



Communication Rhodium-Catalyzed Dynamic Kinetic Resolution of Racemic Internal Allenes towards Chiral Allylated Triazoles and Tetrazoles

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Abstract: A general Rh-catalyzed addition reaction of nitrogen containing heterocycles to internal allenes is reported. Starting from racemic internal allenes a dynamic kinetic resolution (DKR) provides *N*-allylated triazoles and tetrazoles. Simultaneous control of N^1/N^x -position selectivity, enantioselectivity and olefin geometry gives access to important building blocks of target-oriented synthesis. The synthetic utility is demonstrated by a gram-scale reaction and a broad substrate scope tolerating multiple functional groups. Deuterium labeling experiments and experiments with enantioenriched allenes as starting material support a plausible reaction mechanism.

Keywords: asymmetric catalysis; dynamic kinetic resolution; internal allenes; rhodium; hydroamination



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1. Introduction

5-membered nitrogen containing heterocycles are found in a variety of bioactive compounds. Molecules containing triazoles exhibit antifungal [1], anxiolytic [2], antibacterial [3], and anticancerogenic [4] activity. Tetrazoles display antifungal [5], immuno-suppressive [6], and antiviral [7] properties. In addition, the isosterism of tetrazoles to carboxylic acids makes them a suitable motif in drug design [8]. In particular, the subclass of α -chiral *N*-alkylated triazoles and tetrazoles features a broad range of biological activity (Figure 1) [5,9–12].



Figure 1. Bioactive compounds possessing an α -chiral triazole or tetrazole scaffold [5,9–11].

Due to the importance of these moieties, different strategies for obtaining them have been developed in the past (Scheme 1). Zhao and coworkers published the transition metal catalyzed allylic substitution with sodium benzotriazolide [13,14]. Despite the excellent enantioselectivities in some cases, the method lacks regioselectivity and requires deprotonation of the triazole in a previous step. Khan recently reported the allylic substitution of cyclic carbonates with tetrazoles [15]. However, allylic substitutions in general are not in accordance with the principle of atom economy by releasing stoichiometric amounts of waste [16]. A series of organocatalyzed aza-Michael additions overcomes this shortcoming and in some cases convinces with high selectivities, but the scope of these transformations is limited [17–22]. Furthermore, a three-component reaction of tetrazoles, aldehydes, and acid anhydrides should be mentioned, which uses a Dynamic Kinetic Resolution to synthesize α -chiral tetrazoles as hemiaminals [23,24].

Allylic substitution of carbonates Zhao (2011)



Organocatalyzed aza-Michael reaction



Dynamic Kinetic Resolution of Azole Heminaminals



Scheme 1. Selected methods for the synthesis of α -chiral triazoles and tetrazoles [13–24].

In the last decade, our group developed the transition metal-catalyzed addition of a variety of pronucleophiles to allenes and alkynes [25,26]. C- [27–29], N- [30–32], O- [33–35], and *S*-pronucleophiles [36,37] can thus be allylated enantioselectively, which creates an atom economic analogon to the Tsuji-Trost allylation [38–45] and allylic oxidations [46–48]. Furthermore, the synthetic utility of these reactions has already been demonstrated in several total syntheses [49–51]. We recently reported on the rhodium-catalyzed addition of pyrazoles to internal allenes [52]. Due to the importance of triazoles and tetrazoles, we also wanted to extend the Rh-catalysis for these heterocycles. Hence an optimized catalytic protocol for the synthesis of such frameworks is presented using a DKR, a powerful and important method in asymmetric catalysis and synthesis [53–57].

2. Results and Discussion

Coupling benzotriazole (2) with our screening allene, **1**, resulted in 96% yield and perfect enantio-, regio-, and E/Z-selectivity by using $[Rh(COD)Cl]_2$, (R,R)-DIOP, and 50 mol% of PPTS at 60 °C. Phenyltetrazole (4) was coupled at 40 °C and with 20 mol% PPTS with ideal regio- and Z/E-selectivity and good enantiomeric excess (Scheme 2) (For optimization and screening tables, see the Supporting Information).



Scheme 2. Optimized reaction conditions of the Rh-catalyzed hydroamination of racemic 1,3disubstituted allenes. Scale: 0.25 mmol; 1.25 mL of toluene (0.2 M). Yields reported for isolated products. Enantioselectivities were determined by HPLC analysis using a chiral stationary phase. COD = cyclooctadien, PPTS = pyridinium *p*-toluenesulfonate. Gram-scale catalysis (4.03 mmol allene): benzotriazole: 96% yield, N^1/N^2 96:4, E/Z > 95:5, 95% *ee*; phenyltetrazole: 84% yield, Z/E > 95:5, 85% *ee*. For determination of absolute configuration, see the Supporting Information.

After identifying optimized reaction conditions, the broad applicability is demonstrated by several scopes. Initially we subjected a variety of triazoles to the screening allene **1** (Figure 2).



Figure 2. Scope of the addition of Triazoles to rac-1,7-diphenyl-hepta-3,4-diene (1). Reactions were performed at 0.25 mmol scale. Cumulative yield for all isolated isomers. E/Z-selectivities determined by ¹H-NMR. Enantioselectivities were determined by HPLC analysis using a chiral stationary phase. Unless specified, *ee*-values refer to main-stereoisomer of the main-regioisomer. Shown regioisomer is designated as an N^1 -product.

The benzotriazol-derived substrates (6–12) showed up to 96% yield and enantioselectivities up to 97% *ee*. While N^1/N^2 -selectivity was consistently greater than 91:9 for symmetrically substituted triazoles (**3**, 6–8, **13**, **14**), asymmetric substrates added the challenge of N^1/N^3 -regioselectivity. 5-substituted benzotriazoles (**10–12**) provided the corresponding products in an almost statistical N^1/N^3 -distribution. Placing the methylgroup in 4- position (**9**) and thus closer to the reactive site increased N^1/N^3 -selectivity to 4:1. Notably, there was a decrease of E/Z-selectivity for heterosubstituted benzotriazoles (**8**, **11**, **12**), whereas a nearly perfect *E*-selectivity was present in all other cases. The nitrosubstituted benzotriazole (**12**) even led to an inversed olefine geometry, with the *Z*-product being preferred.

We subsequently tested several allenes for compatibility in the reaction with benzotriazole **2** (Figure 3). Dialkyl substituted allenes (**16–18**) yielded perfect regioselectivity and enantiomeric excess of up to 98% *ee*. Even a sterically more demanding (**19**) and a macrocyclic allene (**20**) were tolerated as well. The method has its limitations for sterically very demanding and aryl-substituted allenes (**21**, **22**), as well as for a trisubstituted allene (**23**). For these substrates, yield and selectivity decreased. Next, we subjected several tetrazoles to the corresponding reaction conditions (Figure 4).



Figure 3. Scope of the addition of Benzotriazole (**2**) to different racemic allenes. Reactions were performed at 0.25 mmol scale. Cumulative yield for all isolated isomers. *E*/*Z*-selectivities determined by ¹H-NMR. Enantioselectivities were determined by HPLC analysis using a chiral stationary phase. Unless specified, *ee*-values refer to main-stereoisomer of the main-regioisomer. [a] Reaction was heated for 72 h.



Figure 4. Scope of the addition of Tetrazoles to rac-1,7-diphenyl-hepta-3,4-diene. (1) Reactions were performed at 0.25 mmol scale. Cumulative yield for all isolated isomers. *Z/E*-selectivities were determined by ¹H-NMR. Enantioselectivities were determined by HPLC analysis using a chiral stationary phase. Unless specified, *ee*-values refer to main-stereoisomer of the main-regioisomer. Unless specified full N^2 -selectivity was obtained. [a] Reaction was performed at 60 °C.

Halogen-substituted phenyltetrazoles were coupled in nearly quantitative yields (25–27). Tetrazoles containing thioethers (31, 32) were the only ones to yield products with reduced N^2/N^1 -regioselectivity (about 3:1); however, maintaining quantitative yield and consistently high Z/E- and enantioselectivity. Eventually, we subjected several allenes to the reaction with 5-phenyl-tetrazole (4) (Figure 5).



Figure 5. Scope of the addition of 5-phenyl-2H-tetrazole to different racemic allenes. Reactions were performed at 0.25 mmol scale. Cumulative yield for all isolated isomers. *E*/*Z*-selectivities determined by ¹H-NMR. Enantioselectivities were determined by HPLC analysis using a chiral stationary phase. Unless specified, *ee*-values refer to main-stereoisomer of the main-regioisomer. Unless specified full N^2 -selectivity was obtained.

Except for one sterically more challenging substrate (**38**), all products were obtained in perfect Z-selectivity. Only the di-cyclohexyl substituted substrate (**38**) showed shares of the *E*-product, indicating the limitation of the catalyst controlling the olefin geometry for sterically more demanding allenes. Some mechanistic control experiments were carried out (Scheme 3).



Scheme 3. Control experiments: Without PPTS, only the allene could be reisolated. After reactions with deuterated pronucleophiles, the deuterium was observed exclusively at the former central atom of the allene.

If the catalysis was performed without PPTS, no reaction occurred, revealing the important role of the additive for the reaction. Furthermore, we prepared deuterated nucleophiles, which we subjected to the respective catalysis conditions. The deuterium atoms were found exclusively at the former central atom of the allene. This is in contrast to earlier results with terminal allenes, where deuterium was found at several positions [58–60]. Using enantiomerically enriched allenes in the catalysis, both enantiomers of allene yielded the (S)-product for the triazole and the (R)-product for the tetrazole regardless of the configuration of the allene used (Table 1).

When the achiral dppb ligand was used instead of the chiral DIOP ligand in the reactions with enantiomerically enriched allene, the racemic products were obtained, indicating a racemization step in the catalytic cycle. These findings lead us to propose the following reaction mechanism (Scheme 4).

A Rh^I-DIOP complex is first formed from [Rh(COD)Cl]₂ and (*R*,*R*)-DIOP (inner box of Scheme 4). With the help of PPTS, the pronucleophile is then added by oxidative addition to form the Rh-hydride species **A**. Now, *syn*-hydrometallation from the sterically less demanding side occurs at the respective allene enantiomers. This occurs in such a way that the hydrogen atom results at the former central atom of the allene. Initially, two diastereomeric *Z*-configured σ -complexes **B** and *dia*-**B** are formed, which are in equilibrium with their corresponding *syn*, *anti*-configured π -complexes **C** and *dia*-**C**. Finally, a σ - π - σ -isomerization and a bond rotation lead to the identical pseudo-*meso*- π -allyl complex **D** for both diastereomers. Dynamic kinetic resolution is ensured via this *syn*, *syn*-configured π -complex, since the initial hydrometallation products **B** and *dia*-**B** can be converted into each other via **D**. If a triazole is the pronucleophile in the catalysis, reductive elimination occurs of pseudo-

meso- π -allyl complex **D**, with the chiral ligand ensuring enantioselectivity. In contrast, when a tetrazole is used as a pronucleophile, reductive elimination preferentially occurs from *syn-anti-* π -complex **C**. This could explain why the (*S*)-*E* product is formed for the triazole and the (*R*)-*Z* product for the tetrazole.



Table 1. Control experiments with enantioenriched allene.

Control experiments with enantiomerically enriched allenes led to the products with the same absolute configuration for (R,R)-DIOP or to the racemic products for the achiral dppb ligand.



Scheme 4. Proposed reaction mechanism of Rh-catalyzed hydroamination of internal allenes with triazoles and tetrazoles. R.E. = Reductive elimination.

3. Materials and Methods

3.1. Materials

Toluene was freshly distilled over Sodium/Benzophenone and degassed with argon prior to use. Solvents employed for work-up and column chromatography were purchased in technical grade quality and distilled by rotary evaporator before use. $[Rh(COD)Cl]_2$ was purchased from Sigma-Aldrich (St. Louis, MO, USA). (*R*,*R*)-DIOP was prepared according to the procedure shown in the Supplementary Materials.

3.2. Methods

A 20 mL screw-cap Schlenk tube was dried under a vacuum, backfilled with argon (Argon 5.0 Sauerstoffwerke Friedrichshafen, Friedrichshafen, Germany), and cooled to room temperature using a standard Schlenk line apparatus. The tube was filled with [Rh(COD)Cl]₂ (6.2 mg, 0.013 mmol, 5.0 mol%), (R,R)-DIOP (12.5 mg, 0.025 mmol, 10.0 mol%), PPTS (31.5 mg, 0.125 mmol, 50.0 mol% or 12.6 mg, 0.05 mmol, 20.0 mol%), and triazole (0.500 mmol, 2.0 equiv.) or tetrazole (0.30 mmol, 1.2 equiv.). The tube was put on a vacuum and backfilled with argon again. Freshly distilled toluene (1.25 mL) and allene (0.25 mmol, 1.0 equiv.) were added by syringe under a flow of argon, and then the tube was sealed by a screw cap. The mixture was stirred at 60 °C (for triazoles) or 40 °C (for tetrazoles) for 16 h. The tube was cooled to room temperature, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography using AcOEt and hexanes as eluent on silica gel. In the case of the synthesis of racemic samples dppb was used as the catalyst.

4. Conclusions

To conclude, we developed a highly selective Rh-catalysis to add triazoles and tetrazoles to internal allenes. In only one step, allylated triazoles and tetrazoles were constructed in an enantio-, stereo-, and regioselective fashion. Mechanistic studies with deuterated pronucleophiles and enantioenriched substrates led us to propose a DKR mechanism. Further investigations in terms of compatible pronucleophiles that can be subjected to this catalytic system is the goal of future research in our laboratories.

Supplementary Materials: The following supporting information can be downloaded at: https: //www.mdpi.com/article/10.3390/catal12101209/s1, screening tables, preparation of ligand and substrates, analytical data, ¹H and ¹³C NMR spectra, determination of absolute configuration, HPLC chromatograms of products and enantioenriched allenes, more detailed materials and methods [61–66].

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