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C–H Activation

Rhodium(III)-Catalyzed Synthesis of Skipped Enynes via C(sp^3)–H Alkynylation of Terminal Alkenes

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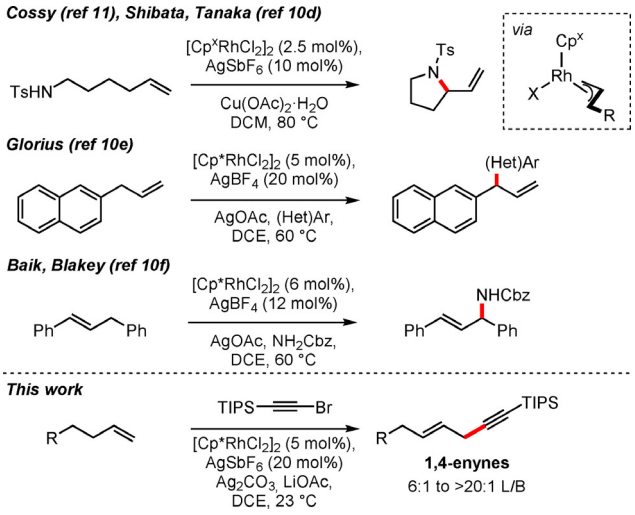
Abstract: *The Rh^{III}-catalyzed allylic C–H alkynylation of non-activated terminal alkenes leads selectively to linear 1,4-enynes at room-temperature. The catalytic system tolerates a wide range of functional groups without competing functionalization at other positions. Similarly, the vinylic C–H alkynylation of α,β- and β,γ- unsaturated amides gives conjugated Z-1,3-enynes and E-enediynes.*

Strategies to attain regioselectivity in transition metal-catalyzed C–H bond functionalization usually rely on anchimeric assistance,[1] either exerted by a pre-existing directing group or by taking advantage of a transient directing group.[1d,2] While facing atom- and step-economy challenges, these approaches have been established as powerful tools for the production of value-added products from simple precursors,[3] and in the synthesis of advanced pharmaceutical compounds[4] and natural products.[5] Most methods have focused on the functionalization of C(sp^2)–H bonds,[1,6] where the more challenging C(sp^3)–H bond activation strategy have been growing in the last decade.[1,3c,7]

Less common and more ambitious is the selective C–H bond functionalization beyond the aid of directing groups.[8,9] Recently, [Cp^xRh] and [Cp^xIr] complexes have gained attention in this area due to their ability to coordinate with terminal double bonds and form π-allyl complexes under mild conditions.[10] Since the report of Cossy on the formation of pyrrolidines and tetrahydropyridines by the action of different [Cp*Rh] complexes,[11] other methods have been developed for C–H bond functionalization via π-allyl [Cp^xRh]- and [Cp^xIr]-complexes (Scheme 1).[12] Of particular significance are the findings of Shibata and Tanaka,[10d] Glorious,[10e] and Baik and Blakey,[10f] where different [Cp^xRh]-π-allyl complexes where isolated and proved to be catalytically active towards allylic C–H amination and arylation.

Here, we report on a directing group-free transformation for the direct construction of C(sp^3)-C(sp) bonds from simple terminal alkenes under [Cp*Rh]-catalyzed conditions.[13] This new protocol is suitable for the synthesis of 1,4-enynes from terminal alkenes without prior functionalization, which are valuable synthons[14] traditionally prepared by cross coupling,[15] allylic alkynylation,[16] allylic alkylation,[17] and nucleophilic substitution.[18]



Scheme 1. Different strategies for Rh-catalyzed allylic C–H functionalization.

Grounding from our recent work on C(sp^2/sp^3)-C(sp) bond formation,[19] we first investigated the reactivity of hex-5-en-1-ol (**1a**) and bromoalkyne **2a** with [Cp^*RhCl_2]$_2$ (5 mol%), $AgSbF_6$ (20 mol%), Ag_2CO_3 (50 mol%) and LiOAc (40 mol%) in 1,2-dichloroethane (DCE) at 23 °C. Under these mild conditions, we observed formation of skipped enyne **3a** in 47% isolated yield with excellent stereoselectivity ($E/Z > 30:1$), moderate linear vs. branched selectivity and modest linear vs. 1,3-bis alkynylated product distribution (Table 1, entry 1).[20] The observed linear selectivity in the alkynylation of **1a** is noteworthy since internal functionalization is typically favored for allylic C–H amination[12c] and arylation[21] of non-activated terminal alkenes.

Several observations concerning the optimum reaction are noteworthy. Using AgOAc instead of LiOAc and Ag_2CO_3 led to slightly lower conversion (10–15% of unreacted starting material remained) but formation of the 1,3-bis alkynylated product was suppressed (Table 1, entry 2). The higher basicity of Ag_2CO_3 compared to AgOAc may account for the small formation of the latter. No reaction was observed in the absence of LiOAc with substrate **1a**, and either decomposition or no reaction occurred when stoichiometric or no $AgSbF_6$ was used, respectively (Table 1, entry 3–5). The reaction proceeded with lower efficiency when using [Cp^*IrCl_2]$_2$ as the catalyst (Table 1, entry 6) and low conversion was observed in the presence of $LiSbF_6$ (Table 1, entry 7). Complex $Cp^*Rh(OAc)_2(OH)$[22] was inactive in the absence of $AgSbF_6$ (Table 1, entry 8), although adding $LiSbF_6$

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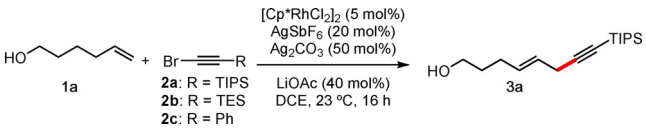
Table 1: Rh-catalyzed allylic C–H alkynylation of **1a** with **2**.



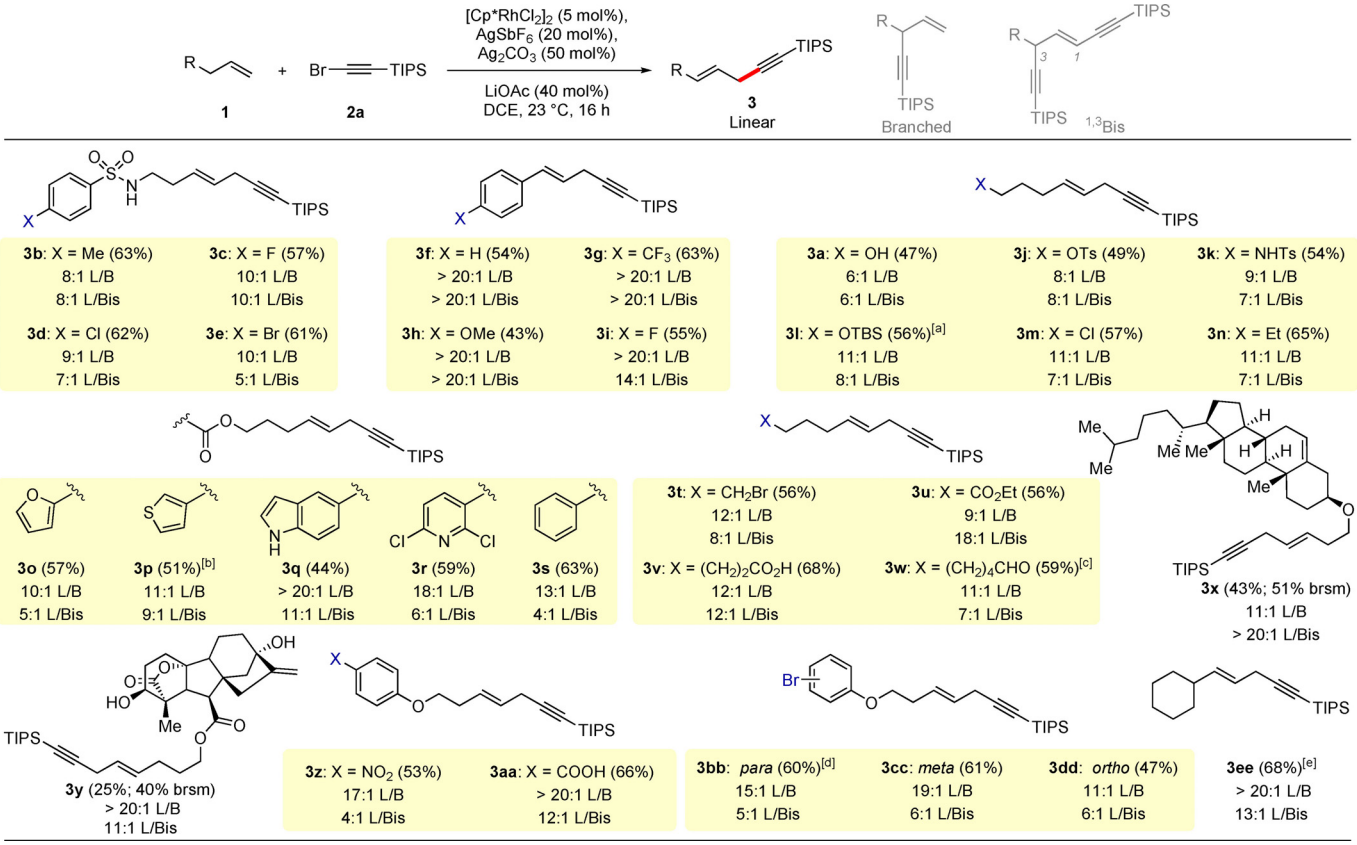
	Variation	R[a]	**3a** yield [%]	L/B	L/Bis
1	None	TIPS	68 (47)	6:1	6:1
2	With AgOAc, no LiOAc, Ag_2CO_3	TIPS	60	5:1	–
3	No LiOAc	TIPS	nr		
4	No $AgSbF_6$	TIPS	nr		
5	$AgSbF_6$ (120 mol%), no Ag_2CO_3	TIPS	–		
6	$[Cp^*IrCl_2]_2$	TIPS	–[b]		
7	$LiSbF_6$	TIPS	26[c]	–	–
8	$Cp^*Rh(OAc)_2(OH_2)$, no $AgSbF_6$	TIPS	nr		
9	$Cp^*Rh(OAc)_2(OH_2)$, $LiSbF_6$[d]	TIPS	61 (39)	8:1	8:1
10	None	TES	55	2:1	–
11	None	Ph	60	1:1	–

Yields determined by ^1H NMR with trichloroethylene as internal standard. Yields of isolated product in parentheses. [a] 1.2 equiv of **2a–c**. [b] Low conversion observed. [c] Starting material remained. [d] $LiSbF_6$ (40 mol%). L: linear product (**3a**), B: branched product; Bis: 1,3-bis product (see Scheme 2). nr: no reaction. DCE: 1,2-dichloroethane.

restored the reaction performance with slight better selectivity (Table 1, entry 9). This last result may suggests a pivotal role of hexafluoroantimonate salts not only in the activation of the catalyst but in the activation of the bromoalkyne too.

Other alkyne donors **2b**,**c** resulted in similar conversions but with lower selectivity (Table 1, entries 10 and 11), which implies that terminal functionalization is sterically driven.[23]

Next, other alkenes were investigated (Scheme 2). Different types of sulfonamides were obtained in good yield and selectivity (**3b–e**, **3k**). It is important to note that no allylic C–H amination was detected with these substrates, a cyclization that has been reported to occur under similar conditions.[10d,11] Exclusive linear selectivity was obtained when trying different allyl-substituted arenes, as represented by formation of products **3f–i**. The mildness of the reaction condition allowed a wide functional group acceptance, including primary halides (**3m**, **3t**), TBS- and tosyl-masked primary alcohols (**3j**, **3l**), aliphatic ester (**3u**), acid (**3v**), aldehyde (**3w**), nitro (**3z**), and different bromoaryl ethers (**3bb–dd**). Most interesting, alkenes with an appended aromatic ring bearing directing groups generally used for the activation of $C(sp^2)$–H bonds, such as a MeO- and -CO_2H groups, were selectively functionalized at the allylic C–H position (**3h** and **3aa**) without any alkynylation at the aromatic ring. Yet, stronger directing groups as -$C(O)(i\text{-}Pr)_2N$ and -C(O)NHAc delivered complex mixtures of mono- and bis alkynylated products.[23] Furane (**3o**), thiophene (**3p**), indole (**3q**), and pyridine (**3r**) 1,4-enynes ester derivatives were as well accessed in good yields and selectivities. Aromatic alkynylation guided by the ester moiety was only observed for thiophene **1p**, where incorporation at the activated α-position was detected to a small

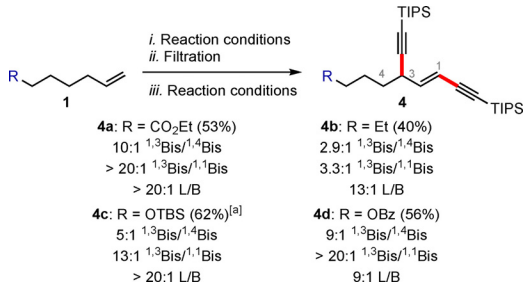


Scheme 2. Substrate scope of allylic C–H alkynylation of non-activated terminal alkenes. [a] 63% yield in the absence of LiOAc, 10:1 L/B, 10:1 L/Bis. [b] Alkynylation at the α-position was also observed.[23] [c] Starting material remained (70% brsm). [d] Reaction performed at 2.5 mmol scale. [e] 72% yield in the absence of LiOAc, 17:1 L/B, >20:1 L/Bis.

extent.[23] Polyfunctional complex substrates such as cholesterol derivative **1x** and gibberellic acid ester **1y** provided the desired skipped enynes **3x** and **3y**, respectively. Although modest yields were observed, it is worthy to note that the major compound formed originated from the allylic C–H alkynylation of the terminal bond, leaving untouched the internal and 1,1-disubstituted alkenes. In addition, readily available alkenes such as *n*-octane and allylcyclohexane reacted cleanly to give selectively the corresponding 1,4-enynes **3n** and **3ee** in 65% and 68% yield, respectively. This method is robust, as demonstrated in the preparation of product **3bb** from **1bb** in a 2.5 mmol scale in comparable yield and selectivity.[23]

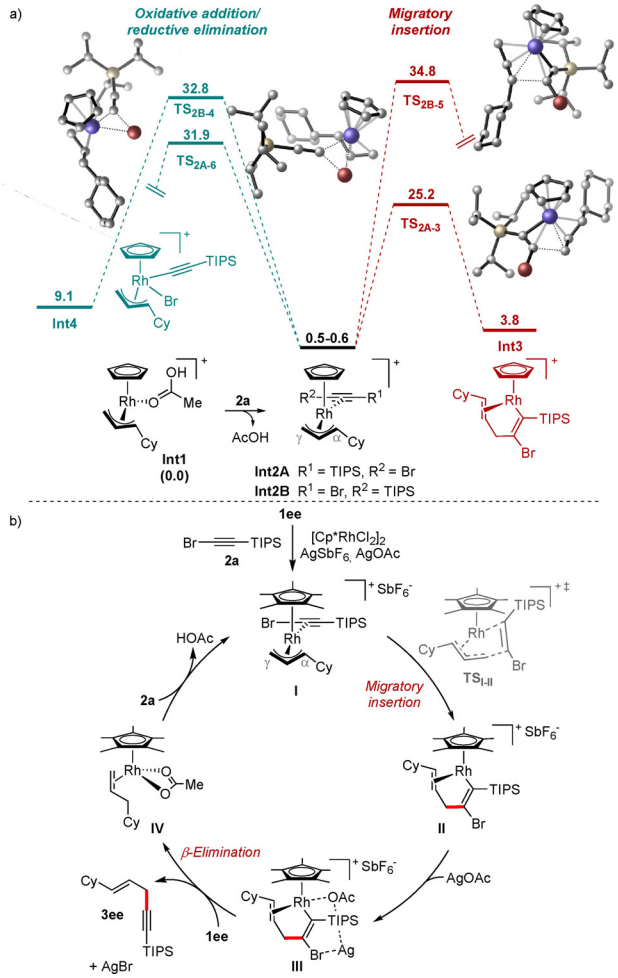
Interestingly, products **3l** and **3ee** were obtained in similar yields in the presence or in the absence of LiOAc, whereas the use of this salt was essential for the formation of compounds **3a**, **3b** or **3f**. This suggest that LiOAc might be necessary to prevent formation of inactive Rh^{III} species in cases in which the substrate bears potentially coordinating groups.[24]

1,3-Bisalkynylation was promoted after a consecutive set up and products **4a–d** could be accessed in moderate to good yields and selectivity (Scheme 3).[20] In this case, formation of 1,1-bis- and 1,4-bisalkynylated compounds were observed as minor products.



Scheme 3. [23] Substrate scope of 1,3-bisalkynylation of non-activated terminal bonds. Reaction conditions: **2a** (110 mol%), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), Ag_2CO_3 (50 mol%), LiOAc (40 mol%), DCE (0.2 M), 23 °C, 16 h. [a] Starting from **3l**.

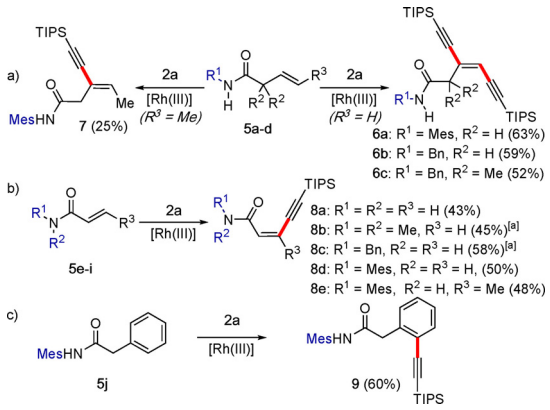
Density functional theory calculations25 where undertaken to better understand the operative mechanism of this transformation (Scheme 4). Using **1ee** as the substrate and AgOAc as the additive, the activation barriers of migratory insertion/β-elimination and oxidative addition/reductive elimination pathways were compared (Scheme 4a).[10,11] Starting from π-allyl **Int1**, analogous to known catalytically active Rh^{III}-intermediates in C–H allylic functionalization,[10d–f] coordination with **2a** can generate **Int2A** and **Int2B**. Next, the theoretical results suggested that terminal functionalization by γ-migratory insertion towards **Int3** ($\Delta G^{\ddagger} = 25.2$ kcal mol^{-1}) would be kinetically favored over the formation of the Rh^{V} species **Int4** ($\Delta G^{\ddagger} = 32.8$ kcal mol^{-1}), an intermediate that upon reductive elimination would also lead to the linear product. α-Migratory insertion was as well calculated for **1ee** and proved to be kinetically disfavored compared to γ-migration ($\Delta G^{\ddagger} = 34.8$ kcal mol^{-1}), presumably by an increase of steric hindrance at the transition



Scheme 4. a) DFT calculations for the Rh^{III}-catalyzed alkynylation of alkenes [ωB97xD/6–311G++(d,p)(H, C, O, Si) + LANL2DZ(d)(Br) + LANL2TZ-(f)(Rh, Ag)// 6-31G(d)(H, C, O, Si) + LANL2DZ(Rh, f; Ag, f; Br, d)]. b) Proposed catalytic cycle.

state. This result is in excellent agreement with the observed regioselectivity for ***1ee*** (>20:1). Following the preferred mechanistic pathway, a catalytic cycle for the formation of skipped enynes is proposed in Scheme 4b. First, formation of complex **I** by interaction of **1ee** and **2a** with $[Cp^*RhCl_2]_2$, AgOAc and $AgSbF_6$, is followed by γ-migratory insertion towards **II**. The latter is then stabilized to **III** by coordination of AgOAc, and a β-bromo-elimination is promoted forming product **3ee** and AgBr. A new molecule of **1ee** enters producing **IV**, and starts the cycle after C–H allylic activation and complexation with **2a**.

The catalytic system employed was also compatible for the formation of $C(sp^2)$-C(sp) bonds.[19b] Observing that terminal alkenes with appended tosyl amides were well tolerated in the undirected allylic C–H alkynylation and arylamides were unreactive,[23] a slightly modified protocol was tested with terminal alkenes having amide groups at different distances from the carboxamide. Thus, we found that β,γ-unsaturated amides **5a–c** were bisalkynylated and form conjugated *E*-enediynes **6a–c**, (Scheme 5a). Interestingly, *trans*-**5d** led to *E*-configured 1,3-enyne **7**, although in

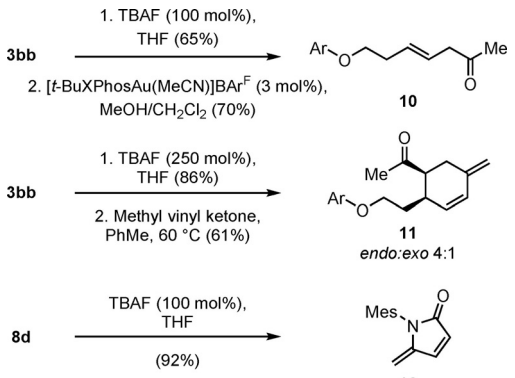


Scheme 5. Substrate scope of vinyl C–H alkynylation of activated and non-activated alkene bonds. Reaction conditions: **2a** (250 mol%), $[Cp^*RhCl_2]_2$ (3 mol%), $AgSbF_6$ (24 mol%), Ag_2CO_3 (100 mol%), LiOAc (100 mol%), DCE, 80°C, 16 h. [a] 100°C.

modest yield. On the other hand, α,β-unsaturated amides **5e–i** were mono-alkynylated giving stereoselectively *Z*-1,3-enynes **8a–e** in moderate yields (Scheme 5b).[26] A different outcome was observed with 2-phenylacetamide **5j**, which gave exclusively *ortho*-alkynyl **9** in 60% yield (Scheme 5c). Pivalanilides led to the expected products of *ortho*-alkynylation under these reaction conditions.[23,27]

To illustrate the synthetic utility of the obtained 1,3- and 1,4-enynes, further transformations were conducted (Scheme 6). Deprotection of **3bb** with stoichiometric TBAF (100 mol%) led to the corresponding terminal alkyne in 65% yield, which was converted to the β,γ-unsaturated enone **10** in 70% yield when exposed to [*t*-BuXPhosAu(MeCN)]BAr^F in methanol. Alternatively, treatment of **3bb** with excess TBAF (250 mol%) afforded the respective conjugated allene in 86% yield,[28] and underwent a [4+2] cycloaddtion with methyl vinyl ketone to give adduct **11** in 61% yield (*endo*:4:1).[29] Moreover, 1,3-enyne **8a** delivered pyrrolone **12** in 92% yield after TBAF treatment.[30]

In summary, we have developed a [Cp*Rh]-catalyzed linear selective allylic C–H bond alkynylation under mild conditions allowing straightforward access to synthetically usefull 1,4-enynes. This reaction tollerates a broad range of functional groups, including known aryl-directing groups without functionalization at the aromatic ring. Theoretical experiments suggested a migratory insertion mechanism to be kinetically favored against an oxidative addition/reductive elimination pathway. 1,3-Bisalkynylation was also accessed and may be complementary to known 1,1-bisalkynylation procedures. Finally, α,β- and β,γ-unsaturated amides give *Z*-1,3-enynes and *E*-bis-enediynes, respectively.[31]



Scheme 6. Derivatization of 1,4-enynes from C–H alkynylation. Ar: 4-Br-C_6H_4.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,4-enynes · alkynylation · allylic functionalization · rhodium · undirected C–H activation

[1] For representative reviews on directing group-assisted C–H functionalization, see: a) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107–1295; b) Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603–6743; c) L. D. Caspers, B. J. Nachtsheim, *Chem. Asian J.* **2018**, *13*, 1231–1247; d) O. K. Rasheed, B. Sun, *ChemistrySelect* **2018**, *3*, 5689–5708; e) M. Kapoor, A. Singh, K. Sharma, M. Hua Hsu, *Adv. Synth. Catal.* **2020**, *362*, 4513–4542.

[2] For selected reviews on transient directing groups, see: a) Q. Zhao, T. Poisson, X. Pannecoucke, T. Besset, *Synthesis* **2017**, *49*, 4808–4826; b) P. Gandeepan, L. Ackermann, *Chem* **2018**, *4*, 199–222; c) T. Bhattacharya, S. Pimparkar, D. Maiti, *RSC Adv.* **2018**, *8*, 19456–19464; For selected recent examples on remote C–H bond functionalization, see: d) H. Shi, Y. Lu, J. Weng, K. L. Bay, X. Chen, K. Tanaka, P. Verma, K. N. Houk, J. Q. Yu, *Nat. Chem.* **2020**, *12*, 399–404; e) R. R. Annapureddy, C. Jandl, T. Bach, *J. Am. Chem. Soc.* **2020**, *142*, 7374–7378.

[3] For reviews, see: a) R. H. Crabtree, *J. Chem. Soc. Dalton Trans.* **2001**, 2437–2450; b) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507–514; c) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654–2672; d) J. Zhang, L. J. Kang, T. C. Parker, S. B. Blakey, C. K. Luscombe, S. R. Marder, *Molecules* **2018**, *23*, 922; e) S. Yuan, Y. Li, J. Peng, Y. M. Questell-Santiago, K. Akkiraju, L. Giordano, D. J. Zheng, S. Bagi, Y. Román-Leshkov, Y. Shao-Horn, *Adv. Energy Mater.* **2020**, *10*, 2002154; f) S. Shaaban, C. Davies, H. Waldmann, *Eur. J. Org. Chem.* **2020**, 6512–6524.

[4] For reviews, see: a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009; *Angew. Chem.* **2012**, *124*, 9092–9142; b) E. J. E. Caro-Diaz, M. Urbano, D. J. Buzard, R. M. Jones, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5378–5383; c) J. Yamaguchi, K. Amaike, K. Itami in *Transition Metal*

Heterocycle Synthesis via *C–H Activation* (Ed.: X.-F. Wu), Wiley-VCH, Weinheim, **2016**, pp. 505 – 550; d) D. Basu, S. Kumar, V. SaiSudhir, R. Bandichhor, *J. Chem. Sci.* **2018**, *130*, 71; e) M. Moir, J. J. Danon, T. A. Reekie, M. Kassiou, *Expert Opin. Drug Discovery* **2019**, *14*, 1137 – 1149.

[5] For reviews, see: a) K. Godula, D. Sames, *Science* **2006**, *312*, 67 – 72; b) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976 – 1991; c) D. Y. K. Chen, S. W. Youn, *Chem. Eur. J.* **2012**, *18*, 9452 – 9474; d) P. Tao, Y. Jia, *Sci. China Chem.* **2016**, *59*, 1109 – 1125; e) K. Chen, X. Lei, *Curr. Opin. Green Sustain. Chem.* **2018**, *11*, 9 – 14; f) S. K. Sinha, G. Zanoni, D. Maiti, *Asian J. Org. Chem.* **2018**, *7*, 1178 – 1192; g) H. Zhai, Y. Li, F. Fang in *Efficiency in Natural Product Total Synthesis* (Eds.: P.-Q. Huang, Z.-J. Yao, R. P. Hsung), Wiley, Hoboken, **2018**, pp. 261 – 272; h) D. J. Abrams, P. A. Provencher, E. J. Sorensen, *Chem. Soc. Rev.* **2018**, *47*, 8925 – 8967.

[6] For reviews, see; a) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651 – 3678; b) G. Song, X. Li, *Acc. Chem. Res.* **2015**, *48*, 1007 – 1020; c) S. Rej, N. Chatani, *Angew. Chem. Int. Ed.* **2019**, *58*, 8304 – 8329; *Angew. Chem.* **2019**, *131*, 8390 – 8416; d) M. R. Sk, S. S. Bera, S. Basuli, A. Metya, M. S. Maji, *Asian J. Org. Chem.* **2020**, *9*, 1701 – 1717.

[7] For reviews, see: a) T. G. Saint-Denis, R. Y. Zhu, G. Chen, Q. F. Wu, J. Q. Yu, *Science* **2018**, *359*, eaao4798; b) J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62 – 101; *Angew. Chem.* **2018**, *130*, 64 – 105.

[8] For an outlook on undirected C–H functionalization, see: a) J. F. Hartwig, M. A. Larsen, *ACS Cent. Sci.* **2016**, *2*, 281 – 292; for recent examples on undirected C–H functionalization, see: b) A. Mondal, H. Chen, L. Flämig, P. Wedi, M. Van Gemmeren, *J. Am. Chem. Soc.* **2019**, *141*, 18662 – 18667; c) R. Oeschger, B. Su, I. Yu, C. Ehinger, E. Romero, S. He, J. Hartwig, *Science* **2020**, *368*, 736 – 741.

[9] For representative reviews on undirected Pd-catalyzed π-allyl C–H bond functionalization of non-activated alkenes, see: a) C. J. Engelin, P. Fristrup, *Molecules* **2011**, *16*, 951 – 969; b) A. Breder, *Synlett* **2014**, *25*, 899 – 904; c) F. Liron, J. Oble, M. M. Lorion, G. Poli, *Eur. J. Org. Chem.* **2014**, 5863 – 5883; d) R. A. Fernandes, J. L. Nallasivam, *Org. Biomol. Chem.* **2019**, *17*, 8647 – 8672.

[10] For literature related to isolated Cp^XM (M = Rh, Ir) complexes, see: a) R. A. Periana, R. G. Bergman, *J. Am. Chem. Soc.* **1984**, *106*, 7272 – 7273; b) J. B. Wakefield, J. M. Stryker, *J. Am. Chem. Soc.* **1991**, *113*, 7057 – 7059; c) Y. F. Han, G. X. Jin, *Chem. Soc. Rev.* **2014**, *43*, 2799 – 2823; d) Y. Shibata, E. Kudo, H. Sugiyama, H. Uekusa, K. Tanaka, *Organometallics* **2016**, *35*, 1547 – 1552; e) A. Lerchen, T. Knecht, M. Koy, J. B. Ernst, K. Bergander, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 15248 – 15252; *Angew. Chem.* **2018**, *130*, 15468 – 15472; f) R. J. Harris, J. Park, T. A. F. Nelson, N. Iqbal, D. C. Salgueiro, J. Bacsa, C. E. Macbeth, M. H. Baik, S. B. Blakey, *J. Am. Chem. Soc.* **2020**, *142*, 5842 – 5851.

[11] T. Cochet, V. Bellosta, D. Roche, J. Y. Ortholand, A. Greiner, J. Cossy, *Chem. Commun.* **2012**, *48*, 10745 – 10747.

[12] a) A. Archambeau, T. Rovis, *Angew. Chem. Int. Ed.* **2015**, *54*, 13337 – 13340; *Angew. Chem.* **2015**, *127*, 13535 – 13538; b) Q. Cui, W. Liao, Z. Y. Tian, Q. Li, Z. X. Yu, *Org. Lett.* **2019**, *21*, 7692 – 7696; c) T. A. F. Nelson, M. R. Hollerbach, S. B. Blakey, *Dalton Trans.* **2020**, *49*, 13928 – 13935.

[13] For the preparation of 1,4-enynes from non-activated alkenes, see: a) X. Le Zhou, L. Ren, P. S. Wang, *J. Org. Chem.* **2017**, *82*, 9794 – 9800; b) A. A. Almasalma, E. Mejía, *Chem. Eur. J.* **2018**, *24*, 12269 – 12273.

[14] For selected systematic studies on transformations of 1,4-enynes, see: a) A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614 – 12615; b) S. Gao, H. Liu, C. Yang, Z. Fu, H. Yao, A. Lin, *Org. Lett.* **2017**, *19*, 4710 – 4713; c) X. F. Wei, X. W. Xie, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc.* **2017**, *139*, 4647 – 4650; d) X. Fang, Q. Li, R. Shi, H. Yao, A. Lin, *Org. Lett.* **2018**, *20*, 6084 – 6088.

[15] For systematic studies on 1,4-enyne formation by cross-coupling, see: a) A. Commercon, J. Normant, J. Villieras, *J. Organomet. Chem.* **1975**, *93*, 415 – 421; b) T. P. Heffron, J. D. Trenkle, T. F. Jamison, *Tetrahedron* **2003**, *59*, 8913 – 8917; c) M. Shirakura, M. Suginome, *Angew. Chem. Int. Ed.* **2010**, *49*, 3827 – 3829; *Angew. Chem.* **2010**, *122*, 3915 – 3917; d) R. Agata, S. Lu, H. Matsuda, K. Isozaki, M. Nakamura, *Org. Biomol. Chem.* **2020**, *18*, 3022 – 3026.

[16] For recent systematic studies on 1,4-enyne formation by allylic alkynylation, see: a) A. Harada, Y. Makida, T. Sato, H. Ohmiya, M. Sawamura, *J. Am. Chem. Soc.* **2014**, *136*, 13932 – 13939; b) Q. Yang, Y. Zhou, J. Chen, X. He, J. Xu, F. Y. Kwong, B. Fan, *Eur. J. Org. Chem.* **2015**, 5330 – 5333; c) T. Nakane, Y. Tanioka, N. Tsukada, *Organometallics* **2015**, *34*, 1191 – 1196; d) P. Xie, Z. Sun, S. Li, L. Zhang, X. Cai, W. Fu, X. Yang, Y. Liu, X. Wo, T. P. Loh, *Org. Lett.* **2020**, *22*, 1599 – 1604.

[17] For selected systematic studies on 1,4-enyne formation by allylic alkylation, see a) B. M. Trost, S. Hildbrand, K. Dogra, *J. Am. Chem. Soc.* **1999**, *121*, 10416 – 10417; b) R. Takeuchi, K. Tanabe, *Angew. Chem. Int. Ed.* **2000**, *39*, 1975 – 1978; *Angew. Chem.* **2000**, *112*, 2051 – 2054; c) M. A. Kacprzynski, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 10676 – 10681; d) N. F. Langille, T. F. Jamison, *Org. Lett.* **2006**, *8*, 3761 – 3764; e) H. Li, A. Alexakis, *Angew. Chem. Int. Ed.* **2012**, *51*, 1055 – 1058; *Angew. Chem.* **2012**, *124*, 1079 – 1082; f) Y. Makida, Y. Takayama, H. Ohmiya, M. Sawamura, *Angew. Chem. Int. Ed.* **2013**, *52*, 5350 – 5354; *Angew. Chem.* **2013**, *125*, 5458 – 5462.

[18] For systematic studies on 1,4-enyne formation nucleophilic substitution, see: a) S. Peng, L. Wang, J. Wang, *Org. Biomol. Chem.* **2012**, *10*, 225 – 228; b) G. Huang, X. Wang, Y. Pan, H. Wang, G. Yao, Y. Zhang, *J. Org. Chem.* **2013**, *78*, 2742 – 2745.

[19] a) E. Tan, A. I. Konovalov, G. A. Fernandez, R. Dorel, A. M. Echavarren, *Org. Lett.* **2017**, *19*, 5561 – 5564; b) E. Tan, O. Quinonero, M. E. de Orbe, A. M. Echavarren, *ACS Catal.* **2018**, *8*, 2166 – 2172; c) E. Tan, M. Zanini, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2020**, *59*, 10470 – 10473; *Angew. Chem.* **2020**, *132*, 10556 – 10559.

[20] For the selective formation of 1,1-bis alkylation compounds, see: Y. Li, H. Wei, D. Wu, Z. Li, W. Wang, G. Yin, *ACS Catal.* **2020**, *10*, 4888 – 4894.

[21] To the best of our knowledge, linear selectivity in Cp^*Rh^{III}-catalyzed allyl-aryl coupling is only favored in systems in which the final alkene is conjugated to an aryl ring: a) ref. [10e]; b) T. Knecht, T. Pinkert, T. Dalton, A. Lerchen, F. Glorius, *ACS Catal.* **2019**, *9*, 1253 – 1257.

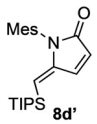
[22] a) P. M. Boyer, C. R. Roy, J. M. Bielski, J. S. Merola, *Inorg. Chim. Acta* **1996**, *245*, 7 – 15; b) G. A. M. Jardim, E. N. Da Silva, J. F. Bower, *Chem. Sci.* **2016**, *7*, 3780 – 3784.

[23] See the Supporting Information for additional details.

[24] For the role of acetate in the cyclometallation with $[Cp^*RhCl_2]_2$, $[Cp^*IrCl_2]_2$, and $[RuCl_2(p\text{-cymene})]_2$, see: D. L. Davies, O. Al-Duaij, J. Fawcett, M. Giardiello, S. T. Hilton, D. R. Russell, *Dalton Trans.* **2003**, 4132 – 4138.

[25] See the Supporting Information for all the computational details and the complete study.

[26] Substrate **5d** also delivered **8d′** in 7% yield under these conditions.[23]



8d′

[27] For directed ortho-alkynylation of anylines, see: a) R. Amemiya, A. Fujii, M. Yamaguchi, *Tetrahedron Lett.* **2004**, *45*, 4333 – 4335; b) M. Tobisu, Y. Ano, N. Chatani, *Org. Lett.* **2009**, *11*, 3250 – 3252; c) F. Xie, Z. Qi, S. Yu, X. Li, *J. Am. Chem. Soc.* **2014**, *136*, 4780 – 4787; d) Z. Ruan, S. Lackner, L. Ackermann, *ACS Catal.* **2016**, *6*, 4690 – 4693.
[28] For the preparation of related conjugated allenes, see ref. [20].
[29] K. Yoshida, P. A. Grieco, *Chem. Lett.* **1985**, *14*, 155 – 158.
[30] a) Y. Hoshino, Y. Shibata, K. Tanaka, *Angew. Chem. Int. Ed.* **2012**, *51*, 9407 – 9411; *Angew. Chem.* **2012**, *124*, 9541 – 9545; b) C. Feng, D. Feng, Y. Luo, T. P. Loh, *Org. Lett.* **2014**, *16*, 5956 – 5959.
[31] Since acceptance of this manuscript, a related study was published: S. Mondal, T. Pinkert, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2021**, https://doi.org/10.1002/anie.202015249; *Angew. Chem.* **2021**, https://doi.org/10.1002/ange.202015249.

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