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Palladium- and Rhodium-Catalyzed Dynamic Kinetic Resolution of Racemic Internal Allenes Towards Chiral Pyrazoles

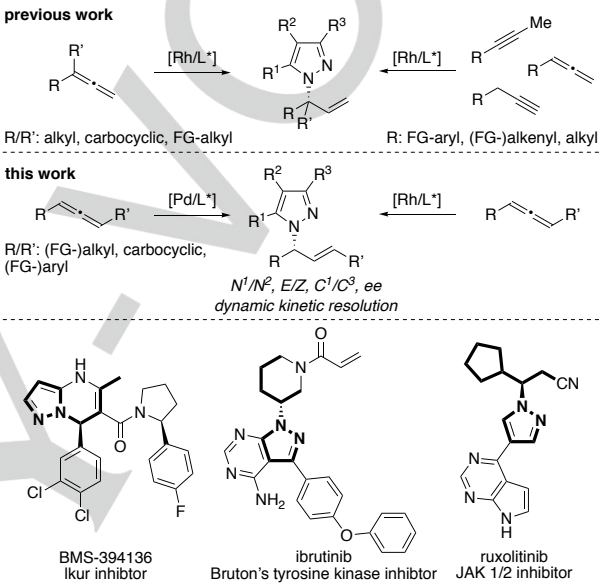
Lukas J. Hilpert, Simon V. Sieger, Alexander M. Haydl and Bernhard Breit*

Abstract: A complementing Pd- and Rh-catalyzed *dynamic kinetic resolution (DKR)* of racemic allenes leading to *N*-allylated pyrazoles is described. Such compounds are of enormous interest in medicinal chemistry as certified drugs and potential drug candidates. The new methods feature high chemo-, regio- and enantioselectivities aside from displaying a broad substrate scope and functional group compatibility. A mechanistic rational accounting for allene racemization and *trans*-alkene selectivity is discussed.

We recently reported a series of addition reactions of O-, N-, S- and C-pronucleophiles to allenes and their isomeric alkynes[1,2] which can be seen as atom economic[3] variants of the Tsuji-Trost allylation[4] and allylic oxidations.[5] In the presence of a suitable chiral rhodium-catalyst these reactions proceed with perfect branched regioselectivity and in many cases with excellent control of enantioselectivity.[6] However, most of these reactions furnish allylic products with a mono-substituted terminal alkene functionality. However, it would be synthetically very attractive to access also disubstituted allylic alkene moieties, which might be accessible upon addition of pronucleophiles to 1,3-disubstituted allenes possessing axial chirality.[7] An ideal asymmetric transformation would start from racemic 1,3-disubstituted allenes and transform them to the corresponding allylation products in a *dynamic kinetic resolution (DKR)*[8,9] process. This would demand a catalyst allowing for fast allene racemization relative to pronucleophile addition as well as a significantly enhanced catalyst activity since 1,3-disubstituted allenes have shown to be significantly less reactive. As particularly attractive pronucleophiles we selected pyrazoles since many α-chiral *N*-alkylated pyrazoles have shown to have impressive medicinal properties such as BMS-394136 (Ikur inhibitor)[10], ibrutinib (Bruton's tyrosine kinase inhibitor)[11] or ruxolitinib (JAK1/2 kinase inhibitor; Scheme 1).[12-14]

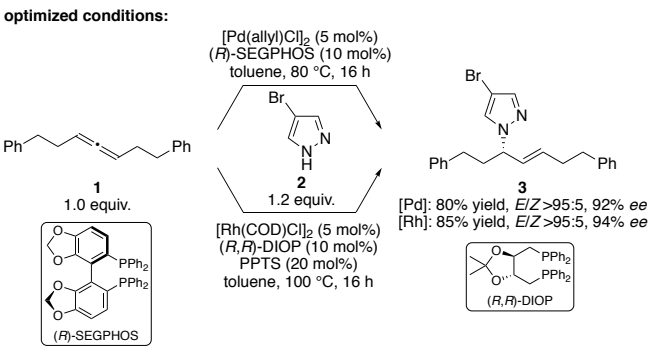
Herein we disclose the development of two catalyst systems based on either palladium or rhodium that permit a dynamic kinetic allylation of functionalized symmetrical and unsymmetrical pyrazoles using racemic 1,3-disubstituted allenes in high chemo-, regio- and stereoselectivity. The two methods complement each other and allow for a very broad substrate scope with wide functional group tolerance.

In initial experiments we selected symmetrical racemic allene **1** and bromo-pyrazole **2** as privileged substrates. Intensive screening of suitable reaction conditions led to the identification of two optimal catalyst systems (Scheme 2): a palladium/SEGPHOS and a rhodium/DIOP system of which all components are readily commercially available.



Scheme 1. Rh- and Pd- catalyzed hydroamination of allylic precursors and bioactive compounds possessing complex α-chiral *N*-allylated pyrazole scaffolds.

In both cases allylation product **3** was obtained in high yield, excellent *E/Z* as well as enantioselectivity.[15]



Scheme 2. Optimized reaction conditions of the Pd- and Rh-catalyzed hydroamination of 1,3-disubstituted allenes. (Additional) reaction conditions: Scale: 0.25 mmol; 1.25 mL of toluene (0.2 M). Reported yields are isolated yields. The *ee* values were determined by chiral HPLC. PPTS = pyridinium *p*-tolouenesulfonate. Gram-scale catalysis (4.03 mmol): [Pd]: 81% yield, *E/Z* >95:5, 92% *ee*; [Rh]: 84% yield, *E/Z* >95:5, 93% *ee*.

With the optimal reaction conditions in hand, first the substrate scope of the palladium system was studied. We

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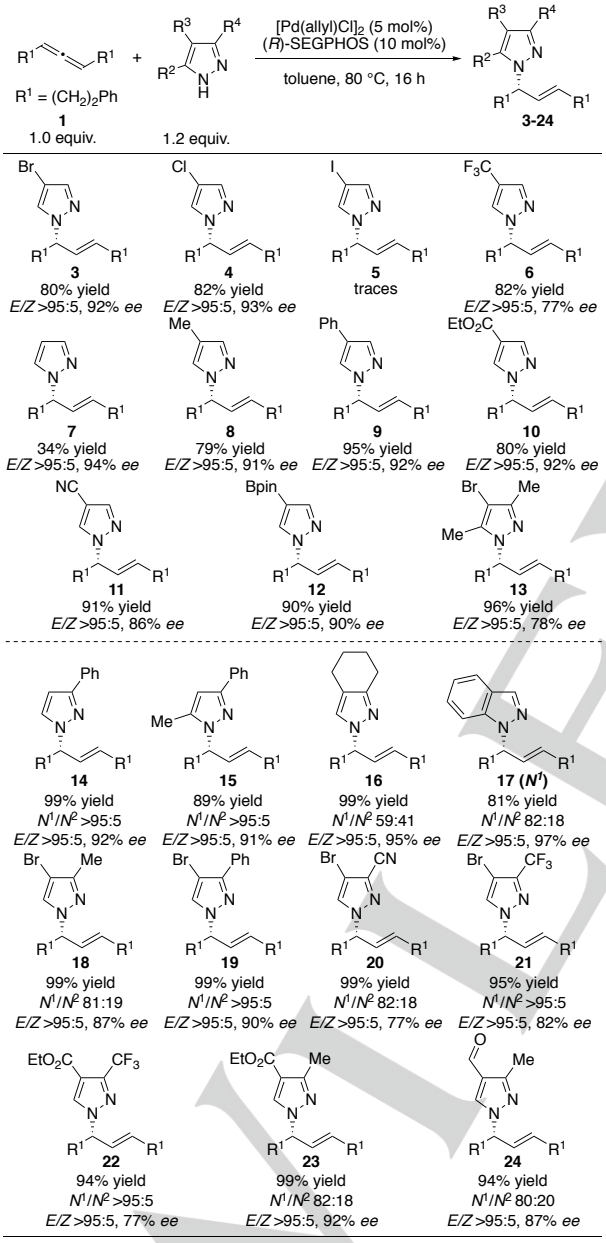
identified a broad range of differently substituted pyrazoles (Table 1) and different symmetrical and unsymmetrical internal allenes (Table 2) as suitable coupling partners. Several functional groups were tolerated such as halogens (**3**-**6**), esters (**10, 22-23**), nitriles (**11, 20**) and pinacolboranes (**12**), which in turn allow further modifications by Suzuki-Miyaura cross-coupling reactions.[16]

Table 1. Scope of the Pd-catalyzed hydroamination of 1,7-diphenyl-hepta-3,4-diene (**1**) with different symmetric and unsymmetrical pyrazoles.[a-e]

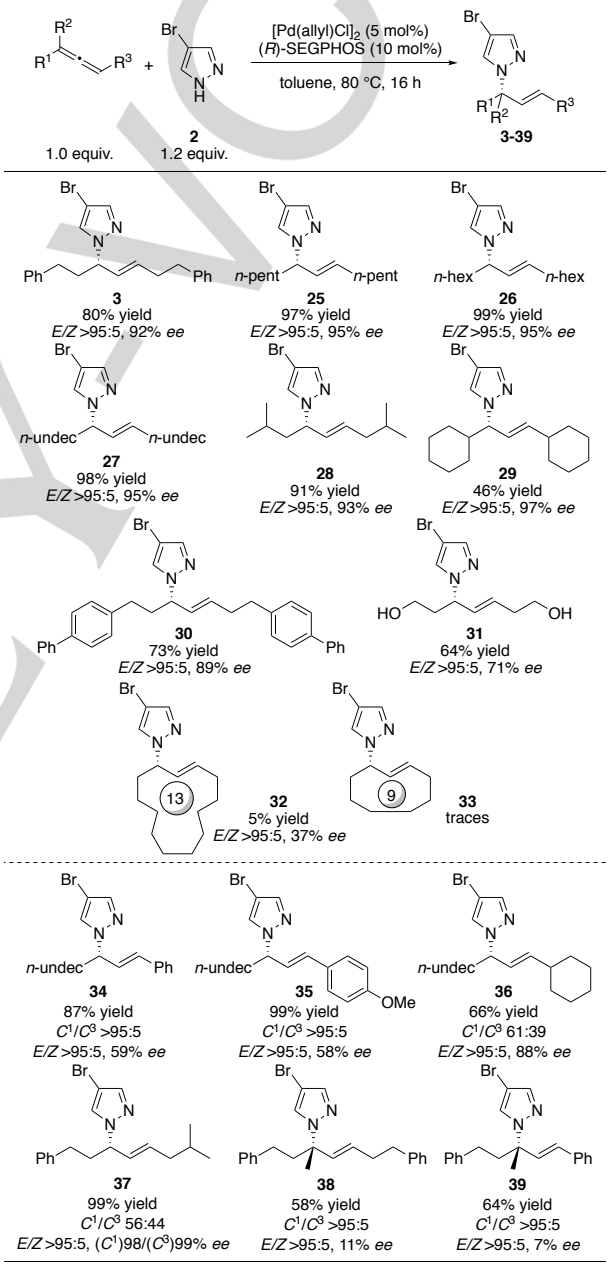


[a] Reported yields are isolated and combined yields. [b] *E*/*Z*-ratio was determined by ^{1}H-NMR analysis oft the crude reaction mixture. [c] Enantiomeric excess was determined by chiral HPLC. [d] Assignment of N^1- or N^2-product by HMBC or NOE experiments. [e] For determination of absolute configuration see supporting information.

Not surprisingly, 4-iodopyrazole (**5**) did only form in trace amounts due to side reactions caused by oxidative addition of the palladium catalyst. However, in most cases the desired products were obtained in excellent yields, *E*-selectivities and enantiomeric excesses.

Furthermore, the coupling of unsymmetrically substituted pyrazoles was studied. Alongside consistent and excellent selectivities and yields we obtained N^1/N^2-ratios of up to >95:5 for several products.

Table 2. Scope of the Pd-catalyzed hydroamination of different symmetric and unsymmetrical internal allenes with 4-bromopyrazole (**2**).[a-e]



[a] Reported yields are isolated and combined yields. [b] *E*/*Z*-ratio was determined by ^{1}H-NMR analysis oft the crude reaction mixture. [c] Enantiomeric excess was determined by chiral HPLC. [d] Assignment of C^1- or C^3-product by HMBC or NOE experiments. [e] For determination of absolute configuration see supporting information.

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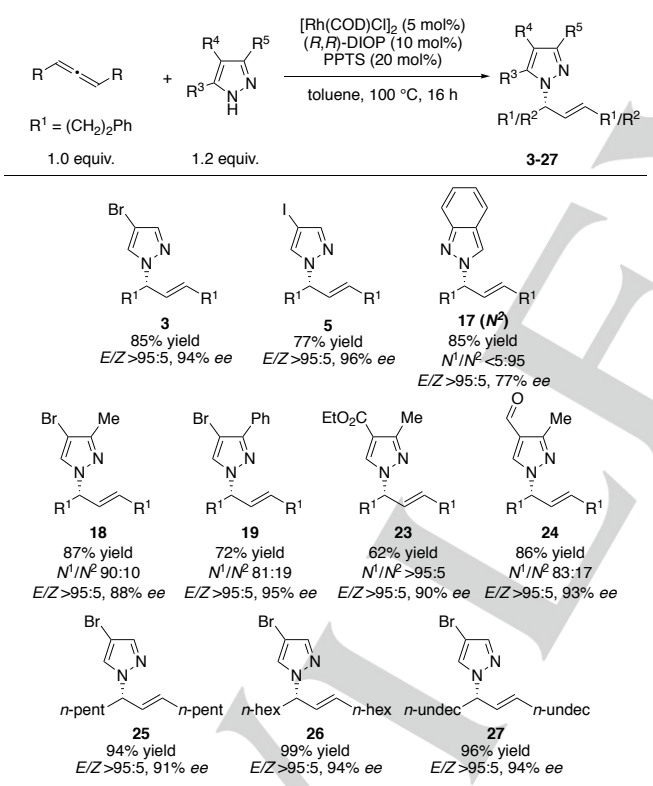
This might be the result of sterical control since coupling occurred generally at the sterically least hindered *N*-atom (=N^1). However, indazole (**17**) was an exception. Here coupling occurred such that the more stable aromatic allylation product was obtained.[17] Furthermore, an unprotected aldehyde function was well compatible with the reaction conditions (**24**). Moreover, several symmetrical dialkyl-substituted allenes proved to be decent reaction partners (Table 2, **25**-**28**). However, increasing steric demand of the alkyl substituents (**29**) led to decreased yields while enantioselectivity maintained a high level. Even an unprotected diol substrate was tolerated (**31**).

A limitation is represented by carbocyclic allenic substrates which gave only trace amounts of coupling products (**32**, **33**), presumably owing to the difficulty of installation of an *E*-alkene function in carbocyclic structure. For unsymmetrically, alkyl-aryl substituted allenes very good C^1/C^3-regioselectivities were obtained (**34**, **35**) but coupling occurred in lower enantioselectivities. For unsymmetrical, dialkyl-substituted allenes the C^1/C^3-regioselectivity was rather low (**36**), however, in this case good to excellent enantioselectivities were observed.

Table 3. Scope of the Rh-catalyzed hydroamination of different symmetric internal allenes with different symmetric and unsymmetrical pyrazoles.[a-f]

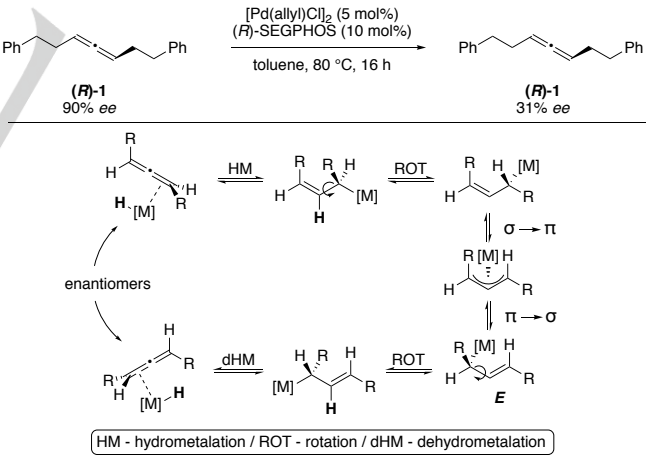


[a] Reported yields are isolated and combined yields. [b] *E*/*Z*-ratio was determined by ^{1}H-NMR analysis oft the crude reaction mixture. [c] Enantiomeric excess was determined by chiral HPLC. [d] Assignment of N^1- or N^2-product by HMBC or NOE experiments. [e] Assignment of C^1- or C^3-product by HMBC or NOE experiments. [f] For determination of absolute configuration see supporting information.

Also two trisubstituted allenes were tested: Surprisingly, coupling occurred on the more substituted allene termini in both cases, furnishing allylation products **37** and **38** in excellent C^1/C^3-regioselectivities and *E*/*Z*-selectivities. However, the associated enantioselectivities were low.

Concomitantly, the scope for the rhodium-catalyzed hydroamination was explored (Table 3). Gratifyingly, the rhodium-catalyst allowed to access iodide derivative **5**, for which the palladium catalyst had failed. For several allylation products even higher yields, regio- and enantioselectivities were observed compared to the palladium catalysis. Interestingly, reversed N^1/N^2-selectivity was found upon addition of indazole (**17**). In this case the sterically less hindered but less aromatic allylation product **17 (N^2)** was formed in high selectivity.

To gain preliminary insights into the underlying reaction mechanism the enantioenriched allene **(*R*)-1** was prepared. By applying the Pd-catalysis conditions a significant erosion of the enantiomeric purity of **1** was observed, indicative of a racemization process (Scheme 3). However, in case of applying the corresponding Rh-catalysis conditions, only allene decomposition was observed,[18] which however, does exclude a racemization prior to nucleophile addition.[19] Such an allene racemization was observed by us previously applying a related rhodium-catalyst system.[20] A plausible reaction mechanism to explain allene isomerization as well as the preferred *E*-alkene formation is depicted in Scheme 3.[21-27] In this respect, hydrometalation of the allene followed by bond rotation, σ–π–σ isomerization and additional bond rotation leads to a σ-allyl complex possessing an *E*-alkene geometry. From here dehydrometalation (β-H-elimination) furnishes the enantiomeric allene complex. Alternatively, a reductive elimination of the metal-coordinated pyrazole ligand would furnish the observed *E*-allylic products.



Scheme 3. Racemization experiment of enantioenriched **(*R*)-1** and proposed isomerization of 1,3-disubstituted allenes. (Additional) reaction conditions: Scale: 0.25 mmol; 1.25 mL of toluene (0.2 M). The *ee* values were determined by chiral HPLC.

To conclude, we accomplished a complementing Pd- and Rh-catalyzed *DKR* of racemic internal allenes through hydroamination with pyrazoles furnishing chiral *N*-allyl pyrazoles in a completely atom economic fashion and with highest selectivities. The reactions tolerate a broad variety of functional groups such as halogens, esters, aldehydes, nitriles,

pinacolboranes and free alcohols. The obtained products could find use as important building blocks for the synthesis of small-molecule pharmaceuticals containing pyrazoles.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Dynamic Kinetic Resolution • Palladium • Rhodium • Pyrazole • Internal Allene • Asymmetric Catalysis

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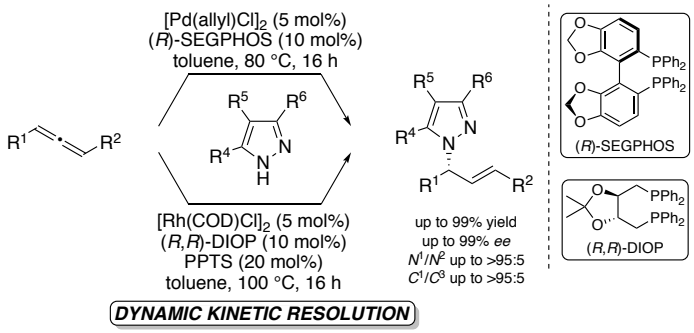

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