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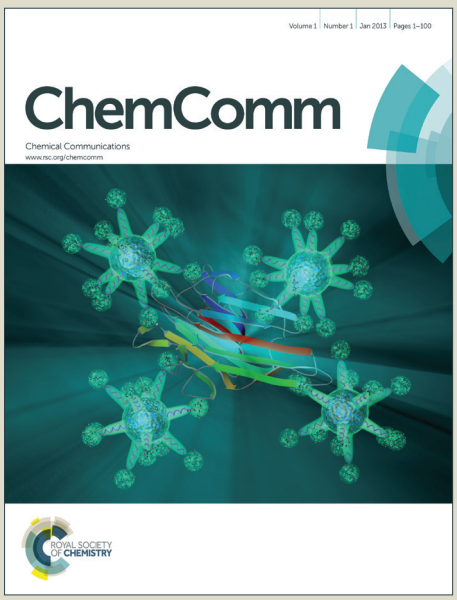

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Enantioselective Formation of Tertiary and Quaternary Allylic C-N Bonds via Allylation of Tetrazoles

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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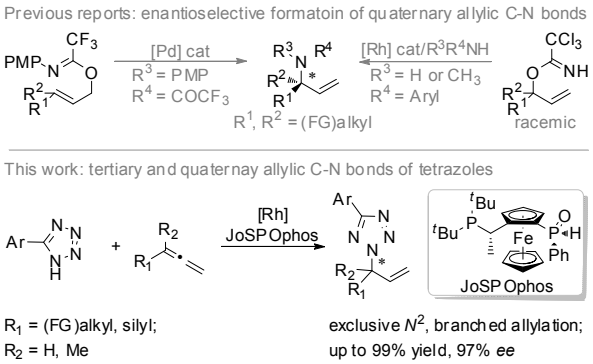
Rhodium-catalyzed regio- and enantioselective coupling of tetrazoles with allenes are reported. Asymmetric construction of tertiary and quaternary allylic C-N bonds were achieved using a Rh(I)/JoSPOphos catalyst. This method permits the atom-economic synthesis of various valuable N^2-allylic tetrazoles.

Since the discovery of tetrazoles by J. A. Bladin in 1885,[1] their wide applications have attracted much attention.[2] In the last decades, the development of new synthetic methods towards various tetrazole derivatives has been of great interest,[3] notably azide-nitrile cycloadditions.[3a] As a stable-to-metabolism analog of carboxy or *cis*-amido groups, the introduction of a tetrazole fragment into various organic compounds has been extensively used in drug design[2b-d, 4a-c] and in the synthesis of nonnatural amino acids.[4d] In the top 200 pharmaceutical products by worldwide sales in 2009, more than ten of them were tetrazole containing compounds.[4e]

N-alkyl substituted tetrazoles, as an important subclass of tetrazole derivatives, have shown a broad spectrum of biological activities.[4a-d] Representatively, various tetrazole substituted piperidine deravatives have metabotropic glutamate receptors (mGLuRs) and kainate receptors (KARs) antagonistic effect.[4b] Tetrazoles derived α-amino acids exhibit antagonistic activity towards *N*-methyl-D-aspartate receptors (NMDARs).[4d] Additionally, the use of *N*-alkyl substituted tetrazoles for ligand design have emerged to be intriguing in coordination and supramolecular chemistry[2e-f]. However, *N*-alkylation of tetrazoles has been rarely investigated.[5] To this end, efficient synthetic methods for *N*-alkylation of tetrazoles are highly desirable.

Enantiomerically pure *N*-allylic compounds are valuable building blocks as the versatility of allylic moiety. Allylic substitution and Overman rearrangement are prevalent methods for regio- and enantioselective formation of allylic C-N bonds.[6,7] However, the enantioselective formation of quarternary allylic C-N bonds remains a challenge.[8] Recently, elegant approaches towards the asymmetric synthesis of allylic amines with *N*-substituted quaternary stereocenters via palladium catalyzed aza-Claisen rearrangements of linear allylic trifluoroacetimidates[8a,b] and rhodium catalyzed allylic substitution of racemic tertiary allylic trichloroacetimidates[8c] have been reported (Scheme 1). In our previous studies, we reported rhodium catalyzed atom-economic[9] addition of pronucleophiles to allenes[10] and alkynes[11] as an alternative to allylic substitution. However, the enantioselective formation of quaternary allylic C-N bonds has been so far unsuccessful, possibly due to the higher energy barrier for the formation of rhodium-allyl intermediates or greater propensity for β-hydride elimination.[12] We assumed that the relative acidic tetrazoles (pKa ≈ 5.0) may favor the oxidative addition[13a] and reductive elimination[13b] steps in the catalytic cycle, making the enantioselective formation of quaternary allylic C-N bonds possible. Herein we report an enantioselective formation of tertiary and quaternary allylic C-N bonds via rhodium catalyzed coupling of tetrazoles with allenes, which allows the asymmetric synthesis of *N*-allylated tetrazoles in an atom-economic manner.



Scheme 1. Enantioselective formation of tertiary and quaternary allylic C-N bonds. FG = functional group. PMP = *p*-methoxyphenyl.

We commenced our study with 5-phenyltetrazole and cyclohexylallene in the presence of [{Rh(COD)Cl}$_2$] (1.0 mol%) in 1,2-dichloroethane (DCE) at 80 °C using (*R*,*R*)-DIOP (**L1**, 3.0 mol%) as the

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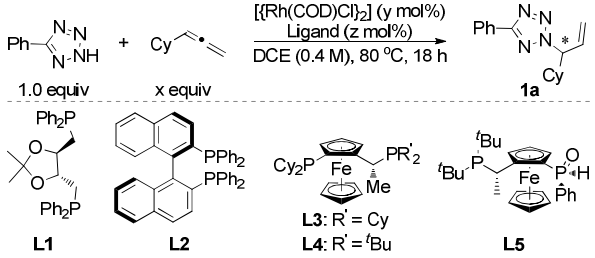
Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, NMR spectra, and HPLC traces. See DOI: 10.1039/x0xx00000x

chiral ligand, which was previously proved to be optimal for the coupling of carboxylic acids with terminal allenes. The reaction gave up to 91% isolated yield of the desired product **1a**, but only disappointing enantioselectivity (12% *ee*) was obtained (Table 1, entry 1). However, the high reactivity of 5-phenyltetrazole as a pronucleophile encouraged us to test various chiral bidentate ligands. (*R*)-Binap (**L2**) has shown high reactivity but low enantioselectivity (Table 1, entry 2). The Josiphos type ligands **L3** and **L4** gave only low to moderate *ee* (Table 1, entry 3-4). To our delight, a promising enantioselectivity was obtained employing a JoSPOphos ligand **L5**, albeit the yield was still low (Table 1, entry 5). After screening all the parameters of the reaction conditions, we were please to find out that slightly higher loading of allene and rhodium catalyst can increase the reaction yield up to 80% without any detrimental effect of the enantioselectivity at 60 °C (Table 1, entry 6).

Table 1. Optimization of Enantioselective Formation of Allylic C-N bonds.

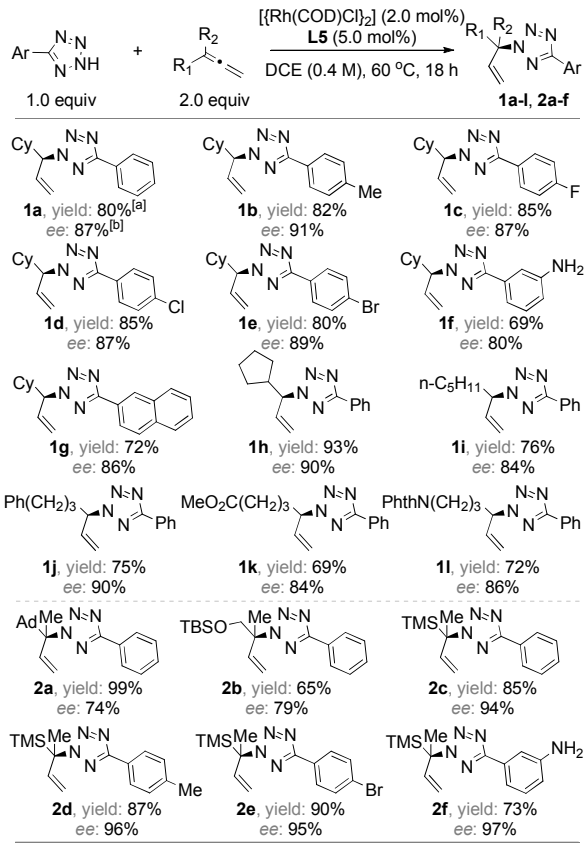


Entry	Ligand	x	y	z	Yield/%[a]	*ee*/%[b]
1	**L1**	1.2	1.0	3.0	91	12
2	**L2**	1.2	1.0	3.0	82	41
3	**L3**	1.2	1.0	3.0	97	10
4	**L4**	1.2	1.0	3.0	55	51
5	**L5**	1.2	1.0	3.0	42	87
6[c]	**L5**	2.0	2.0	5.0	80	87

[a] Isolated product. [b] Determined by chiral HPLC. [b] Reaction at 60 °C. Cy = cyclohexyl.

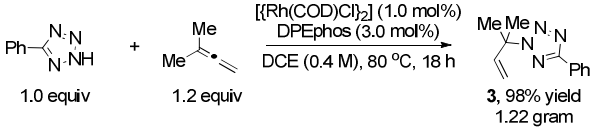
Having the optimized conditions in hand, we then investigated the scope of the addition of different tetrazoles with mono-substituted allenes (Scheme 2). A broad range of tetrazoles were coupled with cyclohexylallene with moderate to good yield, different functional groups were well tolerated, for example halogen (**1c**-**e**), and free amino group (**1f**). Mono-substituted allenes were smoothly coupled with up to 93% yield and 90% *ee*, allenes bearing ester and phthaloyl-protected amino groups were well tolerated.

For the synthesis of quaternary allylic C-N bonds, dialkyl-substituted allenes could couple with phenyltetrazole to afford the quaternary allylic C-N bonds, albeit enantioselectivities were moderate (**2a**-**b**). Due to the wide application of allylsilanes,[14] we turned our attention on the coupling of TMS-methyl-substitued terminal allene with tetrazoles. To our surprise, the reactions provided the desired allylsilanes bearing quaternary allylic C-N bonds in up to 90% yield, excellent enantioselectivities and with good functional group tolerance (**2a**-**f**).



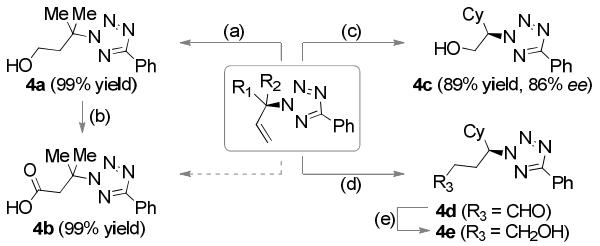
Scheme 2. Scope of Enantioselective Formation of Tertiary and Quaternary Allylic C-N bonds. [a] Isolated yield. [b] Determined by chiral HPLC. Phth = phthaloyl; Ad = adamantly; TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl.

Due to the importance of prenylation in biochemistry,[15] we examined the coupling of phenyltetrazole with 1,1-dimethylallene using a racemic ligand bis[(2-diphenylphosphino)phenyl)] ether (DPEphos).[16] The desired N^2-prenylated tetrazole derivative **3** was isolated in 98% yield and 1.22 gram scale, which indicates the practicality of this method (Scheme 3).



Scheme 3. Prenylation of phenyltetrazole in gram scale.

To exhibit the utility of the tetrazole allylated products, prenylated product **3** was subjected for hydroboration to obtain the β–hydroxyl derivative **4a** in 99% yield, which can be converted to the corresponding β–carboxylic acid **4b** in 99% yield. The α–hydroxyl derivative **4c** was synthesized from **1a** via ozonylysis and reduction. Hydroformylation of **1a** using 6-(diphenylphosphino)pyridin-2(1*H*)-one (6-DPPon) ligand[17] followed by reduction led to the formation of **4e** (Scheme 4).



Scheme 4. Derivatization of N^2-allylated tetrazoles. (a) **3**, 9-BBN (2.5 equiv), THF, - 78 °C to rt, overnight; then H_2O_2, NaOH, EtOH, 0 °C to rt, 6 h. (b) **4a**, Iodobenzene diacetate (2.2 equiv), TEMPO (0.2 equiv), $NaHCO_3$ (2.0 equiv), MeCN:H_2O (1:1), 0 °C, 2h; then rt, 2h. (c) **1a**, O_3, - 78 °C, 5 min; $NaBH_4$ – 78 °C to rt, MeOH:CH_2Cl_2 (1:1). (d) **1a**, $[Rh(CO)_2acac]$ (0.5 mol%), 6-DPPon (10 mol%), CO/H_2 (20 bar), toluene (0.1 M), 80 °C, 20 h, 70% yield. (e) **4d**, $NaBH_4$ (2.0 equiv), MeOH, 0 °C to rt, 2 h, 87% yield, 87% *ee*.

An isotopic labelling experiment with [D]phenyltetrazole and cyclohexylallene under optimized conditions revealed that deuterium was incorporated exlusively at the internal position of the alkene.[16] Based on the results of the labeling experiment and previous reports,[10b-f] the following mechanism can be proposed. Oxidative addition of phenyltetrazole to Rh(I) generates Rh(III)-H complex. Hydrometalation of the less substituted double bond could generate allyl-Rh complex, which could liberate the desired branched product **1a** via reductive elimination.[16]

To conclude, we have developed the first coupling of tetrazoles with mono-substituted and 1,1-disubstituted allenes via a rhodium/JoSPOphos catalyst system. This method allows the synthesis of various valuable tetrazole derivatives bearing tertiary and quaternary allylic C-N bonds, which is of wide interest for medicinal and synthetic chemistry. Enantioselective formation of quaternary allylic C-N bonds using other nitrogen pronucleophiles, particularly towards the asymmetric synthesis of primary amines is underway.[18]

This work was supported by the DFG, the International Research Training Group "Catalysts and Catalytic Reactions for Organic Synthesis" (IRTG 1038) and the Krupp Foundation. We thank Umicore, BASF and Wacker for generous gifts of chemicals. Kun Xu thank Dr. Vahid Khakyzadeh, Dr. Yuanzhi Xia, Dr. Changkun Li and Yu-Hsuan Wang for their kind help.

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18 Detailed investigations about the reaction mechanism and the origin of asymmetric induction of nitrogen pronucleophiles with allenes will be reported in the future.