88 "3MET", and GO 853/12-1. We thank UMICORE for donating chemicals, BMBF and the state of NRW (Center of Solvation Science "ZEMOS"), the CSC (fellowships to G.Z. and Z.H.) for financial support, and M. Wüstefeld for HRMS measurements.

REFERENCES

(1) (a) Posternak, A. G.; Garlyauskayte, R. Y.; Yagupolskii, L. M. BTISA-Catalyzed Friedel–Crafts Bimolecular Cyclization of Cinnamic Acid under Superelectrophilic Solvation Conditions. *J. Fluor. Chem.* **2010**, *131*, 274–277. (b) Leoni, L. M.; Hamel, E.; Genini, D.; Shih, H.; Carrera, C. J.; Cottam, H. B.; Carson, D. A. Indanocine, a Microtubule-Binding Indanone and a Selective Inducer of Apoptosis in Multidrug-Resistant Cancer Cells. *JNCI J. Natl. Cancer Inst.* **2000**, *92*, 217–224.

(2) Patil, S. A.; Patil, R.; Patil, S. A. Recent Developments in Biological Activities of Indanones. *Eur. J. Med. Chem*. **2017**, *138*, 182–198.

(3) Kerr, D. J.; Hamel, E.; Jung, M. K.; Flynn, B. L. The Concise Synthesis of Chalcone, Indanone and Indenone Analogues of Combretastatin A4. *Bioorg. Med. Chem*. **2007**, *15*, 3290–3298.

(4) (a) Sartori, G.; Maggi', R.; Bigi', F.; Porta', C.; Taob, X.; Bernardi', G. L.; Ianelli', S.; Nardelli', M. Selective Synthesis of 1-Indanones via Tandem Knoevenagel Condensation-Cycloalkylation of P-Dicarbonyl Compounds and Aldehydes. *Tetrahedron* **1995**, *51*, 12179–12192. (b) Kangani, C. O.; Day, B. W. Mild, Efficient Friedel–Crafts Acylations from Carboxylic Acids Using Cyanuric Chloride and AlCl3. *Org. Lett*. **2008**, *10*, 2645–2648. (c) Chassaing, S.; Kumarraja, M.; Pale, P.; Sommer, J. Zeolite-Directed Cascade Reactions: Cycliacyarylation versus Decarboxyarylation of α,β-Unsaturated Carboxylic Acids. *Org Lett*. **2007**, *9*, 3889–3892. (d) Yin, W.; Ma, Y.; Xu, J.; Zhao, Y. Microwave-Assisted One-Pot Synthesis of 1-Indanones from Arenes and α,β-Unsaturated Acyl Chlorides. *J. Org. Chem*. **2006**, *71*, 4312–4315. (e) Ramulu, B. V.; Niharika, P.; Satyanarayana, G. Superacid-Promoted Dual C–C Bond Formation by Friedel–Crafts Alkylation/Acylation of Cinnamate Esters: Synthesis of Indanones. *Synthesis* **2015**, *47*, 1255–1268. (f) Prakash, G. K. S.; Yan, P. Superacidic Trifluoromethanesulfonic Acid-Induced Cycli-Acyalkylation of Aromatics. *Catal. Lett*. **2003**, *87*, 109–112. (g) Ramulu, B. V.; Reddy, A. G. K.; Satyanarayana, G. Superacid-Promoted Dual C–C Bond Formation by Friedel–Crafts Alkylation and Acylation of Ethyl Cinnamates: Synthesis of Indanones. *Synlett*. **2013**, *24*, 868–872. (h) Sani Souna Sido, A.; Chassaing, S.; Kumarraja, M.; Pale, P.; Sommer, J. Solvent-Dependent Behavior of Arylvinylketones in HUSY-Zeolite: A Green Alternative to Liquid Superacid Medium. *Tetrahedron Lett*. **2007**, *48*, 5911–5914.

(5) (a) Tiwari, P. K.; Aidhen, I. S. A Weinreb Amide Based Building Block for Convenient Access to β,β-Diarylacroleins: Synthesis of 3-Arylindanones. *Eur. J. Org. Chem*. **2016**, 2637–2646. (b) Rajesh, N.; Prajapati, D. Indium-Catalyzed, Novel Route to β,β-Disubstituted Indanones via Tandem Nakamura Addition–hydroarylation–decarboxylation Sequence. *Chem. Commun*. **2015**, *51*, 3347–3350.

(6) Gagnier, S. V.; Larock, R. C. Palladium-Catalyzed Carbonylative Cyclization of Unsaturated Aryl Iodides and Dienyl Triflates, Iodides, and Bromides to Indanones and 2-Cyclopentenones. *J. Am. Chem. Soc*. **2003**, *125*, 4804–4807.

(7) (a) Kundu, K.; McCullagh, J. V.; Morehead, A. T. Hydroacylation of 2-Vinyl Benzaldehyde Systems: An Efficient Method for the Synthesis of Chiral 3-Substituted Indanones. *J. Am. Chem. Soc*. **2005**, *127*, 16042–16043. (b) Oonishi, Y.; Ogura, J.; Sato, Y. Rh(I)-Catalyzed Intramolecular Hydroacylation in Ionic Liquids. *Tetrahedron Lett*. **2007**, *48*, 7505–7507. (c) Yang, J.; Yoshikai, N. Cobalt-Catalyzed Enantioselective Intramolecular Hydroacylation of Ketones and Olefins. *J. Am. Chem. Soc*. **2014**, *136*, 16748–16751.

(8) (a) Minatti, A.; Zheng, X.; Buchwald, S. L. Synthesis of Chiral 3-Substituted Indanones via an Enantioselective Reductive-Heck Reaction. *J. Org. Chem*. **2007**, *72*, 9253–9258. (b) Yu, Y.-N.; Xu, M.-H. Enantioselective Synthesis of Chiral 3-Aryl-1-Indanones through Rhodium-Catalyzed Asymmetric Intramolecular 1,4-Addition. *J. Org. Chem*. **2013**, *78*, 2736–2741. (c) Yue, G.; Lei, K.; Hirao, H.; Zhou, J. (Steve). Palladium-Catalyzed Asymmetric Reductive Heck Reaction of Aryl Halides. *Angew. Chem. Int. Ed*. **2015**, *54*, 6531–6535.

(9) González, J.; Santamaría, J.; Ballesteros, A. Gold(I)-Catalyzed Addition of Silylacetylenes to Acylsilanes: Synthesis of Indanones by C–H Functionalization through a Gold(I) Carbenoid. *Angew. Chem. Int. Ed*. **2015**, *54*, 13678–13681.

(10) Liu, Y.; Chen, L.; Liu, Y.; Liu, P.; Dai, B. Synthesis of 3-Aryl-1-Indanones via CsF-Promoted Coupling of Arylboronic Acids with N -Tosylhydrazones. *J. Chem. Res*. **2018**, *42*, 40–43.

(11) Yu, L.; Han, M.; Luan, J.; Xu, L.; Ding, Y.; Xu, Q. Ca(OH)2-Catalyzed Condensation of Aldehydes with Methyl Ketones in Dilute Aqueous Ethanol: A Comprehensive Access to α,β-Unsaturated Ketones. *Sci. Rep*. **2016**, *6*, 30432.

(12) (a) Chen, G.; Zhuang, Z.; Li, G.-C.; Saint-Denis, T. G.; Hsiao, Y.; Joe, C. L.; Yu, J.-Q. Ligand-Enabled β-C-H Arylation of α-Amino Acids Without Installing Exogenous Directing Groups. *Angew. Chem. Int. Ed.* **2017**, *56*, 1506–1509. (b) Liu, T.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. Palladium(II)-Catalyzed Site-Selective C(Sp3)–H Alkynylation of Oligopeptides: A Linchpin Approach for Oligopeptide-Drug Conjugation. *Angew. Chem. Int. Ed*. **2017**, *56*, 10924–10927.

(13) 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.

(14) (a) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. Two Methods for Direct Ortho -Arylation of Benzoic Acids. *J. Am. Chem. Soc*. **2007**, *129*, 9879–9884. (b) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed Coupling of Benzoic Acid C–H Bonds with Alkynes, Styrenes, and 1,3-Dienes. *Angew. Chem. Int. Ed*. **2018**, *57*, 1688–1691.

(15) (a) 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. – Eur. J*. **2017**, *23*, 549–553. (b) 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.

(16) (a) 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. – Eur. J*. **2017**, *23*, 17449–17453. (b) Qiu, Y.; Tian, C.; Massignan, L.; Rogge, T.; Ackermann, L. Electrooxidative Ruthenium-Catalyzed C–H/O–H Annulation by Weak O -Coordination. *Angew. Chem. Int. Ed*. **2018**, *57*, 5818–5822. (c) Qiu, Y.; Stangier, M.; Meyer, T. H.; Oliveira, J. C. A.; Ackermann, L. Iridium-Catalyzed Electrooxidative C–H Activation by Chemoselective Redox-Catalyst Cooperation. *Angew. Chem. Int. Ed*. **2018**, *57*, 14179–14183.

(17) Zhang, Y.; Zhao, H.; Zhang, M.; Su, W. Carboxylic Acids as Traceless Directing Groups for the Rhodium(III)-Catalyzed Decarboxylative C–H Arylation of Thiophenes. *Angew. Chem. Int. Ed.* **2015**, *54*, 3817–3821.

(18) (a) Zhang, G.; Jia, F.; Gooßen, L. J. Regioselective C–H Alkylation via Carboxylate-Directed Hydroarylation in Water. *Chem. – Eur. J*. **2018**, *24*, 4537–4541. (b) Trita, A. S.; Biafora, A.; Pichette Drapeau, M.; Weber, P.; Gooßen, L. J. Regiospecific Ortho-C–H Allylation of Benzoic Acids. *Angew. Chem. Int. Ed*. **2018**, *57*, 14580–14584. (c) 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.

(19) (a) Han, W.-J.; Pu, F.; Li, C.-J.; Liu, Z.-W.; Fan, J.; Shi, X.-Y. Carboxyl-Directed Conjugate Addition of C–H Bonds to α,β-Unsaturated Ketones in Air and Water. *Adv. Synth. Catal*. **2018**, *360*, 1358–1363. (b) Shi, G.; Zhang, Y. Carboxylate-Directed C–H Functionalization. *Adv. Synth. Catal.* **2014**, *356*, 1419–1442. (c) Pichette Drapeau, M.; Gooßen, L. J. Carboxylic Acids as Directing Groups for C–H Bond Functionalization. *Chem. – Eur. J*. **2016**, *22*, 18654–18677. (d) Chen, C.; Liu, P.; Tang, J.; Deng, G.; Zeng, X. Iridium-Catalyzed, Weakly Coordination-Assisted Ortho-Alkynylation of (Hetero)Aromatic Carboxylic Acids without Cyclization. *Org. Lett*. **2017**, *19*, 2474–2477. (e) Yu, J.-L.; Zhang, S.-Q.; Hong, X. Mechanisms and Origins of Chemo- and Regioselectivities of

Ru(II)-Catalyzed Decarboxylative C–H Alkenylation of Aryl Carboxylic Acids with Alkynes: A Computational Study. *J. Am. Chem. Soc.* **2017**, *139*, 7224–7243. (f) Kim, K.; Vasu, D.; Im, H.; Hong, S. Palladium(II)-Catalyzed Tandem Synthesis of Acenes Using Carboxylic Acids as Traceless Directing Groups. *Angew. Chem. Int. Ed*. **2016**, 55, 8652–8655. (g) Qin, X.; Li, X.; Huang, Q.; Liu, H.; Wu, D.; Guo, Q.; Lan, J.; Wang, R.; You, J. Rhodium(III)-Catalyzed Ortho C–H Heteroarylation of (Hetero)Aromatic Carboxylic Acids: A Rapid and Concise Access to π-Conjugated Poly-Heterocycles. *Angew. Chem. Int. Ed*. **2015**, *54*, 7167–7170.

(20) Zhang, G.; Hu, Z.; Belitz, F.; Ou, Y.; Pirkl, N.; Gooßen, L. J. Rhodium-Catalyzed Annelation of Benzoic Acids with α,β-Unsaturated Ketones with Cleavage of C–H, CO–OH, and C–C Bonds. *Angew. Chem. Int. Ed*. **2019**, *58*, 6435–6439.

(21) (a) Ueura, K.; Satoh, T.; Miura, M. An Efficient Waste-Free Oxidative Coupling via Regioselective C–H Bond Cleavage: Rh/Cu-Catalyzed Reaction of Benzoic Acids with Alkynes and Acrylates under Air. *Org. Lett*. **2007**, *9*, 1407–1409. (b) Li, Q.; Yan, Y.; Wang, X.; Gong, B.; Tang, X.; Shi, J.; Xu, H. E.; Yi, W. Water as a Green Solvent for Efficient Synthesis of Isocoumarins through Microwave-Accelerated and Rh/Cu-Catalyzed C–H/O–H Bond Functionalization. *RSC Adv*. **2013**, *3*, 23402–23408. (c) Han, W.-J.; Pu, F.; Fan, J.; Liu, Z.-W.; Shi, X.-Y. Rhodium(III)-Catalyzed Tandem C–H Olefination and Oxidative Cycliza-tion of Aromatic Acids with Acrylates for the Synthesis of (E)-3-Ylidenephthalides. *Adv. Synth. Catal*. **2017**, *359*, 3520–3525. (d) Jiang, Q.; Zhu, C.; Zhao, H.; Su, W. RhIII-Catalyzed C–H Olefination of Benzoic Acids under Mild Conditions Using Oxygen as the Sole Oxidant. *Chem. – Asian J*. **2016**, *11*, 356–359. (e) Bettadapur, K. R.; Lanke, V.; Prabhu, K. R. A Deciduous Directing Group Approach for the Addition of Aryl and Vinyl Nucle-ophiles to Maleimides. *Chem. Commun*. **2017**, *53*, 6251–6254.

(22) For Rh-catalyzed ortho-functionalizations, see: (a) Qi, X.; Li, Y.; Bai, R.; Lan, Y. Mechanism of Rhodium-Catalyzed C–H Functionalization: Advances in Theoretical Investigation. *Acc. Chem. Res*. **2017**, *50*, 2799–2808. (b) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild Metal-Catalyzed C–H Activation: Examples and Concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900–2936. (c) 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. (d) Peneau, A.; Guillou, C.; Chabaud, L. Recent Advances in [Cp*MIII] (M = Co, Rh, Ir)-Catalyzed Intramolecular Annulation Through C–H Activation. *Eur. J. Org. Chem*. **2018**, 5777–5794. (e) Mamone, P.; Danoun, G.; Gooßen, L. J. Rhodium-Catalyzed Ortho Acylation of Aromatic Carboxylic Acids. *Angew. Chem. Int. Ed*. **2013**, *52*, 6704–6708.

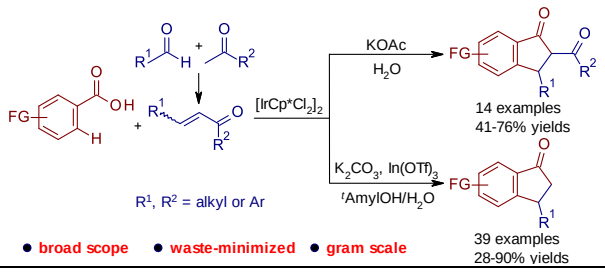
(23) For related deacylation processes or CO-OH substitutions, see: (a) Armaly, A. M.; Bar, S.; Schindler, C. S. Aluminum Chloride-Mediated Dieckmann Cyclization for the Synthesis of Cyclic 2-Alkyl-1,3-Alkanediones: One-Step Synthesis of the Chiloglottones. *Org. Lett*. **2017**, *19*, 3958–3961. (b) Tang, M.; Sun, R.; Li, H.; Yu, X.; Wang, W. An Unconventional Redox Cross Claisen Condensation–Aromatization of 4-Hydroxyprolines with Ketones. *J. Org. Chem*. **2017**, *82*, 8419–8425. (c) Hussein, M. A.; Huynh, V. T.; Hommelsheim, R.; Koenigs, R. M.; Nguyen, T. V. An Efficient Method for Retro-Claisen-Type C–C Bond Cleavage of Diketones with Tropylium Catalyst. *Chem. Commun*. **2018**, *54*, 12970–12973. (d) Zhang, L.; Li, F.; Wang, C.; Zheng, L.; Wang, Z.; Zhao, R.; Wang, L. Lipase-Mediated Amidation of Anilines with 1,3-Diketones via C–C Bond Cleavage. *Catalysts* **2017**, *7*, 115. (e) Cai, G.-X.; Wen, J.; Lai, T.-T.; Xie, D.; Zhou, C.-H. Sequential Michael Addition/Retro-Claisen Condensation of Aromatic β-Diketones with α,β-Unsaturated Esters: An Approach to Obtain 1,5-Ketoesters. *Org. Biomol. Chem*. **2016**, *14*, 2390–2394. (f) Kawata, A.; Takata, K.; Kuninobu, Y.; Takai, K. Indium-Catalyzed Retro-Claisen Condensation. *Angew. Chem. Int. Ed*. **2007**, *46*, 7793–7795. (g) Smith, K. M.; Miura, M.; Tabba, H. D. Deacylation and Deformylation of Pyrroles. *J. Org. Chem*. **1983**, *48*, 4779–4781.

(24) Wang, J.-N.; Chen, S.-Q.; Liu, Z.-W.; Shi, X.-Y. Divergent Syntheses of Spiroindanones and 2-Substituted 1-Indanones by Ruthenium-Catalyzed Tandem Coupling and Cyclization of Aromatic Acids with α,β-Unsaturated Ketones. *J. Org. Chem*. **2019**, *84*, 1348–1362.

(25) For For Ir-catalyzed *ortho*-functionalizations, see: (a) Huang, L.; Hackenberger, D.; Gooßen, L. J. Iridium-Catalyzed Ortho-Arylation of Benzoic Acids with Arenediazonium Salts. *Angew. Chem. Int. Ed*. **2015**, *54*, 12607–12611. (b) Simmons, E. M.; Hartwig, J. F. Iridium-Catalyzed Arene *Ortho*-Silylation by Formal Hydroxyl-Directed C–H Activation. *J. Am. Chem. Soc*. **2010**, *132*, 17092–17095.

(26) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. Efficient Catalytic Addition of Aromatic Carbon-Hydrogen Bonds to Olefins. *Nature* **1993**, *366*, 529–531.

TOC


KOAc
H2O
14 examples
41-76% yields
[IrCp*Cl2]2
K2CO3, In(OTf)3
tAmylOH/H2O
39 examples
28-90% yields
R1, R2 = alkyl or Ar
broad scope
waste-minimized
gram scale