Iridium(I)-Catalyzed Intramolecular Cycloisomerization of Enynes: Scope and Mechanistic Course

David F. Fernández,[†§] Catarina A. B. Rodrigues,[†§] Martín Calvelo,[†] Moisés Gulías,[†] José L. Mascareñas,[*†] Fernando López[*†‡]

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

[‡] Instituto de Química Orgánica General CSIC, Juan de la Cierva 3, 28006, Madrid, Spain

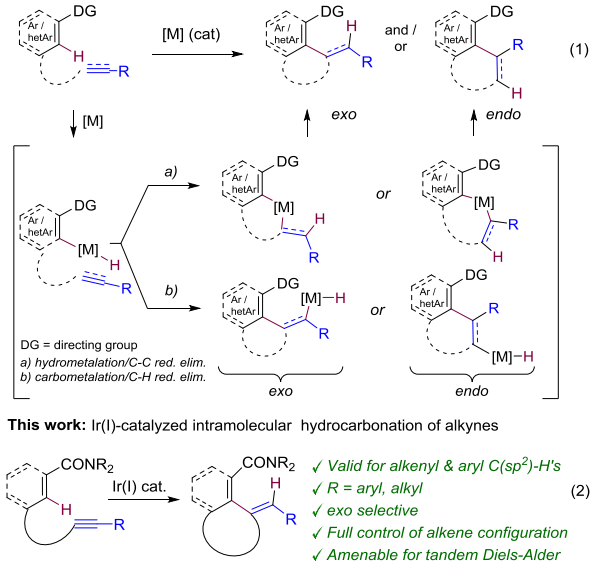
ABSTRACT: We report an Ir(I)-catalyzed cycloisomerization methodology that provides access to carbocyclic systems bearing *exo*-alkene moieties from alkynyl-equipped acyclic precursors. The method relies on the C-H activation of olefinic and (hetero)aromatic C(sp^2)–H bonds, followed by an exo-cyclization to a tethered alkyne, and provides interesting cyclic diene products that are amenable of further elaboration. Importantly, DFT calculations suggests that, in contrast to related hydrocarbonations of alkenes in which either migratory insertions or C-C reductive eliminations have been suggested to be rate determining, in our reactions, the energetic barrier of these steps is lower than that of the previous C–H activation.

KEYWORDS: Iridium, C–H activation, hydrocarbonation, catalysis, cyclization

The development of methods for C–C bond formation based on metal-promoted C–H bond activations is revolutionizing modern synthetic chemistry.[1] Of special interest are those methods that involve a metal catalyzed simple addition of C(sp^2)–H bonds across the C–C unsaturated moiety of alkenes or alkynes, owing to their simplicity, constructive power, and full atom-economy.[2] While the hydrocarbonation of alkenes present the interest of creating new stereocenters, the analog reactions with alkynes are of also great synthetic value as the alkenyl moiety of the product provides for further manipulations.

Most studies in this area have been focused on intermolecular processes, and on the use Pd, Ru or Rh catalysts.[1,2] In contrast, reports on iridium-promoted additions of C(sp^2)–H bonds across alkynes are very scarce, and essentially limited to precursors with (hetero)aromatic moieties. Noticeably, iridium promoted additions of alkenyl C–H bonds to alkynes have not yet been described.[3] More remarkable, regardless of the type of metal catalyst used, intramolecular additions to alkynes based on C–H activation processes, are almost unknown. The only examples so far described consist of a Rh(I)-catalyzed cyclization of α,β-unsaturated imines containing tethered alkynes[4] and a recent report on a Ir(I) or Rh(I)-catalyzed C–H alkenylation of indoles.[5,6]

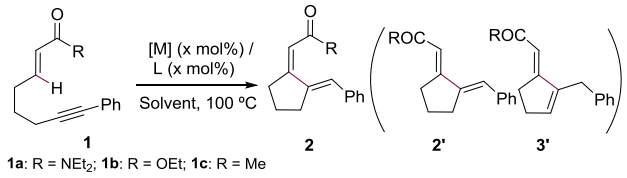
From a mechanistic point of view, these hydrocarbonation processes catalyzed by low-valent transition metal complexes have been generally proposed to involve a C–H oxidative addition step, followed by either an *exo*- or *endo* hydrometalation of the C–C unsaturated bond. Finally, a C–C reductive elimination would deliver the cyclic products (Scheme 1, eq 1. route a). However, recent mechanistic work suggested that a path based on a carbometalation/C–H reductive elimination sequence (route b, *exo* type), could better explain the Ir-catalyzed hydrocarbonation of alkenes.[7] Considering these intriguing mechanistic aspects, the scarce precedents on intramolecular hydroarylation and especially, hydroalkenylation of alkynes,[4-6] and the constructive power of the cyclizations, we were prompted to investigate the performance of iridium catalysts in this type of reactions.[8] Herein we report an Ir(I)-catalyzed intramolecular addition of olefinic, aromatic and heteroaromatic precursors to tethered alkynes. These cycloisomerizations provide carbocyclic products containing an *exo*-olefin, with complete stereoselectivity. The synthetic potential of the strategy is further stressed by coupling the cyclization process with a Diels–Alder cycloaddition in a single pot, which provides a direct and fully stereoselective entry to relatively complex polycarbocyclic systems bearing up to four stereocenters. Importantly, we provide DFT calculations that point to the C–H activation as the step with higher activation barrier. This contrasts to the hydrocarbonation of alkenes,[8] which has been proposed to proceed through a rate limiting carbometalation followed by C–H reductive elimination.[9]



Scheme 1. Mechanistic scenario for metal-catalyzed hydrocarbonations (eq. 1, *exo* and *endo*), and our work (eq. 2).

Considering the scarcity of intramolecular hydrocarbonations proceeding through the activation olefinic C(sp^2)–H bonds,[10] we selected the alkenyl derivative **1a** as model substrate. The complex [Ir(cod)$_2$]BArF / d^{F}ppe, previously found successful for the hydrocarbonation of alkenes,[8,11] was moderately efficient, providing the expected *exo*-cyclization product **2a** in 61% yield (24 h heating at 100 ºC in 1,2-DCE, Table 1, entry 1). In addition to **2a**, traces of the *trans* isomer **2a'** (< 6%) could also be observed in the crude, whereas the *endo*-cyclization product (i.e. **4a**) was not detected. Among bisphosphines,[12] only BINAP improved this result (70%, entry 2), a value that could be improved up to 92% yield by using dioxane as solvent (entry 3). The use of monodentate phosphine ligands such as Ph_3P proved unsuccessful (entry 4).

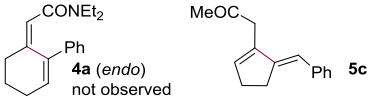
Table 1. Preliminary screening with **1a**[a]



1a: R = NEt_2; **1b**: R = OEt; **1c**: R = Me

Entry	1	[M] (x mol%)	Conv.	L	Products, % yield[b]
1[c]	**1a**	[Ir(cod)$_2$]BArF (5)	77%	d^{F}ppe	**2a,** 61 / **2a'**, 6
2[c]	**1a**	[Ir(cod)$_2$]BArF (5)	80%	*rac*-BINAP	**2a,** 70 /**2a'**, 2
3	**1a**	[Ir(cod)$_2$]BArF (5)	99%	*rac*-BINAP	**2a,** 92 / **2a'**, 4
4[d]	**1a**	[Ir(cod)$_2$]BArF (5)	0%	PPh_3	-
5	**1a**	[Ir(cod)$_2$]BF4 (5)	99%	*rac*-BINAP	**2a**, 60 / **2a'**, 3 / **3a'**, 12
6	**1a**	[Ir(cod)$_2$]OTf (5)	99%	*rac*-BINAP	**2a,** 85 / **2a'**, 3 / **3a'**, 8
7[e]	**1a**	[Ir(cod)$_2$]BArF (5)	74%	*rac*-BINAP	**2a**, 71
8[f]	**1b**	[Ir(cod)$_2$]BArF (5)	99%	*rac*-BINAP	-[g]
9[f,h]	**1c**	[Ir(cod)$_2$]BArF (5)	99%	*rac*-BINAP	**5c**, 42
10[i]	**1a**	$RuH_2CO(PPh_3)_3$ (5)	99%	-	**2a'**, 7 / **3a'**, 61

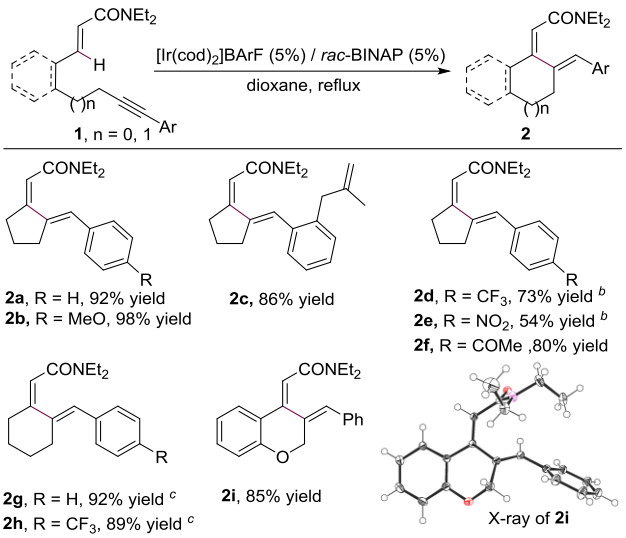
[a] Conditions: **1a** was added to a solution of [M] (x mol%) and L (x mol%) in dioxane, unless otherwise noted, and the mixture was heated at 100 ºC for 24 h. [b] Isolated yields. [c] Carried out in 1,2-DCE (100 ºC, sealed tube). [d] Carried out with 10 mol% of Ph_3P. [e] Carried out with NaOAc (20%). [f] Carried out at 120 ºC. [g] A complex mixture of products is obtained. [h] Reaction time: 6 days. [i] Carried out in refluxing toluene. d^{F}ppe: $(C_6F_5)_3P(CH_2)_2P(C_6F_5)_3$.



The counterion influences the outcome, with BF_4^- or TfO^- leading to lower yields and the formation of small amounts of secondary products like **3a'** (entries 5 and 6). Contrary to the C–H alkenylation of indoles, which required the use of NaOAc (20 mol%) to avoid partial isomerization of the product,[5] this base is detrimental for the cyclization (entry 7). The nature of the directing group is critical, as substrates with an ethyl ester (**1b**) or a ketone (**1c**), instead of the amide, were unreactive at 100 ºC. Increasing the temperature up to 120 ºC led to some reactivity, albeit we observed mixtures of products (entry 8) or the formation of isomers like **5c** (entry 9). Importantly, Rh and Ru catalysts previously found to be effective in intermolecular alkenylations,[13] failed to give the desired products. We only observed some reactivity with $RuH_2CO(PPh_3)_3$, which produced mostly the isomeric product **3a'** (61%, entry 10).[14] These results confirm that methods that work in intermolecular reactions do not necessarily translate to intramolecular cases.

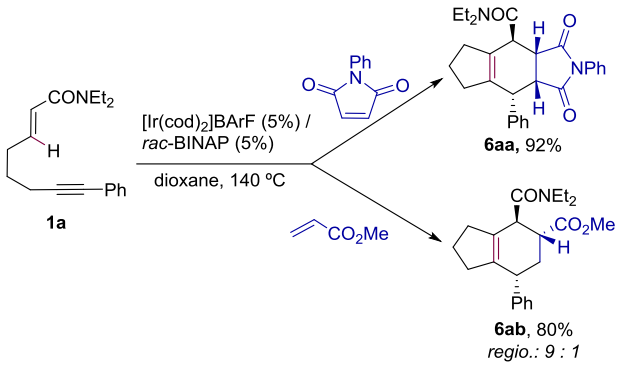
The reaction is tolerant to both electron-donating and electron withdrawing substituents at the aryl group of the alkyne (Table 2), although, in the case of electron deficient substituents, obtaining good conversions required further heating. Nevertheless, the corresponding *exo*-dienyl cyclopentanes (**2b–2f**) were isolated with moderate to excellent yields and complete selectivities. Importantly, the reaction tolerates a one-carbon elongation of the tether, and the cyclohexane products (**2g–2h**) were obtained in excellent yields, even under relatively mild temperatures (80 ºC). Finally, substrates with aryl linkers do also react to provide chromane derivatives like **2i** in excellent yield (Table 2).[15]

Table 2. Intramolecular hydroalkenylation of alkynes[a]



[a] Conditions: **1** was added to a solution of [Ir(cod)$_2$]BArF (5 %) and *rac*-BINAP (5 %) in dioxane and the mixture was refluxed for 19 h. Isolated yields. [b] Carried out at 120 ºC (sealed tube). [c] Carried out at 80 ºC.

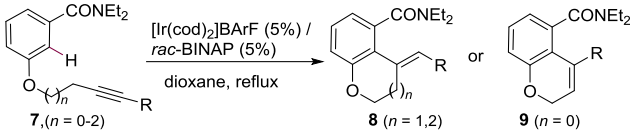
The presence of the exocyclic diene in the reaction products (**2**) suggested the possibility of further synthetic elaboration. Despite the diene is not electronically well posed to react with electron deficient alkenes, we observed that heating of **2a** with N-phenyl maleimide (4 equiv.) in dioxane at 140 ºC, provides the *endo*-cycloadduct **6aa** in 90% yield.[12] Remarkably, both reactions, the cycloisomerization and the cycloaddition, can be carried out in the same pot. Therefore, direct heating of **1a** with [Ir(cod)$_2$]BArF / *rac*-BINAP in presence of *N*-phenyl maleimide (4 equiv) in dioxane at 140 ºC, for 24 h, produces the tricyclic adduct **6aa** in 92% isolated yield (Scheme 2). Similarly, using methyl acrylate as reaction partner, we observed the product **6ab** in 80% yield and 9:1 regioselectivity (major isomer shown, Scheme 2). It is important to remark the total chemoselectivity of the cycloisomerization in presence of excess of an externally added alkene, as this could also participate in competing intermolecular hydrocarbonations. Overall, the method provides a straightforward protocol to generate stereochemically rich polycarbocyclic products from simple acyclic starting materials, with full atom-economy.[16]

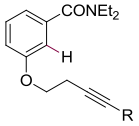
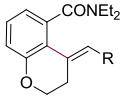
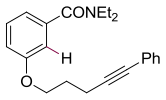
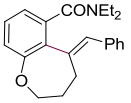
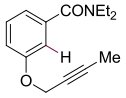
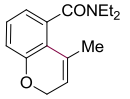


Scheme 2. Tandem, one-pot Ir(I)-catalyzed C-H hydrocarbonation / Diels-Alder

We also analyzed related reactions involving the activation of aromatic and heteroaromatic C(sp^2)–H bonds. Importantly, the aryl carboxamide **7a** undergoes a very efficient reaction to give the chromane derivative **8a** (88% yield, Table 3, entry 1). Similarly to the olefinic series, the presence of electron-withdrawing groups at the aryl substituent of the alkyne somehow reduces the efficiency of the process (**8b**, 48% yield, entry 2). Aliphatic substituents at the alkyne terminal position (*e.g.* methyl) are well tolerated, so that cyclization products like **8c** could be obtained in 78% yield (entry 3). Notably, the reaction was also effective in substrates with longer tethers like **7d**, with the benzoxepine derivative **8d** being obtained in 68% yield (entry 4). Interestingly, precursors with shorter tethers such as **7e** led to an alternative *endo*-cyclization product (**9e**) albeit in low yield (entry 5).[17]

Table 3. Alkenylation of (hetero)aromatic systems[a]



entry		R	7	Product	8/9	Yield (%)[b]
1		Ph	**7a**		**8a**	88
2		*p*CF_3Ph	**7b**		**8b**	48 [c]
3		Me	**7c**		**8c**	78
4			**7d**		**8d**	68
5			**7e**		**9e**	35

[a] Conditions: **7** was added to a solution of [Ir(cod)$_2$]BArF (5 %) and *rac*-BINAP (5 %) in dioxane, and the mixture was heated under reflux for 24 h. [b] Isolated yields. [c] Carried out at 80 ºC (73% conversion).

Importantly, the intramolecular hydrocarbonation of alkynes can also be efficiently accomplished in heteroaromatic systems, such as pyrroles. Thus, tetrahydroindolizine product **8f** and **8g** were efficiently obtained from the corresponding pyrrol-tethered alkynyl precursors upon heating at 80 ºC in presence of [Ir(cod)$_2$]BArF / *rac*-BINAP (Figure 1). The reactions also gave small amounts of isomeric dihydroindolizines.[18] Gratifyingly, seven- and even eight-membered pyrrol-fused systems **8h** and **8i** could also be assembled in good yields and complete selectivity. Thus, the methodology provides a simple, efficient and atom-economical approach to challenging heteroaromatic systems bearing fused medium-sized carbocycles, structures that are difficult to assemble through alternative methodologies.

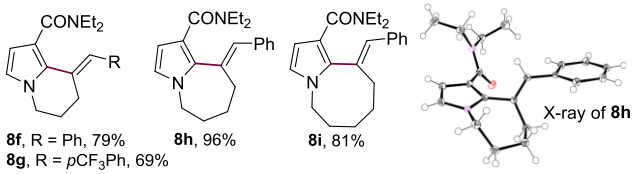
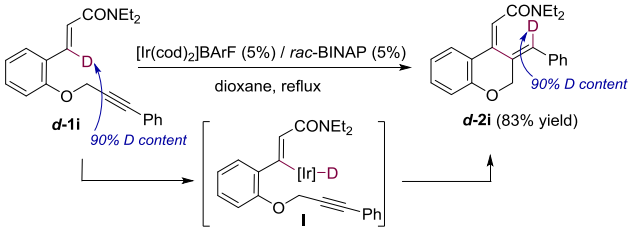


Figure 1. Intramolecular hydrocarbonation of alkynes with pyrroles; X-ray of **8h**.

Mechanistically informative, treatment of deuterated precursor ***d*-1i** under standard reaction conditions provided the expected cycle with complete and exclusive incorporation of deuterium at the vinylic position, confirming that an Ir(III)–hydride intermediate of type **I** is involved (Scheme 3).[19] However, the evolution of this intermediate to the product could either occur via a hydroiridation or a carboiridation process.



Scheme 3. Mechanistic probe.

To shed light into these competitive pathways, we performed a DFT theoretical analysis using the model substrate **1a'**, and dppe as ligand.[12,20] As can be seen in the Figure 2, the C–H activation step exhibits the highest energy barrier of the process (**TS1**, 21.9 kcal·mol^{-1}),[21] and leads to intermediate **Int-1**, which might conformationally relax to the most stable Ir(III) intermediates **Int-1b** and **Int-1a**, respectively. From **Int-1b**, a pathway based on an hydroiridation of the alkyne followed by a subsequent C–C reductive elimination seems very plausible, with calculated energy barriers of 9.0 and 12.1 kcal·mol^{-1}, respectively (red pathway). Alternatively, from the more stable iridium-hydride isomer of type **Int-1a** ($\Delta\Delta G$ = 10.8 Kcal·mol^{-1}), which bears the carbonyl and the hydride in trans disposition, a carboiridation / C–H reductive elimination sequence can also be proposed. While the carbometalation presents an energy barrier of 20.0 kcal·mol^{-1}, close to that of the previous iridium oxidative addition step, the final C–H reductive elimination has the lowest barrier of the catalytic cycle, 7.6 kcal·mol^{-1}, and both steps proceed through energetic maxima significantly below to that of **TS1** (16.9 kcal·mol^{-1} for **TS2a** and 0.4 for **TS3a**, blue pathway). Therefore, the TOF-determining transition state of the process is that associated to the initial oxidative addition (**TS1**),[22] and both the hydrometalation and the carbometalation pathways are viable. However, the C–H reductive elimination presents a lower energetic barrier than the C–C forming process. This mechanistic sce-

nario is compatible with a H/D KIE value of ~2, which was measured for the cyclizations of model substrates **1i** and *d*-**1i**.[12] Overall, these results suggest a different energetic profile than that previously proposed for intramolecular carboxamide-assisted hydrocarbonation of alkenes,[8,9] wherein the carbometalation and C–C reductive elimination steps have energy barriers larger than that of the C–H insertion. In the current case, the fact that there is a migratory insertion of an alkyne instead of an alkene, and that the reductive elimination involves a sp^2–rather than a sp^3–carbon, might account for the difference.

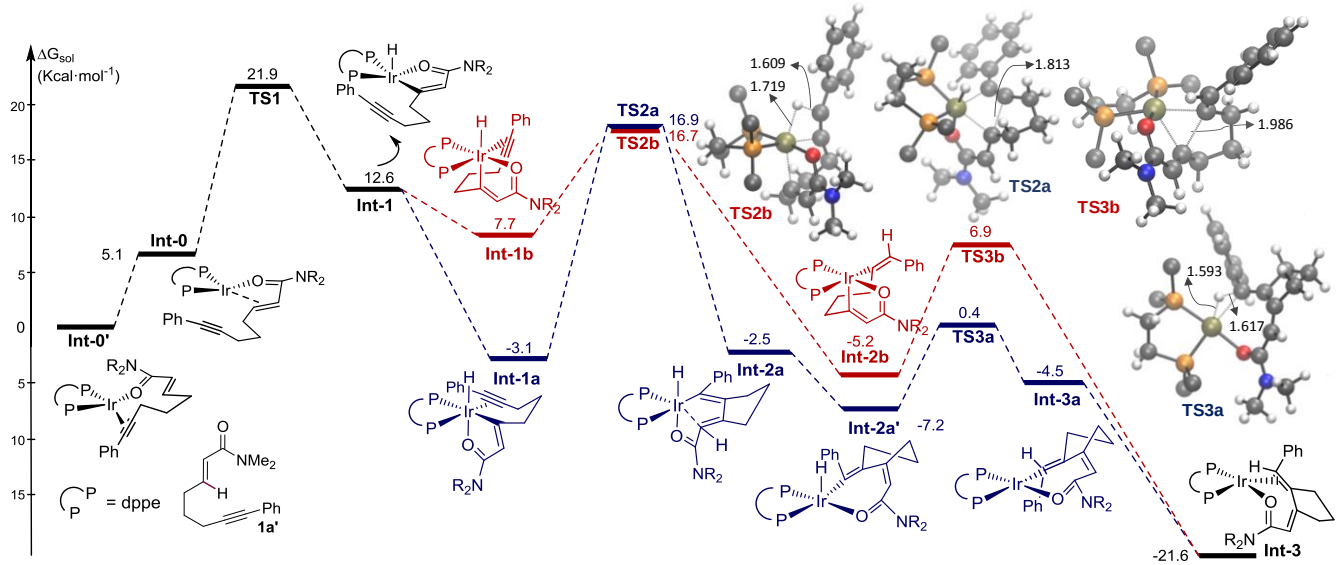


Figure 2. Energy profile ΔG^{solv} (kcal·mol^{-1}) for the hydrocarbonation of **1a'** (R = Me).[18] Phenyl rings of dppe are omitted for clarity. Key bond distances in Å

In summary, we have developed the first examples of iridium-catalyzed cycloisomerizations of enynes involving a C–H activation process. The reactions provide cyclic systems bearing an *exo*-dienyl moiety with defined stereochemistry. The method, which relies on a carboxamide-assisted C–H activation, is also suitable for substrates with aromatic and heteroaromatic C–H bonds. Importantly, the reaction allows the construction of five to eight-membered rings, and can be coupled to [4 + 2] cycloadditions in an one-pot process, thus allowing a straightforward, stereoselective entry to relatively complex polycyclic systems. Finally, DFT calculations confirmed the initial oxidative addition as rate determining step, and that both, the carbometalation and hydrometalation paths, are energetically feasible, albeit the former presents an easier C–H reductive elimination.

AUTHOR INFORMATION

Corresponding Author

* E-mail: Prof. J. L. Mascareñas. joseluis.mascarenas@usc.es,
Dr. F. Lopéz.: fernando.lopez@csic.es

Notes

The authors declare no competing financial interest.

Author Contributions

[§]These authors contributed equally.

ASSOCIATED CONTENT

Supporting Information. Full experimental procedures, optimization of the catalyst and characterization of all new compounds, including ^{1}H-, ^{13}C-NMR spectra.This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Intramolecular hydrocarbonations of C–C unsaturated bonds using olefinic C(sp^2)–H bonds are very scarce. See ref 4 for examples with alkynes. For alkenes, see: (a) Fujii, N.; Kakiuchi, F.; Chatani, N.; Murai, S. Transition Metal-Catalyzed Intramolecular C-H/Olefin Coupling. *Chem. Lett.* **1996**, *25*, 939-940. (b) Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Asymmetric Synthesis of (−)-Incarvillateine Employing an Intramolecular Alkylation via Rh-Catalyzed Olefinic C−H Bond Activation. *J. Am. Chem. Soc.* **2008**, *130*, 6316-6317. (c) Aissa, C.; Fürstner, A. A Rhodium-Catalyzed C−H Activation/Cycloisomerization Tandem. *J. Am. Chem. Soc.* **2007**, *129*, 14836-14837. (d) Aissa, C.; Ho, K. Y. T.; Tetlow, D. J.; Pin-Nó, M. Diastereoselective Carbocyclization of 1,6- Heptadienes Triggered by Rhodium-Catalyzed Activation of an Olefinic C-H Bond. *Angew. Chem. Int. Ed.* **2014**, *53*, 4209-4212.

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(12) See the Supporting Information for further details.

(13) For Ru, see: (a) Kakiuchi, F.; Uetsuhara, T.; Tanaka, Y.; Chatani, N.; Murai, S. Ruthenium-Catalyzed Addition of Olefinic C–H Bonds in Conjugate Enones to Acetylenes to Give Conjugate Dienones. *J. Mol. Catal. A: Chem.* **2002**, 511–514. (b) Neisius, N. M.; Plietker, B. The Ruthenium-Catalyzed Hydrovinylation of Internal Alkynes by Acrylates: An Atom Economic Approach to Highly Substituted 1,3- Dienes. *Angew. Chem. Int. Ed.* **2009**, *48*, 5752–5755. (c) Nishida, M.; Adachi, N.; Onozuka, K.; Matsumura, H.; Mori, M. Intramolecular Cyclizations of Enynes Using $RuClH(CO)(PPh_3)_3$. *J. Org. Chem.* **1998**, *63*, 9158-9159. For Rh, see: (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Stereoselective Alkylation of α,β-Unsaturated Imines via C−H Bond Activation. *J. Am. Chem. Soc.* **2006**, *128*, 5604- 605. (e) Shibata, Y.; Otake, Y.; Hirano, M.; Tanaka, K. Amide-Directed Alkenylation of sp^2 C−H Bonds Catalyzed by a Cationic Rh(I)/BIPHEP Complex Under Mild Conditions: Dramatic Rate Acceleration by a 1-Pyrrolidinecarbonyl Group. *Org. Lett.* **2009**, *11*, 689-692.

(14) (a) Control experiments suggest that product **3a'** can be obtained from **2a'** under reaction conditions. (b) With this Ru catalyst, **2a** was never detected, even at lower temperatures or shorter reaction times, suggesting that it proceeds through a different mechanism. See Ref. 13c.

(15) Traces of isomers of type **2'** could only be detected in the reaction crudes of **1e** and **1f**.

(16) Wender, P. A.; Gamber, G. G.; Scanio, M. J. C. Serial [5+2]/[4+2] Cycloadditions: Facile, Preparative, Multi-Component Syntheses of Polycyclic Compounds from Simple, Readily Available Starting Materials. *Angew. Chem. Int. Ed.* **2001**, *40*, 3895-3897.

(17) Probably, an *exo* migratory insertion is highly impeded due to conformation constrains imposed by the shorter tether (vide infra).

(18) Control experiments suggest that the isomeric side-products are obtained from **8f** and **8g**, under reaction conditions. This isomerization is also observed under soft acidic conditions ($CHCl_3$ that contains traces of hydrochloric acid). See the Supp. Info.

(19) An alternative mechanisms based on hydrometalations (e.g. ref 13c) or through oxidative metalacycles are very unlikely since would provide isomers of type **2'**.

(20) Optimization of geometries was carried out at the M06 / 6-31G(d,p) level (SDD for Ir), and single point calculations at M06 / 6-311++G(d,p);SDD for Ir. Reported values correspond to solvation-corrected relative free-energies obtained at this level (solvent = dioxane). See the Supp. Info.

(21) The C–H activation can also occur from **Int-0'**, wherein the alkyne is coordinated to the Ir, with an almost identical barrier. See the Supp. Info.

(22) (a) Kozuch, S. Steady State Kinetics of Any Catalytic Network: Graph Theory, the Energy Span Model, the Analogy between Catalysis and Electrical Circuits, and the Meaning of "Mechanism", *ACS Catal.* **2015**, *5*, 5242–5255. (b) Kozuch, S.; Shaik, S. How to Conceptualize Catalytic Cycles? The Energetic Span Model, *Acc. Chem. Res.* **2011**, *44*, 101-110.

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