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Mitsunobu Reaction of 1,2,3-NH-Triazoles: A Regio- and Stereoselective Approach to Functionalized Triazole Derivatives

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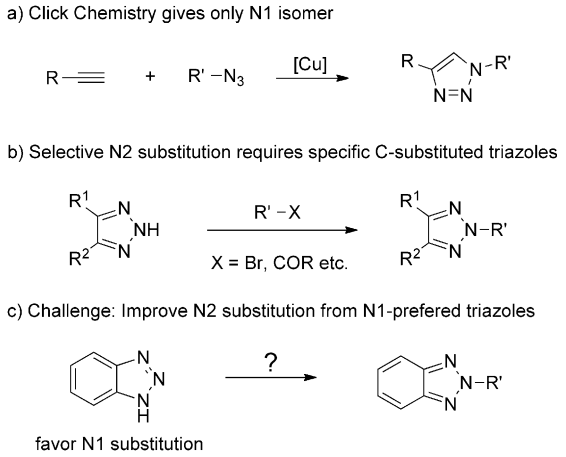
On the occasion of the 10th anniversary of click chemistry

The discovery of the copper-catalyzed alkyne/azide cycloaddition ("click" chemistry)[1] earlier this century has clearly advanced the research of 1,2,3-triazoles and made these five-membered heterocycles among the "hottest" compounds in chemistry-,[2] materials-,[3] and biological[4] research during the last decade.[5] This robust method has been widely applied to various areas as an efficient strategy for combining different functionalities under mild conditions. Recently, driven by the great success of the synthesis of 1,2,3-triazoles, more attentions have been put into investigating the fundamental reactivity of this interesting heterocycle.[6] Various attractive applications have been reported that are associated with the unique 1,2,3-triazole core structure, including the formation of carbene intermediates[7] and adjusting the transition metal reactivity with triazole ligands.[8] These studies further extended the versatility of 1,2,3-triazole building blocks. Fast-growing research in this area has led to the urgent need for effective syntheses of different triazole analogous, especially those that provide good regio and stereo-selectivity.

One challenge for the functionalization of triazoles is the regioselective synthesis of the N2-isomers. Whilst click-chemistry techniques give only the N1 isomers, NH-triazole functionalization relies heavily on the reactivity of the triazoles, and, most of the time, the N1 isomers are still the major products. Recent reports in the literature have described strategies focused on the development of suitable substitute groups at the C4 and C5 positions to promote good N2 selectivity (Scheme 1).[9] Therefore, new strategies that can encourage N2 selectivity from "N1-substitution-favored" NH-triazoles are highly desirable. Herein, we report the Mitsunobu reaction of NH-triazoles with alcohols as an effective method not only for the synthesis of enantiomeric pure chiral triazole derivatives, but also for selective N2 substitution through the modification of the carbon electrophiles instead of changing the substituents on the NH-triazoles.



Scheme 1. The challenge in improving N2 regioselectivity of N1-preferred triazoles.

Our group has recently reported several effective strategies[10] for introducing different functional groups onto the triazole ring. Through these investigations, a clear reactivity difference was revealed between N1 and N2 isomers. For example, we recently discovered that N2-aryl triazole (NAT) could provide very efficient UV/blue fluorescence whilst N1 isomers gave almost no emission at all.[11] In addition, we also applied the 1,2,3-triazoles as ligands to form transition metal complexes and interesting new reactivities were obtained,[12] which clearly demonstrated the strong potential applications for 1,2,3-triazole in organic synthesis and transition metal catalysis. The interesting coordination ability of 1,2,3-triazoles and unique complex activity led to the strong

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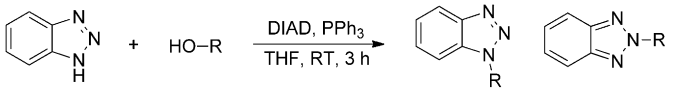
desire to prepare enantiomerically pure triazole derivatives. These two challenges, improving N2 selectivity for a triazole that has an N1-substitution preference and introducing chiral groups on the triazole ring, led us to investigate the Mitsunobu reaction between the NH-triazoles and alcohols.

Considering the usually good stereoselectivity associated with the Mitsunobu reaction,[13] where complete inversion of the alcohol stereogenic center occurred through S_N2 addition, we postulated that this strategy might be applied on the introduction of chiral substitute groups on triazoles. The rather high acidity (pKa 8~10) and the excellent nucleophilicity of the NH-1,2,3-triazole makes them suitable coupling partners with alcohols under Mitsunobu conditions. In addition, although the N1 nitrogen of the triazole is usually more-basic (higher electron density) than the N2 nitrogen, the center nitrogen atom is much-less sterically hindered. Therefore, N2 substitution is kinetically favored. As a result, the highly stereochemistry-sensitive Mitsunobu reactions could potentially favor the kinetic product and increase the N2 selectivity. To verify this hypothesis, the reaction between benzyl alcohol **2a** and benzotriazole **1a** was performed under standard Mitsunobu conditions (DIAD, PPh_3 in THF, Scheme 2a).

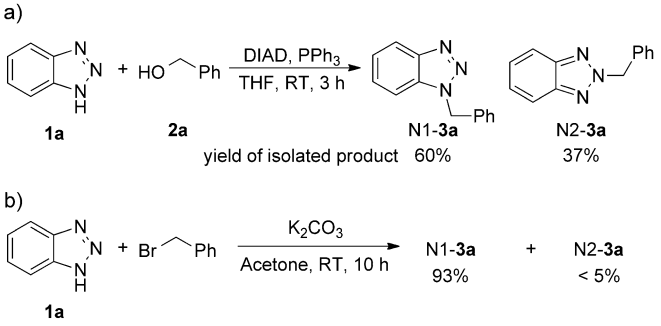
As expected, the dehydration product **3a** was isolated in excellent yields (97% combined N1 and N2 isomers) under Mitsunobu conditions. Notably, N1 and N2 isomers were readily purified by column chromatography (significantly different polarity between the N1 and N2 isomers). Compared with the alkylation conditions, where only trace amounts of N2-**3a** were isolated (Scheme 2b), the Mitsunobu conditions gave a significantly higher overall yield of the N2 isomers. To determine how different alcohols influenced the reactivity and regioselectivity of the Mitsunobu reaction, various alcohols were applied to react with **1a** (Table 1).

Table 1. Reaction substrate scope with benzotriazole (BTA).[a]



	Yield[b] (N1+N2) [%]	Ratio[c] N2/N1		Yield[b] (N1+N2) [%]	Ratio[c] N2/N1
3a	97	1:1.6	**3h**	88	1.6:1
3b	84	1:1.3	**3i**	96	1.6:1
3c	95	1:1.9	**3j**	93	2:1
3d	93	1:1.8	**3k**	85	1.8:1
3e	96	1:1.7	**3l**	80	1.2:1
3f	94	1:1.5	**3m**	79	2.6:1
3g	97	1:1.2			

[a] Standard reaction condition: 1 equiv of alcohols, 1.2 equiv of triazoles, 1.2 equiv of triphenylphosphine (PPh_3) and 1.2 equiv of diisopropyl azodicarboxylate (DIAD) were mixed in the distilled tetrahydrofuran (THF). [b] Yield of isolated product. [c] Ratios determined by NMR analysis of crude reaction mixtures.

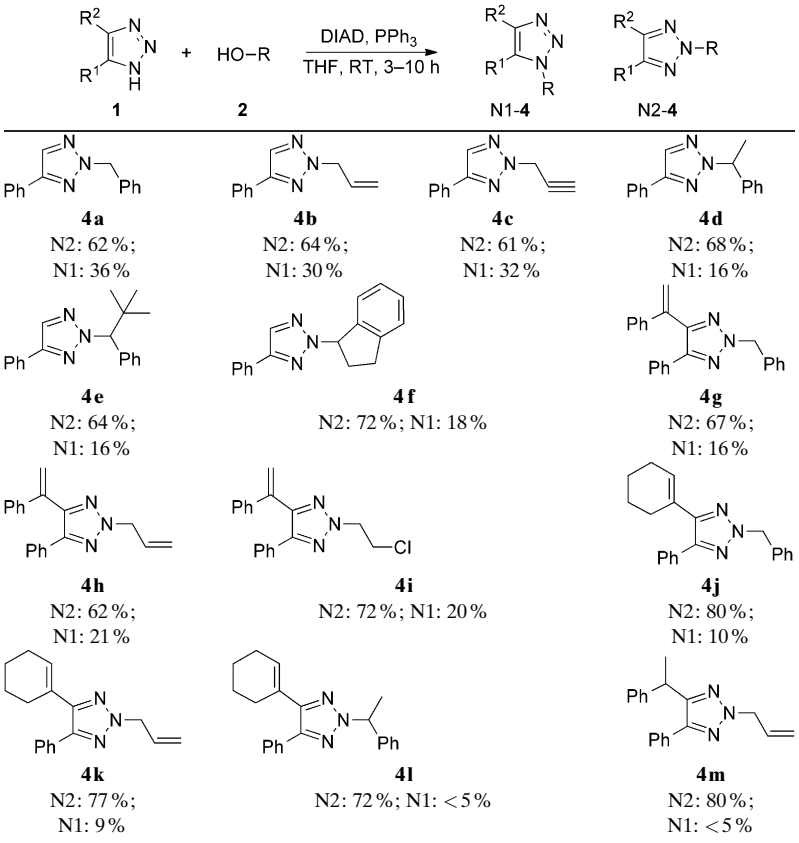


Scheme 2. Mitsunobu reaction and alkylation of benzotriazole.

As shown in Table 1, the Mitsunobu conditions were suitable for a large group of alcohols, giving the coupling products in generally excellent yields (N1+N2 > 85%). Significantly higher yields of the N2 products (compared with the alkylation conditions) were obtained in all cases. In addition, the secondary alcohols, although they required longer reaction times (8 to 12 h), gave the N2 isomers as the major products, which supported our hypothesis that the stereochemistry-sensitive Mitsunobu reaction promotes the kinetic N2 addition even for highly N1-preferred benzotriazoles. Different NH-triazoles were then considered to further extend the reaction substrate scope (Table 2).

In all cases, significantly higher N2 selectivity was obtained. For example, as we have reported previously, the reaction between 4-phenyl-NH-triazole (**1b**) and benzyl bromide ($PhCH_2Br$) gave N1-substituted benzyl **4a** as the major product (N2/N1 = 1:5). Under the Mitsunobu conditions, the desired N2 isomer became the major product (N2/N1 = 1.7:1). Good to excellent yields of the isolated N2 isomers were obtained. This strategy not only provided an al-

Table 2. Reaction substrate scope with various triazoles.[a,b]



[a] Standard reaction conditions: alcohol (1 equiv), triazoles (1.2 equiv), of triphenylphosphine (PPh_3; 1.2 equiv) and of diisopropyl azodicarboxylate (DIAD; 1.2 equiv) were mixed in distilled tetrahydrofuran (THF). [b] Yields determined by NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard; ratios determined by NMR analysis of the crude reaction mixtures.

ternative approach for NH-triazole functionalization, but also, more importantly, allowed N2 functionalization through altering different reaction parameters instead of adjusting the substitution groups on 1,2,3-triazoles (currently the dominant approach in the literature for the synthesis of N2 isomers). The significance of this strategy in altering the N1/N2 selectivity was further highlighted in the synthesis of bis-N2-triazole derivatives (Scheme 3).

In general, N1/N1-bis-triazoles can be readily prepared using double-click-chemistry reactions from diynes. On the other hand, the N2/N2-bis-triazoles are extremely challenging to prepare based on the statistic analysis. For example, assuming that mono-substitution gave a N1/N2 ratio of 5:1, the ratio of the bis-functionalization of the same reaction would be N1–N1/N1–N2/N2–N2 = 25:10:1. Therefore, the theoretical yields for N2–N2 product would be only 2.7%. The Mitsunobu conditions, by altering the N1/N2 selectivity, afforded the opportunity to synthesize the N2/N2 isomer for the first time through simple post-triazole derivatization. As indicated in Scheme 3, bis-triazole **5a** was successfully prepared, even with usually N1 dominant benzotriazole. The yields of the N2/N2 isomers were significantly improved with the 4-phenyl-triazole (**5b**) and derivatives (**5d** and **5f**). Notably, only trace amount of the N2/N2 bis-triazoles were observed from the reaction of 4-phenyl-triazole (PTA) with dichloro/dibromo alkanes, owing to the unfavored statistic discussed above.

Encouraged by the good reactivity of the NH-triazole under Mitsunobu conditions, we investigated the stereoselectivity of this transformation. The *trans*-2-methylcyclohexanol **2b** and *trans*-2-methylcyclopentanol **2c** were used to react with benzotriazole (BTA) **1a** and phenyl-triazole (PTA) **1b**. As expected, excellent stereoselectivity were achieved, only the corresponding *cis*-products were obtained with complete stereochemistry inversion (Scheme 4).[14]

These results were exciting because they provided a practical approach for the preparation of enantiomeric pure 1,2,3-triazole derivatives through the coupling of triazoles and chiral alcohols. The enantiomeric pure alcohol **2d** and quinine **2e** were used for the asymmetric synthesis of chiral triazole derivatives. As shown in Scheme 5, the chiral triazoles **7a** and **7b** were prepared with excellent stereochemistry control.

Under the Mitsunobu conditions, the enantiomeric pure alcohol **2d** gave near-complete chirality transfer, forming the chiral triazole **7a** in 96% *ee* (determine by HPLC analysis).[15] As mentioned above, the N1 and N2 isomers were readily separated by column chromatography owing to their large difference in polarity, which made this method very attractive for the preparation of enantiomerically pure triazoles. As observed above, the secondary alcohols improved the yields of the N2 isomers, even for the usually N1-dominant benzotriazoles. The synthesis of **7b** (structure confirmed by X-ray crystallography) highlighted the strength of this method in the preparation of highly functional triazole analogues. It is expected that these compounds can be applied as potential building blocks in asymmetric catalysis, especially considering the interesting reactivity of the 1,2,3-triazoles.

In conclusion, the Mitsunobu reactions between NH-triazoles and alcohols is a practical approach for 1,2,3-triazole functionalization. Unlike the previously reported strategies, where different triazoles were required to achieve good yields of N2 isomers, the Mitsunobu conditions favored the formation of the kinetic products (N2 isomers), even for 1,2,3-triazoles with high N1-preference (such as benzotriazoles). Therefore, this method provides an alternative approach to N2 substitution without changing the reactivity of the triazoles. Moreover, with the excellent stereochemical control, this method allows the asymmetric synthesis of enantiomerically pure triazole derivatives, which can certainly help the further development of 1,2,3-triazoles as new building blocks in chemistry and related research.

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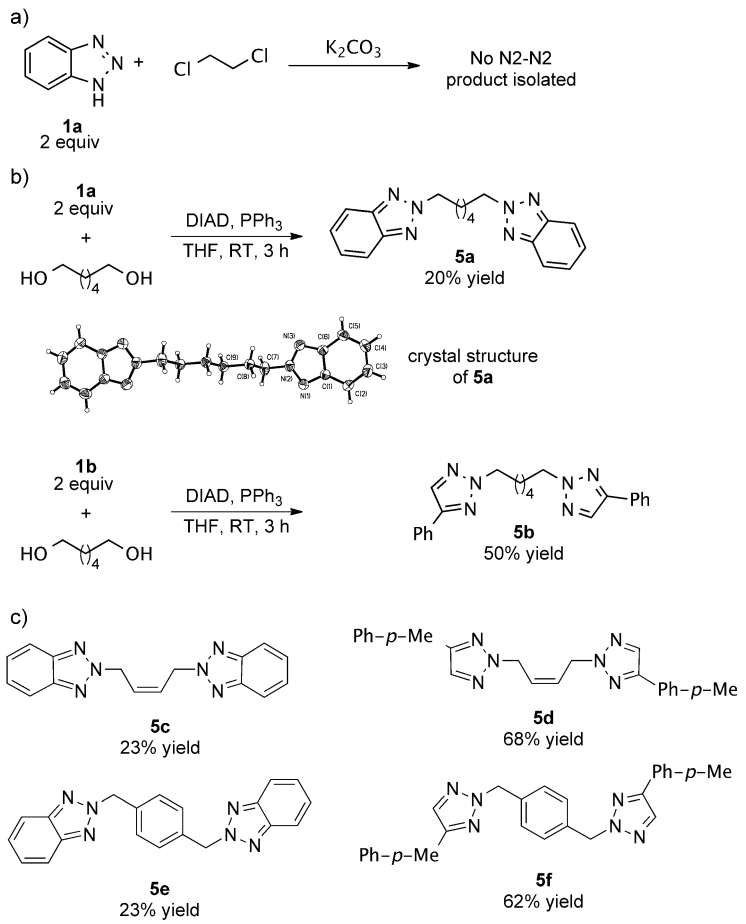
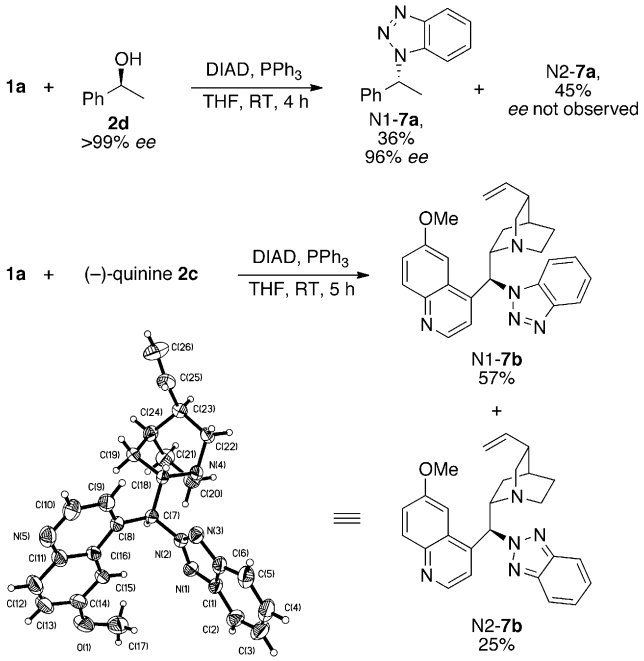
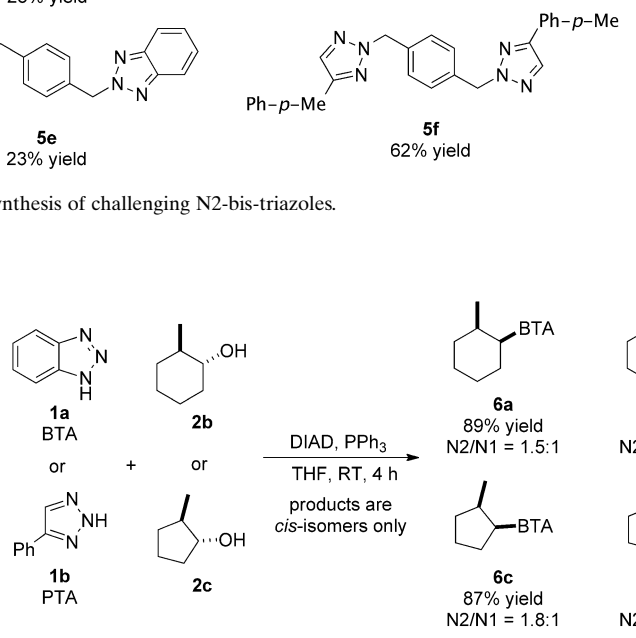


Scheme 3. Synthesis of challenging N2-bis-triazoles.



Scheme 5. Asymmetric synthesis of chiral triazole derivatives.[16]



Scheme 4. Complete stereochemistry inversion.

Experimental Section

General Procedure for the Mitsunobu Reaction of 1,2,3-NH-Triazoles with Alcohols

A 25 mL round-bottomed flask is equipped with a stirring bar, nitrogen inlet, rubber septum. The flask is charged with alcohol (3.0 mmol), NH-triazole (3.6 mmol), triphenylphosphine (PPh_3; 3.6 mmol), and 12 mL of distilled tetrahydrofuran (THF). The flask is immersed in an ice bath, and diisopropyl azodicarboxylate (DIAD; 3.6 mmol) is added dropwise at a rate such that the temperature of the reaction mixture is maintained below 10 °C. Upon completion of the addition, the flask is removed from the ice bath and the solution is stirred at room temperature for 3 h, and monitored by TLC. After the reaction is complete, 30 mL of water is added to quench the reaction. The mixture is extracted three times with ethyl acetate (20 mL). The combined organic layers are washed twice with brine (20 mL) and dried over anhydrous sodium sulfate (Na_2SO_4). Excess solvent and other volatile reaction components are completely removed under reduced pressure. The residue is applied to a flash chromatography column on silica gel (*n*-hexane/ethyl acetate = 10:1) to give the products.

Acknowledgements

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Keywords: 1,2,3-triazoles · click chemistry · enantioselectivity · Mitsunobu reaction · regioselectivity

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[14] The relative stereochemistry of **6a**–**6d** were determined by NMR analysis.

[15] The *ee* of N2–**7a** was not determined owing to the difficulty in separation of the two enantiomers by HPLC. However, large optical rotation of N2–**7a** was observed with $[\alpha]_D^{25} = -55.40$ (CH_2Cl_2, $c = 1.0$), which confirmed that the likely similar excellent stereochemistry inversion was associated with the product.

[16] CCDC 819067 (N2-**7b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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