

Pyridone Allylation

Rhodium-Catalyzed Chemo-, Regio-, and Enantioselective Addition of 2-Pyridones to Terminal Allenes**

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Abstract: A rhodium-catalyzed chemo-, regio-, and enantioselective addition of 2-pyridones to terminal allen es to give branched *N*-allyl 2-pyridones is reported. Preliminary mechanistic studies support the hypothesis that the reaction was initiated from the more acidic 2-hydroxypyridine form, and the initial kinetic *O*-allylation product was finally converted into the thermodynamically more stable *N*-allyl 2-pyridones.

Chiral *N*-substituted 2-pyridones can be found in many biologically active natural products and medicinally interesting molecules (Figure 1).^[1] They are usually prepared by multistep synthesis in which chiral electrophiles or chiral amines are needed.^[2] The straightforward enantioselective

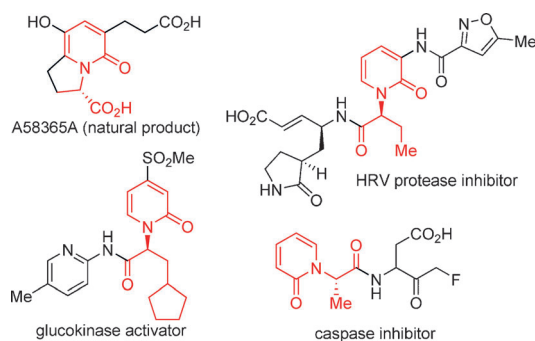
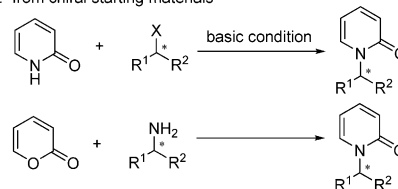


Figure 1. Biologically active molecules with *N*-chiral 2-pyridone moieties.

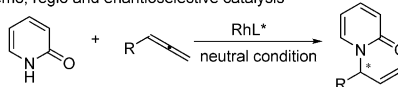
functionalization of 2-pyridones by the aid of a chiral catalyst from achiral starting materials is still very rare.^[3,4] Herein, we report a rhodium-catalyzed chemo-, regio-, and enantioselective addition of 2-pyridones to terminal allen es to furnish α -chiral *N*-allyl 2-pyridones (Scheme 1).

The molecule 2-pyridone exists as a mixture of two tautomers, namely 2-pyridone and the corresponding 2-hydroxypyridine.^[5] The 2-pyridone anion is a well-known

Previous work: from chiral starting materials

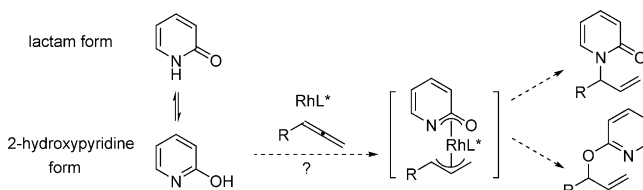


This work: chemo, regio and enantioselective catalysis



Scheme 1. Synthesis of chiral *N*-substituted 2-pyridones.

ambident nucleophile in organic synthesis.^[6] The alkylation of 2-pyridone under basic condition suffers from the *N* vs. *O* selectivity, which normally depends on solvents, bases, substrates, and additives.^[2a] Our group recently developed the rhodium-catalyzed atom-economic and regioselective addition of different pronucleophiles to alkynes or allen es to generate the branched allylic products.^[7] The pronucleophiles need to show pronounced acidity or the ability to undergo an oxidative addition with the rhodium catalyst to be applicable in this transformation. Thus, we anticipated the more acidic 2-hydroxypyridine tautomer, rather than the lactam form, to undergo a rhodium-catalyzed addition to allen es under neutral conditions. Furthermore, there might be an opportunity, based upon the choice of the phosphine ligand, to control the *N* vs. *O* chemo- and enantioselectivity (Scheme 2).



Scheme 2. The rhodium catalyst differentiates two tautomers and determines the *O* vs. *N* ratio.

Our study commenced with 5-chloropyridone **1a** and linear 3-phenylpropyl allene **2a** as model substrates (Table 1). In the presence of 2.5 mol % of $[\text{Rh}(\text{cod})\text{Cl}]_2$ and 7.5 mol % of DPEphos, *O*-allylated product **3aa** and *N*-allylated **4aa** were isolated in a ratio of 1:1 (entry 1). Further ligand screening revealed that electron-rich diphosphine ligands (DTBM ligands) increased both the reactivity and the *N* vs. *O*

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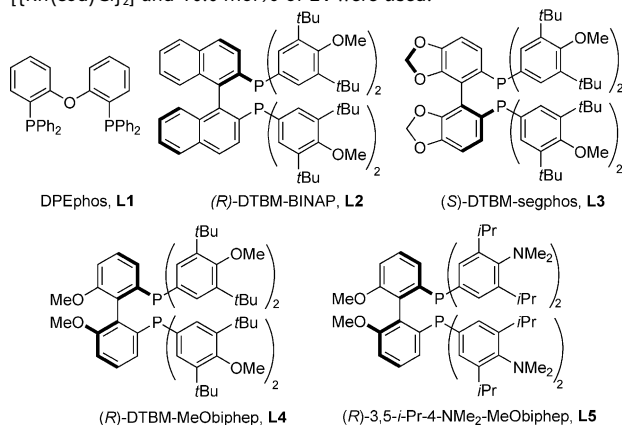
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Table 1: Screening of ligands for the rhodium-catalyzed chemo-, regio-, and enantioselective addition of 2-pyridone to allene.^[a]

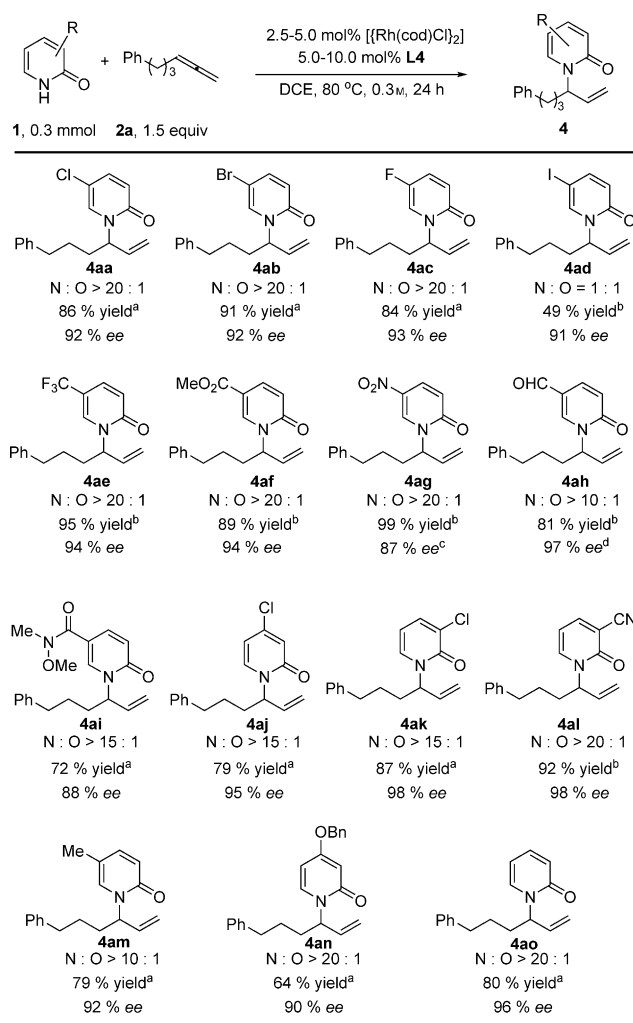
Entry	Ligand	Ratio 3 vs. 4 ^[b]	Yield of 4 ^[c] (%)	<i>ee</i> (%) ^[d]
1	DPEphos (L1)	1:1	17	—
2	L2	1:2	47	92
3	L3	1:9	73	−78
4	L4	1:9	80	92
5	L5	1:3.1	78	93
6 ^[e]	L4	< 1:20	86	92

[a] 0.3 mmol of **1a** and 0.45 mmol of **2a** in 1.0 mL of DCE. [b] The ratio was determined by ¹H NMR. [c] Yield of isolated product. [d] The *ee* values were determined by chiral-phase HPLC analysis. [e] 5.0 mol% of [Rh(cod)Cl]₂ and 10.0 mol% of **L4** were used.



selectivity.^[8] When (*R*)-DTBM-BINAP (**L2**) and (*R*)-3,5-*i*-Pr-4-NMe₂-MeObiphep (**L5**) were used, moderate *N* : *O* ratios (2:1 and 3.1:1) and high levels of enantioselectivity (92% and 93% *ee*) were obtained, while (*S*)-DTBM-segphos (**L3**) gave a high *N* vs. *O* ratio (9:1), but a relatively low 78% *ee* (entries 2, 3, and 5). Finally, (*R*)-DTBM-MeObiphep (**L4**) showed the best combination of *N* vs. *O* selectivity (9:1) and enantioselectivity (92% *ee*). When 5.0 mol% of [Rh(cod)Cl]₂ and 10.0 mol% of **L4** were used, only *N*-allylated product **4aa** could be observed in the ¹H NMR spectrum of the crude reaction mixture (entry 6). In all cases, only branched *O* and *N* allylated products can be detected.

With the optimized conditions in hand, we then examined the scope of 2-pyridones (Scheme 3). Halogenated 2-pyridones gave similar *N* vs. *O* ratios, yields, and *ee* values as the model substrate **1a** (**4ab** and **4ac**). 5-Iodopyridone gave 1:1 *N* vs. *O* ratio, perhaps because the active iodo group competes with the *O*-allylated product to react with rhodium complex (**4ad**). Strong electron-withdrawing groups (trifluoromethyl, ester, nitro, aldehyde, and cyano) accelerated the reaction, and a catalyst loading of 2.5 mol% [Rh(cod)Cl]₂ was sufficient in these cases (**4ae–4ah** and **4ai**). A Weinreb amide can also be tolerated in the reaction, which allows for further reactions with organometallic reagents to furnish ketones (**4ai**). Besides 5-substituted 2-pyridones, 4- and 3-chloropyridones reacted smoothly to give the *N*-allylated



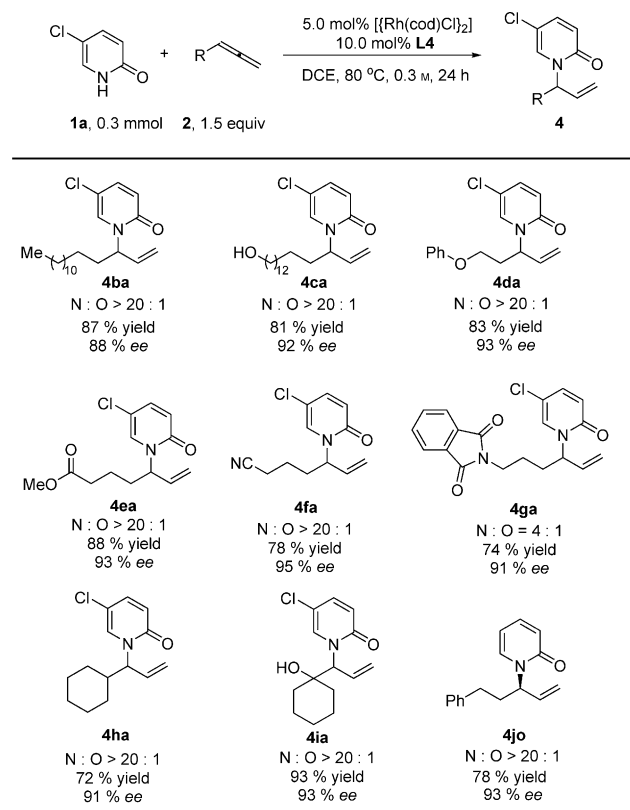
Scheme 3. Scope of 2-pyridones in the rhodium-catalyzed chemo-, regio-, and enantioselective addition of 2-pyridones to allenes.

[a] 5.0 mol% [Rh(cod)Cl]₂ and 10.0 mol% **L4** were used.

[b] 2.5 mol% [Rh(cod)Cl]₂ and 5.0 mol% **L4** were used. [c] 5.0 mol% **L5** was used. [d] The *ee* value was obtained from the corresponding alcohol.

products in high yields and enantioselectivities (**4aj** and **4ak**). However, 6-chloropyridone gave only the *O*-allylated product, presumably for steric reasons.^[9] The reaction is not only limited to electron-withdrawing pyridones. Electron-neutral and electron-donating groups can also be tolerated (**4am** and **4ao**), although 4-benzoxypyridone showed only a moderate conversion (**4an**).

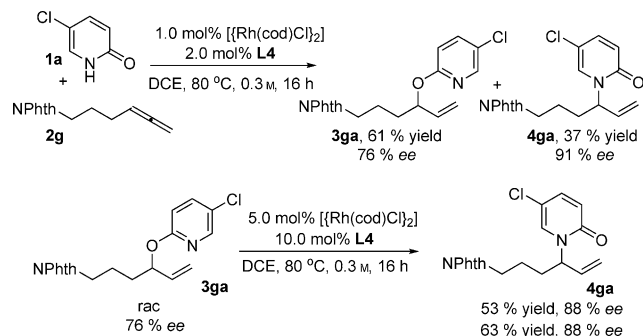
After our investigation of pyridone substrates was complete, we moved on to determine the scope of allene coupling partners (Scheme 4). With 5-chloropyridone as the model substrate, different allenes were tested under the standard condition. A linear *n*-alkyl substituted allene without any functional group worked smoothly to provide the *N* product in high yield but with a slightly diminished enantioselectivity (**4ba**). Different functional groups such as free hydroxy, phenyl ether, ester, cyano, and phthalimide can all be tolerated in this reaction (**4ca–4ga**). The bulky α -branched cyclohexyllallene showed lower reactivity to form the *N*-



Scheme 4. Scope of allenes in the rhodium-catalyzed chemo-, regio-, and enantioselective addition of 2-pyridones to allenes.

allylated product (**4ha**).^[10] To our surprise, an allene equipped with a tertiary alcohol function displayed high reactivity to give the corresponding amino alcohol derivative in excellent yield and enantioselectivity (**4ia**). The absolute configuration of compound **4jo** was assigned to be (*R*) through comparison to known literature examples.^[3] The structure of *N*-allylated (*R*)-**4da** was further confirmed by a single-crystal X-ray diffraction analysis (see the Supporting Information).^[11]

When **1a** and **2g** reacted in the presence of 1.0 mol% $[\text{Rh}(\text{cod})\text{Cl}]_2$ and 2.0 mol% **L4**, along with the expected *N*-allylated product **4ga**, *O*-allylated product **3ga** was isolated in 61 % yield with a 76 % ee as the main product (Scheme 5). Both the racemic and the scalemic 76 % ee **3ga** were subjected to the standard conditions to furnish **4ga** with 88 % ee.^[12]

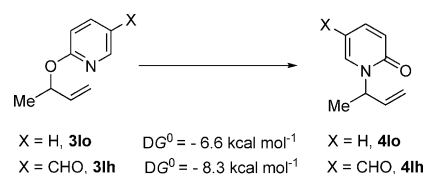


Scheme 5. Conversion of *O*-allylated product into *N*-allylated product.

These results suggest that the *O*-allylated product is the kinetic product and it can be converted into the thermodynamically more stable *N*-allylated product. Furthermore, from **3ga** to **4ga**, it is most likely that an achiral intermediate is produced and the final enantioselectivity of **4ga** is controlled by the chiral catalyst (see below).^[13]

In situ IR spectroscopy was used to gain further insights into the reaction mechanism. Because **L3** showed similar reactivity and is less expensive than **L4**, it was selected as the ligand for these studies. This experiment shows that the *O*-allylated product is formed quickly and is the primary kinetic product. Subsequently, we hypothesize that the kinetic *O*-allylation product is re-introduced to allylic insertion by rhodium and progresses through a common intermediate to give the thermodynamic *N*-alkylated product.^[8]

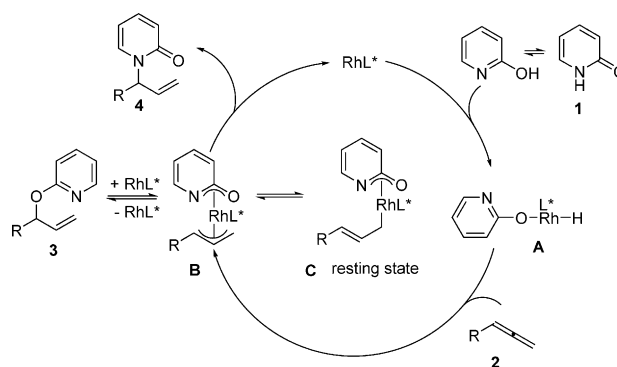
This assumption was confirmed by DFT calculation on the MP2/6-311 + G(2d,p) level (Scheme 6), as the *N*-branched-



Scheme 6. DFT calculation on the stability for *O*- and *N*-allylated 2-pyridones in the gas phase.

allylated pyridone (**4lo**) was 6.6 kcal mol⁻¹ more stable than the corresponding *O*-product (**3lo**).^[6a] An electron-withdrawing group (aldehyde CHO) at the 5-position of the pyridone ring increased the energy difference to 8.3 kcal mol⁻¹ (**3lh** to **4lh**).

On the basis of these observations, the following reaction mechanism is proposed (Scheme 7). The rhodium catalyst

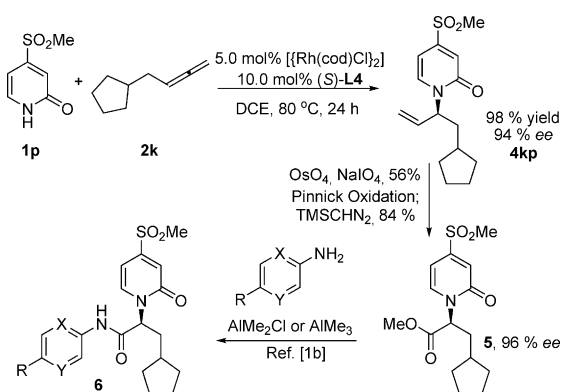


Scheme 7. Proposed mechanism.

reacts with the hydroxypyridine tautomer of **1** to form the intermediate **A**.^[14,15] **A** inserts into allene **2** to give the key allyl rhodium intermediate **B**. Reductive elimination from **B** can either form the *O*-allylated or the *N*-allylated products **3** and **4**, respectively. Our experimental observations suggest that formation of the C–O product **3** is kinetically favored.^[16,17] However, this process becomes reversible

when electron-rich ligands are used. In these cases, **3** can be converted into the thermodynamically more stable **4** by the same intermediate **B**. π -Allyl complex **B** is likely to be in equilibrium with the σ -allyl complex **C**, which might even be the resting state of this catalytic cycle, in agreement with similar observation we have made in the related reaction of alkynes and allenes with carboxylic acids as pronucleophiles.^[13] In **C**, the previous chiral information of the O-allylated product **3** is lost, and once again the chiral catalyst has control of the enantioselectivity en route to the thermodynamic product **4** by way of a dynamic kinetic asymmetric transformation.^[18]

The new pyridone allylation can be applied to the synthesis of the known glucokinase activators **6** (Scheme 8).



Scheme 8. The synthesis of glucokinase activators **6**.

Rhodium-catalyzed selective addition of 2-pyridone **1p** to allene **2k** afforded the key intermediate **4kp** in 98% yield and 94% *ee*. Subsequent oxidation and methylation gave compound **5** with 96% *ee*, which can be converted into compounds **6** by aluminum-mediated amide formation with a variety of aminoheterocycles.^[1b]

In conclusion, we have developed the rhodium-catalyzed direct chemo-, regio- and enantioselective allylation of 2-pyridones with allenes in an atom-economic manner under neutral conditions.^[19] A broad range of 2-pyridones coupled with functionalized allenes to give α -chiral *N*-allylic pyridones. This reaction can be used in the synthesis of biologically active molecules. Further studies will focus on the selective allylation of other ambident nucleophiles.

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- [1] a) P. S. Dragovich, T. J. Prins, R. Zhou, T. O. Johnson, Y. Hua, H. T. Luu, S. K. Sakata, E. L. Brown, F. C. Maldonado, T. Tuntland, C. A. Lee, S. A. Fuhrman, L. S. Zalman, A. K. Patick, D. A. Matthews, E. Y. Wu, M. Guo, B. C. Borer, N. K. Nayyar, T. Moran, L. Chen, P. A. Rejto, P. W. Rose, M. C. Guzman, E. Z. Dovalsantos, S. Lee, K. McGee, M. Mohajeri, A. Liese, J. Tao, M. B. Kosa, B. Liu, M. R. Batugo, J.-P. R. Gleeson, Z. P. Wu, J.

- Liu, J. W. Meador, III, R. A. Ferre, *J. Med. Chem.* **2003**, *46*, 4572–4585; b) J. A. Pfefferkorn, J. Lou, M. L. Minich, K. J. Filipinski, M. He, R. Zhou, S. Ahmed, J. Benbow, A.-G. Perez, M. Tu, J. Litchfield, R. Sharma, K. Metzler, F. Bourbonnais, C. Huang, D. A. Beebe, P. J. Oates, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3247–3252; c) S. O'Connor, P. Somers, *J. Antibiot.* **1985**, *38*, 993–996; d) J. Golec, P. Charifson, J.-D. Charrier, H. Binch, WO01042216, **2001**.
- [2] a) Y.-Q. Yang, M. M. Bio, K. B. Hansen, M. S. Potter, A. Clausen, *J. Am. Chem. Soc.* **2010**, *132*, 15525–15527; b) F. G. Fang, S. J. Danishefsky, *Tetrahedron Lett.* **1989**, *30*, 3621–3624; c) C. A. Martinez, D. R. Yazbeck, J. Tao, *Tetrahedron* **2004**, *60*, 759–764; d) M. L. Minich, I. D. Watson, K. J. Filipinski, J. A. Pfefferkorn, *Tetrahedron Lett.* **2009**, *50*, 2094–2096; e) E. Verissimo, N. Berry, P. Gibbons, M. L. S. Cristiano, P. J. Rosenthal, J. Gut, S. A. Ward, P. M. O'Neill, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4210–4214; f) Y. Yu, C. Zhu, S. Wang, W. Song, Y. Yang, J. Shi, *J. Nat. Prod.* **2013**, *76*, 2226–2233.
- [3] For the only example with two-step asymmetric Overman-type 3,3-rearrangement, see: A. Rodrigues, E. E. Lee, R. A. Batey, *Org. Lett.* **2010**, *12*, 260–263.
- [4] For non-chiral transition-metal-catalyzed rearrangement of 2-allyloxypyridines, see: a) H. F. Stewart, R. P. Seibert, *J. Org. Chem.* **1968**, *33*, 4560–4561; b) G. Balavoine, F. Guibe, *Tetrahedron Lett.* **1979**, *20*, 3949–3952; c) A. C. S. Reddy, B. Narsaiah, R. V. Venkataratnam, *Tetrahedron Lett.* **1996**, *37*, 2829–2832; d) K. Itami, D. Yamazaki, J.-I. Yoshida, *Org. Lett.* **2003**, *5*, 2161–2164.
- [5] a) P. Beak, *Acc. Chem. Res.* **1977**, *10*, 186–192; b) P.-T. Chou, C.-Y. Wei, F.-T. Hung, *J. Phys. Chem. B* **1997**, *101*, 9119–9126.
- [6] a) M. Breugst, H. Mayr, *J. Am. Chem. Soc.* **2010**, *132*, 15380–15389; b) H. Mayr, M. Breugst, A. R. Ofial, *Angew. Chem. Int. Ed.* **2011**, *50*, 6470–6505; *Angew. Chem.* **2011**, *123*, 6598–6634.
- [7] a) A. Lumbroso, P. Koschker, N. R. Vautravers, B. Breit, *J. Am. Chem. Soc.* **2011**, *133*, 2386–2389; b) P. Koschker, A. Lumbroso, B. Breit, *J. Am. Chem. Soc.* **2011**, *133*, 20746–20749; c) M. L. Cooke, K. Xu, B. Breit, *Angew. Chem. Int. Ed.* **2012**, *51*, 10876–10879; *Angew. Chem.* **2012**, *124*, 11034–11037; d) C. Li, B. Breit, *J. Am. Chem. Soc.* **2014**, *136*, 862–865; e) K. Xu, N. Thieme, B. Breit, *Angew. Chem. Int. Ed.* **2014**, *53*, 2162–2165; *Angew. Chem.* **2014**, *126*, 2194–2197; f) K. Xu, N. Thieme, B. Breit, *Angew. Chem. Int. Ed.* **2014**, *53*, 7268–7271; *Angew. Chem.* **2014**, *126*, 7396–7399.
- [8] For details, see the Supporting Information.
- [9] For a related steric effect on rearrangement of 6-substituted alkoxy pyridine, see: a) C. S. Yeung, T. H. H. Hsieh, V. M. Dong, *Chem. Sci.* **2011**, *2*, 544–551; b) S. Pan, N. Ryu, T. Shibata, *Org. Lett.* **2013**, *15*, 1902–1905.
- [10] In Ref. [3], the cyclohexyl group stops the palladium-catalyzed rearrangement for steric reasons. Phenyl allene was tested and it gave low conversion. 1,3-Disubstituted allene gave low conversion, and only O-allyl product was detected.
- [11] For the crystal structure, see the Supporting Information. CCDC 1016609 (**R-4da**) 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.
- [12] Full conversion was obtained. Besides the *N*-allylated product, the elimination products 2-pyridone and 1,3-diene were observed in the ¹H NMR of the crude mixture.
- [13] For the related mechanism study, see: U. Gellrich, A. Meißner, A. Steffani, M. Kähny, H.-J. Drexler, D. Heller, D. A. Plattner, B. Breit, *J. Am. Chem. Soc.* **2014**, *136*, 1097–1104.
- [14] For stoichiometric studies of phenol with transition metal, see: F. T. Ladipo, M. Kooti, J. S. Merola, *Inorg. Chem.* **1993**, *32*, 1681–1688.

- [15] Methyl 2-acetamidoacrylate and *N*-Cbz enecarbamate were tested for amide initiated reactions, but no trace of product was observed.
- [16] For a review on transition-metal-catalyzed addition of O-nucleophiles to allenes, see: M. P. Muñoz, *Org. Biomol. Chem.* **2012**, *10*, 3584–3594.
- [17] A mechanism in which the linear O-allylated product is an intermediate can be ruled out; for details, see the Supporting Information.
- [18] For selected examples of rhodium-catalyzed enantioselective allylic substitutions from racemic substrates, see: a) T. Hayashi, A. Okada, T. Suzuka, M. Kawatsura, *Org. Lett.* **2003**, *5*, 1713–1715; b) J. S. Arnold, H. M. Nguyen, *J. Am. Chem. Soc.* **2012**, *134*, 8380–8383; c) J. S. Arnold, G. T. Cizio, D. R. Heitz, H. M. Nguyen, *Chem. Commun.* **2012**, *48*, 11531–11533; d) J. S. Arnold, E. T. Mwenda, H. M. Nguyen, *Angew. Chem. Int. Ed.* **2014**, *53*, 3688–3692; *Angew. Chem.* **2014**, *126*, 3762–3766.
- [19] For selected examples of asymmetric hydroamination of allenes, see: a) L. M. Lutete, I. Kadota, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 1622–1623; b) N. Nishina, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2006**, *45*, 3314–3317; *Angew. Chem.* **2006**, *118*, 3392–3395; c) R. L. Lalonde, B. D. Sherry, E. J. Kang, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2452–2453; d) Z. Zhang, C. F. Bender, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2007**, *129*, 14148–14149; e) Z. J. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard III, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 13064–13071; f) N. D. Shapiro, V. Rauniyar, G. L. Hamilton, J. Wu, F. D. Toste, *Nature* **2011**, *470*, 245–250; g) K. L. Butler, M. Tragni, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2012**, *51*, 5175–5178; *Angew. Chem.* **2012**, *124*, 5265–5268; h) L. I. Rodríguez, T. Roth, J. L. Fillol, H. Wadepohl, L. H. Gade, *Chem. Eur. J.* **2012**, *18*, 3721–3728; i) C. Michon, F. Medina, M.-A. Abadie, F. Agbossou-Niedercorn, *Organometallics* **2013**, *32*, 5589–5600.