Transition-Metal-Catalyzed Denitrogenative Transannulation: Converting Triazoles into Other Heterocyclic Systems

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1. Introduction

1,2,3-Triazoles are important heterocyclic units endowed with a broad spectrum of biological activities. They have been extensively used in medicinal chemistry and in material science. According to the existing paradigm, the 1,2,3-triazole ring is a very robust heterocyclic unit, thus not surprisingly, its chemistry mostly involves functionalization of the core. However, recently, new chemistry involving ring opening of the 1,2,3-triazole ring in the presence of various transition-metal catalysts has been reported. Most importantly a new direction, a denitrogenative transannulation of triazoles into other N-containing heterocycles, has recently appeared. Although, several methods exist for the construction of various N-containing heterocycles, there is always a need for new, efficient, and general methods for the synthesis of these important classes of compounds. The denitrogenative transannulation approach offers obvious advantages over many existing methods, as it allows efficient, single-step interconversion of easily available 1,2,3-triazoles into a variety of other valuable N-containing heterocyclic systems.

This Minireview covers the transition metal catalyzed denitrogenative transannulation of 1,2,3-triazoles into highly functionalized five- and six-membered-ring heterocycles, as well as fused nitrogen-containing heterocycles, in a single step. The organization of this Minireview is based on the denitrogenative transannulation reaction of different types of triazoles with alkynes, nitriles, alkenes, allenes, and isocyanides. Both, the synthetic applications, as well as the mechanistic aspects of the described transannulation reactions are discussed.

2. Transannulation of Pyridotriazoles

In solution, the pyridotriazoles exist in a closed/opened form equilibrium with the diazocompounds (Scheme 1). Thus, not surprisingly, the former is sometimes capable of undergoing transformations that are characteristic for diazocompounds. It deserves mentioning that the position of this equilibrium depends upon several factors, such as temperature, solvent, and the nature of the substituent (R') at C7 of the triazole ring. It has been reported that the introduction of a halogen atom at C7 (R' = Cl) shifts the equilibrium to the right, which has been explained in terms of nonbonding repulsion between the lone pair of electrons on the halogen and nitrogen atom in the peri-position of the triazole ring (Scheme 1). (1)

Recently, Gevorgyan and co-workers demonstrated that the diazoform 2a,b may be used as a source of a rhodium carbonoid species (Scheme 2). Thus, it was shown that the 7-halo-substituted pyridotriazole 3b, in the presence of a
rhodium catalyst, released dinitrogen from 2b to produce the corresponding rhodium carbenoid 4b. It was confirmed by its insertion into the Si–H bond of triethylsilane, a method developed by Doyle et al. for trapping the rhodium-stabilized carbenes originating from RhII complexes and diazoacetates.\[17\] As expected, the pyridotriazoles 3a and 3b exhibited different reactivity towards triethylsilane under these reaction conditions. Thus, while 3a remained unreactive, 3b was smoothly converted into 5b, the product of the rhodium carbenoid insertion into the Si–H bond. Thus, it became evident the 7-halo-substituted pyridotriazole 3b can indeed serve as a convenient precursor for rhodium carbenoids (Scheme 2).

2.1. Transannulation with Alkynes and Nitriles

After revealing that the pyridotriazole 3b, the surrogate of α-imino diazocompound 2b, can be used as convenient precursors for the rhodium carbenoid 4b, the reactivity of the latter in cycloaddition reactions with alkynes was explored (Scheme 3).\[16\] It was found that treatment of the pyridotriazole 3b with phenyl acetylene in the presence of Rh2(OAc)4, resulted in a mixture of the cyclopropene 6a and indolizine 7a, the products of the [2+1] and the formal [2+3] cycloaddition reactions, respectively. Interestingly, the cyclopropene 6a, under the employed reaction conditions, did not undergo cyclosomerization into indolizine 7a, thereby suggesting independent mechanistic paths for their formation. Selectivity of the transannulation reaction has been dramatically improved by employing a [Rh2(pfb)4] catalyst to give 7a as the sole reaction product in 78% yield. Under these reaction conditions, the 1-carbomethoxy-substituted pyridotriazole 3b underwent smooth transannulation with terminal aryl and alkenyl alkynes to produce indolizines 7 in good to excellent yields (Scheme 3).

Next, the Gevorgyan group explored the possibility of a transannulation reaction of 3, having various substitutions, with nitriles en route to N-fused imidazoles (Scheme 4). It was found that the pyridotriazoles 3 reacted smoothly with a variety of aryl, alkyl, and alkenyl nitriles 8 in the presence of Rh2(OAc)4 to afford the N-fused imidazopyridines 9 in good to high yields (Scheme 4). Importantly, 3-carbomethoxy-, 3-aryl-, as well as 7-bromo-, and 7-methoxy-substituted pyridotriazoles, proved to be equally efficient in this reaction.

It was proposed that this transannulation proceeds through the in situ generated rhodium carbenoid intermediate 10 (Scheme 5). A direct nucleophilic attack\[18\] of the alkyne or nitrile at 10 produces the intermediate ylide 11 (path a, Scheme 5), which then cyclizes to form 7 or 9 via the cyclic zwitterion 12. Alternatively (path b), [2+2] cycloaddi-
tion of the rhodium carbenoid 10 with an alkyne or nitrile produces the metalla-cyclobutene 13, which can also arise from cyclization of 11. Rhodacycle 13 then undergoes σ-bond metathesis to produce the rhodium carbenoid 14, which upon 6π-electrocyclization and subsequent reductive elimination of rhodium furnished either the product 7 or 9. The potential \([2+1]/\text{cycloisomerization sequence via } 16 \text{ (path c)}\) was ruled out since the cyclopropene 6a did not cycloisomerize into 7a under the reaction conditions (see Scheme 3).

3. Transannulation of N-Sulfonyl-1,2,3-triazoles

3.1. Transannulation with Alkynes, Nitriles, and Alkenes

N-Sulfonyl-1,2,3-triazole is an important heterocyclic unit that can easily be synthesized by the copper-catalyzed azide–alkyne cycloaddition reaction. This triazole is exceedingly resistant to thermal degradation and stays intact under harsh hydrolytic, reductive, and oxidative conditions. In 2008, Gevorgyan, Fokin, and co-workers challenged the robustness of this heterocyclic unit. They demonstrated that N-sulfonyl-1,2,3-triazoles 17a in the presence of 1 mol% \(\text{Rh}_2(\text{OAc})_4\) smoothly reacts with styrene to quantitatively produce the trans-cyclopropane carboxaldehyde 18 after silica gel chromatography (Scheme 6). Apparently, the N-sulfonyl-1,2,3-triazole 17a served as a surrogate for the diazoimine species 19, which in turn was converted into the corresponding metal carbenoid 20. A subsequent \([2+1]\) cycloaddition of 20 with styrene, and hydrolysis of the formed iminocyclopropane 21 furnished the reaction product 18 (Scheme 6).

Inspired by this finding, they next attempted a transannulation reaction of the triazole 17a with benzonitrile by employing two different protocols, namely, microwave-assisted and conventional heating. It was found that both methods were equally efficient in providing the transannulation product, imidazole 22a in high yields (Scheme 7).

The developed methods have been applied to transannulation of differently C4-substituted N-sulfonyl-1,2,3-triazoles...
with a number of nitriles (Scheme 8). The reactions appeared to be very general with respect to the triazole and nitrile components. Both the microwave and the conventional heating methods afforded high to excellent yields of the diversely substituted transannulation products (Scheme 8). It deserves mentioning that in contrast to pyridotriazoles (see above), the triazoles 17 under these reaction conditions did not undergo transannulation reaction with terminal alkynes into pyrroles.

The proposed mechanistic rationale is related to the analogous transannulation of nitriles with diazoketones as reported by Helquist, Akermark, and co-workers. According to the path a in Scheme 9, a nucleophilic attack of the nitrile on the rhodium carbenoid 20 leads to the ylide 23, which upon cyclization into the zwitterion 24 and subsequent loss of the metal, furnishes the imidazole 22. Alternatively, ylide 23 may give rise to the rhodium carbenoid 25 through a [1,3] Rh shift. A subsequent cyclization of the intermediate 25 and then reductive elimination produces 22. Also, a possible direct formation of 22 through a [3+2] cycloaddition of 20 with a nitrile was not ruled out (path b).

In 2009, Murakami and co-workers reported a nickel-catalyzed denitrogenative transannulation reaction of N-sulfonyl-1,2,3-triazoles with internal alkynes. They discovered that a combination of a [Ni(cod)2] catalyst with the electron-rich and bulky phosphine ligand P(nBu)Ad2, and AlPh3 as a Lewis acid additive, was efficient for the transannulation of triazoles 17 with internal alkynes into tetrasubstituted pyrroles 26 (Scheme 10). It was found that the yields of the transannulation reaction with symmetrical alkynes...
were generally good, except for an n-hexyl-substituted triazole. Transannulation with unsymmetrical alkynes produced nearly equal amounts of regioisomers (last three structures in Scheme 10), whereas attempts on the employment of terminal alkynes were unsuccessful, presumably because of a facile self-oligimerization side process.[28]

Mechanistically, it is believed that this reaction starts from a ring–chain tautomerization of the triazole 17a into diazocene 19 (Scheme 11), which is captured by nickel to give the nickel carbenoid 27. The latter cyclizes into the azanickelacycle 28. Subsequent insertion of the alkyne into the Ni–C bond leads to the corresponding six-membered nickelacycle 29, which upon reductive elimination of the Ni⁰ furnishes the pyrrole 26. It was hypothesized that the possible role of the Lewis acid in this transformation may involve a promotion of the ring–chain tautomerization of 17a into 19, or an acceleration of the reductive elimination of nickel[30] from 29.

Very recently, Gevorgyan et al. partially solved the problem of transannulation of monocyclic triazoles with terminal alkynes (see below) into pyrroles.[30] It was reported, that employment of the [Rh₂(oct)₄]/AgOAcOCF₃ binary catalyst system enables efficient transannulation of the N-sulfonyl-1,2,3-triazoles 17b with arylalkynes to afford the corresponding transannulation products 30 in good to excellent yields (Scheme 12). Electron-rich alkynes were more efficient in this reaction than their electron-neutral counterparts, whereas electron-deficient arylalkynes did not undergo this transformation at all.

The following plausible mechanism for this transannulation reaction has been proposed (Scheme 13). Upon treatment with [Rh₂(oct)₄] the triazole 17b transforms into the rhodium iminocarbene 20b.[24] A direct nucleophilic attack of the terminal alkyne at the latter produces ylide 31 (path a, Scheme 13)[16,24] which upon cyclization forms a cyclic zwitterionic species 32. Elimination of the rhodium catalyst from 32 produces the reaction product 30. In contrast, the in situ generated silver acetylide may attack 20b to form the rhodium-containing propargylimine species 33 (path b). Alternatively, 33 may arise through a proton loss from 31 (path b'). Proton-assisted 5-endo-dig cyclization of 33 would afford cyclic intermediate 32. However, a deuterium labeling experiment employing the deuterated alkyne resulted in formation of [D]-30 with complete preservation of a deuterium label at C₃, thus undoubtedly ruling out the possible involvement of the paths b and b', both of which would result in partial or complete deuterium scrambling. Although, the crucial role of silver trifluoroacetate in this transformation is not completely understood, this Lewis acid probably activates the electrophilic rhodium carbene moiety, through coordination to the imine, toward the nucleophilic attack by an alkyne. The higher reactivity of electron-rich alkynes in this transformation is due to the ylide reaction (path a).

The synthetic usefulness of this transannulation reaction was showcased by an efficient three-component semi-one-pot synthesis of the pyrrole 35 from tosylazole 34 and two different terminal alkynes by a combined copper-catalyzed click/rhodium-catalyzed transannulation reaction sequence (Scheme 14).

Very recently, Fokin and co-workers showed[31] that highly reactive Rh¹¹ N-triflyl azavinyl carbenes can easily be produced from the NH-1,2,3-triazoles 36 by treatment with triflic anhydride in the presence of Rh¹¹ complexes. These carbene intermediates efficiently engage olefins in highly enantio- and diastereoselective transformations, thus providing easy access to homochiral cyclopropane carboxaldehydes 37 and 2,3-dihydropyrroles 38 (Scheme 15). Although, the transannulation products were formed formed in high yield, the enantioselectivity of the transannulation products varied.

*Scheme 11.* Proposed mechanism of the nickel-catalyzed denitrogenative transannulation of N-sulfonyl-1,2,3-triazole 17a with internal alkynes. Ts = 4-toluenesulfonyl.

*Scheme 12.* Rhodium-catalyzed denitrogenative transannulation of N-sulfonyl-1,2,3-triazole 17b with terminal alkynes.

*Scheme 13.* Proposed mechanism for transannulation of N-sulfonyl-1,2,3-triazoles 17b with terminal alkynes.
depending on the nature of the substituent (R') at C4 of the triazole ring.

4. Transannulation of N-Aroylbenzotriazoles

4.1. Transannulation with Alkynes

Nakamura et al. developed an interesting palladium-catalyzed transannulation reaction of N-aroylbenzotriazoles \[39\] with alkynes to give indoles \[40\] (Scheme 16).\[32\] The authors took advantage of the closed/opened form equilibrium between the acyltriazole \[39\] and its diazonium isomer \[41\], which serves as an equivalent of the haloanilide \[42\] that is employed in indole synthesis reported by Larock et al.\[33\] From an environmental standpoint, the base-free conditions and benign by-product (N2) of this transannulation reaction are the obvious advantages of this method over Larock/C29's classical indole synthesis, which produces stoichiometric amounts of HX* base waste. The reaction conditions for this transannulation require heating \[39a\] and the internal alkynes \[43\] in the presence of [Pd(PPh3)4] at 130 °C without a solvent (Scheme 17). These reaction conditions allow the synthesis of the multisubstituted indoles \[40a\] in good yields. Performing the reaction using solvents, as well as employment of other palladium catalysts, were less efficient. The electronic nature of the substituents showed a pronounced effect on the efficiency of this reaction. Whereas triazoles possessing electron-withdrawing groups reacted well, those substituted with electron-donating groups reacted sluggishly, thus providing poor yields or no reaction even under prolonged reaction times. Reactions with unsymmetrical alkynes showed varied regioselectivity, thus favoring bulkier substituents (R') at C2 of the indole; this trend is analogous to that observed in the Larock’s indole synthesis. Expectedly, this Pd0-catalyzed method did not tolerate terminal alkynes (Scheme 17).

Mechanistically, this palladium-catalyzed transannulation reaction is quite similar to that of the nickel-catalyzed transannulation described above. First, Pd0 oxidatively inserts into the C/C0 N bond of the diazonium moiety of the 2-iminobenzenediazonium species \[41a\], which is thermally generated from the benzotriazole \[39a\].\[34\] Insertion of the alkyne into the Pd/C0 C bond of the resulting intermediate \[44\] leads to the formation of the palladacycle \[46\], which upon the reductive elimination yields indole \[40a\] and regenerates the Pd0 catalyst (Scheme 18).

5. Transannulation of 1,2,3-Benzotriazinones

5.1. Transannulation with Alkynes, allenes, and Alkenes

Murakami and co-workers found that the 1,2,3-benzotriazinones \[47\] are also good substrates for denitrogenative transannulation reactions. Thus, \[47\] in the presence of a nickel catalyst undergoes a facile reaction with alkynes to produce isoquinolones \[48\] (Scheme 19).\[35\] The authors proposed that the reaction is initiated by the insertion of Ni0 into the N/C0 N linkage of \[47\], which upon loss of dinitrogen produces the azanickelacycle \[49\].\[36\] Insertion of the alkyne into the Ni/C0 C bond leads to the formation of a seven-membered nickelacycle intermediate \[50\],\[37\] which after reductive elimination affords the final product \[48\] and regenerates the Ni0 catalyst (Scheme 19).

This reaction appeared to be very general in scope, as various symmetrical and unsymmetrical internal alkynes, as


Scheme 15. Transannulation of the NH-1,2,3-triazoles \[36\] with styrenes. NTTL = N-1,8-naphthoyl-tert-leucine.

Scheme 16. Palladium-catalyzed transannulation versus the Larock indole synthesis.

Scheme 17. Palladium-catalyzed denitrogenative transannulation of the N-aroylbenzotriazoles \[39a\] with internal alkynes.
well as terminal alkynes, gave very high yields of the isoquinolones 48' (Scheme 20). Unsymmetrical alkynes however, showed varied regioselectivity. Remarkably, terminal alkynes provided both excellent yields and regioselectivities in this reaction. It was found that the 1,2,3-benzotriazinones 47 possessing either electron-withdrawing or electron-donating aryl substituents at the nitrogen atom underwent smooth transannulation reactions at room temperature, whereas the reaction of benzyl- and methyl-substituted substrates required higher temperatures. N-unsubstituted benzotriazinone failed to undergo this reaction.

Murakami et al. have also developed the nickel-catalyzed denitrogenative transannulation of 1,2,3-benzotriazinones with allenes.\[38\] First, from the reaction of 47a with stoichiometric amounts of [Ni(cod)\textsubscript{2}] and dppbenz, the authors succeeded in isolating a five-membered azanickelacycle intermediate 49a, the structure of which was confirmed by the single-crystal X-ray analysis (Scheme 21). Treatment of 49a with an allene at 60°C in THF gave an isomeric mixture of the 3,4-dihydroisoquinolin-1(2H)-ones 51a and 52a (54:46) in 99% yield.

A catalytic version of this reaction (5 mol % [Ni(cod)\textsubscript{2}], 20 mol % PMe\textsubscript{3}, THF, 60°C) was then applied for transannulation of different 1,2,3-benzotriazinones 47b with a number of monosubstituted allenes (Scheme 22). Both the electron-withdrawing and electron-donating substituents at the N atom of the triazole moiety and at the aromatic ring of the benzotriazinone worked well, thus producing the differently substituted isoquinolones 51b as a major regioisomer.\[39\] Probably as a result of steric, the regiochemistry was completely reversed in the reaction with tert-butyl- and trialkylsilyl-substituted allenes (Scheme 22).

Employment of the cyclic 1,3-disubstituted allene 53 resulted in an interesting outcome; the nature of the product varied depending upon the type of the phosphine ligand.
employed (Scheme 23). The use of PMe₃ in THF at 60 °C produced the imino ester **54** in 75% yield, whereas employment of the bidentate phosphine ligand (**R,R**)-Me-duphos in toluene at 100 °C afforded **55** as the sole product in 99% yield.

The control experiment revealed that **54** in the presence of [Ni(cod)₂] and (**R,R**)-Me-duphos in toluene at 100 °C was completely isomerized into **55**, thus confirming thermodynamic control in the formation of the latter in the reaction of **47a** and **53**.

The authors have also explored the asymmetric version of this transformation. It was shown that employment of bidentate phosphine ligands, such as (**R,R**)-Me-duphos and (**S,S,R,R**)-tangphos provided good enantioselectivities. Importantly, both the regio- and enantioselectivities were very high when the phosphinooxazoline ligand (**S**)-iPr-foxap was employed (Scheme 24).

As an extension of this methodology, the same group has also developed the nickel-catalyzed transannulation of benzotriazinones with 1,3-dienes. Interestingly, when the complex **49a** was mixed with the 1,3-diene **56** in the absence of a phosphine ligand, the formation of only trace amounts of **57** was detected (Scheme 25). However, addition of the dppf ligand provided **57** in 40% yield (Scheme 25).

Next, the generality of this approach was tested using a catalytic version of this reaction. Thus, employment of [Ni(cod)₂] (10 mol%) and dppf (10 mol%) in THF at 60 °C allowed a facile reaction of differently substituted benzotriazinones **47b** with symmetrical 1,3-dienes **58** to form various N-protected isoquinolones **59** (Scheme 26). Except for the N-benzyl-substituted benzotriazinone (24%), the yields employing all other substrates were high. Benzotriazinones with both electron-donating and electron-withdrawing groups at the benzene ring were equally competent in this reaction. Employment of unsymmetrical dienes **58** was nearly as efficient in providing isoquinolones **59** as major regioisomers over 60. For this transformation, the authors proposed a mechanism similar to that proposed for the nickel-catalyzed transannulation of benzotriazinones with allenes. [38]
It was also shown that in the presence of [Ni(cod)$_2$] and P(nBu)$_3$, the benzotriazinones 47b can undergo an efficient transannulation reaction with activated alkenes (Scheme 27). Thus, electron-deficient alkenes, such as methyl acrylate, acrylonitrile, and acrylamide smoothly underwent transannulation with 47b to give the dehydroisoquinolinones 61 in excellent yields. Pyridyl-containing alkenes were similarly efficient, whereas styrene gave low yield of the product. Electron-neutral and electron-rich alkenes did not participate in this reaction at all. (Scheme 27).[41]

5.2. Transannulation with Isocyanides

The same research group has also shown[42] that isocyanides can also be employed in this transannulation reaction. Thus, 1,2,3-benzotriazinone 47b and benzothiatriazine dioxide 47c, in the presence of a palladium catalyst and a phosphine ligand underwent smooth transannulation with isocyanides 62 to give the corresponding isocyanide incorporated products 63 in excellent yields (Scheme 28). Except for the N-alkyl-substituted triazinones, all other substrates tested exhibited excellent reactivity, thus giving rise to almost quantitative yields of the products. The reaction is also quite general with respect to the isocyanides 62, as aryl, benzyl, cyclohexyl, and even aliphatic isocyanides were competent in this reaction for producing high yields of the transannulation products.

6. Transannulation of 1,2,3,4-Benzothiazinones

6.1. Transannulation with Allenes

In 2010, Murakami and co-workers reported[43] the nickel-catalyzed enantioselective transannulation reaction of 1,2,3,4-benzothiazinone-1,1(2H)-dioxide 64 with monosubstituted allenes to produce 1,2,3,4-benzothiatriazine-1,1(2H)-dioxide derivatives 65 and 66. It was proposed that this reaction is initiated by an oxidative addition of Ni$_0$ into the N–N bond and subsequent elimination of the dinitrogen molecule to yield the five-membered intermediate 67. A subsequent allene insertion into 67 generates the π-allylnickel intermediate 68. An allylic amidation at the more-substituted carbon atom[41b,44] in the latter delivers the reaction product and regenerates the Ni$_0$ catalyst (Scheme 29).

It was found that C$_2$-symmetric bidentate bisphosphine ligands such as (S)-binap,[45] (S,S',R,R')-tangphos,[46] and (R,R)-Me-duphos[47] were not competent in this reaction. However, employment of unsymmetrical P,N-type bidentate ligands resulted in enantioselective transannulation products.
ligands such as (S,S)-1,1,1,3,3-pentafluoropropan-2-ol and 5-nitro-1,1,1-trifluoroacetone afford both good yield and excellent enantioselectivity. This reaction was found to be quite general with respect to the alkyl substituent (R) at the N atom of the triazole moiety, thus producing 66 as the major regioisomer in good enantioselectivity. Reaction of the tert-butyl-containing substrate 64 (R = Bu), probably resulting because of steric reasons, produced 65 as a major regioisomer. The p-tolyl-substituted substrate 64 (R = p-tolyl) was much less efficient in this reaction.

Various monosubstituted allenes were equally effective in transannulation with 64a, thus producing high yields and good enantioselectivities of the corresponding products. Allenes possessing siloxy, benzyloxy, and N-phthalimidoyl substituents showed good enantioselectivities of the corresponding products. The transannulation with 64 was much less efficient in this reaction.

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Scheme 30. Transannulation of 1,2,3,4-benzothiatriazine-1(2H)-dioxide 64a with various allenes.

7. Conclusions

This Minireview highlights the increasing interest in the development of transition metal catalyzed transannulation reactions. This new approach may serve as a complimentary methodology for construction of heterocycles as it allows a general and highly efficient synthesis of complex and highly functionalized aromatic nitrogen heterocycles with diverse substitution patterns. Although additional development of novel, more general, and efficient transannulation protocols is highly warranted, the progress achieved so far in this area holds promise for its extensive application in organic synthesis.

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