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Chemo-, Regio-, and Enantioselective Rhodium-Catalyzed Allylation of Triazoles with Internal Alkynes and Terminal Allenes

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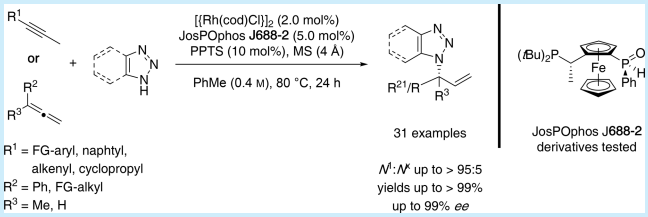
Supporting Information

ABSTRACT: The rhodium-catalyzed asymmetric N^1-selective and regioselective coupling of triazole derivatives with internal alkynes and terminal allenes gives access to secondary and tertiary allylic triazoles in very good enantioselectivities. For this process, three new members of the JosPOphos ligand family have been prepared and employed in catalysis. The optimized reaction conditions enable the coupling of triazoles with internal alkynes as well as with allenes, displaying a high tolerance for functional groups. A gram scale reaction provided N^1-allyltriazole, which was subjected to various transformations highlighting synthetic utility.



Since chiral *N*-substituted triazoles possess broad ranges of biological activities, such as antifungal,[1a] anxiolytic,[1b] antibacterial,[1c] and analgesic properties[1d] (Figure 1), the development of new catalytic methods for their regio- and stereoselective synthesis is in high demand in synthetic organic chemistry.

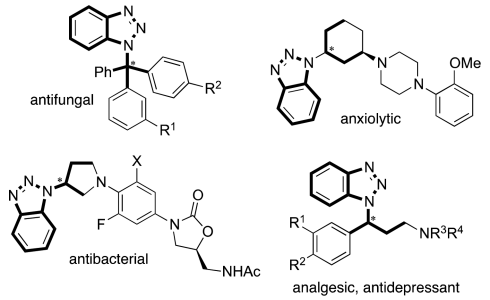
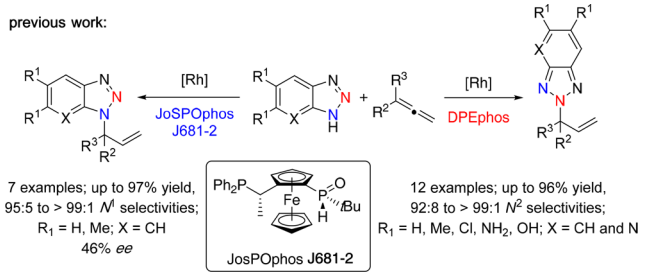


Figure 1. Bioactive compounds possessing an α-chiral benzotriazole scaffold.

The synthesis of such *N*-alkylated chiral triazoles in combination with the desired *N*-selectivity is troublesome since the energy difference between the N^1 and N^2 tautomers in solution is small.[2] Thus, only a limited number of synthetic methods exist, which mostly suffer from a lack of selectivity. *N*-Alkylated chiral triazoles are usually prepared by either nucleophilic substitution of chiral secondary alcohols,[3a] allylic substitution,[3b−d] or organocatalytic Michael addition.[3e−g]

We recently reported on the rhodium-catalyzed and highly regioselective addition of different pronucleophiles to allenes and alkynes,[4] a method that can be viewed as an atom-economic alternative to transition-metal-catalyzed allylic substitution[5] and oxidation[6] to generate branched allylic products. Among these, we described N^1- and N^2-selective rhodium-catalyzed additions of benzotriazoles to aliphatic terminal allenes (Scheme 1) depending on the rhodium catalyst employed.[7,8]

Scheme 1. Previously Reported Regioselective and Regiodivergent Addition of Benzotriazole to Aliphatic Allenes



Given the pharmacological importance of chiral N^1-alkylated triazoles, we decided to develop a related asymmetric catalytic variant. We anticipated that by the choice of an appropriate JosPOphos ligand there might be an opportunity to control enantioselectivity upon N^1-selective addition of triazoles to internal alkynes and terminal allenes.

We herein report on the rhodium-catalyzed regio- and enantioselective addition of triazoles to internal alkynes and terminal allenes providing access to secondary α-chiral N^1-allylated triazoles.

For initial reactivity studies, derivatives of the JosPOphos ligand family were required. These were prepared by a two-step synthesis starting from Ugi's amine (*S*)-(**1**) (Scheme 2). First,

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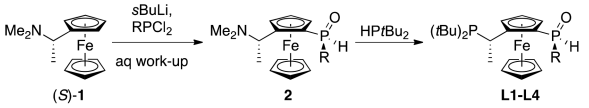
Scheme 2. Synthesis of JosPOphos Ligand SL-J688-2 and Its Derivatives



L1 = SL-J688-2: R = Ph, 62%, *dr* > 2.3:1; after recrystallisation: 41%, *dr* > 95:5;

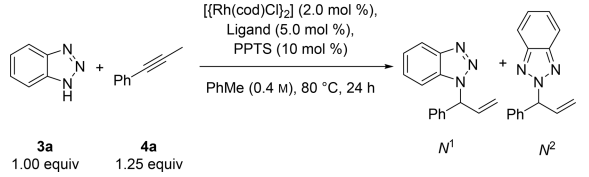
L2: R = 3,5-DiMe-Ph, 20%, *dr* = 5.6:1; **L3**: R = 4-MeO-Ph, 42%, *dr* = 4.8:1;

L4: R = 4-CF_3-Ph, 40%, *dr* = 1.3:1

the secondary phosphine oxide was installed by a directed *ortho*-lithiation followed by trapping with a dichlorophosphine, and subsequent hydrolysis of the remaining P−Cl bond. The NMe_2 moiety was substituted by heating in acetic acid with the corresponding di-*tert*-butylphosphine yielding the desired ligands with retention of configuration due to neighboring group participation of the ferrocene unit.[9] All ligands were isolated as diastereomeric mixtures by virtue of the configuration of the secondary phosphine oxide. For SL-J688-2 (**L1**) a recrystallization was carried out to obtain the main diastereomer in pure form.

With the desired ligands in hand initial reactivity assays were carried out using benzotriazole (**3a**) and 1-phenyl-1-propyne (**4a**) in the presence of [{Rh(cod)Cl}$_2$] (2.0 mol %), PPTS (10 mol %), and the respective chiral ligands (5.0 mol %) in toluene at 80 °C (Table 1). To our delight, we obtained the branched

Table 1. Ligand Screening for Regio- and Enantioselective *N*-Allylation of Benzotriazole (3a) with 1-Phenyl-1-propyne (4a)[a]



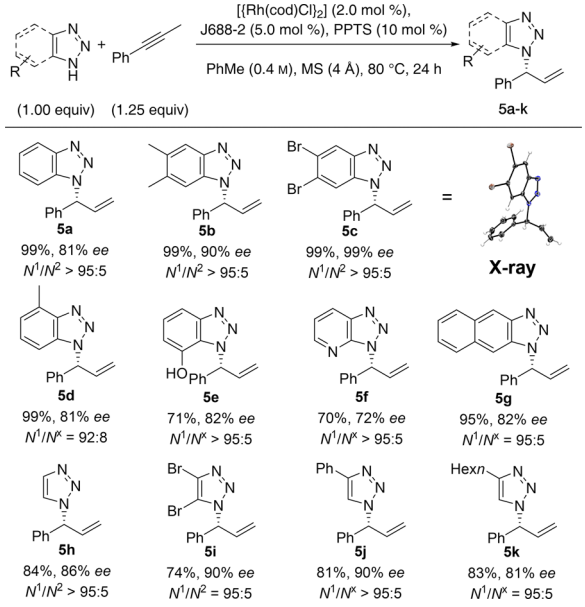
entry	ligand	additive	N^1/N^2[b]	yield (%)[c]	*ee* (%)[d]
1	J681-2	PPTS	–	0	–
2	L1[e]	PPTS	>95:5	99	81
3	L1[e]	–	>95:5	51	*rac*
4	L1 (*dr* = 2.3:1)	PPTS	>95:5	99	81
5	L2	PPTS	>95:5	99	72
6	L3	PPTS	>95:5	99	63
7	L4	PPTS	>95:5	92	73
8	L1 (*dr* = 2.3:1)	PPTS, MS (4 Å)[f]	>95:5	99	81

[a]Reaction conditions: benzotriazole (0.4 mmol) and 1-phenyl-1-propyne (0.5 mmol) in toluene (1.0 mL) at 80 °C, 24 h. [b]Regioselectivity determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Yield of isolated product. [d]Determined by chiral HPLC analysis. [e]*dr* > 95:5. [f]160 mg/mmol of MS (4 Å, pearls) were used. cod = 1,5-cyclooctadiene, PPTS = pyridinium *p*-toluenesulfonate.

N^1-allylated benzotriazole in excellent yield as well as good enantioselectivity (99%, 81% *ee*; entry 2) by using JosPOphos J688-2 (**L1**). The presence of PPTS was crucial to obtain the desired N^1 product in high yield and enantioselectivity (entry 3). Next, we examined whether the configuration of the secondary phosphine oxide affects the reaction in terms of yield, N^1-selectivity, and enantioselectivity. We were pleased to observe the same results with the diastereomeric mixture of **L1** as for the diastereomerically pure J688-2 ligand (**L1**) (entry 4).[10] Based on these results our new JosPOphos derivatives were tested as mixtures of diastereomers. Unfortunately, neither the more sterically demanding ligand **L2** (entry 5) nor the electron-rich or electron-poor ligands (**L3** and **L4**, entries 6 and 7) resulted in higher enantioselectivities. Therefore, we focused on optimizing the reaction with the initial JosPOphos J688-2 (**L1**). Most consistent results were obtained upon addition of molecular sieves (4 Å) (entry 8).[11]

Having the optimized reaction conditions in hand, we started to explore the reaction scope by initially coupling symmetrical and unsymmetrical triazoles to 1-phenyl-1-propyne (Scheme 3). We found a wide range of triazoles to be suitable reaction

Scheme 3. Scope of the Addition of Triazoles to 1-Phenyl-1-propyne



partners furnishing the corresponding allylic triazoles in good to excellent yields, along with very good to excellent regio- and enantioselectivities. At this point the absolute configuration could be determined by X-ray crystal structure analysis of product **5c**.

Furthermore, the coupling reactions of various substituted internal alkynes using 4-phenyltriazole were explored.[12] We were pleased to obtain the desired allylation products in very good yields, along with excellent nitrogen-position selectivity as well as regio- and enantioselectivities (Scheme 4). Cyclopropyl- and enyne-based internal alkynes reacted smoothly to give the desired products (**5l** and **5m**) as well as a broad variety of different aryl substituents.

Based on these results, we were curious if our catalytic system is also capable of the enantioselective hydroamination of terminal allenes (Scheme 5). Indeed, the reaction of benzotriazole with different allenes as well as the reaction of various triazoles with 2-phenylethylallene gave good yields and high regioselectivities along with good enantioselectivity. Even an alkyl iodide moiety (**6c**)—usually prone for enabling side reactions by facile oxidative addition of the rhodium catalyst—was well tolerated and a disubstituted allene (**6d**) was a suitable reaction partner for benzotriazole.[13]

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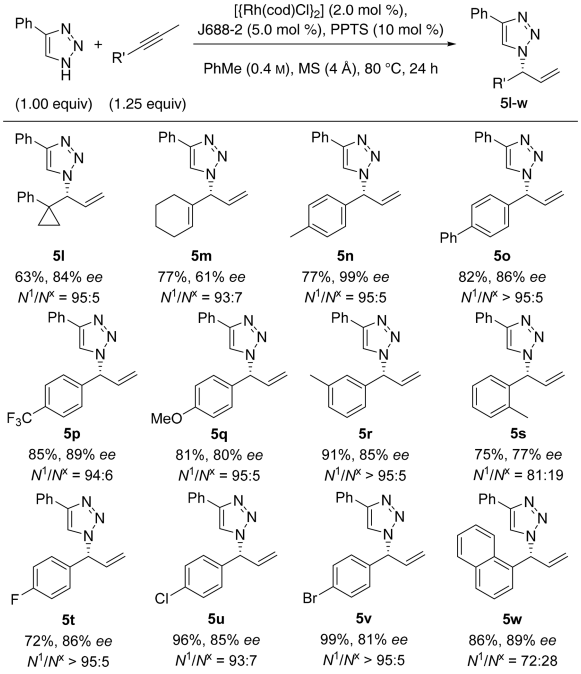
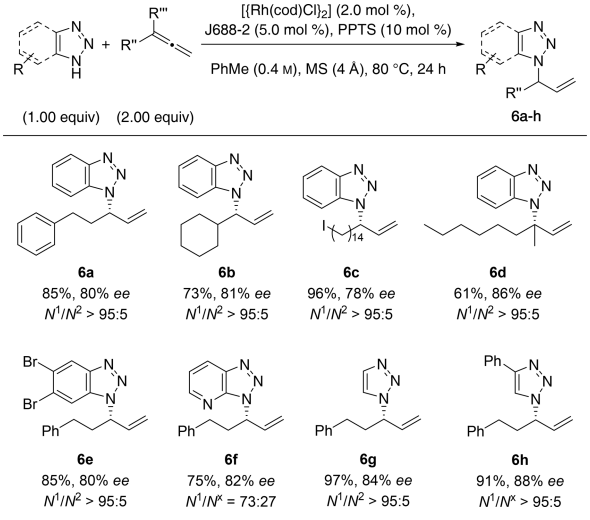
Scheme 4. Scope of the Addition of 4-Phenyltriazole to Different Internal Alkynes



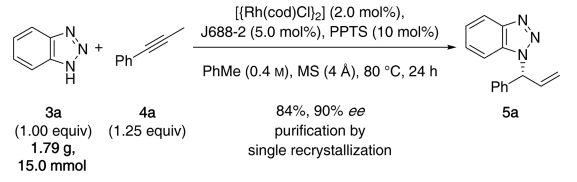
Scheme 5. Scope of the Addition of Triazoles to Terminal Allenes



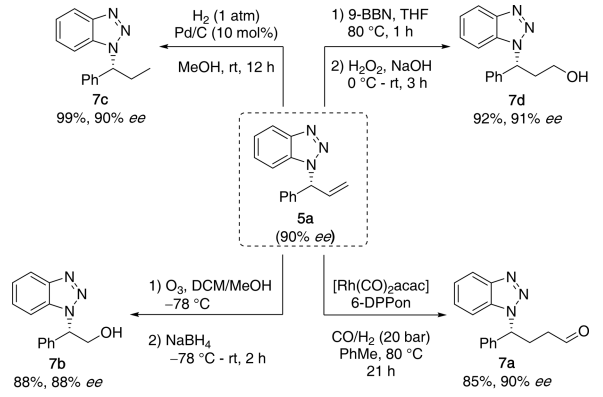
To further explore the synthetic utility of N^1-allylated benzotriazoles, allylic benzotriazole **5a** was prepared on multigram scale (Scheme 6).

The allylic moiety of **5a** was then subjected to assorted transformations (Scheme 7). Hydroformylation of the terminal

Scheme 6. Gram Scale Preparation of 5a and Purification by Single Recrystallization



Scheme 7. Various Functionalizations of Allylated Benzotriazole 5a



double bond, using our self-assembly ligand 6-diphenylphosphinopyridone (6-DPPon), furnished aldehyde **7a** in good yield and with excellent linear/branched selectivity (95:5).[14] Cleavage of the alkene by ozonolysis of **5a** followed by reductive workup led to alcohol **7b** in 88% yield. Hydrogenation furnished **7c** and hydroboration/oxidation gave the alcohol **7d**, while leaving the benzotriazole unit untouched.

To conclude, we developed a regio- and enantioselective addition of triazoles to internal alkynes and terminal allenes in an atom-economic manner by using a rhodium/JosPOphos catalyst system. The reaction displays a broad substrate range of substituted triazoles, alkynes, and allenes to provide N^1-allylated triazoles in very good yields along with high regio- and enantioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03708.

Synthetic procedures for new compounds as well as their analytical data, involving ^{1}H NMR, ^{13}C NMR spectra, and scanned HPLC chromatograms for chiral compounds (PDF)

Accession Codes

CCDC 1530594 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(10) We assume that under the acidic reaction conditions there is an equilibrium of both secondary *P*-oxide diastereomers and the tautomeric phosphinite.

(11) For further details concerning the optimization, see the Supporting Information.

(12) Unfortunately, the addition to terminal alkynes such as prop-2-yn-1-ylbenzene did not provide any product.

(13) NMR analysis of all crude catalysis products never showed any linear triazole allylation product.

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