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Nitrogen Heterocycles

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

*Buddhadeb Chattopadhyay and Vladimir Gevorgyan**

cyclization · nitrogen heterocycles · transition metals · transannulation · synthetic methods

Transition metal catalyzed denitrogenative transannulation of a triazole ring has recently received considerable attention as a new concept for the construction of diverse nitrogen-containing heterocyclic cores. This method allows a single-step synthesis of complex nitrogen heterocycles from easily available and cheap triazole precursors. In this Minireview, recent progress of the transition metal catalyzed denitrogenative transannulation of a triazole ring, which was discovered in 2007, is discussed.

1. Introduction

1,2,3-Triazoles are important heterocyclic units endowed with a broad spectrum of biological activities.[1–5] They have been extensively used in medicinal chemistry,[6,7] biochemistry,[8,9] and in material science.[10] 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.

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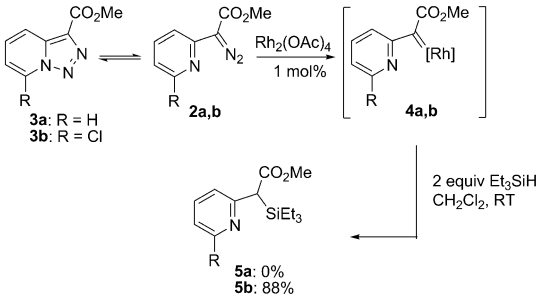
2. Transannulation of Pyridotriazoles

In solution, the pyridotriazoles **1**[11] exist in a closed/opened form equilibrium[12] with the diazocompounds **2**[13] (Scheme 1). Thus, not surprisingly, the former is sometimes

Scheme 1. Closed/opened form equilibrium of pyridotriazoles.

capable of undergoing transformations that are characteristic for diazocompounds.[14] It deserves mentioning that the position of this equilibrium depends upon several factors, such as temperature, solvent, and the nature of the substituent (R^1) at C7[12b] of the triazole ring. It has been reported that the introduction of a halogen atom at C7 ($R^1 = Cl$) 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 **1** (Scheme 1).[15]

Recently, Gevorgyan and co-workers demonstrated[16] that the diazoform **2a,b** may be used as a source of a rhodium carbenoid species (Scheme 2). Thus, it was shown that the 7-halo-substituted pyridotriazole **3b**, in the presence of a

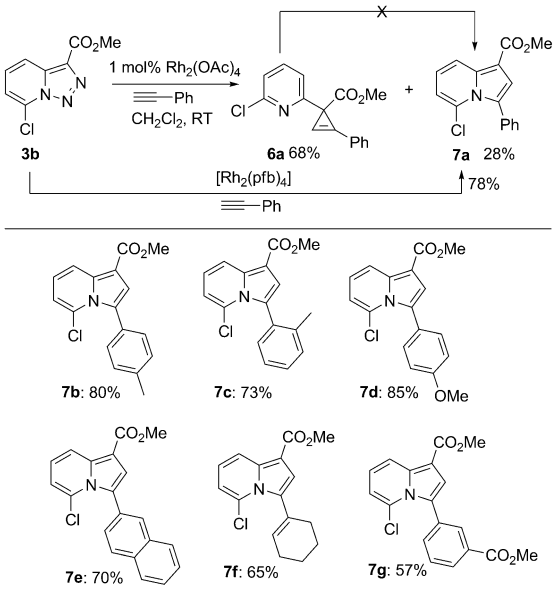


Scheme 2. Rhodium carbenoid insersion into a Si–H bond.

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 Rh^{II} 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 $Rh_2(OAc)_4$, 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 cycloisomerization into indolizine **7a**, thereby suggesting independent mechanistic paths for their formation. Selectivity of the transannulation reaction has been dramatically improved by employing a $[Rh_2(pfb)_4]$ catalyst to give **7a**



Scheme 3. Transannulation of the pyridotriazole **3b** with alkynes. pfb = perfluorobutyrate.

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 $Rh_2(OAc)_4$ 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-substitited 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-

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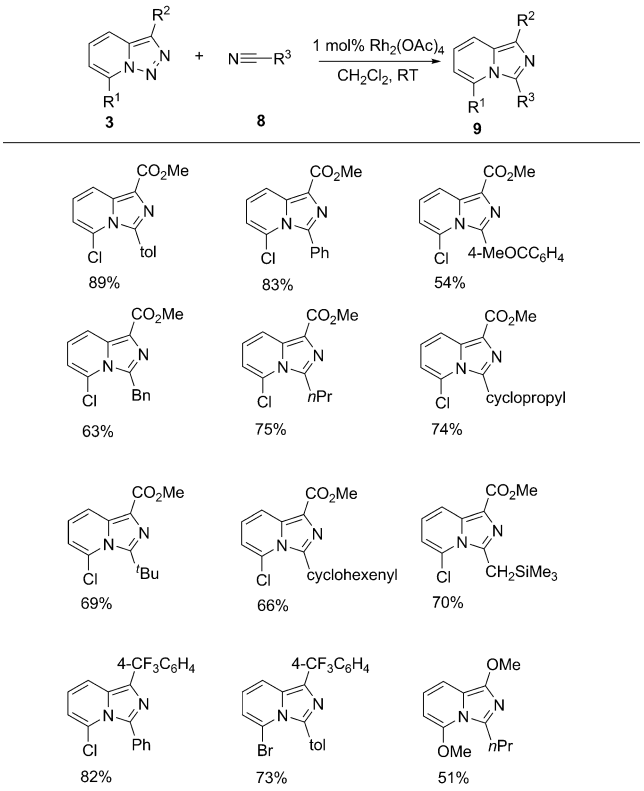
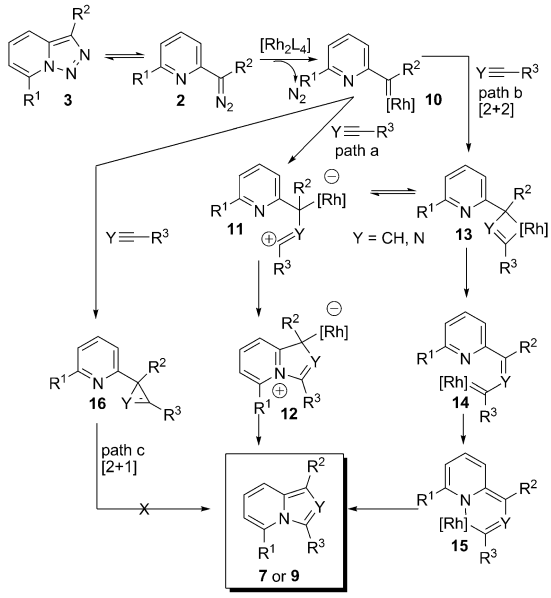
Buddhadeb Chattopadhyay was born in Insura (Hooghly), West Bengal, India. He received his B.Sc. in 2001 from the Burdwan University, his M.Sc. at Visva-Bharati (Santiniketan), and then joined Prof. K. C. Majumdar at the University of Kalyani. His doctoral work focused on the development of common to medium-sized-ring heterocyclic compounds using transition-metal catalysts. He joined Prof. Gevorgyan's group in 2009 as a postdoctoral research associate to work on transition metal catalyzed transannulation and C–H activation chemistry.



Scheme 4. Denitrogenative annulation of pyridotriazoles **3** with nitriles.



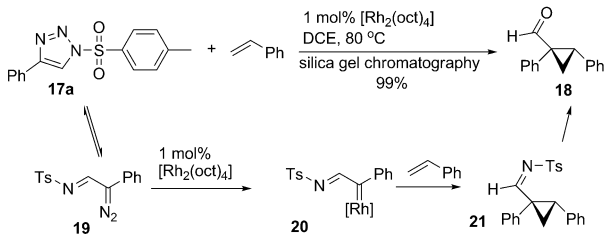
Scheme 5. Proposed mechanism for transannulation of pyridotriazoles **3** with alkynes and nitriles.

tion of the rhodium carbenoid **10** with an alkyne or nitrile produces the metallacyclobutene **13**, which can also arise from cyclization of **11**.[19] 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]/cycloisomerization sequence via **16** (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

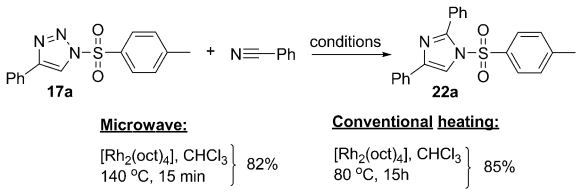
N-Sulfonyl-1,2,3-triazole is an important heterocyclic unit that can easily be synthesized by the copper-catalyzed azide–alkyne cycloaddition reaction.[20] This triazole is exceedingly resistant to thermal degradation and stays intact under harsh hydrolytic, reductive, and oxidative conditions.[21,22] 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% $Rh_2(OAc)_4$ smoothly reacts with styrene to quantitatively produce the *trans*-cyclopropane[23] carboxaldehyde **18** after silica gel chromatography (Scheme 6).[24] 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).



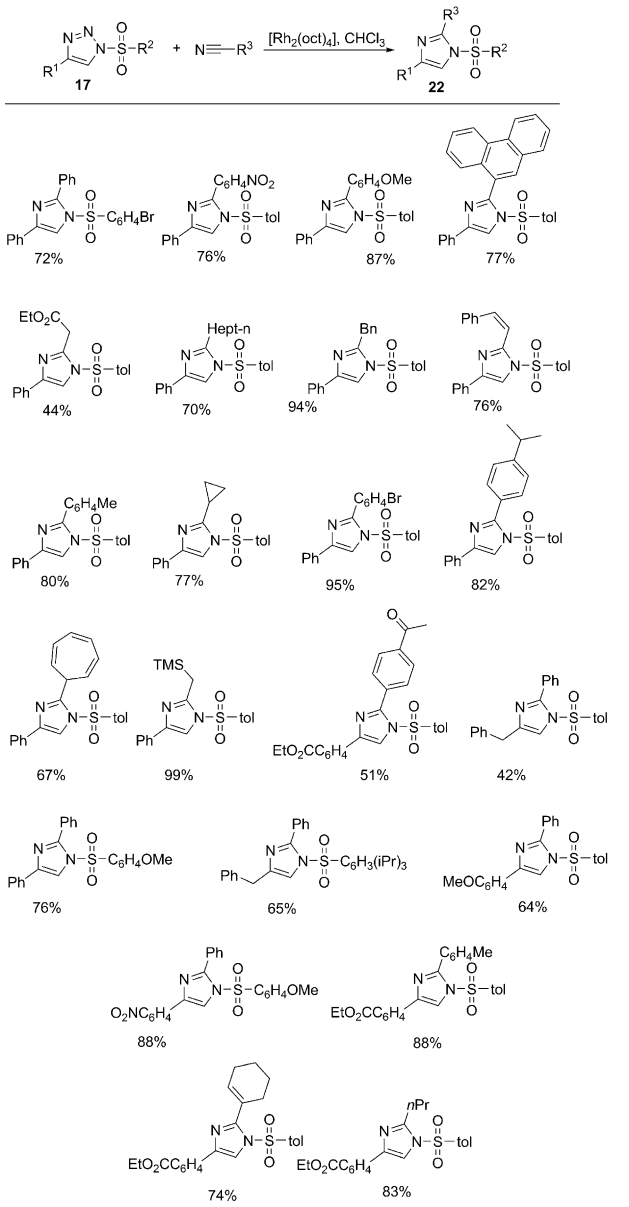
Scheme 6. Denitrogenative cyclopropanation of the N-sulfonyl-1,2,3-triazole **17a** with styrene. DCE = 1,2-dichloroethane, oct = octanoate.

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



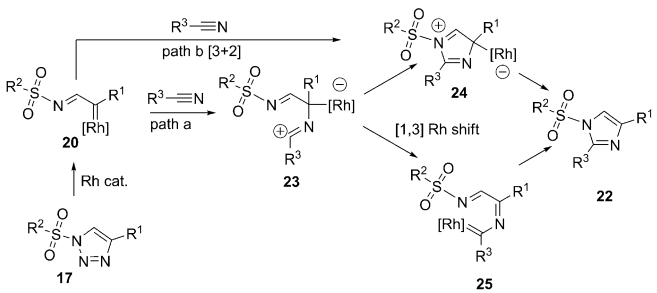
Scheme 7. Transannulation of N-sulfonyl-1,2,3-triazole **17a** with benzonitrile employing microwave-assisted and conventional heating methods.



Scheme 8. Denitrogenative transannulation of N-sulfonyl-1,2,3-triazoles **17** with nitriles. TMS = trimethylsilyl.

17 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 **22** (Scheme 8).[24] 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.

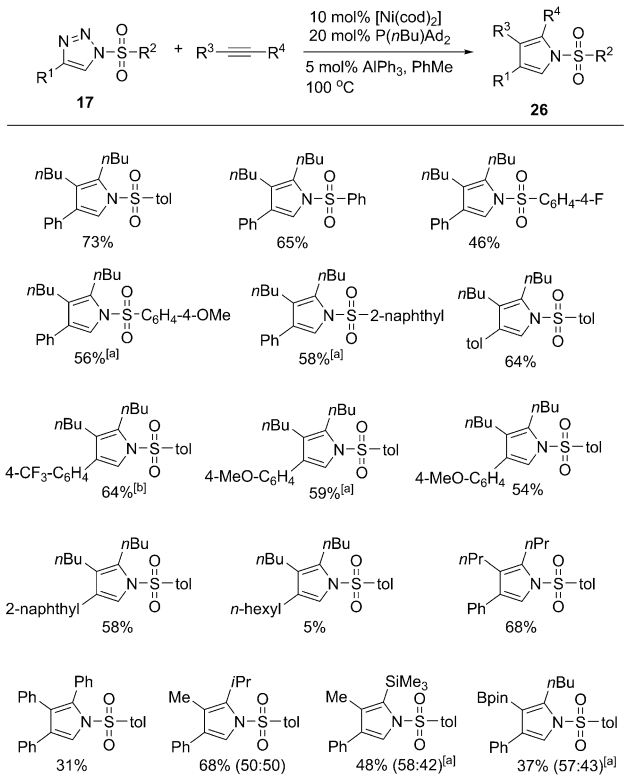
The proposed mechanistic rationale is related to the analogous transannulation of nitiles with diazoketones as reported by Helquist, Akermark, and co-workers.[25] According to the path a in Scheme 9, a nuclephilic attack of the nitrile on the rhodium carbenoid **20**[26] leads to the ylide **23**, which upon cyclization into the zwitterion **24** and subsequent loss of the metal, furnishes the imidazole **22**. Alternatively,



Scheme 9. Proposed mechanism for the transannulation of N-sulfonyl-1,2,3-triazoles **17** with nitriles.

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[27] 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).

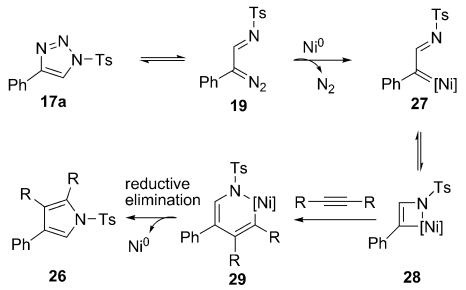
In 2009, Murakami and co-workers reported a nickel-catalyzed denitrogenative transannulation reaction of N-sulfonyl-1,2,3-triazoles with internal alkynes.[28] They discovered that a combination of a $[Ni(cod)_2]$ catalyst with the electron-rich and bulky phosphine ligand $P(n\text{Bu})Ad_2$, and $AlPh_3$ 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



Scheme 10. Nickel-catalyzed transannulation of the N-sulfonyl-1,2,3-triazoles **17** with internal alkynes. The yields are those of the isolated product. [a] $[Ni(cod)_2]$ (15 mol%) and $P(n\text{Bu})Ad_2$ (30 mol%). [b] 110 °C. Ad = adamantyl, cod = 1,5-cyclooctadiene.

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 diazoimine **19** (Scheme 11), which is captured by nickel to give the

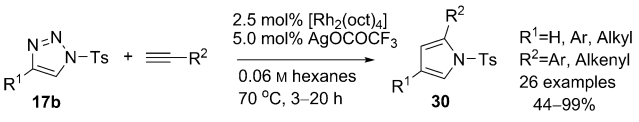


Scheme 11. Proposed mechanism of the nickel-catalyzed denitrogenative transannulation of N-sulfonyl-1,2,3-triazole **17a** with internal alkynes. Ts = 4-toluenesulfonyl.

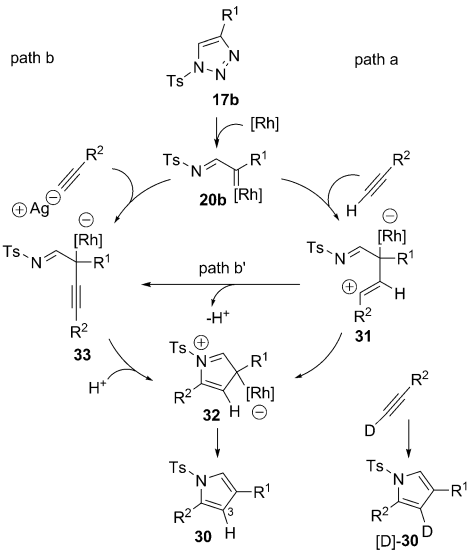
nickel carbenoid **27**. The latter cyclizes into the azanickelacycle **28**. Subsequent insertion of the alkyne into the Ni–C bond leads to the corresponding six-membered nickelacycle **29**, which upon reductive elimination of the Ni^0, furnishes the pyrrole **26**. It was hypothesized that the possible 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[29] 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 $[Rh_2(oct)_4]/AgOCOCF_3$ 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 $[Rh_2(oct)_4]$, the triazole **17b** transforms into the rhodium iminocarbene **20b**.[24] A direct nucleophlic attack of the terminal alkyne at the latter produces ylide **31** (path a,



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

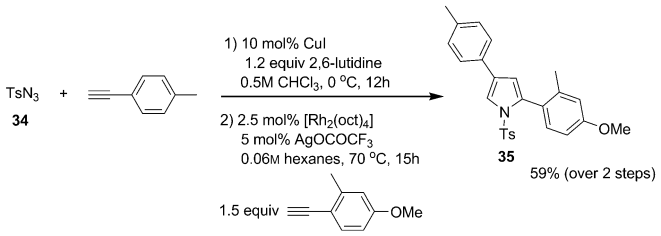


Scheme 13. Proposed mechanism for transannulation of N-sulfonyl-1,2,3-triazoles **17b** with terminal alkynes.

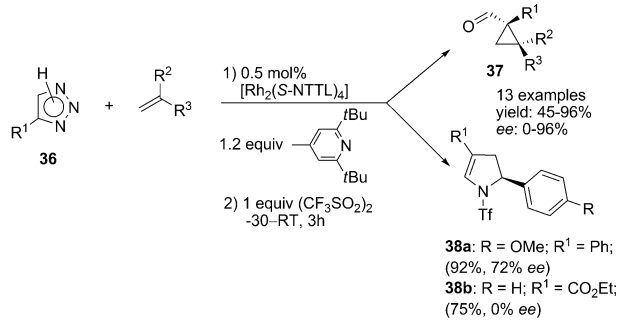
Scheme 13),[4,24] which upon cyclization forms a cyclic zwitterionic species **32**. Elimination of the rhodium catalyst from **32** produces the reaction product **30**. In contrast, the in situ generated silver acetylide may attack **20b** to form the rhodium-containing propargylimine species **33** (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 reasonably fits into the most plausible reaction being 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 tosylazide **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 Rh^{II} *N*-triflyl azavinyl carbenes can easily be produced from the *N*H-1,2,3-triazoles **36** by treatment with triflic anhydride in the presence of Rh^{II} 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 14. Semi-one-pot transannulation toward synthesis of pyrroles.



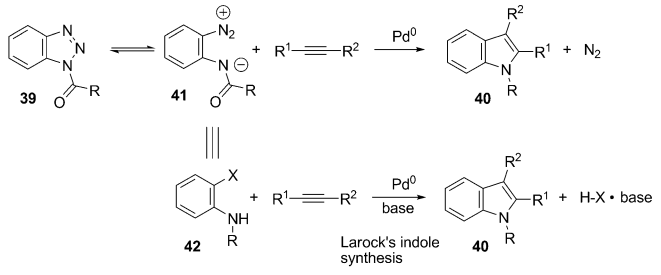
Scheme 15. Transannulation of the NH-1,2,3-triazoles **36** with styrenes. NTTL = *N*-1,8-naphthoyl-*tert*-leucine.

depending on the nature of the substituent (R^1) at C4 of the triazole ring.

4. Transannulation of N-Aroylbenzotriazoles

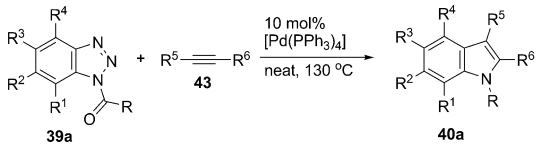
4.1. Transannulation with Alkynes

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 (N_2) of this transannulation reaction are the obvious advantages of this method over Larock's classical indole synthesis, which produces stoichiometric amounts of HX●base waste.



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

The reaction conditions for this transannulation require heating **39a** and the internal alkynes **43** in the presence of $[Pd(PPh_3)_4]$ 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



Scheme 17. Palladium-catalyzed denitrogenative transannulation of the N-aroylbenzotriazoles **39a** with internal alkynes.

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^6) at C2 of the indole; this trend is analogous to that observed in the Larock's indole synthesis. Expectedly, this Pd^0-catalyzed method did not tolerate terminal alkynes (Scheme 17).

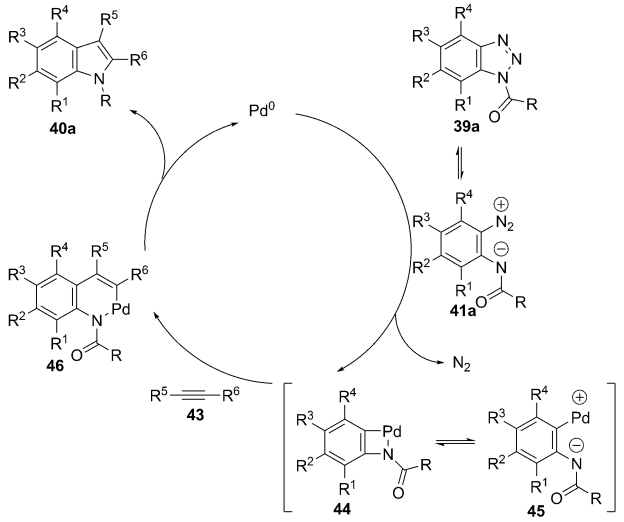
Mechanistically, this palladium-catalyzed transannulation reaction is quite similar to that of the nickel-catalyzed transannulation described above. First, Pd^0 oxidatively inserts into the C–N bond of the diazonium moiety of the 2-iminobenzenediazonium species **41a**, which is thermally generated from the benzotriazole **39a**.[34] Insertion of the alkyne **43** into the Pd–C bond of the resulting intermediate **44** or **45** leads to the formation of the palladacycle **46**, which upon the reductive elimination yields indole **40a** and regenerates the Pd^0 catalyst (Scheme 18).

5. Transannulation of 1,2,3-Benzotriazinones

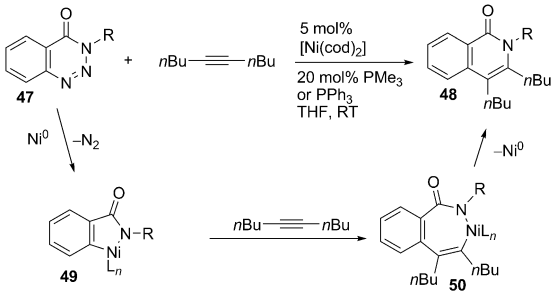
5.1. Transannulation with Alkynes, allenes, and Alkenes

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 Ni^0 into the N–N linkage of **47**, which upon loss of dinitrogen produces the azanickelacycle **49**.[36] Insertion of the alkyne into the Ni–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 Ni^0 catalyst (Scheme 19).

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



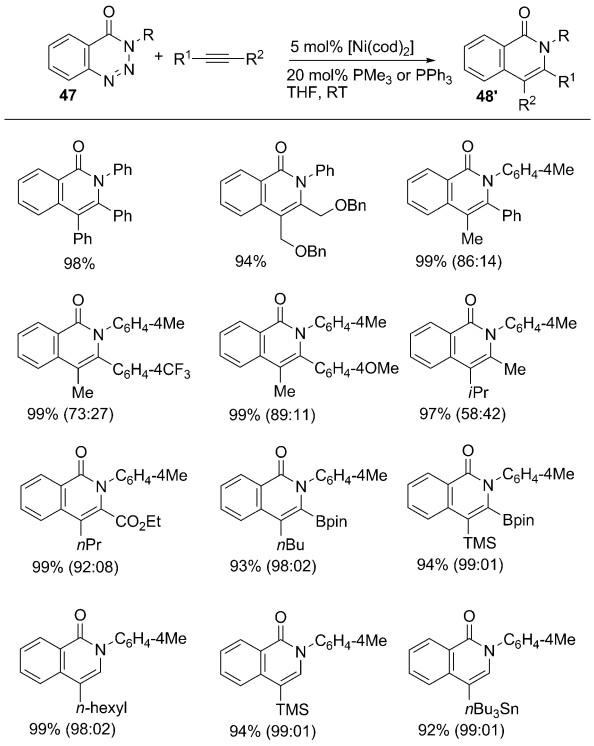
Scheme 18. Proposed mechanism of the palladium-catalyzed transannulation of N-aroylbenzotriazoles **39a** with internal alkynes.



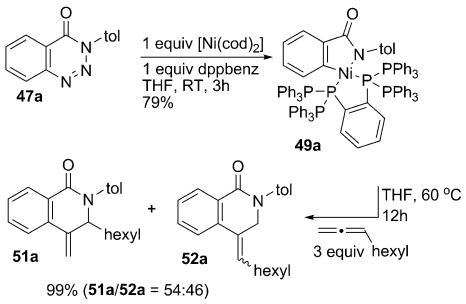
Scheme 19. Nickel-catalyzed transannulation of the 1,2,3-benzotriazinones **47** with an internal symmetrical alkyne.

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 $[Ni(cod)_2]$ 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(2*H*)-ones **51a** and **52a** (54:46) in 99 % yield.



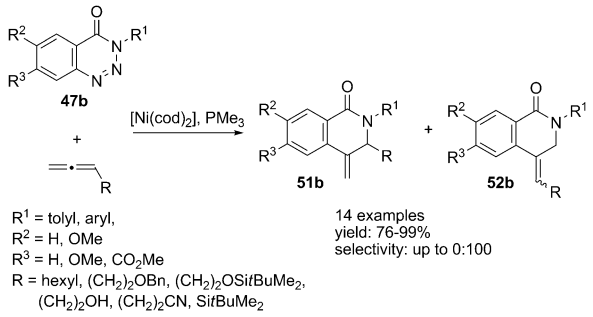
Scheme 20. Nickel-catalyzed denitrogenative transannulation of 1,2,3-benzotriazinones **47** with alkynes. pin = pinacol.



Scheme 21. Nickel-catalyzed denitrogenative transannulation of the 1,2,3-benzotriazinones **47a** with allenes. dppbenz = 1,2-bis(diphenylphosphino)benzene.

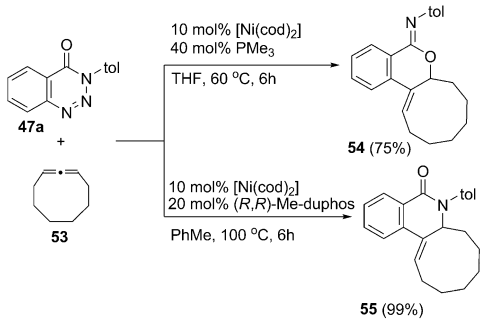
A catalytic version of this reaction (5 mol % $[Ni(cod)_2]$ 20 mol % PMe_3, THF, 60 °C) was then applied for transannulation of different 1,2,3-benzotriazinones **47b** with a number of monosubstituted allenes (Scheme 22). Both the electron-withdrawing and electron-donating substituents at the N atom 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 sterics, 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



Scheme 22. Scope of the nickel-catalyzed transannulation of 1,2,3-benzotriazinones **47b** with allenes.

employed (Scheme 23). The use of PMe_3 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.



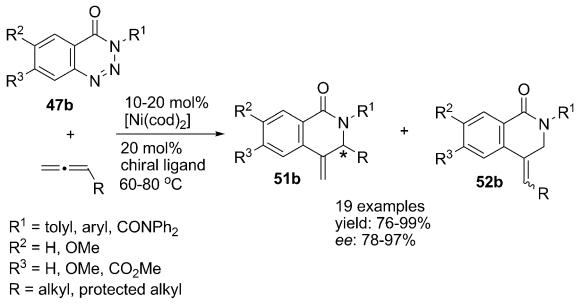
Scheme 23. Nickel-catalyzed denitrogenative transannulation of 1,2,3-benzotriazinones **47a** with internal cyclic allene. See Scheme 29 for structure of (*R*,*R*)-Me-duphos.

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**.

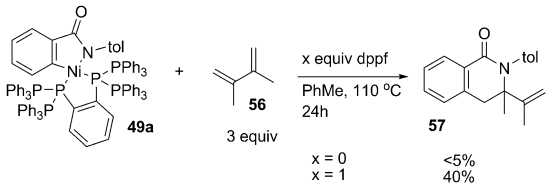
The authors have also explored the asymmetric version of this transformation. It was shown that employment of bidentate phosphine ligands, such as (*R*,*R*)-Me-duphos and (*S*,*S*,*R*,*R*)-tangphos provided good enantioselectivities. Importantly, both the regio- and enantioselectivities were very high when the phosphinooxazoline ligand (*S*,*S*)-*i*Pr-foxap[40] was employed (Scheme 24).[38]

As an extension of this methodology, the same group has also developed the nickel-catalyzed transannulation of benzotriazinones with 1,3-dienes and activated alkenes.[41] 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% (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 benzotri-

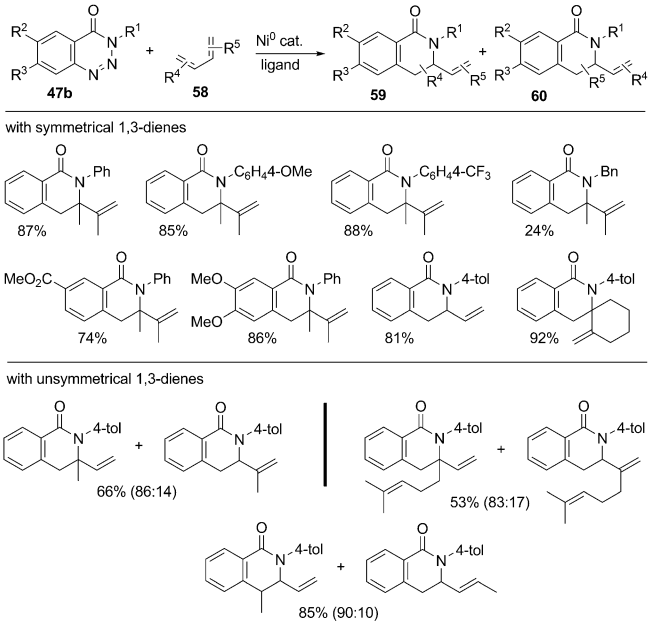


Scheme 24. Enantioselective synthesis of isoquinolones.



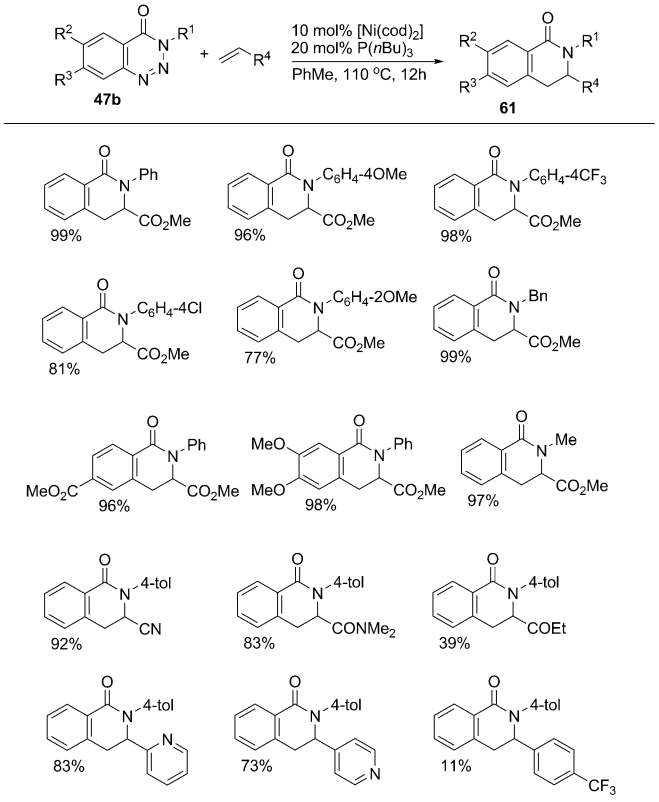
Scheme 25. Transannulation of benzotriazinones with 1,3-dienes. dppf = 1,1′-bis(diphenylphosphino)ferrocene.

azinones **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]



Scheme 26. Scope of transannulation of the benzotriazinones **47b** with 1,3-dienes.

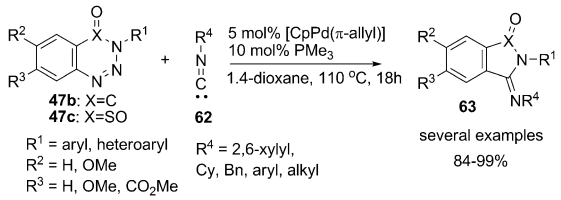
It was also shown that in the presence of $[Ni(cod)_2]$ and $P(nBu)_3$, the benzotriazinones **47b** can undergo an efficient transannulation reaction with activated alkenes (Scheme 27). Thus, electron-deficient alkenes, such as methyl acrylate, acrylonotrile, and acrylamide smoothly underwent transannulation 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]



Scheme 27. Nickel-catalyzed denitrogenative transannulation with alkenes.

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.



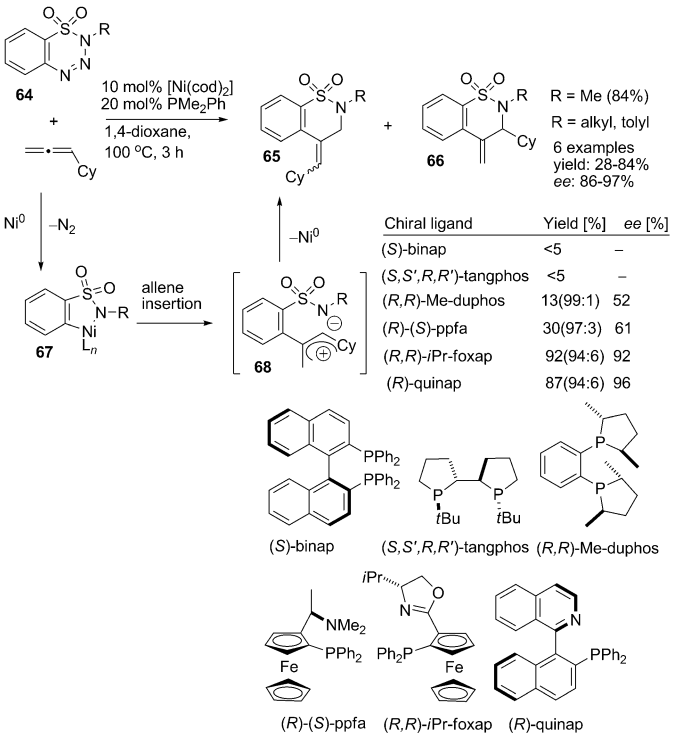
Scheme 28. Palladium-catalyzed transannulation with isocyanides. Cp = cyclopentadienyl.

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-benzothiatriazine-1,2(2*H*)-dioxide **64** with monosubstituted allenes to produce 1,2,3,4-benzothiazine-1,1(2*H*)-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).

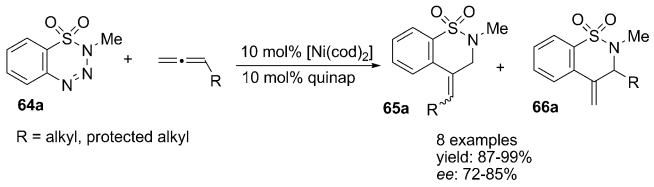
It was found that C_2-symmetric bidentate bisphosphine ligands such as (*S*)-binap,[45] (*S*,*S*′, *R*,*R*′)-tangphos,[46] and (*R*,*R*)-Me-duphos[47] were not competent in this reaction. However, employment of unsymmetrical P,N-type bidentate



Scheme 29. Transannulation of 1,2,3,4-benzothiatriazine-1,1(2*H*)-dioxide **64** with allenes in the presence of various chiral ligands.

ligands such as (*S*,*S*)-*i*Pr-foxap[40] and quinap[48] afforded 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 = *t*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 groups at the alkyl chains also reacted well, although the enantioselectivities were found to be slightly lower (Scheme 30).[43]



Scheme 30. Transannulation of 1,2,3,4-benzothiatriazine-1,2(2*H*)-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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