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Unlocking the N^2 Selectivity of Benzotriazoles: Regiodivergent and Highly Selective Coupling of Benzotriazoles with Allenes**

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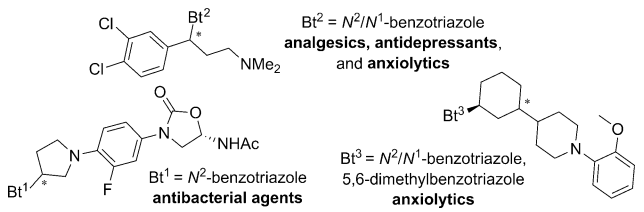
Abstract: *The rhodium-catalyzed, highly N^2- and N^1-selective coupling of benzotriazoles with allenes is reported. The exceptionally high N^2 and N^1 selectivities were achieved by using a rhodium(I)/DPEphos and rhodium(I)/JoSPOphos catalyst, respectively. This method permits the atom-economic synthesis of valuable branched N^2- and N^1-allylated benzotriazole derivatives and allows for preliminary studies of their reactivity.*

Benzotriazoles and their derivatives have been widely used in organic synthesis, materials science, biological research, and medicinal chemistry.[1] *N*-Alkyl-substituted benzotriazoles possess a broad spectrum of biological activities[2a–f] including anti-inflammatory,[2b] antifungal,[2d] antibacterial,[2e] and analgesic properties[2f] (Scheme 1). Unfortunately, the

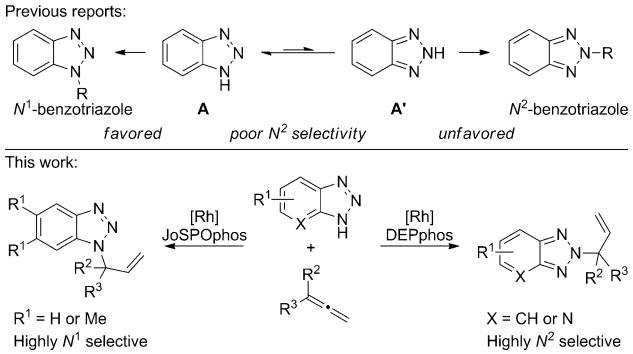


Scheme 1. Examples of biologically active *N*-alkylated benzotriazoles.

difficulty in achieving the *N*-selective, particularly N^2-selective, alkylation of benzotriazoles has limited their application. In this regard, efficient synthetic methods for the *N*-selective alkylation of benzotriazoles are highly desirable.

N-Selective control over 1,2,3-triazoles, especially benzotriazoles, is a challenging topic in organic synthesis because of the equilibrium between N^1 (N^3) and N^2 tautomers.[3] In comparison with non-benzo-1,2,3-triazoles, the N^2 selectivity of benzotriazoles is more difficult to achieve as a result of the decreased aromaticity of the N^2 tautomer.[3] In general, a mixture of N^1- and N^2-substituted benzotriazoles is obtained, although the N^1-substituted benzotriazole is most often the dominant product.[4–6] The aromaticity of the benzenoid tautomer (**A**) was estimated to be 9.5 kcal mol^{-1} greater than that of the quinoid-like tautomer (**A′**), which renders the N^2-selective substitution of benzotriazole a very challenging process.[3a] Although substantial efforts have been made to solve this problem, only a poor N^2 selectivity for benzotriazoles was achieved (Scheme 2).[7] In our studies of the rhodium-catalyzed atom-economic[8] addition of pronucleophiles to allenes and alkynes[9,10] as an alternative to allylic substitution,[11] we assumed that a suitable phosphine-modified rhodium(I) catalyst may distinguish the energy difference between the N^2 and N^1 intermediates in the catalytic cycle, which may result in N^2 and N^1 alkylation. Herein we report an unprecedented N^2- and N^1-selective coupling of benzotriazoles with allenes, which allows for regiodivergent allylation with high levels of selectivity (Scheme 2).

The initial experiments were performed with benzotriazole and cyclohexylallene in the presence of [{Rh(cod)Cl}$_2$] (1.0 mmol %) and dppf (3 mmol %) in 1,2-dichloroethane (DCE) at 80 °C. To our delight, the reaction gave a 93 % yield of the product as determined by NMR spectroscopy, although the selectivity was still low (Table 1, entry 1). The feasibility of benzotriazole as a pronucleophile encouraged us to screen achiral bidentate diphosphine ligands with different bite angles. However, most of the ligands only resulted in poor selectivities (Table 1, entries 2 and 3) or traces of product.[12] We were pleased to observe that high N^1 selectivity was obtained using DPPPent, although the yield was low (Table 1, entry 4). To our delight, a 90 % yield of the isolated N^2 product (**2a**) was obtained using DPEphos.[12] Further optimization led to a lower catalyst loading and an allene ratio with a high selectivity of N^2 relative to its isomers (N^2/N^x = 94:6) and without a detrimental effect on the reactivity (Table 1, entry 5). The corresponding regiocomplementary N^1



Scheme 2. *N*-Selective substitution of benzotriazoles.

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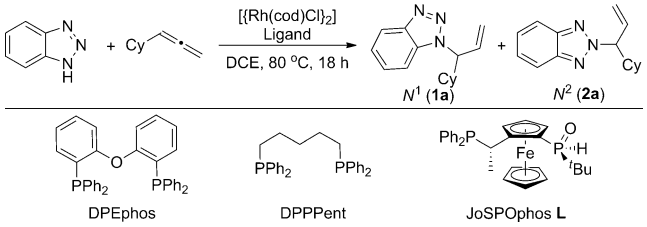
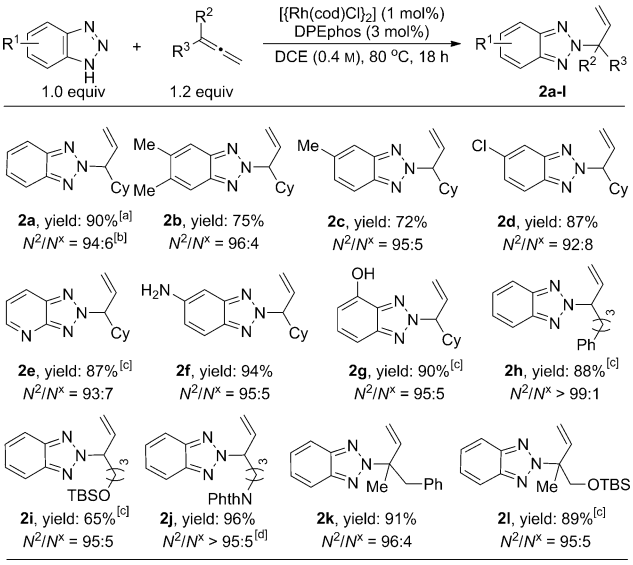
Table 1: Ligand controlled N^2- and N^1-selective coupling of benzotriazole with cyclohexylallene.

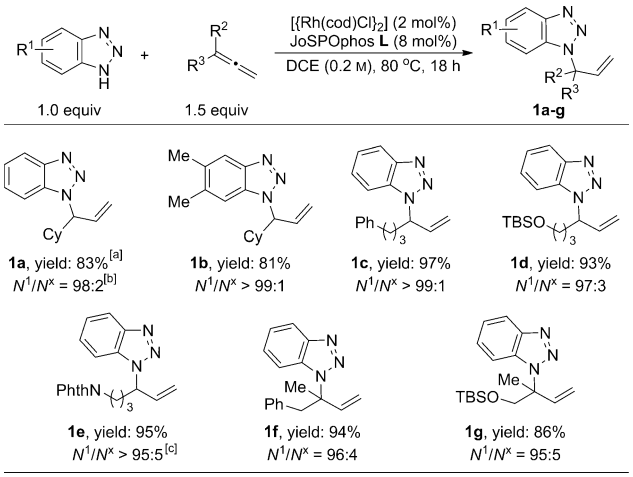


Entry[a,b,c]	Ligand	Yield/[%][d]	N^1/N^2[e]
1[a]	dppf	93	39:61
2[a]	dppp	95	66:34
3[a]	dppb	94	71:29
4[a]	DPPPent	31	93:7
5[b]	DPEphos	(90)[f]	6:94[g]
6[c]	JoSPOphos **L**	(83)[f]	98:2[h]

[a] Conditions: [{Rh(cod)Cl}$_2$] (1.0 mol%), ligand (3.0 mol%), benzotriazole (0.25 mmol), cyclohexylallene (0.3 mmol), DCE (1.0 mL). [b] Conditions: [{Rh(cod)Cl}$_2$] (1.0 mol%), DPEphos (3.0 mol%), benzotriazole (0.5 mmol), cyclohexylallene (0.6 mmol), DCE (1.25 mL). [c] Conditions: [{Rh(cod)Cl}$_2$] (2.0 mol%), JoSPOphos **L** (8.0 mol%), benzotriazole (0.4 mmol), cyclohexylallene (0.6 mmol), DCE (2.0 mL). [d] Yield of the N^1 and N^2 products in the crude reaction mixture as determined by ^{1}H NMR spectroscopy and using 1,3,5-trimethoxybenzene as an internal standard. [e] Determined by GC-MS of the crude reaction mixture. [f] Yield is that of the isolated product. [g] The GC-MS ratio is N^2/N^x (N^x: isomers of **2a**). [h] The GC-MS ratio is N^1/N^x (N^x: isomers of **1a**). cod = 1,5-cyclooctadiene, Cy = cyclohexyl, dppb = 1,4-bis(diphenylphosphino)butane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, dppp = 1,3-bis(diphenylphosphino)propane.



Scheme 3. Scope of the rhodium-catalyzed N^2-selective coupling of benzotriazoles with allenes. [a] The yield is that of the isolated product. [b] The ratio of N^2 and its isomers (N^2/N^x) was determined by GC-MS analysis of the crude reaction mixture. [c] Conditions: [{Rh(cod)Cl}$_2$] (2.5 mol%), DPEphos (10 mol%), allene (1.5 equiv). [d] Determined by ^{1}H NMR spectroscopy after purification. Phth = phthaloyl, TBS = *tert*-butylsilyl.



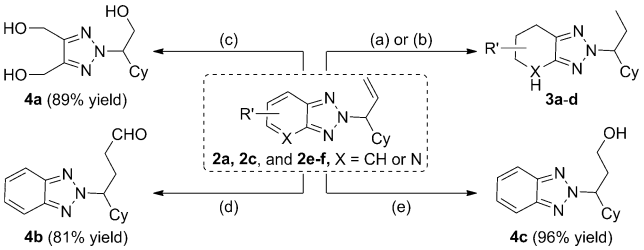
Scheme 4. Scope of the rhodium-catalyzed N^1-selective coupling of benzotriazoles with allenes. [a] The yield is that of the isolated product. [b] The ratio of N^1 and its isomers (N^1/N^x) was determined by GC-MS analysis of the crude reaction mixture. [c] Determined by ^{1}H NMR spectroscopy after purification.

product (**1a**) was obtained, after intensive optimization,[12] in 83% yield and 98:2 (N^1/N^x) selectivity by using JoSPOphos **L**[13a] (Table 1, entry 6). Control experiments indicated that both a rhodium precursor and ligand are necessary for the coupling reactions.[12]

With the optimized conditions in hand, we then investigated the scope of the addition of different benzotriazoles with allenes.[13b] A broad range of benzotriazole derivatives were suitable substrates for the synthesis of N^2-allylated products with good to excellent yields and high selectivities (Scheme 3). Both symmetrically (**2a**,**b**) and asymmetrically (**2c**–**g**) substituted benzotriazole derivatives were smoothly coupled with cyclohexylallene to give branched and N^2-allylated products, although a higher catalyst and allene loading were needed in some cases (**2e**, **2g**–**I**, and **2l**). Halogen (**2d**), free amino (**2f**), and hydroxy (**2g**) groups were well tolerated. To our delight, a pyridine-conjugated triazole was also allylated with high N^2 selectivity (**2e**). A range of terminal allenes was readily prepared in one or two steps from commercially available starting materials.[12] Allenes bearing protected alcohols (**2i** and **2l**) and phthalimide (**2j**) were compatible. 1,1-Disubstituted allenes (**2k**,**l**) were also suitable substrates, and furnished useful quaternary carbon centers.

Symmetric benzotriazole derivatives and different allenes were tested in the rhodium-catalyzed N^1-selective coupling reactions. The regiocomplementary branched N^1-allylated products were obtained in high yields and high N^1 selectivities (Scheme 4, **1a**–**g**).[13c]

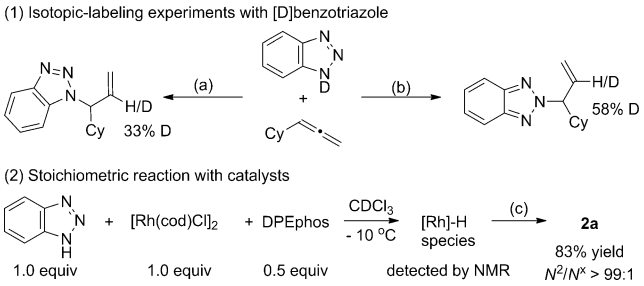
To explore the reactivity of the "less-aromatic" N^2-allylated benzotriazoles (Scheme 5), **2a** and **2e** were subjected to hydrogenation with Pd/C under H_2 (1 atm) at room temperature. The conjugated benzene and pyridine ring were completely hydrogenated under these mild conditions in 99% (**3a**) and 73% (**3b**) yield, respectively. Different substituents on the benzene ring of N^2-allylated benzotriazoles (**2c** and **2f**) also allowed the synthesis of the corresponding hydrogenated products (**3c**,**d**), which are difficult to prepare by other methods.[14a] Ozonolysis of **2a** followed by reductive work up with $NaBH_4$ led to **4a** in 89% yield.[14b] Furthermore, the



Scheme 5. Transformations of N^2-allylated benzotriazoles. a): Pd/C (10 mol%), H_2 (1 atm), MeOH, RT, 16 h; **3a** (product of **2a**), 99% yield; **3b** (**2e**), 73% yield. b): Pd/C (10 mol%), H_2 (30 atm), EtOH, 60°C, 16 h; **3c** (**2c**), 99% yield; **3d** (**2f**), 80% yield. c): O_3, MeOH, −78°C; then $NaBH_4$ (product of **2a**). d) [{Rh(cod)acac] (0.68 mol%), 6-DPPon (3.4 mol%), H_2/CO (1:1, 1 atm), THF, RT, 24 h, linear/branched = 87:13. e): 9-BBN (2.0 equiv), THF, RT, 16 h; then H_2O_2, NaOH, EtOH, RT, 3 h. acac = acetylacetonate, 9-BBN = 9-borabicyclo-[3.3.1]nonane

allylic double bond can be easily modified to other useful functional groups (**4b**,**c**).

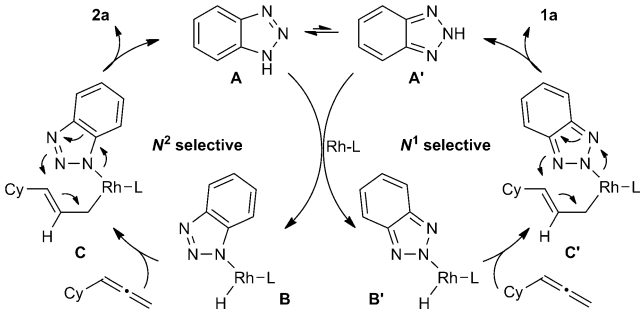
To study the possible mechanism (Scheme 6), isotopic-labeling experiments were conducted with [D]benzotriazole and cyclohexylallene under optimized conditions. Deuterium incorporation was only observed at the internal position of



Scheme 6. Mechanistic investigations. a) Scope of the N^1-selective coupling, 32% yield. b) Optimized conditions for N^2-selective coupling, 78% yield. c) Cyclohexylallene (1.2 equiv), −40°C to room temperature.

the alkene.[12] The stoichiometric reaction of benzotriazole with [{Rh(cod)Cl}$_2$] and DPEphos in $CDCl_3$ was monitored by NMR spectroscopy.[12] The ^{1}H NMR spectrum (263 K) of the reaction after five minutes reaction at room temperature showed a major rhodium hydride species at $\delta = -14.17$ ppm ($^1J_{Rh\text{-}H} = 14.0$ Hz), which indicates the oxidative addition of the N–H bond of benzotriazole to the rhodium center.[15a] The subsequent addition of cyclohexylallene to the mixture at −40°C led to immediate consumption (a few seconds) of the Rh-H species, which suggests hydrometalation of Rh-H to cyclohexylallene.[15b–d] Warming the mixture to room temperature led to the formation of the coupling product **2a** in 83% yield ($N^2/N^x > 99{:}1$).[12]

On the basis of the labeling experiments, the following mechanism can be proposed (Scheme 7). Oxidative addition of the tautomers (**A** or **A**′) of benzotriazole to Rh^I generates a Rh^{III} complex (**B** or **B**′).[15a] Hydrometalation of the less-substituted double bond could generate a σ-allyl-Rh complex



Scheme 7. Proposed mechanism for the rhodium-catalyzed N^1- and N^2-selective coupling of benzotriazoles with allenes.

(**C** or **C**′),[15e–g] which could generate the desired branched *N*-allylic benzotriazoles on reductive elimination.[16] The *N* selectivity is dictated by the energy difference between the two catalytic cycles: the N^2-selective product is formed via **A**-**B**-**C**, and the N^1-selective product is produced via **A**′-**B**′-**C**′. However, the origin of why the two bidentate ligands favor one pathway over the other remains unclear at this moment, and must be addressed in future studies.

To conclude, we have developed the first highly N^2-selective coupling of benzotriazoles with allenes by using a rhodium/DPEphos catalyst system. The regiocomplementary N^1 allylation was also achieved in high yields and high selectivities by using a rhodium/JoSPOphos ligand. A broad range of new N^2- and N^1-allylated benzotriazoles was prepared in an atom-economic manner. This method may extend the application of alkyl-substituted benzotriazoles. Mechanistic investigations and asymmetric variants are currently underway and will be reported in due course.

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[12] See the Supporting Information for details.

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