An Iridium-Catalyzed Tandem Dehydrogenation/Hydroarylation Approach to Synthetically Versatile C2-Alkenyl N–H Indoles

Carlos Lázaro-Milla, José L. Mascareñas, Fernando López

An Iridium-Catalyzed Tandem Dehydrogenation / Hydroarylation Approach to Synthetically Versatile C2-Alkenyl N-H Indoles

Carlos Lázaro-Milla,[†,§] José L. Mascareñas*[†] and Fernando López*[†,‡]

† Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS) and Departamento de Química Orgánica. Universidade de Santiago de Compostela, 15782, Santiago de Compostela, Spain

§ Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040, Madrid, Spain

‡ Misión Biológica de Galicia, Consejo Superior de Investigaciones Científicas (CSIC), 36080, Pontevedra, Spain

KEYWORDS Iridium, Hydroarylation, indoles, C-H functionalization, cycloadditions.

Dedicated, in memoriam, to Dr. Alejandro Gutiérrez González

ABSTRACT: Readily available *N*-carbamoyl indolines can be converted into highly valuable 2-alkenyl and 2-alkyl indoles in a one pot reaction, through an auto-tandem catalytic cascade promoted by an iridium complex. The process entails a dehydrogenation reaction initiated by an iridium-promoted C(sp^3)-H activation, the addition of the resulting indole to an alkyne -or alkene- partner, and a spontaneous loss of the carbamoyl directing group. Interestingly, the resulting C2-alkenyl indoles can participate in a variety of metal-catalyzed annulations initiated by C–H activation, including formal [4+1] and [4+2] cycloadditions, as well as cross-dehydrogenative cyclizations, thus enabling a divergent access to a collection of functionally rich nitrogen-containing heterocycles.

Tandem reactions involving transition metal catalysts are highly attractive synthetic transformations because of their capacity to enhance the structural and functional complexity of readily available precursors in an atom- and step-economical manner.[1] Most of these reactions involve different types of metal catalysts operating in an orthogonal or sequential manner. One-pot tandem processes promoted by a single transition metal reagent that operates under unaltered reaction conditions, namely, auto-tandem processes, are much less common.[1a,2]

This is the case of reactions that combine metal-catalyzed alkane dehydrogenations with a second catalytic event that requires the presence of the newly generated unsaturation. Most of these tandem processes have been carried out using two different catalysts and, even in some cases, they need to operate in a flask-separated manner because of incompatibility issues.[3] Examples in which these types of tandem reactions are promoted by a single metal catalyst are very rare, especially when they involve C–H activation processes. Indeed, the only example involving a dehydrogenation and a C-H activation of the *in situ* generated alkene was reported more than 25 years ago by Murai and coworkers, and consists of a Rh-catalyzed dehydrogenation/carbonylation sequence on piperazine precursors (Scheme 1, equation 1).[4]

Suginome and Ohmura reported a related tandem methodology to build *N*-methyl indoles from 2-ethyl-*N*-methylanilines, which involves an iridium-catalyzed dehydrogenation / intramolecular hydrocarbonation sequence (Scheme 1, equation 2).[5] Elegantly, they also used a similar strategy for the synthesis of 2,3-dihydrobenzofurans from alkyl aryl ethers (Scheme 1, equation 3).[6] However, in contrast to the Murai's method, in these iridium-promoted reactions, the alkenyl moiety created in the dehydrogenation step is used as a hydrocarbonation partner, rather than as substrate for the C–H activation.

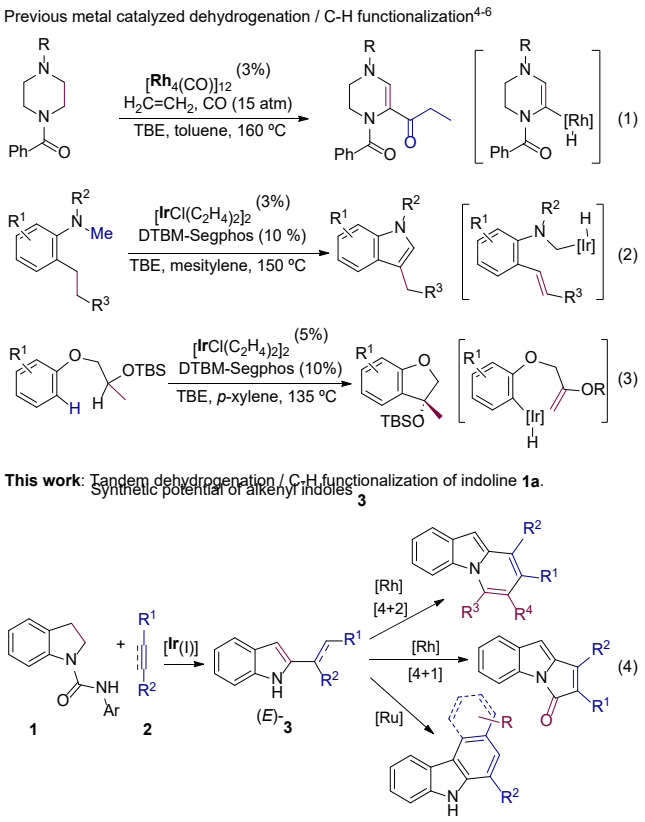
Therefore, and despite the well-known ability of Ir(I) complexes to oxidatively insert into C(sp^2)-H bonds, tandem processes involving oxidative additions of *in situ* generated alkenyl C–H bonds to this metal center have never been described.[7]

Herein we demonstrate that iridium catalysts can promote one-pot, intermolecular reactions entailing a tandem sequence that involves a dehydrogenation, a C–H activation and an alkyne (or alkene) addition step. Specifically, we show that this cascade process can be leveraged to transform *N*-carbamoyl indolines into 2-alkenyl and 2-alkyl N-H indoles (Scheme 1, equation 4). The reaction also entails an intriguing, spontaneous loss of the *N*-linked directing group at the end of the sequential process. The results also raised interesting mechanistic aspects, especially with regard to the nature and order of the catalytic events.

Importantly, we also demonstrate that this type of N-H indole products, which are not trivially made using alternative methods,[8] hold an unanticipated but powerful and versatile synthetic potential, and can engage in a variety of

metal-catalyzed annulations that lead to different types of pyridoindole, pyrroloindoline and benzocarbazoles derivatives in excellent yields (Scheme 1, equation 4). Finally, we have used our Ir-catalyzed tandem process for a two-step, one pot synthesis of the bio-relevant carbazole Sorazolon E.

Scheme 1. Previous metal catalyzed dehydrogenation / hydrocarbonation methods and current process.



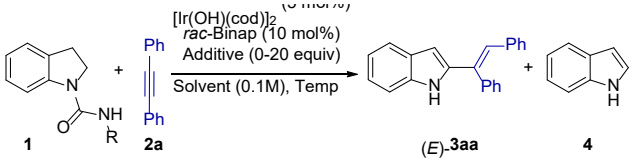
Our research started after observing that the reaction of the *N*-carbamoyl indoline **1a** with diphenylacetylene (**2a**), in presence of [Ir(cod)OH]$_2$ / *rac*-Binap, and at 120 ºC, instead of providing hydroalkylation products,[9] led to the C2-alkenylated N-H indole (*E*)-**3aa**, in a moderate 44% yield (55% conversion), together with traces of indole (**4**) as side product (Table 1, entry 1).[10] Changing the solvent from dioxane to 1,2-DCE, under otherwise identical conditions, led to full recovery of the starting material (entry 2). However, the reaction works in toluene, resulting in a slightly higher yield of **3aa** (51% yield, 61% conversion), together with a 9% yield of indole (**4**, entry 3).

Curiously, the addition of small amounts of water (20 equivalents) allowed full conversion of **1a** and a significant increase of the reaction yield (73 %, entry 4). Moreover, the reaction could be equally performed at lower temperatures, just by increasing the reaction times (entries 5 and 6). On the contrary, the use of alternative protic additives, such as MeOH, instead of water, had a negative impact in the yield (entry 7 and Table S2).[11] In all these reactions, we could detect *cis*-stilbene in the crude reaction mixtures, suggesting that diphenylacetylene **2a** acts both as a hydrocarbonation partner and a hydride scavenger. The use of other common hydrogen scavengers, such as *t*-butyl ethylene (TBE), was less effective (entry 8).

We next analysed the influence of electron-donating (*p*-OMe, **1a'**) or electron-withdrawing groups (*p*-CF$_3$, **1a"**) at the phenyl ring of the *N*-aryl carboxamide moiety. Interestingly, while the presence of the *para*-methoxy group did not have any significant effect on the reaction (entry 9), the incorporation of a CF$_3$ group proved to be advantageous, leading to an improved 85% yield (entry 10). Substrate **1a'"**, bearing an *N*-Benzyl carboxamide (entry 11), or just indoline, that lacks directing groups (entry 12), failed to give any conversion.

The use of the bisphosphine ligand is key for the observed reactivity, as in its absence the reaction provides a poor 5% conversion (entry 13). Not only Binap, but also related ligands such as DM-Binap, H8-Binap or Segphos provided similar results (Table S1). However, structurally different bisphosphines like DPPF, Xantphos or dppe, among others, led to very poor yields (Table S1). Thus, *rac*-Binap was selected as the optimal ligand for the process. Finally, we also confirmed that the use of an iridium-based catalyst is essential, since a similar rhodium complex [Rh(OH)(cod)]$_2$ failed to yield any product (entry 14).

Table 1. Preliminary screening of a tandem Dehydrogenative hydroarylation of indolines 1.[a]



entry	1, R	Solv.	Add.	T (°C)	t (h)	Conv. (%)	3aa (%)	4 (%)
1	**1a**, Ph	Diox	-	120	4	55	44	2
2	**1a**, Ph	DCE	-	120	4	0	0	0
3	**1a**, Ph	Tol	-	120	4	63	51	9
4	**1a**, Ph	Tol	H_2O	120	3	100	73	4
5	**1a**, Ph	Tol	H_2O	100	24	100	70	3
6	**1a**, Ph	Tol	H_2O	90	24	100	72	3
7	**1a**, Ph	Tol	MeOH	120	4	25	12	2
8	**1a**, Ph	Tol	TBE[b]	120	3	59	45	3
9	**1a'**, *p*-$MeOC_6H_4$	Tol	H_2O	110	1	100	72	9
10	**1a"**, *p*-$CF_3C_6H_4$	Tol	H_2O	110	1	100	85	6
11	1a'", Bn	Tol	H_2O	110	24	0	0	2
12	Indoline[c]	Tol	H_2O	110	24	0	0	0
13[d]	**1a"**, *p*-$CF_3C_6H_4$	Tol	H_2O	110	24	5	0	0
14[e]	**1a"**, *p*-$CF_3C_6H_4$	Tol	H_2O	110	1	0	0	1

[a] Conditions: *N*-carbamoyl indoline (**1**, 1 equiv), **2a** (3 equiv), additive (0-20 equiv), [Ir(OH)(cod)]$_2$ (5%), *rac*-Binap (10%). [b] Carried out using TBE (8 equiv) as additive. Equal results were obtained using TBE and H_2O (20 equiv). [c] Carried out using

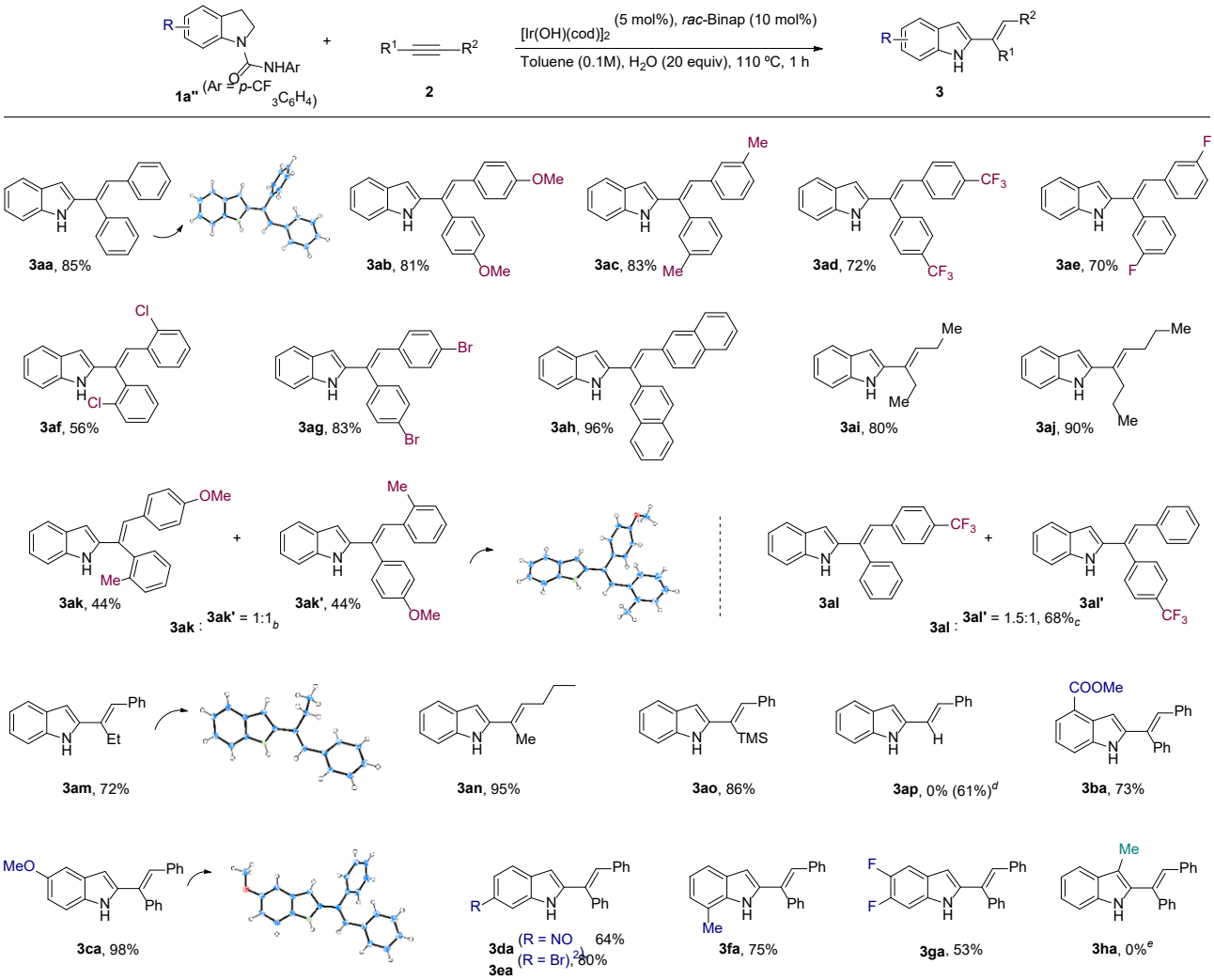
NH-indoline as **1**. [d] Carried out without *rac*-Binap. [e] $[Rh(OH)(cod)]_2$ instead of $[Ir(OH)(cod)]_2$.

After this screening, we analysed the scope of the Ir-catalyzed tandem process, initially using different 1,2-di-substituted alkyne partners (Scheme 2). Thus, we were glad to observe that several symmetrical bis-aryl alkynes (**2b-f**), bearing either electron-donating (e.g, *p*-MeO, *m*-Me) or electron-withdrawing groups (e.g. *m*-F, *p*-CF_3), as well as bromine or chlorine atoms (e.g. *p*-Br, *o*-Cl), participate in the process, providing the expected (*E*)-C2-alkenylated-NH-indoles, **3ab–3ag**, in good yields. Alkynes with larger aromatic substituents such as a β-naphthyl moiety, or with alkyl, instead of aryl groups, were also successful partners. Thus, the reaction of **1a"** with symmetrically aliphatic alkynes such as 3-hexyne (**2i**) or with 4-octyne (**2j**) gave the respective indole products **3ai** and **3aj** in good to excellent yields. Non-symmetrical internal alkynes, such as a bis-aryl alkyne bearing two different electron donating groups at the aryl rings (e.g. *o*-Me and *p*-MeO groups, **2k**) led to a 1:1 mixture of the corresponding regioisomers (**3ak**, **3ak'**). One of the isomers, **3ak'**, could be characterized by X-ray analysis.[11]

The regioselectivity can be improved by differentiating the electron character of the substituents (**3al**:**3al'** = 1.5:1), and, fully controlled by playing with steric differences. Thus, the reaction of **1a"** with but-1-yn-1-ylbenzene (**2m**) delivered exclusively the product **3am**, wherein the new C–C bond was formed at the less sterically hindered alkyne site. The structure of **3am** was unambiguously determined by X-ray crystallography, which also confirmed the *E*-stereochemistry of the alkene moiety.[11] Remarkably, the reaction of dialkyl alkynes like 2-hexyne also proceeded with complete regioselectivity toward the less congested product **3an**, which was isolated in 95% yield.

Curiously, when trimethylsilylphenylacetylene (**2o**) was used as alkyne partner, the product **3ao**, bearing the bulkier TMS group at the indole-adjacent position was obtained with excellent yield and complete regioselectivity. Terminal alkynes, such as phenylacetylene, are not suitable substrates for this reaction, probably due to the facile insertion of Ir(I) complexes into the C(sp)-H bond, which leads to secondary reactions.[12] Nonetheless, the product (**3ap**) can be easily obtained from its TMS analogue (e g. **3ao**) by desilylation with a fluoride source.[11]

Scheme 2. Tandem dehydrogenative / hydroarylation process with diverse alkynes[a]

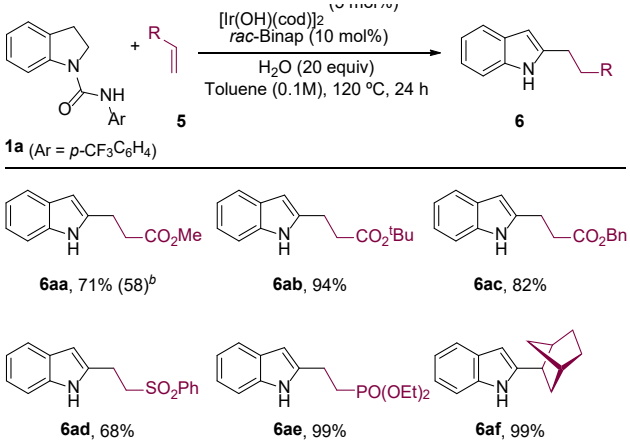


[a] *Conditions*: All reactions were conducted with 3 equiv of alkyne **2**. [b] Isomers can be independently isolated. [c] Yield of the mixture of isomers. [d] Yield of **3ap** obtained through a fluoride (TBAF, THF, 60 ºC) promoted desilylation of **3ao** (see the Supp. Info for details). [e] The 3-methyl indoline precursor (**1h**) was recovered (85%), together with a 10% yield of its 3-methyl NH-indole derivative.

We next explored the behaviour of differently functionalized indolines, using diphenylacetylene as an alkyne partner. Gratifyingly, indolines bearing both electron-withdrawing and electron-donating groups in any of their C4 to C7 positions give the expected (*E*)-C2-alkenylated-NH-indoles (**3ba – 3ga**) in good to high yields. The structure of (*E*)-**3ca** could be further confirmed by X-ray single crystal analysis. Worth to note, a C3-methyl substituted indoline (**1h**) did not participate in the process (**3ha**, 0% yield), possibly due to steric hindrance imposed by this group.

At this stage, it was pertinent to find out whether the method could also be extended to alkene partners. Nicely, the tandem reaction works using methyl acrylate, with the expected indole **6aa** obtained in 43% yield (58% conversion, Scheme 3). This value could be improved by carrying out the reaction with higher excess of alkene, at 120 ºC for 24 hours (71 % yield). The reaction works with other alkenes bearing electron-withdrawing groups, phenyl sulfone or a phosphonate ester (**6aa-6ae**, 68-99% yield). Furthermore, although styrene did not participate in the process, non-conjugated alkenes like norbornene, quantitatively afforded the desired C2-alkylated indole (**6af**).

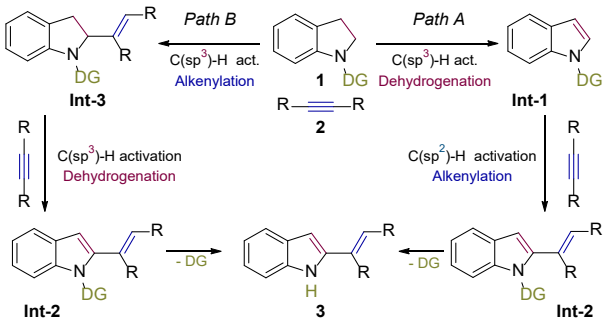
Scheme 3. Tandem dehydrogenative hydroarylation using alkene partners[a]



[a] *Conditions*. Reactions were conducted with 8 equiv. of alkene, unless otherwise noted. [b] Carried out at 110 ºC with 3 equiv of **5a**.

Regarding the mechanism, two hypothetical alternatives were initially considered. The first one (Scheme 4, path A) would involve an initial dehydrogenation of indoline **1**,[13] followed by a hydroarylation of the alkyne (or alkene) partner with the generated indole intermediate (**Int-1**). This path involves two C–H activations promoted by the Ir(I) catalyst, one in the Csp^3–H bond of the initial indoline and the other in the Csp^2–H of the indole resulting from the dehydrogenation. The C2-alkenylated indole product (**Int-2**) would then loss the carbamate, releasing the observed product **3**. Alternatively, path B would consist of an initial hydrocarbonation to give **Int-3**, followed by a dehydrogenation to **Int-2**. The first step of this path, leading to **Int-3**, would indeed be consistent with previously reported C2-alkylation of indolines with alkenes.[9a]

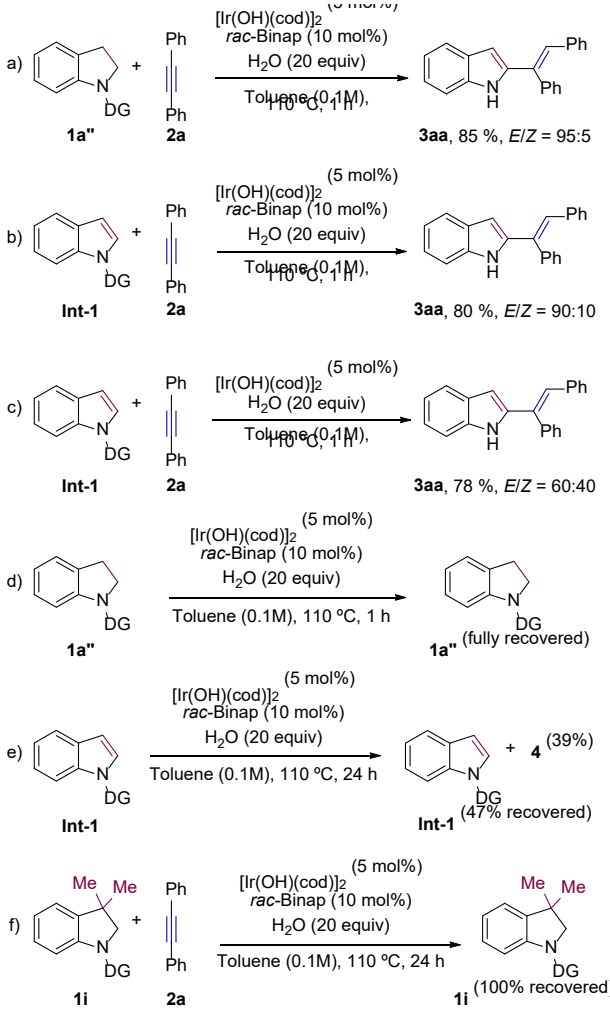
Scheme 4. Proposed pathways for the formation of C2-functionalized-NH-indoles 3



To gain insights into the real mechanism, we synthesized the carbamoyl indole precursor **Int-1** (DG = CONH-*p*-$CF_3C_6H_4$, path A), which was submitted to the reaction conditions (Scheme 5, b). We observed the formation of the C2-alkenylated indole **3aa** in good yield, a result which supports path A. Interestingly, whereas the precursor indoline **1a**" doesn't evolve if the reaction is performed in the absence of Binap (Table 1 entry 13), the indole **Int-1** reacts with diphenylacetylene (**2a**) when treated with $[Ir(OH)(cod)]_2$ (5 mol%) in toluene at 110 °C, to give the C2-alkenylated indole product **3aa** in 80% yield (Scheme 5, c). This result highlights a crucial role of Binap for the dehydrogenation step.

Control experiments confirmed that the presence of the carbamoyl directing group is essential to observe any reactivity, either with indoline or indoles. The intrinsic reactivity profiles of **1a**" and **Int-1** were evaluated by submitting them to standard conditions, but in the absence of diphenylacetylene (Scheme 5, d and e). While in the case of indoline **1a**", we observed no conversion, the indole **Int-1**, gave a considerable amount of the deprotected indole **4** (39% yield). This result suggests that the release of the directing group occurs only after the oxidative aromatization. Finally, and in consonance with the above control reactions, the 3,3-dimethylindoline **1i**, for which the dehydrogenation is not feasible, was fully recovered when treated under standard reaction conditions.

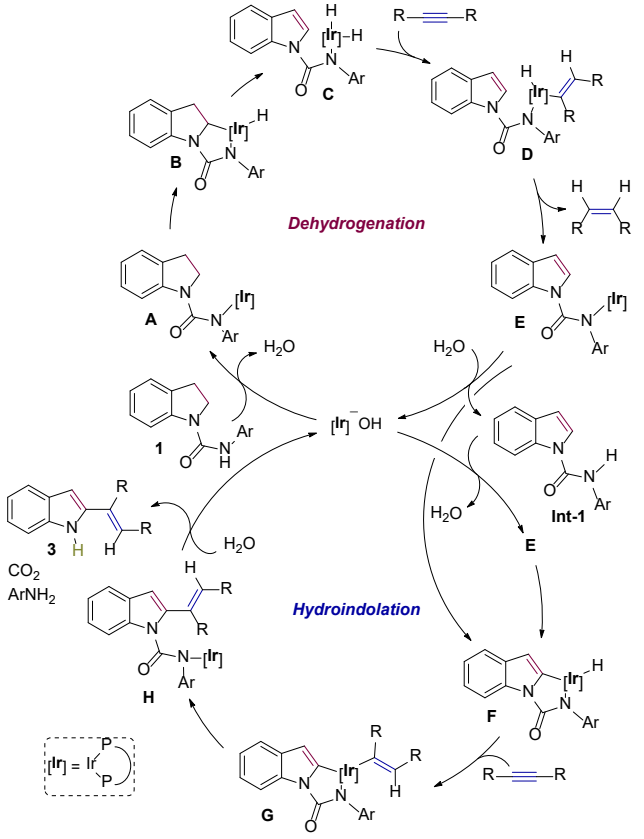
Scheme 5. Control mechanistic experiments a-f[a]



[a] DG = CONH-*p*-$CF_3C_6H_4$.

Therefore, these results suggest a catalytic cycle involving the initial reaction of indoline **1** with *in situ* generated hydroxoiridium complex to yield an amidoiridium complex **A** (Scheme 6). Oxidative addition of the methylene C(sp^3)-H bond to this Ir(I) complex forms alkyl-(hydrido)iridium(III) species **B** that undergoes a β-hydride elimination towards the amidoiridium bis-hydride species **C**. A migratory insertion of the alkyne unit to give **D** (or its regioisomer **D'**[11]), followed by reductive elimination accounts for an overall redox neutral process, and is in consonance with the detection of *cis*-stylbene in the crude reaction mixture (GC-MS and NMR). The resulting amidoiridium complex **E** might be in equilibrium with its protonated species **Int-1**, as the corresponding indole was confirmed to work in the alkenylation process (Scheme 5, b). An oxidative addition step from **E** results in the alkenyl-(hydrido)iridium(III) species **F**. The insertion of a second unit of alkyne and a subsequent reductive elimination would deliver the amidoiridium intermediate **H**,[14] which undergoes the hydrolysis of the carbamoyl directing group to yield the observed product **3** and resetting the catalytic cycle. The detection of *p*-CF_3-aniline by GC-MS in the crude mixtures is consistent with this decarbamoylation.

Scheme 6. Mechanistic proposal

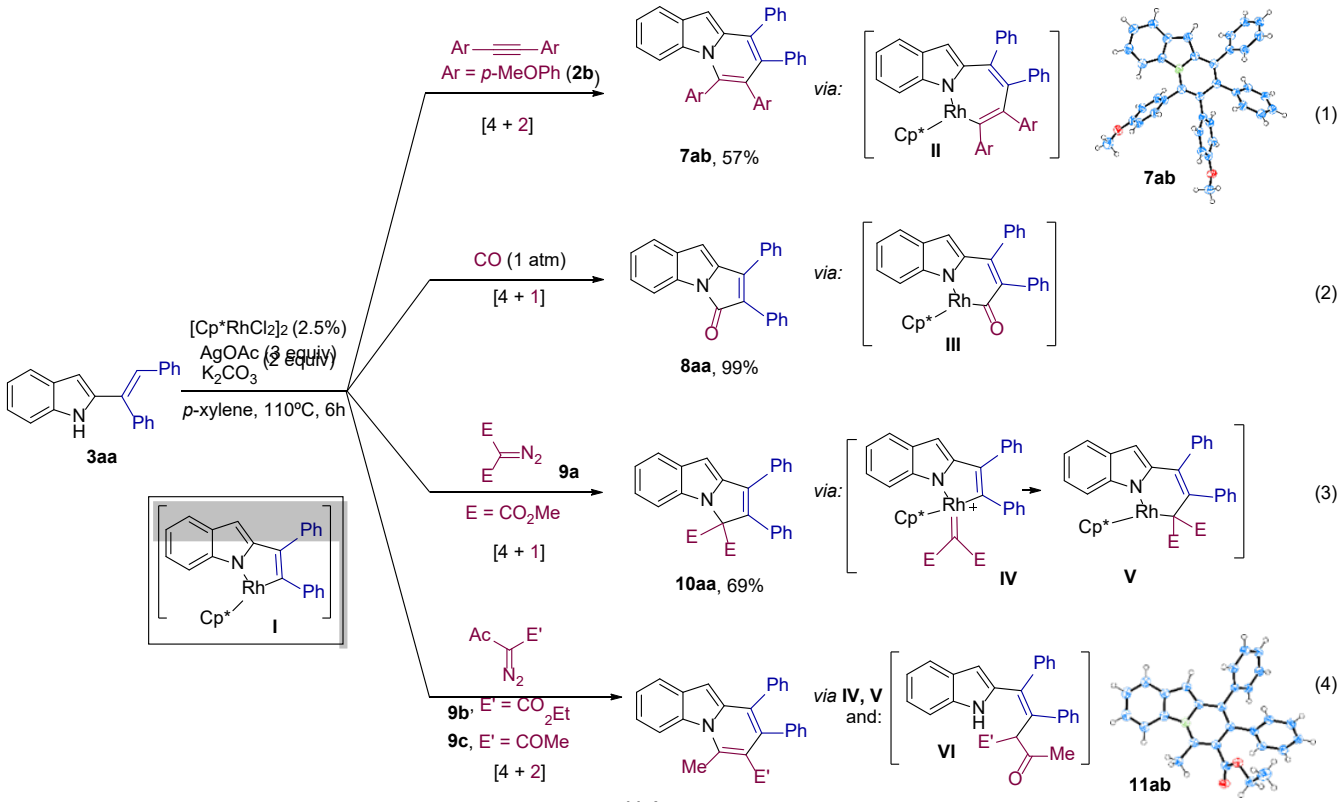


With an optimal and versatile protocol for the practical assembly of *N*-unsubstituted C2-alkenyl indoles, the stage was set to explore the synthetic possibilities of these products. We were especially attracted by the possibility of performing formal annulation reactions initiated by a C–H activation of the alkenyl moiety. Although this type of processes have been used for C2–aryl indoles,[15] related methodologies with C2-alkenyl indoles are essentially unknown. Indeed, the synthetic derivatizations of these systems have been limited to particular thermal Diels-Alder cycloadditions and acid-promoted condensations.[16]

We initially explored the viability of formal metal-promoted annulations with alkynes to give could pyrido[1,2-*a*]indole products of type **7** (Scheme 7), scaffolds that are frequently found in relevant natural and synthetic products.[17] Moreover, due to their luminescent properties, this type of products have also been used in the construction of relevant molecular materials.[18] Initial transformation attempts, carried out using indole **3aa** and alkyne **2b** (bis-*p*-methoxyphenylacetylene), and several palladium catalysis previously used in related transformations of C2-aryl indoles,[18b, 19] were unsuccessful.[11] However, we were glad to observe that the desired [4+2] annulation could be performed under rhodium(III) catalysis. In particular, using the catalyst generated from $[Cp^*RhCl_2]_2$, AgOAc, and K_2CO_3, in *p*-xylene at 110 ºC, the desired pyrido[1,2-*a*]indole **7ab** was obtained in 57% yield (Scheme 7, equation 1).[20, 15k] Its structure was unambiguously confirmed by X-ray analysis.[11]

Importantly, this catalytic system can also promote alternative annulations of **3aa** with partners other than alkynes. For instance, the use of a CO (1 atm), instead of the alkyne, allowed the quantitative formation of the pyrrolo[1,2-*a*]indole-3-one derivative **8aa**, which results from a formal [4+1] annulation (Scheme 7, equation 2).[15k] It is also possible to use diazocompounds such as dimethyl diazomalonate as coupling partners, to give pyrrolo[1,2-*a*]indole products like **10aa** in quantitative yield (Scheme 7, equation 3). This type of formal [4+1] annulations had never been described, even with C2-aryl indoles.[21] Curiously, when using as partner the keto-ester diazo derivative **9b**, instead of the formal [4+1] cycloadduct, we observed the pyrido[1,2-*a*]indole **11ab** (58% yield, Scheme 7, equation 4).[15l] Its structure could be unambiguously determined by X-ray crystallography.[11] The efficiency of this particular annulation could be further improved by changing the Rh(III) precatalyst to an iridium counterpart, $[Cp^*IrCl_2]_2$, using AcOH as additive and 1,2-DCE as solvent. Under these conditions, the pyridoindole **11ab** was obtained in 99% yield. Moreover, with this iridium catalyst,[15m] the participation of other diketo diazocompounds like **9c**, is also viable, affording the expected formal [4+2] annulation product **11ac** in 87% yield (Scheme 7, equation 4). Its structure was also confirmed by X-ray analysis.[11]

Scheme 7. Rh(I) and Ir(I)-catalyzed formal cycloadditions of C2-alkenyl indoles 3 with alkynes, CO and diazomethane derivates



7ca (R_1, R^2, R^5 = Ph; R_3 = OMe; R_4 = H), 64%
7cd (R^1, R^2 = Ph; R_3 = OMe; R_4 = H; R_5 = *p*-$CF_3C_6H_4$), 88%
7cj (R_1, R^2 = Ph; R_3 = OMe; R_4 = H; R_5 = *n*-Pr), 52%
7eb (R_1, R^2 = Ph; R_3 = H; R_4 = Br; R_5 = *p*-MeOC_6H_4, 79%
7hb (R_1, R^2 = 2-Naphthyl; R_3, R^4 = H; R_5 = *p*-MeOC_6H_4), 95%
7mb, (R^1 = Et; R_2 = Ph; R_3, R^4 = H; R_5 = *p*-MeOC_6H_4), 36%,

8ca (R_1, R^2 = Ph; R_3 = OMe; R_4 = H), 70%
8ea (R_1, R^2 = Ph; R_3 = H; R_4 = Br), 90%
8ah (R^1, R^2 = 2-Naphthyl; R_3, R^4 = H), 79%
8am (R^1 = Et; R_2 = Ph; R_3, R^4 = H), 90%
8ai (R^1, R^2 = Et; R_3, R^4 = H), 35%

11cb (R^1, R^2 = Ph; R_3 = OMe; R_4 = H), 75%
11eb (R^1, R^2 = Ph; R_3 = H; R_4 = Br), 99%
11hb (R^1, R^2 = 2-Naphthyl; R_3, R^4 = H), 89%
11mb (R^1 = Et; R_2 = Ph; R_3, R^4 = H), 86%
11ib (R_1, R^2 = Et; R_3, R^4 = H), 72%[a]

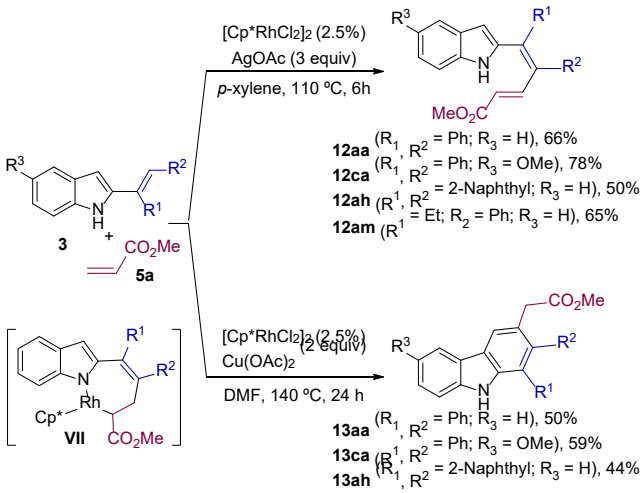
[a] Carried out with **9b** (6 equiv), $[Cp^*IrCl_2]_2$ (4 mol%), AgOAc (60 mol%) and AcOH (2 equiv).

Mechanistically, we propose that all these reactions involve an initial N–H indole metalation, followed by a C–H activation to give a common five-membered metallacyclic intermediate of type **I** (Scheme 7). A migratory insertion of the alkyne or of carbon monoxide would respectively deliver rhodacyclic intermediates **II** and **III** that, after their corresponding reductive eliminations, provide products **7** and **8**. In the case of the diazoderivatives (**9**), the reaction of intermediate **I** with diazomalonate would evolve to the corresponding metal carbene (**IV**), prior to a migratory insertion towards **V**. At this point, if a C-N reductive elimination takes place, the reaction affords the product **10**. However, with ketodiazomethanes the reaction seems to proceed via an alternative protodemetallation path towards **VI**, a process that is more efficient using the Ir(III) catalyst and AcOH as proton source.

Importantly, these transformations are not limited to the diphenyl substituted indole **3aa**. Indeed, as it is preliminary outlined in Scheme 7, several pyrido[1,2-*a*]indoles derivatives of type **7**, exhibiting a variety of substitutions were synthesized in good to excellent yields. Likewise, different type of pyrrolo[1,2-*a*]indolones **8** and pyrido[1,2*a*]indoles **11**, respectively resulting from [4+1] and [4+2] cycloadditions between **3** and carbon monoxide or the diazo ester **9b**, could also be obtained in good yields.

Electron-activated alkenes, like methyl acrylate, can also be used as coupling partners in the Rh(III)-catalyzed reactions of the alkenylindoles **3**. However, instead of a formal annulation process, the Heck-like addition product (*E,E*)-**12aa** was obtained, as single stereoisomer (Scheme 8). The formation of this diene indicates that the putative intermediate **VII** prefers to evolve now through a β-hydride elimination. Curiously, by replacing the Ag(I) oxidant by $Cu(OAc)_2$ and using DMF as the solvent, we exclusively obtained the unexpected carbazole, **13aa**, whose structure was unambiguously confirmed by X-ray crystallographic analysis.[11] This type of carbazoles are appealing structures that can exhibit intriguing physical properties, particularly as light emitting materials for electroluminescence devices.[18] Control experiments confirmed that **13aa** derives from the initially formed diene **12aa**,[11] which would probably undergo a formylation at its C3 position, with DMF serving as formyl source,[22] prior to a Rh-promoted cyclodehydration.

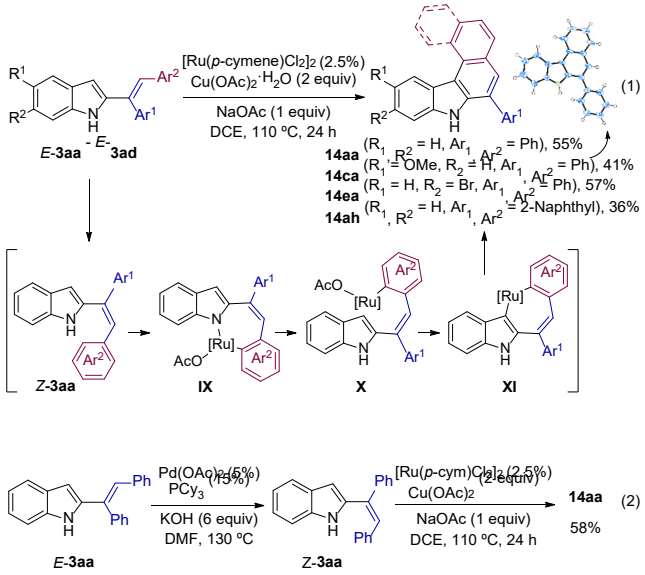
Scheme 8. Rh-catalyzed C-H-olefin functionalization with methyl acrylate as coupling partner



Further exploration of the synthetic potential of indoles **3** led us to find out that they can also engage in interesting ruthenium(II)-promoted transformations. Thus, treatment of **3aa** with catalytic amounts of $[Ru(p\text{-cymene})Cl_2]_2$, in the presence of $Cu(OAc)_2$ and NaOAc, leads to the benzo[*c*]carbazole derivative **14aa** (55% yield), which was also characterized by X-ray analysis (Scheme 9, equation 1). The reaction could also be extended to other related alkenylindoles.[23]

Control experiments suggest that this novel process might involve an initial *E*-to-*Z* isomerization of **3aa**,[11] which enables a subsequent dehydrogenative ring closure. Indeed, the Ru-catalyzed dehydrogenative coupling of an independently prepared *cis* isomer (***Z*-3aa**),[11,24] gave the benzocarbazole **14aa** in 58% yield (Scheme 9, equation 2). The dehydrogenative step from *Z*-**3** would consist of an initial *ortho*-C-H activation of the terminal phenyl group to give the seven-membered ruthenacyclic **IX**. Protonation followed by a second concerted metalation deprotonation at the indole C3-position would deliver the ruthenacycle **XI** that, upon C-C reductive elimination, yields the observed product.

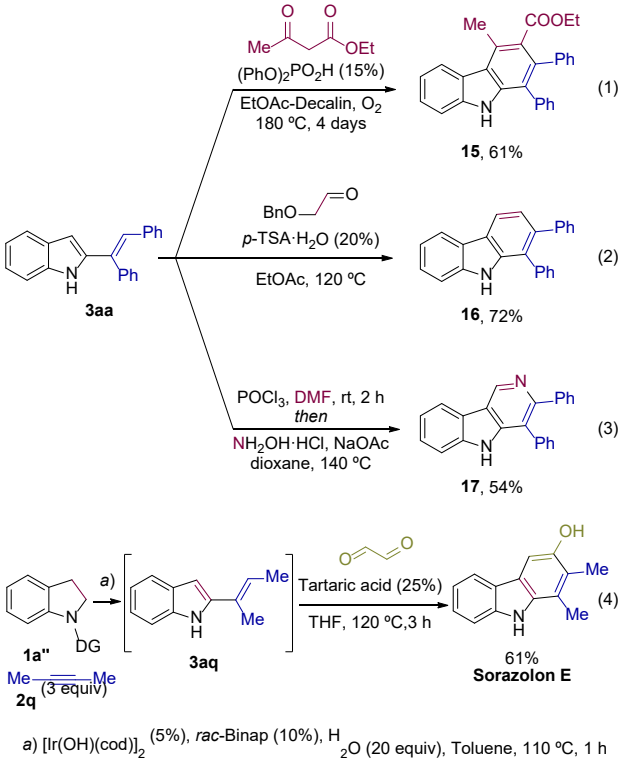
Scheme 9. Ru-catalyzed dehydrogenative ring closure for Benzo[*c*]carbazole formation



Indoles **3** can also be manipulated using metal-free methods (Scheme 10).[25] Thus, treatment of **3aa** with ethyl acetoacetate and diphenyl phosphoric acid led to the polysubstituted carbazole **15**, whereas the reaction with benzyloxyacetaldehyde in presence of *p*-TSA produces **16** (Scheme 10, equations 1 and 2). Product **3aa** could also be transformed into γ-carboline derivatives, like **17** (Scheme 10, equation 3), which exhibit a skeletal framework that is very common in antivirals and antiproliferative agents.[26]

Finally, the synthetic utility of our tandem process was further demonstrated by the synthesis of Sorazolon E, a carbazole isolated from *Sorangium Cellulosum* that exhibits antibacterial activities, as well as cytotoxicity against mice fibroblast cell lines. Treatment of **1a"** with dimethylacetylene (**2q**) under standard conditions gave the expected (*E*)-2-alkenyl-indole **3aq**. Then, replacement of toluene by a THF solution of glyoxal and tartaric acid, and further heating at 120 ºC for 3 h, provided Sozarolon E in 61% overall yield (Scheme 10, equation 4). The procedure is much faster and efficient that previous protocols, based on Wittig reactions that produce mixture of both (*E*) and (*Z*) isomers.[27]

Scheme 10. Metal-free synthesis of carbazole derivatives *via* C3-indole derivatization. Synthesis of Sorazolon E



a) $[Ir(OH)(cod)]_2$ (5%), *rac*-Binap (10%), H_2O (20 equiv), Toluene, 110 ºC, 1 h

In conclusion, we have uncovered a one-pot, auto-tandem catalytic process that allows to couple readily available *N*-carbamoyl indolines with alkynes or activated alkenes to give a variety of highly valuable (*E*)-C2-alkenyl and alkyl NH-indoles. The success of the reaction relies on a sequential orchestration of several reactions that occur with a perfect timing and orthogonality, namely: a dehydrogenation initiated by an iridium promoted C(sp^3)-H activation, the regeneration of the Ir(I) catalyst by excess of the unsaturated partner, a hydroarylation triggered by a C(sp^2)-H activation, and a final, spontaneous decarbamoylation. Despite the distinct nature of the organometallic steps involved in the process, they can be promoted by the same Ir catalyst, which is quite uncommon in other cascade processes.

We have also demonstrated that the produced C2-alkenylindoles present a rich and versatile chemistry, and can be readily transformed into a variety of highly appealing azaheterocycles. For instance, using a common Rh(III) catalytic conditions, they can engage in a variety of novel [4+2] and [4+1] annulations with alkynes, carbon monoxide and diazomethane derivatives, all of them involving C–H activations. On the other hand, in the presence of Ru-catalysts they can undergo cross-dehydrogenative cyclizations towards benzocarbazole derivatives. Finally, using other reagents they can be converted into different type of polysubstituted carbazoles. Eventually, we also demonstrate the utility of the tandem methodology in a two-step, one-pot synthesis of Sorazolon E.

AUTHOR INFORMATION

Corresponding Author

José L. Mascareñas - Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS) and Departamento de Química Orgánica. Universidade de Santiago de Compostela, Spain; Email: joseluis.mascarenas@usc.es; orcid.org/0000-0002-7789-700X
Fernando López - Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS). Universidade de Santiago de Compostela, Spain; Email: fernando.lopez@csic.es; and Misión Biológica de Galicia, Consejo Superior de Investigaciones Científicas (CSIC), 36080, Pontevedra, Spain, orcid.org/0000-0002-0235-6858

Authors

Carlos Lázaro Milla Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS). Universidade de Santiago de Compostela, Spain; Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040, Madrid, Spain; Email**:** carloslazaromilla@ucm.es; orcid.org/0000-0003-3698-1405

ASSOCIATED CONTENT

(Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

Full experimental procedures, optimization of the catalyst and characterization of all new compounds, including ^{1}H-, ^{13}C-NMR spectra.

ACKNOWLEDGMENT

This work received financial support from Spanish grants (Grants PID2020-118579GB-I00 and PID2019-108624RB-I00 and PID2022-137318OB-I00 funded by MCIN / AEI / 10.13039 / 501100011033, Grant IHRC22-00009 funded by MCIN/ISCIII and by the "European Union Next Generation EU/PRTR", ORFEO-CINQA network RED2022-134287-T and Margarita Salas contract to CLM), the Consellería de Cultura, Educación e Ordenación Universitaria (Grant ED431C 2021/25 and Grant ED431G 2019/03: Centro Singular de Investigación de Galicia accreditation 2019-2022) and the European Regional Development Fund-ERDF corresponding to the multiannual financial framework 2014-2020).

REFERENCES

(1) (a) Fogg, D. E.; dos Santos, E. N., Tandem catalysis: a taxonomy and illustrative review. *Coord. Chem. Rev.* **2004**, *248*, 2365-2379. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C., Concurrent Tandem Catalysis. *Chem. Rev.* **2005**, *105*, 1001-1020. (c) Parker, P. D.; Hou, X. T.; Dong, V. M., Reducing Challenges in Organic Synthesis with Stereoselective Hydrogenation and Tandem Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 6724-6745. (d) Sommer, H.; Julia-Hernández, F.; Martin, R.; Marek, I., Walking Metals for Remote Functionalization. *ACS Cent. Sci.* **2018,** *4*, 153-165. (e) Tietze, L. F.; Rackelmann, N., Domino reactions in the synthesis of heterocyclic natural products and analogs. *Pure Appl. Chem.* **2004**, *76*, 1967-1983.

(2) (a) Fiorito, D.; Scaringi, S.; Mazet, C., Transition metal-catalyzed alkene isomerization as an enabling technology in tandem, sequential and domino processes. *Chem. Soc. Rev.* **2021,** *50*, 1391-1406. (b) Campos, J. F.; Berteina-Raboin, S., Tandem Catalysis: Synthesis of Nitrogen-Containing Heterocycles. *Catalysts* **2020**, *10*, 631.

(3) (a) Kumar, A.; Bhatti, T. M.; Goldman, A. S., Dehydrogenation of Alkanes and Aliphatic Groups by Pincer-Ligated Metal Complexes. *Chem. Rev.* **2017**, *117*, 12357-12384. (b) Dobereiner, G. E.; Crabtree, R. H., Dehydrogenation as a Substrate-Activating Strategy in Homogeneous Transition-Metal Catalysis. *Chem. Rev.* **2010**, *110*, 681-703. (c) Wang, Y.; Huang, Z.; Liu, G.; Huang, Z., A New Paradigm in Pincer Iridium Chemistry: PCN Complexes for (De)Hydrogenation Catalysis and Beyond. *Acc. Chem. Res.* **2022**, *55*, 2148-2161. (d) 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. (e) Dobereiner, G. E.; Yuan, J.; Schrock, R. R.; Goldman, A. S.; Hackenberg, J. D., Catalytic Synthesis of *n*-Alkyl Arenes through Alkyl Group Cross-Metathesis. *J. Am. Chem. Soc.* **2013**, *135*, 12572-12575. (f) Ohmura, T.; Kijima, A.; Suginome, M., Integrated Catalytic C–H Transformations for One-Pot Synthesis of 1-Arylisoindoles from Isoindolines via Palladium-Catalyzed Dehydrogenation Followed by C–H Arylation. *Org. Lett.* **2011**, *13*, 1238-1241. (g) Ohmura, T.; Kijima, A.; Suginome, M., Synthesis of 1-Borylisoindoles via Palladium-Catalyzed Dehydrogenation/C–H Borylation of Isoindolines. *J. Am. Chem. Soc.* **2009**, *131*, 6070-6071. (h) Dinh, L. V.; Li, B.; Kumar, A.; Schinski, W.; Field, K. D.; Kuperman, A.; Celik, F. E.; Goldman, A. S., Alkyl–Aryl Coupling Catalyzed by Tandem Systems of Pincer-Ligated Iridium Complexes and Zeolites. *ACS Catal.* **2016**, *6*, 2836-2841. (i) Tang, X.; Jia, X.; Huang, Z., Thermal, Catalytic Conversion of Alkanes to Linear Aldehydes and Linear Amines. *J. Am. Chem. Soc.* **2018**, *140*, 4157-4163. (j) Jia, X.; Huang, Z., Conversion of alkanes to linear alkylsilanes using an iridium–iron-catalysed tandem dehydrogenation–isomerization–hydrosilylation. *Nature Chem.* **2016**, *8*, 157-161. (k) Leitch, D. C.; Lam, Y. C.; Labinger, J. A.; Bercaw, J. E., Upgrading Light Hydrocarbons via Tandem Catalysis: A Dual Homogeneous Ta/Ir System for Alkane/Alkene Coupling. *J. Am. Chem. Soc.* **2013**, *135*, 10302-10305.

(4) (a) Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S., Rhodium-catalyzed reaction of N(2-pyridinyl)piperazines with CO and ethylene. A novel carbonylation at a C-H bond in the piperazine ring. *Organometallics* **1997**, *16*, 3615-3622. (b) Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S., Rhodium-catalyzed reaction of N-acylpiperazines with CO and ethylene. Carbonylation at a C-H bond directed by an amido group. *Tetrahedron Lett.* **1997**, *38*, 7565-7568.

(5) Ohmura, T.; Yagi, K.; Kusaka, S.; Suginome, M., Tandem C–H Transformations by a Single Iridium Catalyst: Direct Access to Indoles and Indolines from *o*-Alkyl-*N*-methylanilines. *ACS Catal.* **2020**, *10*, 3152-3157.

(6) (a) Kusaka, S.; Ohmura, T.; Suginome, M., Iridium-catalyzed Enantioselective Intramolecular Cross-dehydrogenative Coupling of Alkyl Aryl Ethers Giving Enantioenriched 2,3-Dihydrobenzofurans. *Chem. Lett.* **2022**, *51*, 601-604. For a Rh-catalyzed hydroarylation of alkenes with indolines, which is followed by a dehydrogenation process, see: (b) Song, Z.; Samanta, R.; Antonchick, A. P., Rhodium(III)-Catalyzed Direct Regioselective Synthesis of 7-Substituted Indoles. *Org. Lett.* **2013**, *15*, 5662-5665.

(7) For an isolated example observed in an Ir-catalyzed hydrocarbonation of alkenes, see: (a) Yamauchi, D.; Yamakawa, K.; Nishimura, T., Iridium-Catalyzed Enantioselective Direct alpha-C-H Alkylation of Saturated Cyclic Amines with Alkenes. *Org. Lett.* **2022**, *24*, 6828-6833. For an isolated case of a dehydrogenative C–C bond formation combined with a further dehydrogenation event, see: (b) Cooper, P.; Crisenza, G. E. M.; Feron, L. J.; Bower, J. F., Iridium-Catalyzed α-Selective Arylation

of Styrenes by Dual C–H Functionalization. *Angew. Chem. Int. Ed.* **2018**, *57*, 14198-14202. See also, (c): Yamakawa, K.; Nishimura, T. Iridium-Catalyzed Branch-Selective and Enantioselective C2-Alkylation of N-Benzimidazolyl Indoles. *Adv. Synth. Catal.* **2023**, *365*, 2013-2017. (d) Pan, S.; Ryu, N.; Shibata, T., Ir(I)-Catalyzed C–H Bond Alkylation of C2-Position of Indole with Alkenes: Selective Synthesis of Linear or Branched 2-Alkylindoles. *J. Am. Chem. Soc.* **2012**, *134*, 17474-17477.

(8) (a) Schipper, D. J.; Hutchinson, M.; Fagnou, K., Rhodium(III)-Catalyzed Intermolecular Hydroarylation of Alkynes. *J. Am. Chem. Soc.* **2010**, *132*, 6910-6911. (b) Ding, Z.; Yoshikai, N., Mild and Efficient C2-Alkenylation of Indoles with Alkynes Catalyzed by a Cobalt Complex. *Angew. Chem. Int. Ed.* **2012,** *51*, 4698-4701. (c) Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M., Pyrroloindolone Synthesis via a Cp*Co(III)-Catalyzed Redox-Neutral Directed C–H Alkenylation/Annulation Sequence. *J. Am. Chem. Soc.* **2014**, *136*, 5424-5431. (d) Liang, L.; Fu, S.; Lin, D.; Zhang, X.-Q.; Deng, Y.; Jiang, H.; Zeng, W., Ruthenium(II)-Catalyzed Direct Addition of Indole/Pyrrole C2–H Bonds to Alkynes. *J. Org. Chem.* **2014**, *79*, 9472-9480. (e) Sharma, S.; Han, S.; Shin, Y.; Mishra, N. K.; Oh, H.; Park, J.; Kwak, J. H.; Shin, B. S.; Jung, Y. H.; Kim, I. S., Rh-catalyzed oxidative C2-alkenylation of indoles with alkynes: unexpected cleavage of directing group. *Tetrahedron Lett.* **2014**, *55*, 3104-3107. (f) Zhang, W.; Wei, J.; Fu, S.; Lin, D.; Jiang, H.; Zeng, W., Highly Stereoselective Ruthenium(II)-Catalyzed Direct C2-syn-Alkenylation of Indoles with Alkynes. *Org. Lett.* **2015**, *17*, 1349-1352. (g) García-Rubia, A.; Arrayás, R. G.; Carretero, J. C., Palladium(II)-Catalyzed Regioselective Direct C2 Alkenylation of Indoles and Pyrroles Assisted by the N-(2-Pyridyl)sulfonyl Protecting Group. *Angew. Chem. Int. Ed.* **2009**, *48*, 6511-6515. (h) Sharma, S.; Han, S.; Kim, M.; Mishra, N. K.; Park, J.; Shin, Y.; Ha, J.; Kwak, J. H.; Jung, Y. H.; Kim, I. S., Rh-catalyzed oxidative C–C bond formation and C–N bond cleavage: direct access to C2-olefinated free (NH)-indoles and pyrroles. *Org. Biomol. Chem.* **2014**, *12*, 1703-1706.

(9) (a) Nakamura, I.; Yamauchi, D.; Nishimura, T., Hydroxoiridium-Catalyzed sp^3 C-H Alkylation of Indoline Derivatives with Terminal Alkenes. *Asian J. Org. Chem.* **2018**, *7*, 1347-1350. For reviews covering iridium-catalysed hydrocarbonation of C–C unsarturated partners by C(sp^3)-H bond activation, see: (b) Fernández, D. F.; Mascareñas, J. L.; López, F., Catalytic addition of C-H bonds across C-C unsaturated systems promoted by iridium(i) and its group IX congeners. *Chem. Soc. Rev.* **2020**, *49*, 7378-7405. (c) Gonnard, L.; Guerinot, A.; Cossy, J., Transition metal-catalyzed alpha-alkylation of amines by C(sp^3)-H bond activation. *Tetrahedron* **2019**, *75*, 145-163. (d) Kapoor, M.; Singh, A.; Sharma, K.; Hsu, M. H., Site-Selective C(sp^3)-H and C(sp^2)-H Functionalization of Amines Using a Directing-Group-Guided Strategy. *Adv. Synth. Catal.* **2020**, *362*, 4513-4542. (e) Antermite, D.; Bull, J. A., Transition Metal-Catalyzed Directed C(sp^3)–H Functionalization of Saturated Heterocycles. *Synthesis* **2019**, *51*, 3171-3204.

(10) The structure and stereochemistry of (*E*)-**3aa** was confirmed by X-ray crystallographic analysis. See the Supporting Information for further details.

(11) See the Supporting Information for further details.

(12) (a) Zhao, W.; Lu, H. X.; Zhang, W. W.; Li, B. J., Coordination Assistance: A Powerful Strategy for Metal-Catalyzed Regio- and Enantioselective Hydroalkynylation of Internal Alkenes. *Acc. Chem. Res.* **2023**, *56*, 308-321. (b) Trost, B. M.; Masters, J. T., Transition metal-catalyzed couplings of alkynes to 1,3-enynes: modern methods and synthetic applications. *Chem. Soc. Rev.* **2016**, *45*, 2212-2238.

(13) For selected examples of TMC acceptorless dehydrogenation of related heterocycles, see: (a) Zhang, D. L.; Iwai, T.; Sawamura, M. Ir-Catalyzed Reversible Acceptorless Dehydrogenation/Hydrogenation of N-Substituted and Unsubstituted Heterocycles Enabled by a Polymer-Cross-Linking Bisphosphine. *Org. Lett.*, **2020**, 22, 5240-5245. (b) Fujita, K.-I.; Wada, T.; Shiraishi, T., Reversible Interconversion between 2,5-Dimethylpyrazine and 2,5-Dimethylpiperazine by Iridium-Catalyzed Hydrogenation / Dehydrogenation for Efficient Hydrogen Storage. *Angew. Chem. Int. Ed.*, **2017**, *56*, 10886-10889. (c) Xu, R.; Chakraborty, S.; Yuan, H.; Jones, W. D. Acceptorless, Reversible Dehydrogenation and Hydrogenation of *N*-Heterocycles with a Cobalt Pincer Catalyst. *ACS Catal.*, **2015**, *5*, 6350-6354.

(14) Alternatively, a carboiridation step followed by a C-H reductive elimination, instead of the hydroiridation/C-C reductive elimination, can also account for the formation of intermediate **H** from **F**.

(15) For selected examples, see: (a) Li, B.; Zhang, B.; Zhang, X.; Fan, X., Regio-selective synthesis of diversely substituted benzo[a]carbazoles through Rh(III)-catalyzed annulation of 2-arylindoles with α-diazo carbonyl compounds. *Chem. Commun.* **2017**, *53*, 1297-1300. (b) Han, Q.; Guo, X.; Tang, Z.; Su, L.; Yao, Z.; Zhang, X.; Lin, S.; Xiang, S.; Huang, Q., Rhodium-Catalyzed Regioselective Ortho C–H Olefination of 2-Arylindoles via NH-Indole-Directed C–H Bond Cleavage. *Adv. Synth. Catal.* **2018**, *360*, 972-984. (c) Chen, G.; Zhang, X.; Jia, R.; Li, B.; Fan, X., Selective Synthesis of Benzo[*a*]Carbazoles and Indolo[2,1-*a*]-Isoquinolines via Rh(III)-Catalyzed C–H Functionalizations of 2-Arylindoles with Sulfoxonium Ylides. *Adv. Synth. Catal.* **2018**, *360*, 3781-3787. (d) Yang, X.; Li, Y.; Kong, L.; Li, X., Access to Quaternary Stereogenic Centers via Rhodium(III)-Catalyzed Annulations between 2-Phenylindoles and Ketenes. *Org. Lett.* **2018**, *20*, 1957-1960. (e) Obata, A.; Sasagawa, A.; Yamazaki, K.; Ano, Y.; Chatani, N., Nickel-catalyzed oxidative C–H/N–H annulation of N-heteroaromatic compounds with alkynes. *Chem. Sci.* **2019**, *10*, 3242-3248. (f) Shinde, V. N.; Rangan, K.; Kumar, D.; Kumar, A., Rhodium(III)-Catalyzed Dehydrogenative Annulation and Spirocyclization of 2-Arylindoles and 2-(1H-Pyrazol-1-yl)-1H-indoles with Maleimides: A Facile Access to Isogranulatimide Alkaloid Analogues. *J. Org. Chem.* **2021**, *86*, 2328-2338. (g) Zhang, F.; Zhu, X.; Luo, B.; Wang, C., Rh(iii)-catalyzed regioselective C–H activation dialkenylation/annulation cascade for rapid access to 6H-isoindolo[2,1-*a*]indole. *RSC Adv.* **2021**, *11*, 25194-25198. (h) Xia, Y.-Q.; Dong, L., Ruthenium(II)-Catalyzed Indolo[2,1-*a*]isoquinolines Synthesis by Tandem C–H Allylation and Oxidative Cyclization of 2-Phenylindoles with Allyl Carbonates. *Org. Lett.* **2017**, *19*, 2258-2261. (i) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M., Rhodium-Catalyzed Oxidative Coupling/Cyclization of 2-Phenylindoles with Alkynes via C–H and N–H Bond Cleavages with Air as the Oxidant. *Org. Lett.* **2010**, *12*, 2068-2071. (j) Ackermann, L.; Wang, L.; Lygin, A. V., Ruthenium-catalyzed aerobic oxidative coupling of alkynes with 2-aryl-substituted pyrroles. *Chem. Sci.* **2012**, *3*, 177-180. (k) Huang, Q.; Han, Q.; Fu, S.; Yao, Z.; Su, L.; Zhang, X.; Lin, S.; Xiang, S., Rhodium-Catalyzed NH-Indole-Directed C–H Carbonylation with Carbon Monoxide: Synthesis of 6H-Isoindolo[2,1-*a*]indol-6-ones. *J. Org. Chem.* **2016**, *81*, 12135-12142. (l) Zhang, Z.; Liu, K.; Chen, X.; Su, S.-J.; Deng, Y.; Zeng, W., Rhodium(III)-catalyzed indole-directed carbenoid aryl C–H insertion/cyclization: access to 1,2-benzocarbazoles. *RSC Adv.* **2017**, *7*, 30554-30558. (m) Li, S.-S.; Xia, Y.-Q.; Hu, F.-Z.; Liu, C.-F.; Su, F.; Dong, L., IrIII-Catalyzed One-Pot Cascade Synthesis of Pentacyclic-Fused Carbazoles from Indoles and Diazoes. *Chem. Asian J.* **2016**, *11*, 3165-3168.

(16) (a) Aygün, A.; Pindur, U., Synthesis and biological evaluation of structural variants of carbazoquinocin C. *J. Het. Chem.* **2003**, *40*, 411-417. (b) Palmer, B. D.; Thompson, A. M.; Booth, R. J.;

Dobrusin, E. M.; Kraker, A. J.; Lee, H. H.; Lunney, E. A.; Mitchell, L. H.; Ortwine, D. F.; Smaill, J. B.; Swan, L. M.; Denny, W. A., 4-Phenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione Inhibitors of the Checkpoint Kinase Wee1. Structure–Activity Relationships for Chromophore Modification and Phenyl Ring Substitution. *J. Med. Chem.* **2006**, *49*, 4896-4911. (c) Li, X.-S.; Han, Y.-P.; Zhu, X.-Y.; Xia, Y.; Wei, W.-X.; Li, M.; Liang, Y.-M., Lewis Acid-Catalyzed Annulation of Propargylic Alcohols with (*Z*)-2-Styryl-1*H*-Indoles. *Adv. Synth. Catal.* **2018**, *360*, 4441-4445. (d) Saha, S.; Banerjee, A.; Maji, M. S., Brønsted Acid Catalyzed One-Pot Benzannulation of 2-Alkenylindoles under Aerial Oxidation: A Route to Carbazoles and Indolo[2,3-a]carbazole Alkaloids. *Org. Lett.* **2018**, *20*, 6920-6924. (e) Saha, S.; Maji, M. S., One-pot access to tetrahydrobenzo[*c*]carbazoles from simple ketones by using O_2 as an oxidant. *Org. Biomol. Chem.* **2020**, *18*, 1765-1768.

(17) (a) Elliott, I. W., Chapter 4 Dibenzopyrrocoline Alkaloids. In *The Alkaloids: Chemistry and Pharmacology*, Brossi, A., Ed. Academic Press: **1987**; Vol. 31, pp 101-116; (b) Ambros, R.; Schneider, M. R.; Von Angerer, S., Indolo[2,1-a]isoquinolines. Syntheses, steroid hormone receptor binding affinities, and cytostatic activity. *J. Med. Chem.* **1990**, *33*, 153-160. (c) Goldbrunner, M.; Loidl, G.; Polossek, T.; Mannschreck, A.; von Angerer, E., Inhibition of Tubulin Polymerization by 5,6-Dihydroindolo[2,1-*a*]isoquinoline Derivatives. *J. Med. Chem.* **1997**, *40*, 3524-3533. (d) Elmegeed, G. A.; Baiuomy, A. R.; Abdel-Salam, O. M. E., Evaluation of the anti-inflammatory and anti-nociceptive activities of novel synthesized melatonin analogues. *Eur. J. Med. Chem.* **2007**, *42*, 1285-1292. (e) Ahmed, E.; Briseno, A. L.; Xia, Y.; Jenekhe, S. A., High Mobility Single-Crystal Field-Effect Transistors from Bisindoloquinoline Semiconductors. *J. Am. Chem. Soc.* **2008**, *130*, 1118-1119. (f) Kraus, G. A.; Gupta, V.; Kohut, M.; Singh, N., A direct synthesis of 5,6-dihydroindolo[2,1-*a*]isoquinolines that exhibit immunosuppressive activity. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5539-5542. (g) Medina, A. E. *Proc. Natl. Acad. Sci. U. S. A.*, **2010**, *107*, 9921–9922; (h) Zhou, J.; Outlaw, V. K.; Townsend, C. A.; Bragg, A. E., Quenching of pH-Responsive Luminescence of a Benzoindolizine Sensor by an Ultrafast Hydrogen Shift. *Chem. Eur. J.* **2016**, *22*, 15212-15215.

(18) (a) Pallavi, P.; Sk, B.; Ahir, P.; Patra, A., Tuning the Forster Resonance Energy Transfer through a Self-Assembly Approach for Efficient White-Light Emission in an Aqueous Medium. *Chem. Eur. J.* **2018**, *24*, 1151-1158. (b) Samala, S.; Pallavi, P.; Kumar, R.; Arigela, R. K.; Singh, G.; Ampapathi, R. S.; Priya, A.; Datta, S.; Patra, A.; Kundu, B., One-pot synthesis of highly fluorescent pyrido[1,2-*a*]indole derivatives through C-H/N-H activation: photophysical investigations and application in cell imaging. *Chem. Eur. J.* **2014**, *20*, 14344-14350. (c) Outlaw, V. K.; Zhou, J.; Bragg, A. E.; Townsend, C. A., Unusual blue-shifted acid-responsive photoluminescence behavior in 6-amino-8-cyanobenzo[1,2-*b*]indolizines. *RSC Adv.* **2016**, *6*, 61249-61253.

(19) (a) Peng, S.; Wang, L.; Huang, J.; Sun, S.; Guo, H.; Wang, J., Palladium-Catalyzed Oxidative Annulation via C–H / N-H Functionalization: Access to Substituted Pyrroles. *Adv. Synth. Catal.* **2013**, *355*, 2550-2557. (b) Wanqing, W.; Yanni, A.; Jianxiao, L.; Huanfeng, J. A synthetic method of 6-phenylindolo[2,1-*a*]isoquinoline compounds, **2017**, Patent CN106866664A.

(20) Related Rh(III) catalytic systems previously described to prepare indolo[2,1-*a*]isoquinoline derivatives from C2-aryl indoles, were not successful with the C2-alkenyl indole **3aa**. See for instance ref 15a.

(21) For related [4+1] annulations of diazoderivatives using benzamides and other systems, see: (a) Hyster, T. K.; Ruhl, K. E.; Rovis, T., A coupling of benzamides and donor/acceptor diazo compounds to form gamma-lactams via Rh(III)-catalyzed C-H activation. *J. Am. Chem. Soc.* **2013**, *135*, 5364-7. (b) Yu, S.; Liu, S.; Lan, Y.; Wan, B.; Li, X., Rhodium-Catalyzed C–H Activation of Phenacyl Ammonium Salts Assisted by an Oxidizing C–N Bond: A Combination of Experimental and Theoretical Studies. *J. Am. Chem. Soc.* **2015**, *137*, 1623-1631. (c) Zhang, Y.; Zheng, J.; Cui, S., Rh(III)-Catalyzed C–H Activation/Cyclization of Indoles and Pyrroles: Divergent Synthesis of Heterocycles. *J. Org. Chem.* **2014**, *79*, 6490-6500.

(22) Ganesan, B.; Senadi, G. C.; Guo, B. C.; Hung, M. Y.; Lin, W. Y., A copper(II)-catalyzed annulative formylation of *o*-alkynylanilines with DMF: a single-step strategy for 3-formyl indoles. *RSC Adv.* **2018**, *8*, 40968-40973.

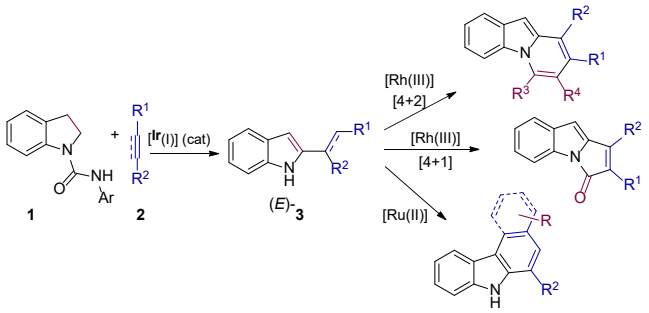
(23) Although some related dehydrogenative cross-couplings have been reported with Pd and Rh, to the best of our knowledge, there is only an isolated case with Ru(II) catalysts, see: (a) Dong, J.; Long, Z.; Song, F.; Wu, N.; Guo, Q.; Lan, J.; You, J., Rhodium or Ruthenium-Catalyzed Oxidative C–H/C–H Cross-Coupling: Direct Access to Extended π-Conjugated Systems. *Angew. Chem. Int. Ed.* **2013**, *52*, 580-584. For a review on TMC oxidative C–H/C–H couplings, see: (b) Yang, Y. D.; Lan, J. B.; You, J. S., Oxidative C-H/C-H Coupling Reactions between Two (Hetero)arenes. *Chem. Rev.* **2017**, *117*, 8787-8863.

(24) For a selected examples of Pd-catalyzed isomerizations of alkenes, see: Matsuura, R.; Karunananda, M. K.; Liu, M.; Nguyen, N.; Blackmond, D. G.; Engle, K. M., Mechanistic Studies of Pd(II)-Catalyzed *E*/*Z* Isomerization of Unactivated Alkenes: Evidence for a Monometallic Nucleopalladation Pathway. *ACS Catal.* **2021**, 4239-4246.

(25) Previously related manipulations were limited to derivatives with only one or two substituents at the alkene. See references 8.

(26) Hingane, D. G.; Parekh, N. P.; Khan, A.; Kusurkar, R. S., Efficient synthetic route toward biologically active γ-carboline derivatives. *Synthetic Commun.* **2016**, *46*, 160-164.

(27) Banerjee, A.; Saha, S.; Maji, M. S., Cascade Benzannulation Approach for the Syntheses of Lipocarbazoles, Carbazomycins, and Related Alkaloids. *J. Org. Chem.* **2022**, *87*, 4343-4359.



TOC graphic