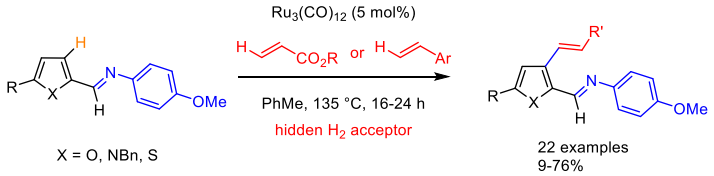
Ru(0)-Catalyzed Alkenylation of 2-Carboxaldimine Heterocyclopentadienes with H_2 Transfer

Roberto Sala,[a,b] Gredy Kiala,[a] Luis F. Veiros,[c] Gianluigi Broggini,[b] Giovanni Poli,[a,*] and Julie Oble[a,*]

[a] Sorbonne Université, Faculté des Sciences et Ingénierie, CNRS, Institut Parisien de Chimie Moléculaire, IPCM, 4 place Jussieu, 75005 Paris, France.

[b] Dipartimento di Scienza e Alta Tecnologia (DISAT), Università degli Studi dell'Insubria, Via Valleggio 9, Como (CO), Italy.

[c] Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais 1, 1049-001 Lisbon, Portugal.



ABSTRACT: A new $Ru_3(CO)_{12}$-catalyzed directed alkenylation of 2-carboxaldimine-heterocyclopentadienes has been accomplished. This process allows to couple furan, pyrrole, indole and thiophene 2-carboxaldimines with electron-poor alkenes such as acrylates, vinylsulfones, and styrenes. This regio- and chemoselective oxidative C–H coupling does not require the presence of an additional sacrificial oxidant. Density functional theory (DFT) calculations allowed to propose a mechanism and unveiled the nature of the H_2 acceptor.

Alkenyl-substituted five-membered heteroarene scaffolds, such as furan, pyrrole, indole and thiophene derivatives, are found in many bioactive and pharmaceutical compounds (Figure 1),[1–7] as well as in various functional organic materials.[8–10] As a consequence, the search for safer and safer, and more atom- and step-economical methods to synthesize these motifs from simple heterocycles and alkenes is a topic of constant great interest. In this context, the formation of new C–C bonds through a transition metal (TM)-catalyzed C–H activation process has received particular attention,[11–14] providing a rapid access to a wide range of highly functionalized heterocyclic motifs.

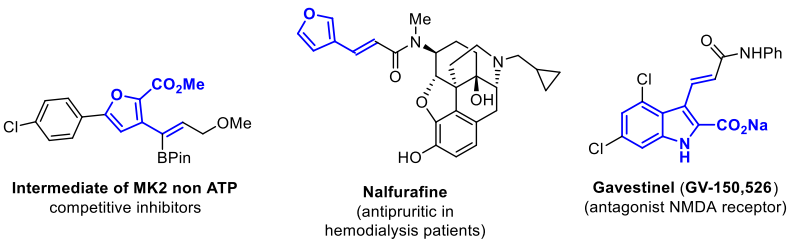


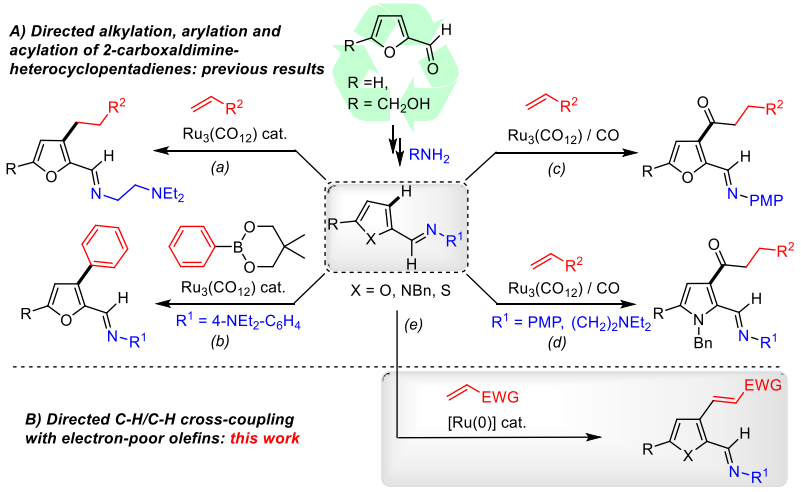
Figure 1. Some bioactive heteroarenes alkenylated at position 3.

The Fujiwara-Moritani reaction, a dehydrogenative cross-coupling, is one of the earliest examples of such a TM-catalyzed C–H functionalizations.[15–22] This type of C–H/C–H cross-coupling[23] is regarded as an ideal method to join an acrylate and an aromatic substrate, via Pd(II), Ru(II), Rh(III), Ir(III), or Co(III) catalysis.[24–27,20] However,

as these dehydrogenative couplings are inherently endergonic, the driving force to push the transformation toward the products side often needs the addition of (super)stoichiometric amounts of an external sacrificial oxidant that accepts the two released H atoms, or the input of electrical energy,[28–30] which drives hydrogen evolution at the cathode. In the former case, sacrificial oxidants such as quinones, Cu(II)-, Mn(IV)-, or Ag(I)-salts are required, which obviously reduces the sustainability of the coupling process. The only green terminal oxidant is molecular oxygen,[31] which is often used in combination with photoredox catalysis.[32–34]

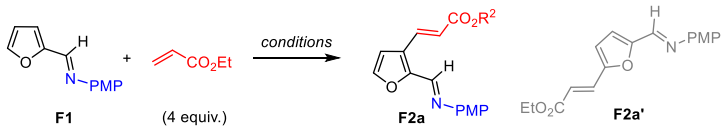
As part of a long term project directed toward the sustainable C–H functionalization of aldimine-armed heterocyclopentadienes of biomass derivation such as furan,[35–37] pyrrole,[38,39] as well as thiophene units, we have recently developed several directed Ru(0)-catalyzed C3-functionalizations (Scheme 1A), such as: the alkylation (*Murai reaction*[40]) of *N,N'*-bidentate furfurylimines with vinylsilane or styrene derivatives (*a*),[41] the arylation of electron-rich furfurylimines with arylboronates (*b*),[42,43] and the acylation (*carbonylative Murai reaction*) of furan- (*c*) or pyrrole-based *p*-methoxyphenyl imines or *N,N'*-bidentate imines (*d*) under CO atmosphere with vinylsilane or styrene partners.[44] However, the directed C3–H alkenylation of 2-formyl-heterocyclopentadiene units, which overwhelms the natural C5 electrophilic preference of these heterocycles,[45] remains a challenge. The few reported C3–H/C–H couplings between 2-substituted heterocyclopentadienes and electron-poor alkenes make use of C2-linked directing groups belonging to the carboxylic acid oxidation level, such as carboxylates, amides, and esters.[46–49] Herein, we disclose a selective, external oxidant free,[50–54] Ru(0)-catalyzed C3-alkenylation of furfural, 5-hydroxymethylfurfural (HMF) derivatives, pyrrole-, indole-, and thiophene 2-carboxaldehydes through their corresponding aldimines (*i.e.* without modification of the formyl redox state), which act as removable directing groups (Scheme 1B, *e*).

Scheme 1. Ru-catalyzed direct functionalization of biomass-derived 2-formyl heteroaromatic compounds: *previous results* and *present work*



In our previous studies, we established that the directed C3–H activation of 2-carboxaldimine-heterocyclopentadienes could be successfully achieved only through a nucleophilic catalysis, which involves an initial oxidative addition step of the targeted C–H bond to the Ru(0) catalyst. In contrast, electrophilic TM-complexes, such as Ru(II) or Pd(II) catalysts, which normally involve an ambiphilic metal–ligand activation / concerted metalation deprotonation (AMLA / CMD) mechanism, appeared uneffective.[13] Classical Fujiwara-Moritani reaction conditions [$Pd(OAc)_2$ cat. / *p*-benzoquinone or $[RuCl_2(p\text{-cymene})]_2$ cat. / $Cu(OAc)_2$], tested in the model coupling between *p*-methoxyphenylfurfurylimine (PMP-imine) **F1** and ethyl acrylate (4 equivalents), gave no C3-alkenylated product **F2a** (Table 1, entry 1). Only traces of the C5-alkenylated product **F2a'** were observed in the case of Ru(II) catalysis (entry 2). Gratifyingly, the use of $Ru_3(CO)_{12}$ (5 mol%), in toluene, gave, after 24 h at 135 °C in a sealed tube under argon atmosphere, the expected dehydrogenative C3 coupling product **F2a** in 44% isolated yield, without any trace of the corresponding C5- functionalized product (entry 3).[55] This result suggests that the nature and the oxidation state of the Ru catalyst are crucial to obtain the desired imine-Ru coordination, which is in turn a *condicio sine qua non* to promote the C3-functionalization. However, the bidentate *N,N'*-imino-amine directing group, which gave satisfactory results in the Murai reaction,[41] provided neither the desired alkenylated (Fujiwara-type) product, nor the alkylated (Murai-type) product (see Supporting Information SI). Comparable results in terms of yield were obtained carrying out the coupling under air or argon atmosphere (compare entries 3 and 4). These results clearly prove that oxygen does not act as oxidant for the ruthenium catalyst. So, how to explain our seemingly acceptorless C–H/C–H coupling? We suspected that excess acrylate acted as an endogenous sacrificial H_2 acceptor (*vide infra*).[56] In line with the above speculation, repetition of the experiment of entry 4, in the presence of only 1 equivalent of acrylate, gave product **F2A** in a decreased yield of 7%. However, the addition of *tert*-butylethylene as a potential hydrogen acceptor,[57] along with the use of only one equivalent of acrylate, was not as effective, as using an excess of the acrylate partner (entry 5).[58] Further optimization studies varying the solvent, the temperature, as well as the reaction time did not reach better results (see SI for details).[59]

Table 1. Fujiwara-Moritani reaction on PMP-imine F1



entry	conditions	results[a]
1	$Pd(OAc)_2$ (5 mol%), *p*-benzoquinone (1 equiv.), PTSA (1 equiv.), AcOH/PhMe, 60 °C, 24	NR
2	$[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $Cu(OAc)_2$ (2 equiv.), PhMe, 135 °C, 24 h	**F2a'**
3	$Ru_3(CO)_{12}$ (5 mol%), PhMe, 135 °C, 24 h (argon atmosphere)	**F2a**
4	$Ru_3(CO)_{12}$ (5 mol%), PhMe, 135 °C, 24 h (air atmosphere)	**F2a**
5[b]	$Ru_3(CO)_{12}$ (5 mol%), 3 equiv. of TBE, PhMe, 135 °C, 24 h (air atmosphere)	**F2a**

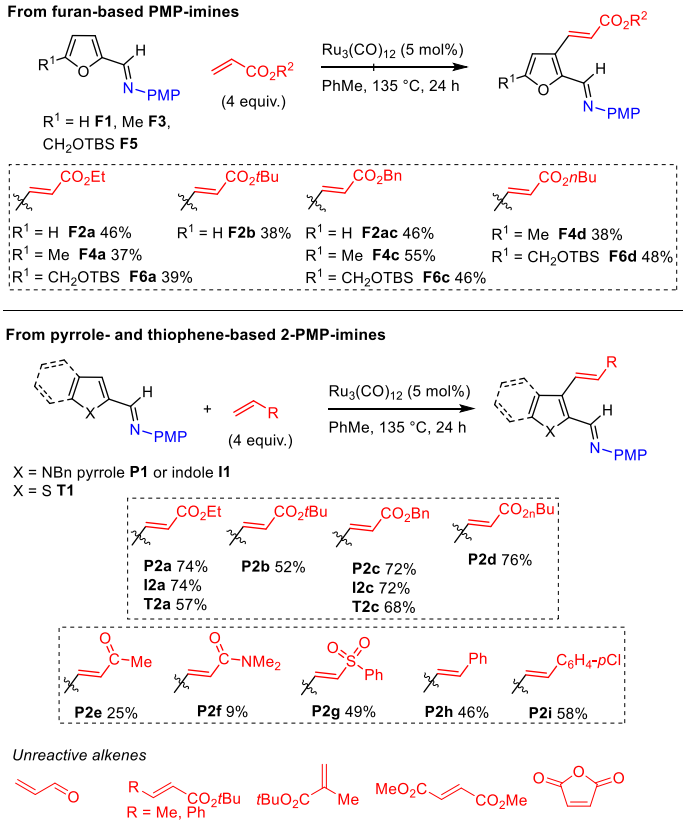
[a] In parentheses, ^{1}H-NMR yield, determined using *p*-dinitrobenzene as internal standard. Isolated yield from silica gel chromatography deactivated with 1% of Et_3N. [b] With 1.1 equiv. of ethyl acrylate. TBE = *tert*-butylethylene

With the optimal conditions in hand [5 mol% $Ru_3(CO)_{12}$, acrylate (4 equiv.), PhMe, 135 °C, 24 h (air)], the scope of this C3–H alkenylation was subsequently studied in the coupling between the PMP-imines of furfural (**F1**), 5-methylfurfural (**F3**), *O*-TBS-protected HMF (**F5**), and ethyl-, *n*-butyl-, *t*-butyl-, and benzyl acrylates (Scheme 2, top). The nature of the C5 substituent in the starting furfurylimines did not sensibly affect the couplings, which led to the expected coupled products **F2a**, **F4a**, and **F6a** from ethyl acrylate, **F2b** from *t*-butyl acrylate, **F4d** and **F6d** from *n*-butyl acrylate, and **F2c**, **F4c**, and **F6c** from benzyl-acrylate, in moderate yields.

Following these encouraging results, we decided to extend our study to pyrrol- and thiophene-based 2-imino heterocyclopentadienes (Scheme 2, bottom). First, pyrrole 2-carboxaldehyde was considered as a suitable starting substrate,[60] given its direct availability from furfural via the Paal-Knorr synthesis,[61] or via a three-step sequence (carbonyl reduction / Achmatowicz rearrangement / Maillard condensation).[62] Indole and thiophene 2-carboxaldehydes were also included, to assess the scope of the coupling within the heterocyclopentadiene family. The couplings of these *N*-based heterocycles were found to be much more efficient and selective than those of the previously studied more fragile furfural derivatives. Accordingly, the coupling between *N*-benzylpyrrole 2-PMP-imine **P1** and ethyl-, *t*-butyl-, *n*-butyl-, and benzyl acrylates led to the expected products (**P2a-d**) in fair to good yields. Similarly, this C–H/C–H coupling could be extended to the 2-PMP-imines of *N*-benzylindole (**I1**), and thiophene (**T1**), which reacted efficiently with ethyl- and benzyl-acrylates to afford the coupled products **I2a**, **I2c**, **T2a**, **T2c**. Further variations at the electron-poor alkene partner were also considered. However α- and β-substituted acrylates, as well as acrolein did not allow the coupling, even under more forcing reaction conditions.

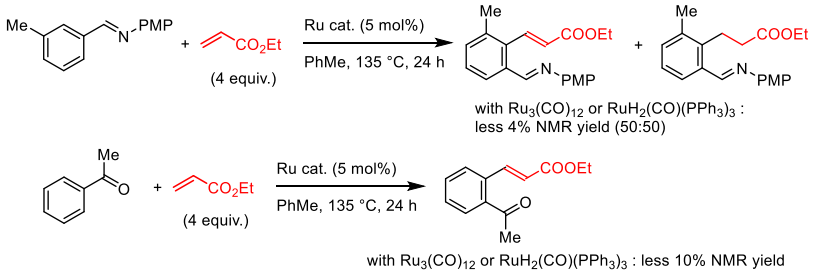
Other monosubstituted electron-poor alkenes were considered as coupling partners for imine **P1** (Scheme 2, bottom). Methyl vinyl ketone gave the expected adduct **P2e** in 25% yield, whereas *N*,*N*'-dimethyl acrylamide gave **P2f** in only 9% yield. Better results were obtained with phenyl vinyl sulfone, which afforded the coupled product **P2g** in 49% yield. Styrene, and 4-chlorostyrene gave the corresponding coupled products **P2h** and **P2i** in 46% and 58% yield, respectively. Thus, in the case of styrenes, by playing with the CO atmosphere, it is possible to switch from a carbonylative Murai coupling[44] to a Fujiwara-Moritani type alkenylation. This feature renders the Ru(0)-catalyzed C3–H functionalization of five-membered heteroarene scaffolds quite general and versatile.

Scheme 2. Ru(0)-catalyzed alkenylation of furan- (top) and pyrrole- and thiophene-based 2-PMP-imines (bottom)



Finally, we wished to verify if the presently developed Ru(0)-catalyzed protocol could also enable the directed Fujiwara-Moritani coupling between simple aryl PMP-imines (or aryl ketones) and electron-poor alkenes. To this purpose, *N*-PMP-(*m*-tolyl)methanimine was synthesized and then submitted to our standard protocol in the presence of ethyl acrylate. A second experiment was repeated replacing the imine with acetophenone (Scheme 3).

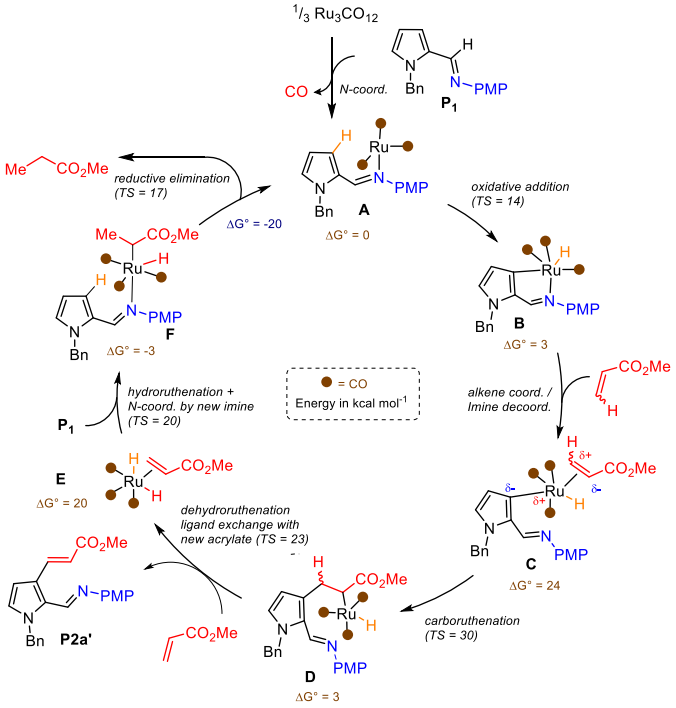
Scheme 3. Attempted Ru(0)-catalyzed alkenylations of benzenic derivatives



The former experiment gave only traces of a mixture of the alkylated (Murai type) and the alkenylated products (Fujiwara-Moritani type), while the second experiment gave only 10% of the alkenylated one. These results unambiguously demonstrate that our Ru(0)-catalyzed protocol selectively enables the coupling between carboxaldimine-heterocyclopentadienes and electron-poor alkenes. Such a selective and unprecedented reactivity is likely due to the combination of the electron richness of the Ru(0) pre-catalyst and of the heterocyclopentadienes with the electron poor nature of the acrylate derivative.

The mechanism of the C3-alkenylation between pyrrole **P1** and methyl acrylate was also studied via DFT calculations.[64] As in our previous mechanistic studies concerning Ru-catalyzed C–H functionalizations,[41,44] we anticipate the conversion of the trimeric $Ru_3(CO)_{12}$ pre-catalyst into a mononuclear ruthenium carbonyl by Ru–Ru breaking and CO release.[65,66] However, the simplicity of the model used may limit the scope of the calculations. The simplified calculated catalytic cycle is shown in Scheme 4, while the complete reaction free energy profile is presented in the SI.

Scheme 4. Proposed mechanism for the Ru(0)-catalyzed alkenylative coupling between N-based PMP-imine P1 and methyl acrylate. All free energy values (kcal/mol) relative to A



The proposed mechanism starts with complex **A**, wherein the imine function of substrate **P1** coordinates $Ru(CO)_3$. Oxidative addition of the C3–H bond to the metal affords the corresponding Ru(II) hydride intermediate **B**. This is a slightly endergonic step (ΔG = 3 kcal/mol) with a barrier of 14 kcal/mol. The reaction proceeds with olefin η^2-coordination, which occurs with simultaneous break of imine coordination to give intermediate **C**. This is followed by the regioselective carboruthenation of the acrylate to generate intermediate **D**, which overcomes a barrier of 30 kcal/mol.[67] This is the highest energy transition state along the path and corresponds to the TOF determining transition state (TDTS) of the process. The subsequent dehydroruthenation releases the final product **P2a'**, while a new acrylate unit that enters the cycle coordinates the newly generated Ru(II)-dihydride **E** (see SI for more details). Hydroruthenation of **E** followed by metal coordination by the imine function of a new entering molecule of imine **P1** gives intermediate **F**. Finally, passing through a barrier of 17 kcal/mol, a reductive elimination generates methyl propionate and regenerates the starting Ru(0) complex. So,

overall, in the catalytic cycle one molecule of imine reacts with two molecules of acrylate to generate one molecule of alkenylated coupling product and one molecule of methyl propionate.

In summary, we have developed a novel Ru(0)-catalyzed method for the selective C3-alkenylation of oxygen-, nitrogen- and sulfur-based heterocyclopentadiene 2-PMP-imines, in the presence of acrylic acid derivatives. In the case of the pyrrole ring, the coupling could be extended to a variety of electron-poor alkene partners with good results. This method does not need the presence of an additional external sacrificial oxidant, as a second unit of the acrylic acid derivative enters the catalytic cycle, accepting the two H atoms expelled in the C–H/C–H coupling. This hidden acceptor part of the cycle is key, as it renders the process thermodynamically favorable, allowing the closure of the catalytic cycle.

This protocol is not only regioselective for the C3–H functionalization, but also chemoselective, as it does not touch carbocyclic arylimines. In particular, in the case of styrenes, by playing with the CO atmosphere, one can switch from a carbonylative Murai coupling to a Fujiwara-Moritani type alkenylation. Finally, DFT computations allowed to propose a plausible mechanism for this process, and unveiled the hidden acceptor.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Further optimizations, DFT study details, atomic coordinates of all optimized species, experimental procedures, compound characterization (PDF).

AUTHOR INFORMATION

Corresponding Author

* E-mail: giovanni.poli@ sorbonne-universite.fr,

julie.oble@sorbonne-universite.fr

ORCID

Roberto Sala: 0000-0001-9397-1364

Luis F. Veiros: 0000-0001-5841-3519

Gianluigi Broggini: 0000-0003-2492-5078

Giovanni Poli: 0000-0002-7356-1568

Julie Oble: 0000-0002-4002-255X

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript

Notes

Any additional relevant notes should be placed here.

ACKNOWLEDGMENT

The authors would like to acknowledge H2020-WIDESPREAD-05-2020-Twinning project Biomass4Synthons (B4S: grant agreement 951996) for financial support, as well as CNRS and Sorbonne Université. Support through the Marie Skłodowska-Curie Innovative Training Network European Training Networks (ITN-ETN) C—H Activation for Industrial Renewal (CHAIR: grant agreement 860762), is also gratefully acknowledged. Centro de Química Estrutural acknowledges the financial support of Fundação para a Ciência e Tecnologia (UIDB/00100/2020). RS thanks Università dell'Insubria for the financial support related to the mobility.

REFERENCES

(1) Xiao, D.; Palani, A.; Huang, X.; Sofolarides, M.; Zhou, W.; Chen, X.; Aslanian, R.; Guo, Z.; Fossetta, J.; Tian, F.; Trivedi, P.; Spacciapoli, P.; Whitehurst, C. E.; Lundell, D. Conformation Constraint of Anilides Enabling the Discovery of Tricyclic Lactams as Potent MK2 Non-ATP Competitive Inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3262–3266.

(2) Nagumo, Y.; Katoh, K.; Iio, K.; Saitoh, T.; Kutsumura, N.; Yamamoto, N.; Ishikawa, Y.; Irukayama-Tomobe, Y.; Ogawa, Y.; Baba, T.; Tanimura, R.; Yanagisawa, M.; Nagase, H. Discovery of Attenuation Effect of Orexin 1 Receptor to Aversion of Nalfurafine: Synthesis and Evaluation of D-nor-Nalfurafine Derivatives and Analyses of the Three Active Conformations of Nalfurafine. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 127360.

(3) Bordi, F.; Mugnaini, M.; Terron, A.; Barnaby, R.; Reggiani, A. GV150526: A Neuroprotective Agent. *CNS Drug Rev.* **2006**, *6*, 135–152.

(4) Di Fabio, R.; Conti, N.; De Magistris, E.; Feriani, A.; Provera, S.; Sabbatini, F. M.; Reggiani, A.; Rovatti, L.; Barnaby, R. J. Substituted Analogues of GV150526 as Potent Glycine Binding Site Antagonists in Animal Models of Cerebral Ischemia. *J. Med. Chem.* **1999**, *42*, 3486–3493.

(5) Xie, Y.; Huang, B.; Yu, K.; Shi, F.; Xu, W. Discovery of a Series of Novel Compounds with Moderate Anti-Avian H5N1 Influenza Virus Activity in Chick Embryo. *Med. Chem. Res.* **2013**, *22*, 3485–3496.

(6) Solomon, V. Raja.; Lee, H. Anti-Breast Cancer Activity of Heteroaryl Chalcone Derivatives. *Biomed. Pharmacother.* **2012**, *66*, 213–220.

(7) Mai, A.; Massa, S.; Ragno, R.; Cerbara, I.; Jesacher, F.; Loidl, P.; Brosch, G. 3-(4-Aroyl-1-Methyl-1 *H* -2-Pyrrolyl)- *N* -Hydroxy-2-Alkylamides as a New Class of Synthetic Histone Deacetylase Inhibitors. 1. Design, Synthesis, Biological Evaluation, and Binding Mode Studies Performed through Three Different Docking Procedures. *J. Med. Chem.* **2003**, *46*, 512–524.

(8) Roncali, J. Synthetic Principles for Bandgap Control in Linear π-Conjugated Systems. *Chem. Rev.* **1997**, *97*, 173–206.

(9) Mitschke, U.; Bäuerle, P. The Electroluminescence of Organic Materials. *J. Mater. Chem.* **2000**, *10*, 1471–1507.

(10) Katz, H. E.; Bao, Z.; Gilat, S. L. Synthetic Chemistry for Ultrapure, Processable, and High-Mobility Organic Transistor Semiconductors. *Acc. Chem. Res.* **2001**, *34*, 359–369.

(11) Dalton, T.; Faber, T.; Glorius, F. C–H Activation: Toward Sustainability and Applications. *ACS Cent. Sci.* **2021**, *7*, 245–261.

(12) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A Comprehensive Overview of Directing Groups Applied in Metal-Catalysed C–H Functionalisation Chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603–6743.

(13) Roudesly, F.; Oble, J.; Poli, G. Metal-Catalyzed CH Activation/Functionalization: The Fundamentals. *J. Mol. Catal. Chem.* **2017**, *426*, 275–296.

(14) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C–H Bond Functionalization Chemistry for the Expedient Construction of C–C Bonds. *Chem. Rev.* **2020**, *120*, 1788–1887.

(15) Moritani, I.; Fujiwara, Y. Aromatic Substitution of Styrene-Palladium Chloride Complex. *Tetrahedron Lett.* **1967**, *8*, 1119–1122.

(16) Fujiwara, Y.; Moritani, I.; Matsuda, M. Aromatic Substitution of Olefin—III. *Tetrahedron* **1968**, *24*, 4819–4824.

(17) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. Aromatic Substitution of Olefin. IV Reaction with Palladium Metal and Silver Acetate. *Tetrahedron Lett.* **1968**, *9*, 3863–3865.

(18) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. Aromatic Substitution of Olefins. VI. Arylation of Olefins with Palladium(II) Acetate. *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169.

(19) Kitamura, T.; Fujiwara, Y. CHAPTER 2. Dehydrogenative Heck-Type Reactions: The Fujiwara–Moritani Reaction. In *Green Chemistry Series*; Li, C.-J., Ed.; Royal Society of Chemistry: Cambridge, 2014; pp 33–54.

(20) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon−Carbon Bonds by Oxidizing Two Carbon−Hydrogen Bonds. *Chem. Rev.* **2011**, *111*, 1215–1292.

(21) Le Bras, J.; Muzart, J. Intermolecular Dehydrogenative Heck Reactions. *Chem. Rev.* **2011**, *111*, 1170–1214.

(22) Tian, T.; Li, Z.; Li, C.-J. Cross-Dehydrogenative Coupling: A Sustainable Reaction for C–C Bond Formations. *Green Chem.* **2021**, No., 10.1039.D1GC01871J.

(23) C–H/C–H cross couplings are sometimes alternatively called: cross-dehydrogenative couplings (CDC), oxidative couplings, or dehydrogenative cross-couplings.

(24) Srivastava, A.; Jana, C. K. *Heterocycles via Cross Dehydrogenative Coupling Synthesis and Functionalization*; Springer Singapore: Singapore.

(25) Ali, W.; Prakash, G.; Maiti, D. Recent Development in Transition Metal-Catalysed C–H Olefination. *Chem. Sci.* **2021**, *12*, 2735–2759.

(26) Mulligan, C. J.; Parker, J. S.; Hii, K. K. (Mimi). Revisiting the Mechanism of the Fujiwara–Moritani Reaction. *React. Chem. Eng.* **2020**, *5*, 1104–1111.

(27) Ma, W.; Gandeepan, P.; Li, J.; Ackermann, L. Recent Advances in Positional-Selective Alkenylations: Removable Guidance for Twofold C–H Activation. *Org. Chem. Front.* **2017**, *4*, 1435–1467.

(28) Tang, S.; Liu, Y.; Lei, A. Electrochemical Oxidative Cross-Coupling with Hydrogen Evolution: A Green and Sustainable Way for Bond Formation. *Chem* **2018**, *4*, 27–45.

(29) Amatore, C.; Cammoun, C.; Jutand, A. Electrochemical Recycling of Benzoquinone in the Pd/Benzoquinone-Catalyzed Heck-Type Reactions from Arenes. *Adv. Synth. Catal.* **2007**, *349*, 292–296.

(30) Meng, Q.-Y.; Zhong, J.-J.; Liu, Q.; Gao, X.-W.; Zhang, H.-H.; Lei, T.; Li, Z.-J.; Feng, K.; Chen, B.; Tung, C.-H.; Wu, L.-Z. A Cascade Cross-Coupling Hydrogen Evolution Reaction by Visible Light Catalysis. *J. Am. Chem. Soc.* **2013**, *135*, 19052–19055.

(31) Yoshimura, R.; Shibata, Y.; Yamada, T.; Tanaka, K. Aerobic Oxidative Olefination of Benzamides with Styrenes Catalyzed by a Moderately Electron-Deficient CpRh(III) Complex with a Pendant Amide. *J. Org. Chem.* **2019**, *84*, 2501–2511.

(32) Guillemard, L.; Wencel-Delord, J. When Metal-Catalyzed C–H Functionalization Meets Visible-Light Photocatalysis. *Beilstein J. Org. Chem.* **2020**, *16*, 1754–1804.

(33) Dwivedi, V.; Kalsi, D.; Sundararaju, B. Electrochemical-/Photoredox Aspects of Transition Metal-Catalyzed Directed C−H Bond Activation. *ChemCatChem* **2019**, *11*, 5160–5187.

(34) De Abreu, M.; Belmont, P.; Brachet, E. Synergistic Photoredox/Transition-Metal Catalysis for Carbon-Carbon Bond Formation Reactions: Synergistic Photoredox/Transition-Metal Catalysis for Carbon-Carbon Bond Formation Reactions. *Eur. J. Org. Chem.* **2020**, *2020*, 1327–1378.

(35) Xu, C.; Paone, E.; Rodríguez-Padrón, D.; Luque, R.; Mauriello, F. Recent Catalytic Routes for the Preparation and the Upgrading of Biomass Derived Furfural and 5-Hydroxymethylfurfural. *Chem. Soc. Rev.* **2020**, *49*, 4273–4306.

(36) Bender, T. A.; Dabrowski, J. A.; Gagné, M. R. Homogeneous Catalysis for the Production of Low-Volume, High-Value Chemicals from Biomass. *Nat. Rev. Chem.* **2018**, *2*, 35–46.

(37) Mika, L. T.; Cséfalvay, E.; Németh, Á. Catalytic Conversion of Carbohydrates to Initial Platform Chemicals: Chemistry and Sustainability. *Chem. Rev.* **2018**, *118*, 505–613.

(38) Yao, Q.; Xu, L.; Guo, C.; Yuan, Z.; Zhang, Y.; Fu, Y. Selective Production of Pyrroles via Catalytic Fast Pyrolysis of Cellulose under Ammonia Atmosphere at Low Temperature. *J. Anal. Appl. Pyrolysis* **2017**, *124*, 409–414.

(39) Song, S.; Fung Kin Yuen, V.; Di, L.; Sun, Q.; Zhou, K.; Yan, N. Integrating Biomass into the Organonitrogen Chemical Supply Chain: Production of Pyrrole and D -Proline from Furfural. *Angew. Chem. Int. Ed.* **2020**, *59*, 19846–19850.

(40) Korvorapun, K.; Samanta, R. C.; Rogge, T.; Ackermann, L. Remote C–H Functionalizations by Ruthenium Catalysis. *Synthesis* **2021**, *53*, 2911–2946.

(41) Pezzetta, C.; Veiros, L. F.; Oble, J.; Poli, G. Murai Reaction on Furfural Derivatives Enabled by Removable N,N'-Bidentate Directing Groups. *Chem. – Eur. J.* **2017**, *23*, 8385–8389.

(42) Siopa, F.; Ramis Cladera, V.-A.; Afonso, C. A. M.; Oble, J.; Poli, G. Ruthenium-Catalyzed C-H Arylation and Alkenylation of Furfural Imines with Boronates: Ruthenium-Catalyzed C-H Arylation and Alkenylation of Furfural Imines with Boronates. *Eur. J. Org. Chem.* **2018**, *2018*, 6101–6106.

(43) Ravasco, J. M. J. M.; Monteiro, C. M.; Siopa, F.; Trindade, A. F.; Oble, J.; Poli, G.; Simeonov, S. P.; Afonso, C. A. M. Creating Diversity from Biomass: A Tandem Bio/Metal-Catalysis towards Chemoselective Synthesis of Densely Substituted Furans. *ChemSusChem* **2019**, *12*, 4629–4635.

(44) Sala, R.; Roudesly, F.; Veiros, L. F.; Broggini, G.; Oble, J.; Poli, G. Ru-Catalyzed Carbonylative Murai Reaction: Directed C3-Acylation of Biomass-Derived 2-Formyl Heteroaromatics. *Adv. Synth. Catal.* **2020**, *362*, 2486–2493.

(45) Itahara, T.; Ouseto, F. Alkenylation of 1-Methyl-2-Pyridone and 2-Formylfuran with Methyl Acrylate and Palladium Acetate. *Synthesis* **1984**, *1984*, 488–489.

(46) Li, F.; Li, X.; Gong, T.; Fu, Y. Selective Conversion of Furoic Acid Derivatives to Multi-Substituted Furanacrylate by a Ruthenium Catalyst. *ChemCatChem* **2019**, *11*, 5124–5130.

(47) Gao, S.; Wu, Z.; Wu, F.; Lin, A.; Yao, H. Catalyst-Controlled Regiodivergent Dehydrogenative Heck Reaction of 4-Arylthiophene/Furan-3-Carboxylates. *Adv. Synth. Catal.* **2016**, *358*, 4129–4135.

(48) Lanke, V.; Ramaiah Prabhu, K. Regioselective Synthesis of 4-Substituted Indoles via C–H Activation: A Ruthenium Catalyzed Novel Directing Group Strategy. *Org. Lett.* **2013**, *15*, 6262–6265.

(49) Padala, K.; Jeganmohan, M. Highly Regio- and Stereoselective Ruthenium(II)-Catalyzed Direct *Ortho* -Alkenylation of Aromatic and Heteroaromatic Aldehydes with Activated Alkenes under Open Atmosphere. *Org. Lett.* **2012**, *14*, 1134–1137.

(50) Lv, N.; Liu, Y.; Xiong, C.; Liu, Z.; Zhang, Y. Cobalt-Catalyzed Oxidant-Free Spirocycle Synthesis by Liberation of Hydrogen. *Org. Lett.* **2017**, *19*, 4640–4643.

(51) Meng, K.; Sun, Y.; Zhang, J.; Zhang, K.; Ji, X.; Ding, L.; Zhong, G. Iridium-Catalyzed Cross-Coupling Reactions of Alkenes by Hydrogen Transfer. *Org. Lett.* **2019**, *21*, 8219–8224.

(52) He, K.-H.; Zhang, W.-D.; Yang, M.-Y.; Tang, K.-L.; Qu, M.; Ding, Y.-S.; Li, Y. Redox-Divergent Hydrogen-Retentive or Hydrogen-Releasing Synthesis of 3,4-Dihydroisoquinolines or Isoquinolines. *Org. Lett.* **2016**, *18*, 2840–2843.

(53) Li, W.-H.; Wu, L.; Li, S.-S.; Liu, C.-F.; Zhang, G.-T.; Dong, L. Rhodium-Catalyzed Hydrogen-Releasing *Ortho* -Alkenylation of 7-Azaindoles. *Chem. - Eur. J.* **2016**, *22*, 17926–17929.

(54) Manikandan, R.; Madasamy, P.; Jeganmohan, M. Ruthenium-Catalyzed *Ortho* Alkenylation of Aromatics with Alkenes at Room Temperature with Hydrogen Evolution. *ACS Catal.* **2016**, *6*, 230–234.

(55) The alkene function in **F2a** is found exclusively in the *E* geometry, and this configuration has been found throughout the study.

(56) In the crude ^{1}H NMR spectra, less than 5% of the C3-alkylated product is visible, which probably comes from the Murai type reactivity.

(57) Burk, M. J.; Crabtree, R. H. Selective Catalytic Dehydrogenation of Alkanes to Alkenes. *J. Am. Chem. Soc.* **1987**, *109*, 8025–8032.

(58) Lin, Q.; Lin, Z.; Pan, M.; Zheng, Q.; Li, H.; Chen, X.; Darcel, C.; Dixneuf, P. H.; Li, B. Alkenes as Hydrogen Trappers to Control the Regio-Selective Ruthenium(II) Catalyzed *Ortho* C–H Silylation of Amides and Anilides. *Org. Chem. Front.* **2021**, *8*, 514–521.

(59) It has to be noted that the functionalization of furfural and HMF derivatives is rather challenging, due to the inherent instability of the furan nucleus that tends to degrade into NMR invisible byproducts (very likely humins). This is not the case for the other heterocycles studied (*vide infra*).

(60) This substrate can thus be considered as a biomass-derived building block, too. See refs 38, 39.

(61) del', M.; Pina, K.; Budylin, V. A.; Rodriges, M.; Terent'ev, P. B.; Bundel', Yu. G. Synthesis and Spectral Properties of 1-Aryl-2-Formylpyrroles. *Chem. Heterocycl. Compd.* **1989**, *25*, 142–146.

(62) Yuen, T.-Y.; Eaton, S. E.; Woods, T. M.; Furkert, D. P.; Choi, K. W.; Brimble, M. A. A Maillard Approach to 2-Formylpyrroles: Synthesis of Magnolamide, Lobechine and Funebral. *Eur. J. Org. Chem.* **2014**, *2014*, 1431–1437.

(63) For imine hydrolysis of the C3-acylated products from the carbonylative Murai reaction, see: 44.

(64) Parr, R. G.; Yang, W. Density Functional Theory of Atoms and Molecules; Oxford University Press: New York, 1989. DFT calculations at the M06/[3-21G(f), 6-311++G(d,p)]//PBE0/[SDD(f), 6-31G(d,p)] level were performed using the GAUSSIAN 09 package. Solvent effects (toluene) were considered by means of the PCM model. A complete account of the computational details and the corresponding list of references are provided as SI.

(65) Álvarez-Rodríguez, L.; Cabeza, J. A.; García-Álvarez, P.; Pérez-Carreño, E.; Polo, D. Amidinatogermylene Derivatives of Ruthenium Carbonyl: New Insights into the Reactivity of $[Ru_3(CO)_{12}]$ with Two-Electron-Donor Reagents of High Basicity. *Inorg. Chem.* **2015**, *54*, 2983–2994.

(66) For a previous DFT study of the Murai reaction, see: a) T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, J. Am. Chem. Soc. 1998, 120, 12692–12693; b) T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, Organometallics 2000, 19, 2318–2329; c) U. Helmstedt, E. Clot, Chem. – Eur. J. 2012, 18, 11449–11458.

(67) All barrier free energy values are related to the initial species, A.