Synthetic Methods

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Regio- and Enantioselective Synthesis of N-Substituted Pyrazoles by Rhodium-Catalyzed Asymmetric Addition to Allenes**

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Abstract: *The rhodium-catalyzed asymmetric N-selective coupling of pyrazole derivatives with terminal allenes gives access to enantioenriched secondary and tertiary allylic pyrazoles, which can be employed for the synthesis of medicinally important targets. The reaction tolerates a large variety of functional groups and labelling experiments gave insights into the reaction mechanism. This new methodology was further applied in a highly efficient synthesis of JAK 1/2 inhibitor (R)-ruxolitinib.*

Nitrogen-containing heterocycles such as chiral N-substituted pyrazoles can be found within the scaffolds of a large variety of biologically active compounds, such as small-molecule pharmaceuticals including ibrutinib (a Bruton's tyrosine kinase inhibiting anticancer agent),[1] ruxolitinib (a JAK 1/2 kinase inhibitor),[2] and MK-0893 (a potent glucagon receptor inhibitor; Figure 1).[3]

The preparation of such chiral pyrazoles either requires multiple steps[4] or is accompanied by the generation of stochiometric amounts of waste,[5] and there are also strong limitations regarding the substrate variability.[6] In this respect we report a rhodium-catalyzed chemo-, regio-, and enantioselective addition of substituted pyrazoles to terminal allenes to furnish secondary and tertiary α-chiral N-allylated pyrazoles.[7]

Our group recently developed the rhodium-catalyzed, atom-economic, and regioselective addition[8] of different pronucleophiles to allenes[9] and alkynes,[10] a method which could be seen as an alternative to the metal-catalyzed allylic substitution[11] and oxidation[12] to generate branched allylic products. Pyrazoles and derivatives exist as a mixture of two tautomers in which the equilibrium between both species is highly dependent upon the substitution pattern of the heterocycle.[13] Along these lines, the outcome of the addition of different pyrazoles to allenes would in theory lead to the formation of two possible regioisomers. We anticipated that there might be an opportunity to control the ratio between the desired N^1 and the undesired N^2 by-product based upon the choice of the phosphine ligand (Scheme 1).

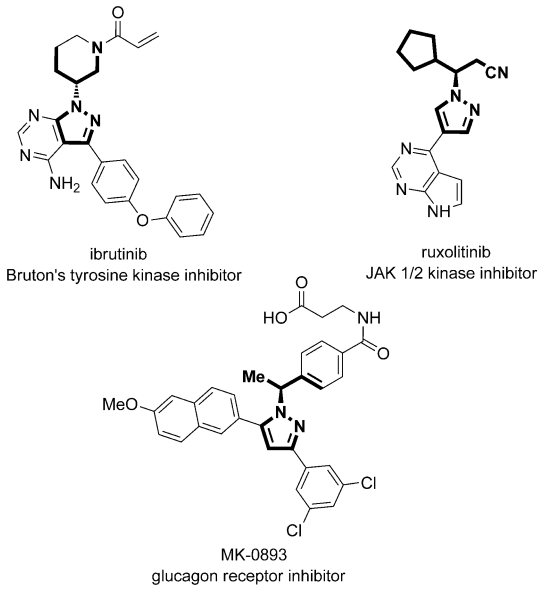
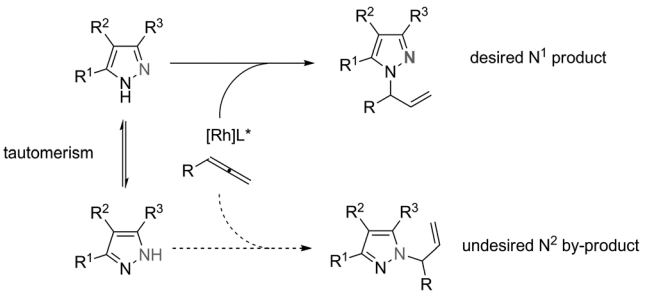


Figure 1. Bioactive compounds possessing an α-chiral pyrazole scaffold.



Scheme 1. Possible differentiation of the two tautomeric pyrazole species by a rhodium catalyst, thus predominantly leading to the desired N^1 product.

Initial reactivity assays were carried out using cyclohexylallene and 4-bromopyrazole in the presence of [{Rh(cod)Cl}$_2$] (2.0 mol%), PPTS (20 mol%), and the nonchiral DPEphos ligand (**L1**; 5.0 mol%) in toluene at 80 °C (Table 1). To our delight we obtained the branched secondary N^1-allylated pyrazole in excellent yield (90%; entry 1). Based on this result the feasibility of 4-bromopyrazole as a promising pronucleophile encouraged us to screen numerous chiral bidentate diphosphine ligands.[14] We were pleased to discover that JoSPOphos (**L2**) led to the desired product in both high

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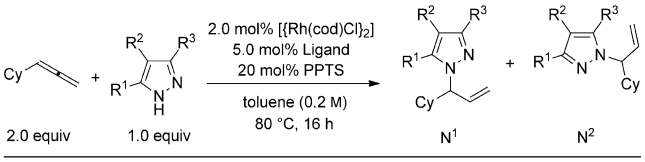
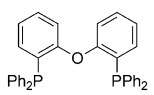
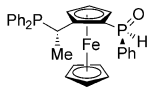
Table 1: Rhodium-catalyzed regio- and enantioselective addition of pyrazole derivatives to cyclohexylallene.[a]





DPEphos, **L1**

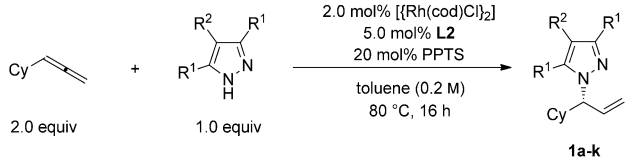


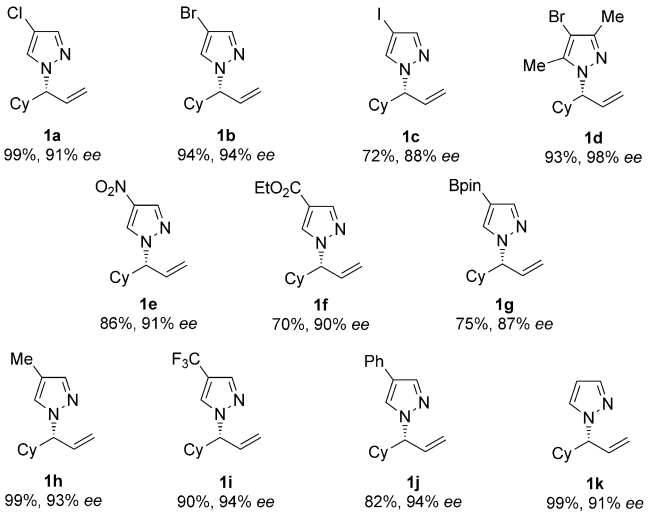
JoSPOphos, **L2**

Entry	R^1, R^2, R^3	Ligand	N^1/N^2[b]	Yield [%][c]	*ee* [%][d]
1	$R^1=R^3=H$, $R^2=Br$	**L1**	–	90	rac.
2	$R^1=R^3=H$, $R^2=Br$	**L2**	–	94	94
3[e]	$R^1=R^3=H$, $R^2=Br$	**L2**	–	70	94
4	$R^1=H$, $R^2=Br$, $R^3=Me$	**L2**	89:11	78 (N^1) 8 (N^2)	88 (N^1) 91 (N^2)
5[f]	$R^1=H$, $R^2=Br$, $R^3=Me$	**L2**	71:29	56 (N^1) 22 (N^2)	87 (N^1) 91 (N^2)

[a] Reaction conditions: cyclohexylallene (1.0 mmol), pyrazole (0.5 mmol), and PPTS (20 mol%) in 2.5 mL of toluene at 80°C, 16 h. [b] Regioselectivity determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of isolated product. [d] The *ee* values were determined by HPLC analysis using a chiral stationary phase. [e] Reaction performed with cyclohexylallene (0.6 mmol, 1.2 equiv), pyrazole (0.5 mmol), PPTS (5 mol%), [{Rh(cod)Cl}$_2$] (0.5 mol%), and **L2** (1.25 mol%) in 2.5 mL of toluene at 80°C, 16 h. [f] Reaction in absence of PPTS. cod = 1,5-cyclooctadiene, Cy = cyclohexyl, PPTS = pyridinium *p*-toluenesulfonate.

Table 2: Scope of the catalytic enantioselective addition of symmetric 4-substituted pyrazole derivatives to cyclohexylallene.[a,b]





[a] Yield of isolated product. [b] The *ee* values were determined by HPLC analysis using a chiral stationary phase. Bpin = pinacolboronate.

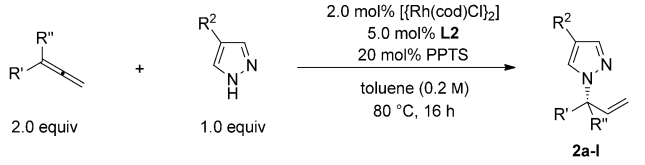
yield (94%) and high enantioselectivity (94% *ee*; entry 2). A catalyst loading of only 0.5 mol% [{Rh(cod)Cl}$_2$] and a lower allene loading (1.2 equiv) led to an acceptable 70% yield and an unchanged *ee* value (entry 3). Further investigations with the unsymmetric 4-bromo-3-methyl-1*H*-pyrazole (entry 4) under optimized reaction conditions furnished the N^1 and N^2 products in a ratio of 89:11; the N^1 product was isolated in 78% yield with 87% *ee* along with the separable minor N^2-allylated by-product. The presence of PPTS plays a significant role in obtaining the desired N^1 product with high regioselectivity (entry 5).

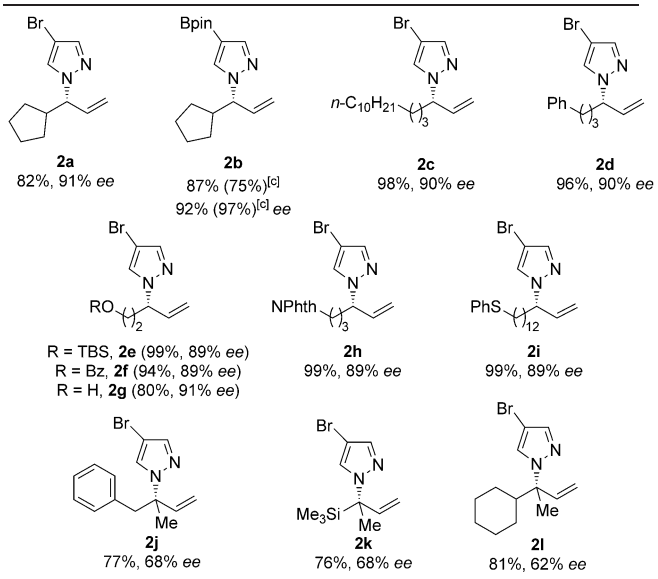
Having the optimal reaction conditions in hand, the scope of this process was studied (Tables 2 and 3). We found a wide range of symmetric substituted pyrazoles to be suitable reaction partners, and they gave the corresponding allylic pyrazoles in good to excellent yields and enantioselectivities (**1a**–**k**; Table 2). Other halogenated 4-pyrazoles, including the iodo-substituted substrate, gave equally high *ee* values (**1c**) and even a trisubstituted halogenated pyrazole reacted to give the desired product in high yield and with an excellent *ee* value of 98% (**1a**,**b** and **1d**). A change of the substitution pattern to electron-withdrawing groups at the 4-position resulted in slightly diminished yields with no detrimental effect on the *ee* values (**1e**,**f**). Even a pinacolboronate was compatible in the reaction (**1g**), and allows further modifications by either transition-metal-catalyzed Suzuki–Miyaura cross-coupling or derivatization to other functional groups.[15] Alkyl, fluoroalkyl, phenyl, and unsubstituted pyrazoles were well tolerated, thus resulting in 82-99% yield and 91-94% *ee* (**1h**–**k**).

Next, we moved on to expand the scope with respect to the terminal allene, including mono- and 1,1-disubstituted allenes, which are readily prepared in one or two steps from either commercial or known starting materials (Table 3).[14] As expected, cyclopentylallene was a suitable coupling partner with different pyrazoles, thus leading to the products **2a** and **2b** in high yields and *ee* values. A single crystallization of the latter product from *n*-heptane increased the *ee* value to 97%, thus demonstrating the utility of this method for the synthesis of essentially enantiopure allylic pyrazole derivatives. Even different linearly substituted allenes led to the desired products in high yields and good enantioselectivities (**2c** and **2d**). Gratifyingly, among different oxygen-functionalized allenes, even an unprotected hydroxy function was well tolerated in the reaction (**2g**). Allenes bearing various other functional groups, such as a phthalimide and a thioether, reacted smoothly with excellent yields and good enantioselectivities (**2h** and **2i**). The 1,1-disubstituted allenes also worked well in terms of yields and enantioselectivities (62–68% *ee*). To the best of our knowledge, these products, representing allylic pyrazoles with a tertiary stereocenter, are not directly accessible by any known pathway (**2j**–**l**).

Based on these results, we further extended the scope to various unsymmetric pyrazoles. To investigate the effects on regio- and enantioselectivity, the substitution pattern of different pyrazole derivatives was varied systematically (Table 4). Structural modification of the model substrate, 4-

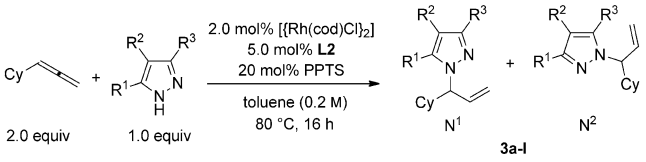
Table 3: Scope of the catalytic enantioselective addition of pyrazoles to substituted terminal allenes.[a,b]

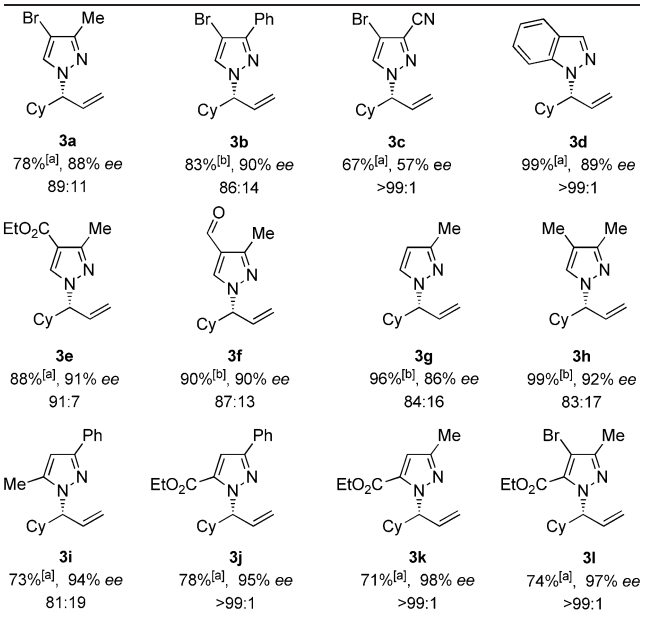




[a] Yield of isolated product. [b] The *ee* values were determined by HPLC analysis using a chiral stationary phase. [c] Value within parentheses is the *ee* value obtained after a single crystallization from *n*-heptane. Bz = benzoyl, TBS = *tert*-butyldimethylsilyl, Phth = phthaloyl.

Table 4: Extended scope of the catalytic enantioselective addition of unsymmetric 3,4- or 3,5-substituted pyrazoles to cyclohexylallene.[a–f]





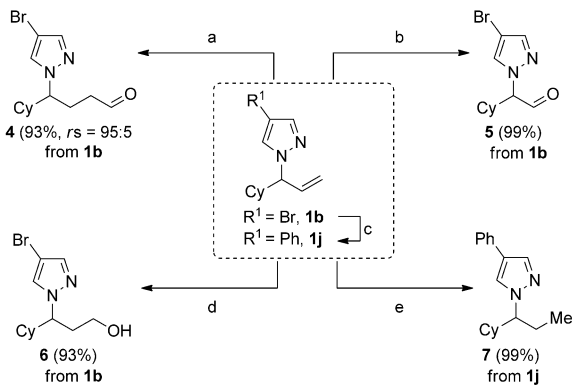
[a] Yield of the isolated N^1 product. [b] Yield of the regioisomeric mixture of N^1 and N^2 products. [c] Regioselectivity determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Assignment of the products as either the N^1 or N^2 product made by using HMBC and NOE experiments. [e] The *ee* values were determined by HPLC analysis using a chiral stationary phase. [f] For the *ee* value of the corresponding N^2 product see the Supporting Information.

bromopyrazole, by changing the carbon scaffold at the 3-position, led to the desired N^1 products in good yields along with good regio- and enantioselectivities (**3a**,**b**). The product **3c** was formed in a regioselective manner, albeit with only moderate yield and *ee* value. To our surprise, even an indazole worked well as a suitable coupling partner in terms of yield (99%) and regioselectivity (>99:1), and furnished **3d** with a high enantiomeric excess of 89% *ee*. Next, we modified the substitution pattern at the 4-position (**3e**–**h**). In terms of yield and N^1 selectivity the electron-poor pyrazoles gave equally high yields as did their electron-rich counterparts, including high regio- and enantioselectivities (**3e**,**f**). Electron-rich pyrazoles also worked well in the reaction and led to the desired N^1 products in excellent yields with high enantiomeric excess, but with a slightly lower regioselectivity (**3g**,**h**). Further modification of the substitution pattern (**3i**–**l**), especially when attaching an electron-withdrawing group to the 5-position (**3j**–**l**), led to N-allylated pyrazoles in good yields along with high regio- and enantioselectivities (up to 98% *ee* and up to 99:1 N^1 selectivity).

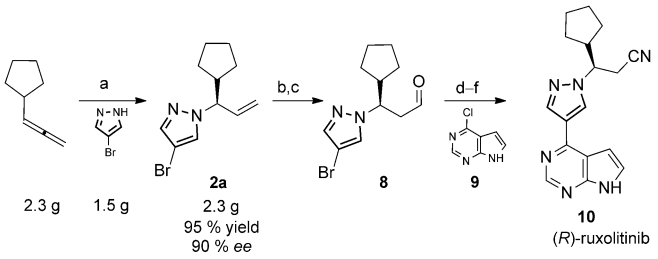
Concerning a possible reaction mechanism, preliminary isotope-labeling experiments were carried out using 4-bromo-[1*D*]-pyrazole under standard rhodium-catalyzed conditions.[14] In accordance with our previous observations, deuterium incorporation was observed at all positions of the alkene.[8a–c]

To explore the synthetic utility of allylated pyrazoles, we subjected **1b** and **1j** to various transformations to get insight into reactivity (Scheme 2). Hydroformylation of the terminal double bond, using our self-assembly ligand 6-diphenylphosphinopyridone (6-DPPon), furnished **4** in high yield (93%) and with an excellent linear/branched selectivity (95:5).[16] C1 cleavage by ozonolysis of **1b** led to **5** in 99% yield.[17a] Furthermore, the double bond was easily modified by other chemoselective transformations (**6** and **7**), thus leaving the pyrazoles untouched.[17b,c] Bifunctional derivatization of the pyrazole moiety gave easy access to the carbon-substituted pyrazole **1j** under Suzuki–Miyaura cross-coupling conditions in high yield.[17d]

Inspired by these synthetic possibilities, this new pyrazole allylation was applied to the synthesis of the JAK 1/2 kinase inhibitor (*R*)-ruxolitinib (**10**; Scheme 3). By using 4-bromopyrazole and cyclopentylallene in the previously described rhodium-catalyzed coupling, **2a** could be synthesized in multigram quantities in a straightforward fashion. Functionalization of the allylic double bond by hydroboration, and subsequent oxidation of the alcohol led to the corresponding aldehyde **8**. The absolute configuration was determined at this



Scheme 2. Various functionalizations of allylated pyrazoles. a) [{Rh(CO)$_2$acac}] (0.5 mol%), 6-DPPon (10 mol%), CO/H_2 (1:1, 20 bar), toluene, 80°C, 21 h, 94% (l/b = 95:5). b) O_3, PPh_3, CH_2Cl_2, −78°C; then RT, 1.5 h, 99%. c) PhB(OH)$_2$, [$PdCl_2(PPh_3)_2$] (5 mol%), K_3PO_4, 1,4-dioxane/H_2O (4:1), 100°C, 18 h, 96%. d) 9-BBN, THF, RT, 2 h; then H_2O_2, NaOH, RT, 2 h, 99%. e) Pd/C (10 mol%), H_2 (1 atm.), MeOH, RT, 18 h, 99%. acac = acetylacetonate, 9-BBN = 9-borabicyclo-[3.3.1]nonane, THF = tetrahydrofuran.



Scheme 3. Gram-scale catalysis and synthesis of (*R*)-ruxolitinib. Reagents and conditions: a) Cyclohexylallene, 4-bromopyrazole, PPTS (20 mol%), [{Rh(cod)Cl}$_2$] (2.0 mol%) and **L2** (5.0 mol%) in toluene (0.2 M) at 80°C, 24 h, 95%, 90% *ee*. b) 9-BBN, THF, RT; then H_2O_2, NaOH, RT, 99%. c) $(COCl)_2$, DMSO, NEt_3, −78°C then RT, 97%. d) NH_4OH, I_2, THF, RT, 90% (79%, 98% *ee* after crystallization from *n*-heptane). e) B_2pin_2, [Pd(dppf)Cl$_2$] (5.0 mol%), KOAc, DMSO, 90°C. f) **9**, [$PdCl_2(PPh_3)_2$] (5.0 mol%), K_2CO_3, 1,4-dioxane/H_2O (2:1), 120°C, 81% (2 steps). DMSO = dimethylsulfoxide, dppf = 1,1′-bis(diphenylphosphino)ferrocene, pin = pinacol.

step by comparison to a literature value.[6e] Subsequent formation of the bromo-substituted nitrile moiety led to a product which could be crystallized from *n*-heptane in 79% yield and an increased *ee* value of 98%. Finally, (*R*)-ruxolitinib (**10**) was obtained after a Suzuki coupling of the generated pinacolboronate with **9** in 81% yield over two steps.[6e]

In summary, we have developed the first highly regio- and enantioselective addition of pyrazoles to terminal allenes in an atom-economic manner by using a rhodium/JoSPOPhos catalyst system. The reaction tolerates a broad range of substituted pyrazoles and allenes, bearing various functional groups, to deliver secondary and tertiary allylated pyrazoles in good to excellent yields along with high regio- and enantioselectivities. We have also demonstrated possible opportunities for derivatization of either the allylic moiety or the pyrazole itself, including the incorporation into a known pyrazole-containing small-molecule pharmaceutical such as (*R*)-ruxolitinib. Further studies on extending this strategic approach to other related nitrogen-containing heterocycles, as well as their application in target-oriented synthesis, are being pursued in our laboratory.

Keywords: allenes · allylic compounds · asymmetric catalysis · heterocycles · rhodium

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Communications

Synthetic Methods

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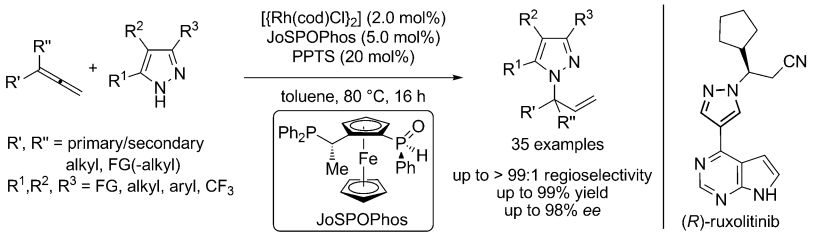
Regio- and Enantioselective Synthesis of N-Substituted Pyrazoles by Rhodium-Catalyzed Asymmetric Addition to Allenes



Add on: The rhodium-catalyzed regio- and enantioselective addition of terminal allenes and functionalized pyrazoles permits the atom-economic synthesis of valuable branched allylic pyrazoles. The synthesis of the small-molecule pharmaceutical (*R*)-ruxolitinib highlights the potential of this method. FG = functional group.

