

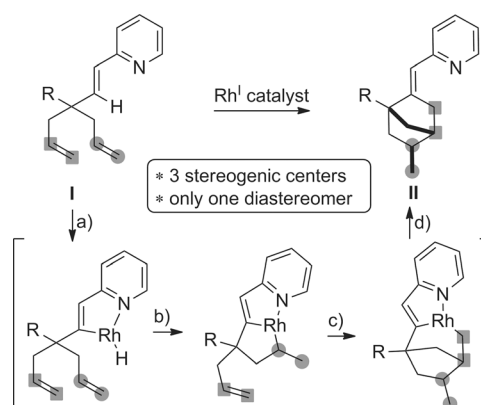
Diastereoselective Carbocyclization of 1,6-Heptadienes Triggered by Rhodium-Catalyzed Activation of an Olefinic C–H Bond**

Christophe Aïssa,* Kelvin Y. T. Ho, Daniel J. Tetlow, and María Pin-Nó

Abstract: The use of α,ω -dienes as functionalization reagents for olefinic carbon–hydrogen bonds has been rarely studied. Reported herein is the rhodium(I)-catalyzed rearrangement of prochiral 1,6-heptadienes into [2,2,1]-cycloheptane derivatives with concomitant creation of at least three stereogenic centers and complete diastereocontrol. Deuterium-labeling studies and the isolation of a key intermediate are consistent with a group-directed C–H bond activation, followed by two consecutive migratory insertions, with only the latter step being diastereoselective.

The metal-catalyzed activation of otherwise inert carbon–hydrogen (C–H) bonds is increasingly recognized as a powerful synthetic method, and numerous transformations involving aromatic C–H bonds have been described.^[1] In contrast, besides hydrovinylation reactions using ethylene,^[2] the metal-catalyzed functionalization of an olefinic C–H bond with a different alkene has been reported on far fewer occasions.^[3] Specifically, besides the addition of 2-isopropenyl-pyridine to 1,5-hexadiene^[3b] and the addition of various olefins to 1,3-dienes,^[2,4] the use of α,ω -dienes as functionalization reagents of olefinic C–H bonds has not yet been explored.

In this context, we anticipated that the treatment of 1,6-heptadiene **I** with a rhodium catalyst would lead to the [2,2,1]-cycloheptane derivative **II** by undergoing the following elementary steps (Scheme 1): a) pyridine-directed C–H bond activation, b) migratory insertion of the first terminal olefin into the metal hydride thus generated, c) migratory insertion of the second olefin,^[5] and d) final reductive elimination. Significantly, the success of this design would enable a strong increase of molecular complexity, as measured by the number of sp^3 -hybridized stereogenic centers created in the rearrangement. Specifically, it would contrast with the classical metal-catalyzed cycloisomerizations of 1,6-



Scheme 1. Proposed catalytic cycle for a diastereoselective carbocyclization of 1,6-heptadienes into [2,2,1]-cycloheptane derivatives.

heptadienes, which are moderately diastereoselective, when the two terminal olefins of the substrate are linked by a prochiral tether.^[6,7] Herein, we report that the implementation of our reaction design leads to the formation of **II** as a single diastereoisomer and we propose a refinement of the initially envisioned mechanism.

Although initial investigations with the model substrate **1a** validated our reaction design, the desired compound **2a** was contaminated by **3a** (Figure 1). This problem was solved by rendering the catalyst cationic through the addition of $AgBF_4$.^[8] Control experiments confirmed that $AgBF_4$ alone cannot act as the catalyst, and that phosphine-free rhodium species are not catalytically competent. Importantly, **2a** was obtained as a single diastereomer, even in the crude reaction mixtures. The stereochemistry of **2a** was confirmed by NOESY and by X-ray crystallography of its hydrochloride salt (Figure 1).^[9]

With these results in hand, we examined the generality of this transformation and observed in all cases the formation of **2** as a single diastereomer in good to excellent yields upon isolation (Scheme 2). The stereochemistry of the compounds **2** was confirmed by NMR spectroscopy and by X-ray crystallography in the case of **2g** (see the Supporting Information). Naphthyl (**1b**), electron-poor and electron-rich phenyl (**1c–f**), 1-oxa-3-indenyl (**1g**), acetal (**1h**), protected amine (**1i**), and alkyl (**1j–m**) groups were all tolerated. The selectivity between **2** and **3** remained excellent ($\geq 95:5$) except in the case of substrates having a nonbulky substituent (**R**), such as a linear ether chain (**1l**) or a simple methyl group (**1m**). Hence, the Thorpe–Ingold effect appears important for the selective formation of **2**. Further confirming this rationale, the reaction of **1** when **R** is a hydrogen atom led to the

[*] Dr. C. Aïssa, K. Y. T. Ho, Dr. D. J. Tetlow, M. Pin-Nó
Department of Chemistry, University of Liverpool
Crown Street, L69 7ZD (UK)
E-mail: aïssa@liverpool.ac.uk

[**] Financial support from EPSRC (DTA studentship to K.Y. T.H.), the University of Liverpool (Studentship to M.P.), the Leverhulme Trust (RPG198), and AstraZeneca is gratefully acknowledged. We thank Johnson-Matthey for the loan of rhodium salts and Dr. C. M. Robertson for X-Ray crystallographic analysis of **2a**·HCl and **2g**.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201400080>.

© 2014 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

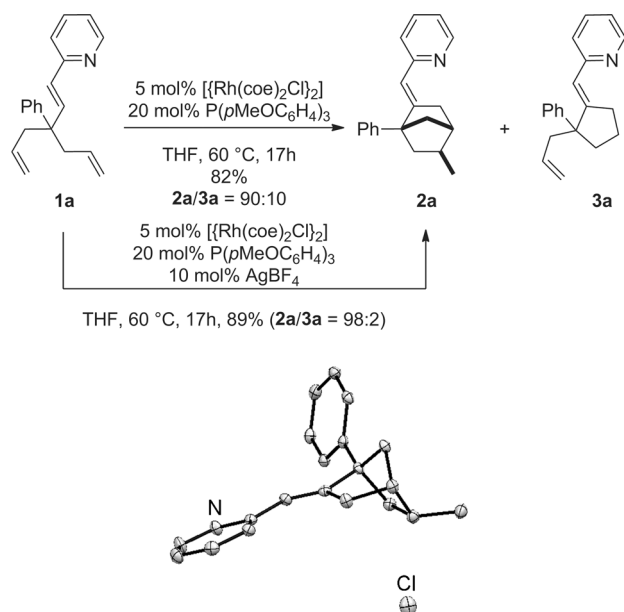
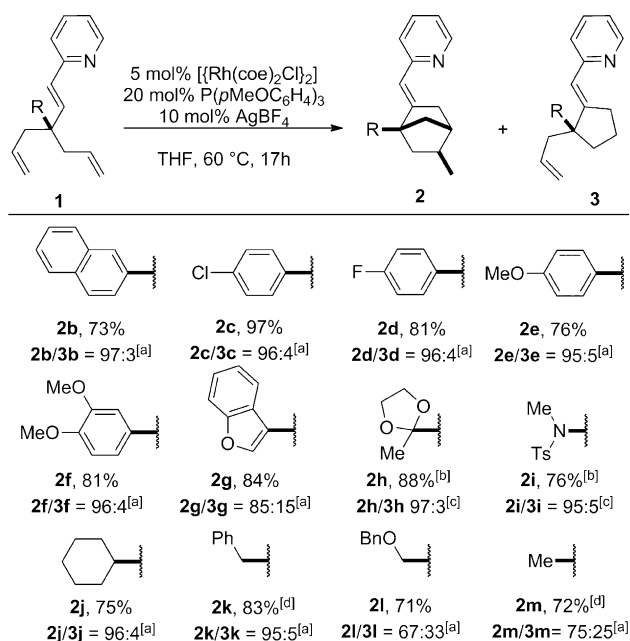


Figure 1. Validation of the reaction design and ORTEP drawing of **2a**·HCl. Only the nitrogen and chlorine atoms are labeled for clarity. Thermal ellipsoids are shown at 50% probability. coe = cyclooctane, THF = tetrahydrofuran.

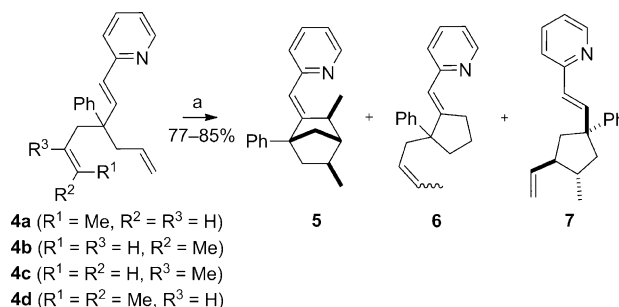


Scheme 2. Diastereoselective carbocyclization of 1,6-dienes. Yields are those for the isolated **2** and **3** (combined) unless otherwise noted. [a] 2/3 ratio of isolated material. [b] Yield of isolated **2**. [c] 2/3 ratio in crude reaction mixture. [d] 15 mol % of $P(pMeOC_6H_4)_3$ was used. Ts = *p*-tolylsulfonyl.

formation of **3** only.^[3d–f] Whereas the **2/3** selectivity observed with **1a–f** remained consistent, the stronger erosion observed with **1g** suggests that electronic factors can play a role.^[10]

When we examined the reactivity of the 1,6-octadiene **4a**, we obtained a complex mixture of products (**5/6/7** = 1:0.7:1.5) in 85% yield as determined by NMR spectroscopy

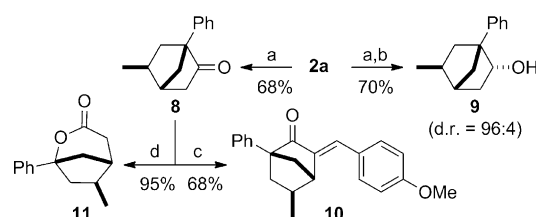
(Scheme 3). Hence, **5** shows four stereogenic centers and was obtained as a single diastereomer, whereas **6** was formed as an equimolar mixture of *cis* and *trans* olefins. More surprising was the presence of **7**, which was also obtained as



Scheme 3. Reaction of substituted the 1,6-dienes **4**. a) $[Rh(coe)_2Cl]_2$ (5 mol %), $P(pMeOC_6H_4)_3$ (20 mol %), $AgBF_4$ (10 mol %), THF, 60 °C, 17 h.

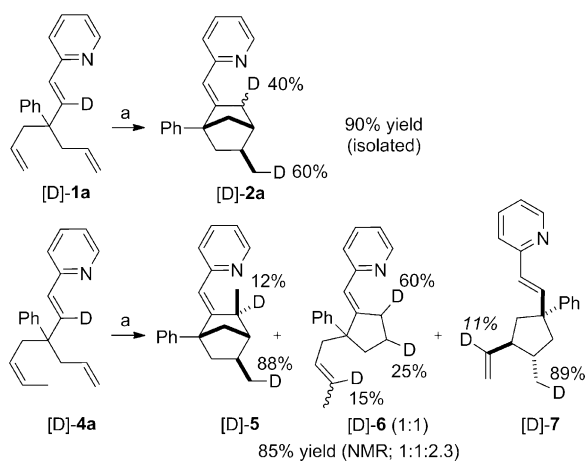
a single diastereomer. When a 1:3 mixture of **4a/4b** was submitted to identical reaction conditions, the same compounds **5**, **6**, and **7** (1:1:3) were obtained in 77% yield (NMR), with a variation in the *trans/cis* ratio of the olefins **6** (3:1). Only sluggish reactions were observed with **4c** or **4d**.

Importantly, the vinyl pyridine moiety can easily be converted into other functional groups. Hence, **2a** was transformed into the ketone **8**, alcohol **9**, α -arylidene ketone **10**, and lactone **11** within one or two steps (Scheme 4).



Scheme 4. Manipulation of **2a**. a) $NaIO_4$ (4 equiv), $RuCl_3$ hydrate (20 mol %), 1,2-DCE, MeCN, water. b) $DiBAL-H$ (4 equiv), toluene. c) $tBuOK$ (0.1 equiv), *p*-anisaldehyde (1 equiv), DMSO. d) *mCPBA* (2.5 equiv), $NaHCO_3$ (5 equiv), CH_2Cl_2 . DCE = dichloroethane, DMSO = dimethylsulfoxide, *mCPBA* = *m*-chloroperbenzoic acid.

We were eager to gain further understanding of the mechanism of these reactions to explain the exquisite diastereoselectivity and the formation of side products such as **7**. Deuterium-labeling experiments with $[D]-1a$ led to the formation of two monodeuterated isomers ($[D]-2a$), wherein the deuterium atom was quantitatively and equally distributed between two positions (Scheme 5). Parallel competition experiments with **1a** and $[D]-1a$ did not indicate any primary kinetic isotope effect ($k_H/k_D = 1.2$). Importantly, the location of the deuterium atom in the $[D]-2a$ isomers did not change with conversion. This observation suggests that the migratory insertion of the first olefin is not only reversible but also occurs much more rapidly than the subsequent steps of the catalytic cycle. In addition, intermolecular transfer of the deuterium atom was not observed in the products for the



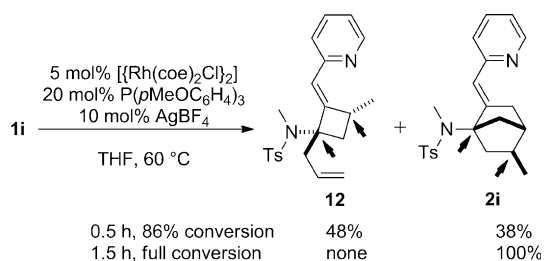
a) $[\text{Rh}(\text{coe})_2\text{Cl}]_2$ (5 mol %), $\text{P}(\text{pMeOC}_6\text{H}_4)_3$ (20 mol %), AgBF_4 (10 mol %), THF, 60 °C, 17 h. Percentages of deuterium incorporation are indicated.

reaction involving an equimolar amount of [D]-1a and 1i, thus confirming the purely intramolecular nature of the hydrometallation step. Hence, [D]-2a and 2i were isolated in 95 and 89 % yield, respectively, in this crossover experiment.

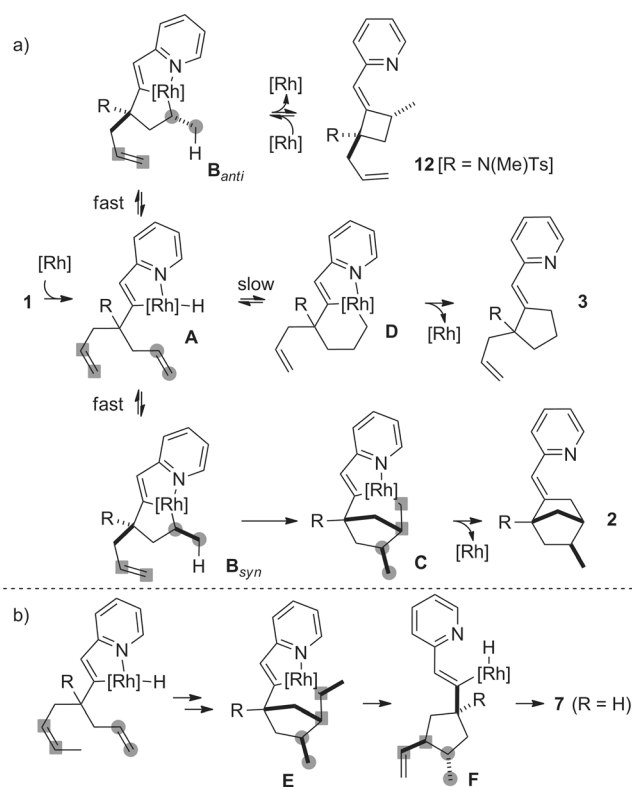
Although 7 appears to result from a formal Alder-ene cycloisomerization of 4a, the location and extent of incorporation of the deuterium atom in [D]-7 upon reaction of [D]-4a (Scheme 5) are not consistent with either an oxidative cyclometallation involving the two olefins of the 1,6-diene moiety^[6c] or an intermolecular addition of a metal hydride intermediate,^[11] and suggests that another mechanism is operative. The other identified components of the mixture were the monodeuterated [D]-5 and [D]-6.

Finally, when examining the kinetic profile of the reaction with the substrate 1i, we observed the transient formation of the four-membered ring 12 (Scheme 6). At 86 % conversion, this compound accounts for up to 48 % of the mass balance, before being converted into 2i. Hence, we could isolate 12 in 33 % yield. Strikingly, the relative configuration of its stereogenic centers (see arrows) is inverted as compared to those in the final product 2i. We observed a similar phenomenon with 1a and 1g, but the formation of four-membered ring compounds analogous to 12 only peaks at 10 % of the mass balance.

These results can be accounted for by the following mechanism (Scheme 7). After pyridine-directed C–H bond activation, the migratory insertion of the first olefin into the rhodium–hydrogen bond of A is not diastereoselective, and



Scheme 6. Transient formation of a four-membered ring intermediate.



Scheme 7. Revised mechanism. $[\text{Rh}] = [\text{Rh}(\text{P}(\text{pMeOC}_6\text{H}_4)_3)_n]\text{BF}_4$.

both B_{syn} and B_{anti} are formed very rapidly and reversibly (Scheme 7a). Then, the migratory insertion of the second olefin is not favored in the case of B_{anti} , which undergoes reductive elimination toward 12, a process particularly favored in the case of $\text{R} = \text{N}(\text{Me})\text{Ts}$. However, 12 can undergo pyridine-directed C–C bond activation and revert back to B_{anti} . In contrast, B_{syn} can undergo migratory insertion of the second olefin more favorably than B_{anti} and give C, which after reductive elimination affords 2. Hence, the exquisite diastereoselectivity of the reaction is dictated by the relative ability of the diastereomers B to undergo intramolecular migratory insertion of the terminal olefin. When R is not sterically demanding, or when the second olefin is too substituted, the evolution of B_{syn} into C is more difficult and the formation of D becomes competitive, thus leading to the formation of 3.^[3d–f,10]

The same mechanistic manifold is operative for substrate 4a, thus leading to the formation of 5 and 6. However, reductive elimination from the intermediate E toward 5 is in competition with the β -hydride elimination toward F, which affords 7 after reductive elimination (Scheme 7b). The predominant incorporation of the deuterium atom on the methyl group of [D]-5 indicates that the unsubstituted olefin undergoes the first migratory insertion into the rhodium–hydrogen bond more rapidly than the substituted olefin. Nevertheless, this step occurs reversibly, thus explaining the olefin isomerization observed in 6. The level of deuterium incorporation at the indicated positions in [D]-6 is in good accordance with previous mechanistic studies on rhodium-catalyzed intramolecular hydrovinylation of olefins.^[3f] Incidentally, the predominant incorporation of the deuterium

atom on the methyl group of [D]-7 enables us to propose that the migratory insertion of the second olefin (i.e., **B**_{syn} to **C**) occurs as depicted in Scheme 7 and not into the C(sp²)-Rh bond of **B**_{syn}.

In conclusion, we have described the first example of metal-catalyzed functionalization of an olefinic C–H bond using a 1,6-heptadiene as a partner. This rearrangement starkly contrasts with classical reactions of similar prochiral substrates in the presence of late-transition-metal catalysts, as it does not lead to the otherwise typical cyclopentene isomers, but converts the 1,6-dienes into [2.2.1]-cycloheptane derivatives, thereby creating at least three stereogenic centers with complete diastereocontrol. After C–H activation, the carbocyclization proceeds by two consecutive migratory insertions, whereby the first is rapid, reversible, and not diastereoselective, and the second leads to the formation of a single diastereoisomer. Importantly, the vinyl pyridine used to trigger the reaction can be easily transformed into other functional groups which are amenable to further synthetic manipulation.

Received: January 4, 2014

Revised: February 20, 2014

Published online: March 13, 2014

Keywords: C–H activation · diastereoselectivity · diene · rearrangement · rhodium

- [1] For examples in most recent reviews, see: a) X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; b) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; c) K. Fagnou, *Top. Curr. Chem.* **2010**, *292*, 35; d) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; e) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; f) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, 46, 677; g) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; h) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; i) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; j) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; k) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651.
- [2] a) T. V. Rajanbabu, *Chem. Rev.* **2003**, *103*, 2845; b) T. V. Rajanbabu, *Synlett* **2009**, 853; c) G. Hilt, *Eur. J. Org. Chem.* **2012**, 4441.
- [3] Selected examples: a) B. M. Trost, K. Imi, I. W. Davies, *J. Am. Chem. Soc.* **1995**, *117*, 5371; b) F. Kakiuchi, Y. Tanaka, T. Sato, N. Chatani, S. Murai, *Chem. Lett.* **1995**, 679; c) T. Sato, F. Kakiuchi, N. Chatani, S. Murai, *Chem. Lett.* **1998**, 893; d) Y.-G. Lim, J.-B. Kang, Y. H. Kim, *Chem. Commun.* **1996**, 585; e) N. Fujii, F. Kakiuchi, N. Chatani, S. Murai, *Chem. Lett.* **1996**, 939; f) N. Fujii, F. Kakiuchi, A. Yamada, N. Chatani, S. Murai, *Chem. Lett.* **1997**, 425; g) N. Fujii, F. Kakiuchi, A. Yamada, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 285; h) Y.-G. Lim, J.-B. Kang, Y. H. Kim, *J. Chem. Soc. Perkin Trans. 1* **1998**, 699; i) Y.-G. Lim, J.-B. Kang, B. T. Koo, *Tetrahedron Lett.* **1999**, *40*, 7691; j) F. Kakiuchi, T. Sato, K. Imi, N. Chatani, S. Murai, *Chem. Lett.* **2001**, 386; k) C.-H. Jun, C. W. Moon, Y.-M. Kim, H. Lee, J. H. Lee, *Tetrahedron Lett.* **2002**, *43*, 4233; l) Y. Yamamoto, S. Sakaguchi, Y. Ishii, *Org. Lett.* **2004**, *6*, 4623; m) Y. Ura, H. Tsujita, K. Wada, T. Kondo, T.-a. Mitsudo, *J. Org. Chem.* **2005**, *70*, 6623; n) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2006**, *128*, 5604; o) C. Aissa, A. Fürstner, *J. Am. Chem. Soc.* **2007**, *129*, 14836; p) H. Tsujita, Y. Ura, S. Matsuki, K. Wada, T.-a. Mitsudo, T. Kondo, *Angew. Chem.* **2007**, *119*, 5252; *Angew. Chem. Int. Ed.* **2007**, *46*, 5160; q) A. S. Tsai, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 6316; r) S. Ogoshi, T. Haba, M. Ohashi, *J. Am. Chem. Soc.* **2009**, *131*, 10350; s) M.-O. Simon, R. Martinez, J.-P. Genêt, S. Darses, *Adv. Synth. Catal.* **2009**, *351*, 153; t) Y.-H. Xu, J. Lu, T.-P. Loh, *J. Am. Chem. Soc.* **2009**, *131*, 1372; u) S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 6295; v) T. Besset, M. Kuhl, F. W. Patureau, F. Glorius, *Chem. Eur. J.* **2011**, *17*, 7167; w) Q.-S. Wang, J.-H. Xie, L.-C. Guo, Q.-L. Zhou, *Org. Biomol. Chem.* **2012**, *10*, 43; x) Y. Hiroi, N. Komine, S. Komiya, M. Hirano, *Org. Lett.* **2013**, *15*, 2486.
- [4] For leading references, see: a) G. Hilt, F.-X. du Mesnil, S. Lüers, *Angew. Chem.* **2001**, *113*, 408; *Angew. Chem. Int. Ed.* **2001**, *40*, 387; b) G. Hilt, S. Lüers, *Synthesis* **2002**, 609; c) B. Moreau, J. Y. Wu, T. Ritter, *Org. Lett.* **2009**, *11*, 337.
- [5] For examples of intramolecular insertion of an alkyl-substituted olefin into putative rhodacyclopentene derivative, see: a) T. Shibata, Y. Tahara, *J. Am. Chem. Soc.* **2006**, *128*, 11766; b) T. Shibata, Y. Tahara, K. Tamura, K. Endo, *J. Am. Chem. Soc.* **2008**, *130*, 3451. For early examples of rhodium-catalyzed reactions involving C–H cleavage and alkene or alkyne insertion, see: c) K. Oguma, M. Miura, T. Satoh, M. Nomura, *J. Am. Chem. Soc.* **2000**, *122*, 10464; d) T. Hayashi, K. Inoue, N. Taniguchi, M. Ogasawara, *J. Am. Chem. Soc.* **2001**, *123*, 9918.
- [6] For leading references, see: a) R. Grigg, J. F. Malone, T. R. B. Mitchell, A. Ramasubbu, R. M. Scott, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1745; b) S. Okamoto, T. Livinghouse, *J. Am. Chem. Soc.* **2000**, *122*, 1223; c) Y. Yamamoto, Y. Nakagai, N. Ohkoshi, K. Itoh, *J. Am. Chem. Soc.* **2001**, *123*, 6372; d) T. Pei, R. A. Widenhoefer, *J. Org. Chem.* **2001**, *66*, 7639; e) M. Michaut, M. Santelli, J.-L. Parrain, *Tetrahedron Lett.* **2003**, *44*, 2157; f) Y. Yamamoto, Y. Nakagai, K. Itoh, *Chem. Eur. J.* **2004**, *10*, 231; g) I. J. S. Fairlamb, G. P. McGlacken, F. Weissberger, *Chem. Commun.* **2006**, 988; h) D. Nečas, M. Turský, I. Tišlerová, M. Kotora, *New J. Chem.* **2006**, *30*, 671.
- [7] For reviews, see: a) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215; b) Y. Yamamoto, *Chem. Rev.* **2012**, *112*, 4736.
- [8] Electron-rich arylphosphines led to catalysts enabling higher conversions. Bidentate ligands are not effective at all. Replacing the pyridine-2-yl directing group in **1a** with a 1-methyl-1*H*-imidazol-2-yl inhibits all reactivity under the reaction conditions described herein; the substrate was recovered untouched.
- [9] Crystallographic data for **2a·HCl**: CCDC 979570 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [10] It is noteworthy that the sp²-hybridized carbon nuclei in the β-position to the pyridine ring have the following chemical shifts ¹³C NMR: δ = 141.8 ppm (**1a**), 142.3 ppm (**1b**), 141.1 ppm (**1c**), 141.6 ppm (**1d**), 142.1 ppm (**1e**), 142.1 ppm (**1d**), 139.6 ppm (**1g**). Hence, this nucleus is most strongly shielded in **1g** and this might be linked to the erosion of selectivity for **2g**.
- [11] a) P. Kisanga, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2000**, *122*, 10017; b) L. A. Goj, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2001**, *123*, 11133; c) K. L. Bray, I. J. S. Fairlamb, J.-P. Kaiser, G. C. Lloyd-Jones, P. A. Slatford, *Top. Catal.* **2002**, *19*, 49; d) K. L. Bray, G. C. Lloyd-Jones, M. P. Muñoz, P. A. Slatford, E. H. P. Tan, A. R. Tyler-Mahon, P. A. Worthington, *Chem. Eur. J.* **2006**, *12*, 8650.