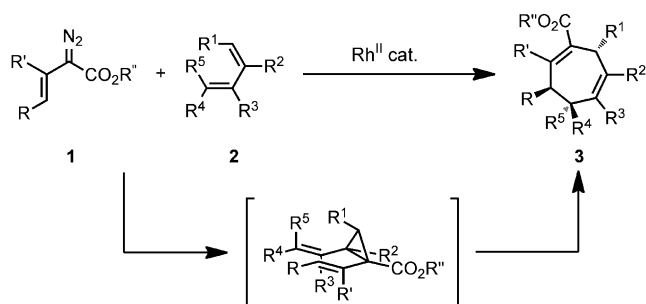


Asymmetric Catalysis

Rhodium-Catalyzed Tandem Cyclopropanation/Cope Rearrangement of 4-Alkenyl-1-sulfonyl-1,2,3-triazoles with Dienes**

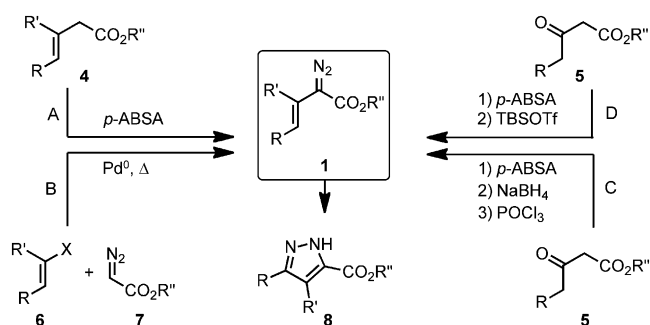
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Metal-catalyzed decomposition of diazo compounds to form transient donor/acceptor rhodium carbenes has been a general strategy for modern metallocarbene chemistry.^[1] The stabilization afforded by a π -donating substituent on the carbenes enhances their selectivity, leading to a number of synthetically useful intermolecular transformations, such as enantioselective cyclopropanation^[2] and C–H insertion.^[3] Alkenyl substituents not only stabilize the carbene, but also participate in a number of novel transformations.^[4] One of the most versatile examples is the formal [4+3] cycloaddition reaction^[5,6] (Scheme 1), which occurs via a tandem cyclopropanation/Cope rearrangement. As such, the reaction has found broad application in the total syntheses of complex natural products.^[6]



Scheme 1. Rhodium(II)-catalyzed formal [4+3] cycloaddition.

The standard approach for generating the alkenylcarbene precursor involves treatment of the corresponding β,γ -unsaturated ester **4** with a diazo transfer reagent, typically *p*-acetamidobenzenesulfonyl azide (*p*-ABSA), in the presence of an amine base, as shown in Scheme 2 (method A).^[7] Although this approach to diazotization is robust for the synthesis of styryldiazoacetates (**4**, R = Ar), it is less reliable when applied to non-conjugated alkenyldiazoacetates. Alternative approaches have been developed, such as palladium-

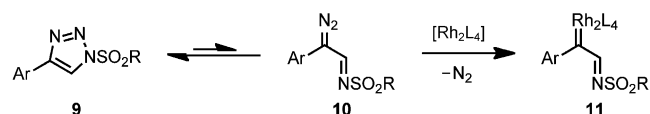


Scheme 2. Alkenyldiazoacetate syntheses and pyrazolization. *p*-ABSA = *p*-acetamidobenzenesulfonyl azide, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

catalyzed cross-coupling of diazoacetates **7** with olefinic (pseudo)halides **6** (method B) and reduction/dehydration of α -diazo- β -ketoesters (**5**, method C). A particularly useful approach involves exposure of 1,3-dicarbonyls **5** to diazo-transfer conditions, followed by formation of the silylenolether (method D).^[2b,8]

A general challenge associated with alkenyldiazoacetates **1**, however, is their propensity to undergo a $6\pi e^-$ electrocyclic cyclization with concomitant aromatization to pyrazoles **8**.^[9] Formation of **8** is irreversible, and moreover, the pyrazole is prone to coordinating with the Rh^{II} complex, impeding catalysis. The rate of pyrazole formation is dependent upon the substituents on the alkenyl group. The unsubstituted and alkyl-substituted vinyldiazoacetates cyclize within hours at ambient temperature and, even when stored at -20°C , require purification prior to use. Thus, although significant latitude is afforded to the diene partner in the formal [4+3] cycloaddition, the product architecture is limited by the accessibility and stability of functionalized alkenyldiazoacetates.

More recently, 1,2,3-triazoles (Scheme 3, **9**) have been shown to act as masked diazo compounds, which are capable of undergoing a “ring-to-chain isomerization” to expose diazo moiety **10**.^[11,12a] In the presence of a dirhodium tetracarboxylate catalyst, the α -diazo imine can be decomposed to generate the metal-bound donor/acceptor carbene intermediate **11**. A number of groups have demonstrated the applica-



Scheme 3. 1-Sulfonyl-1,2,3-triazoles as carbene precursors.

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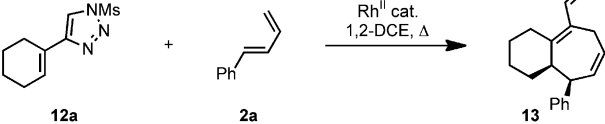
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201304310>.

tion of *N*-sulfonyltriazoles as viable precursors in both classic (cyclopropanation and C–H insertion)^[11] and novel rhodium carbene reactions.^[13]

We have been interested in using 1,2,3-triazoles to expand the scope of donor groups that can be incorporated into donor/acceptor carbenes. To this end, we reported that 4-amido-1-sulfonyl-1,2,3-triazoles can be used to introduce a *N*-phthalimido donor group, which enabled an expedited synthesis of cyclopropyl amino acids.^[13] Analogously, our group discovered that 4-alkenyl-1,2,3-triazoles exhibit a proclivity to undergo intramolecular electrocyclozation, to generate a pyrrole product.^[14] Herein, we describe that 4-alkenyl-1,2,3-triazoles are versatile diazo surrogates that can be used to broaden the range of rhodium-stabilized alkenylcarbenes for the formal [4+3] cycloaddition.

Our exploratory studies commenced with the 4-cyclohexenyl-triazole **12a**, which was previously prepared from the commercially available enyne and demonstrated to be suitable for the rhodium-catalyzed cyclopropanation of styrene.^[11a] Using 1-phenyl-1,3-butadiene (**2a**) as the test substrate and standard conditions for cyclopropanation of alkenes with 1-sulfonyl-1,2,3-triazoles,^[11a] an array of chiral dirhodium tetracarboxylate catalysts were examined (Table 1,

Table 1: Optimization of the formal [4+3] cycloaddition.

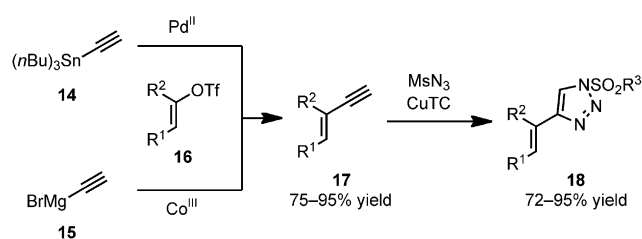


Entry	Rh ^{II} cat.	<i>T</i> [°C]	Yield [%] ^[a]	d.r. ^[b]	ee [%] ^[c]
1	[Rh ₂ {(S)-dosp} ₄]	70	70	> 30:1	–16
2	[Rh ₂ {(S)-btppc} ₄]	70	56	> 30:1	15
3	[Rh ₂ {(S)-pta} ₄]	70	80	> 30:1	40
4	[Rh ₂ {(S)-ptad} ₄]	70	67	> 30:1	66
5	[Rh ₂ {(S)-pttl} ₄]	70	48	> 30:1	82
6	[Rh ₂ {(S)-nttl} ₄]	70	75	> 30:1	92
7	[Rh ₂ {(S)-nttl} ₄]	60	82	> 30:1	97
8	[Rh ₂ {(S)-nttl} ₄]	50	69	> 30:1	97

[a] Yield of isolated **13**. [b] Diastereoselectivity determined by ¹H NMR analysis of the crude residue. [c] Enantioselectivity determined by HPLC analysis on a chiral stationary phase. (S)-btppc = (S)-1-(4-bromophenyl)-2,2-diphenylcyclopropanecarboxylate, DCE = dichloroethane, (S)-dosp = 4-(dodecylphenyl)sulfonyl-(2S)-proline, Ms = methanesulfonyl, (S)-nttl = *N*-naphthoyl-(S)-*tert*-leucinate, (S)-pta = *N*-phthaloyl-(S)-alanine, (S)-ptad = *N*-phthaloyl-(S)-adamantylglycine.

entries 1–6). To this end, [Rh₂{(S)-nttl}₄] (entry 6) was the most efficacious for inducing both high yields and high levels of enantioselectivity for formation of **13** (75 % yield, > 30:1 d.r., 92 % ee).^[15] A decrease in temperature from 70 to 60 °C (entries 6 and 7, respectively) brought about an improvement in both yield and enantioselectivity (82 % yield, > 30:1 d.r., 97 % ee), but further reduction of reaction temperature was detrimental in terms of overall yield (entry 8).

Having established that a 4-alkenyl-1,2,3-triazole could be effectively used in the formal [4+3] cycloaddition, practical syntheses to generate a variety of triazoles **18** were developed,

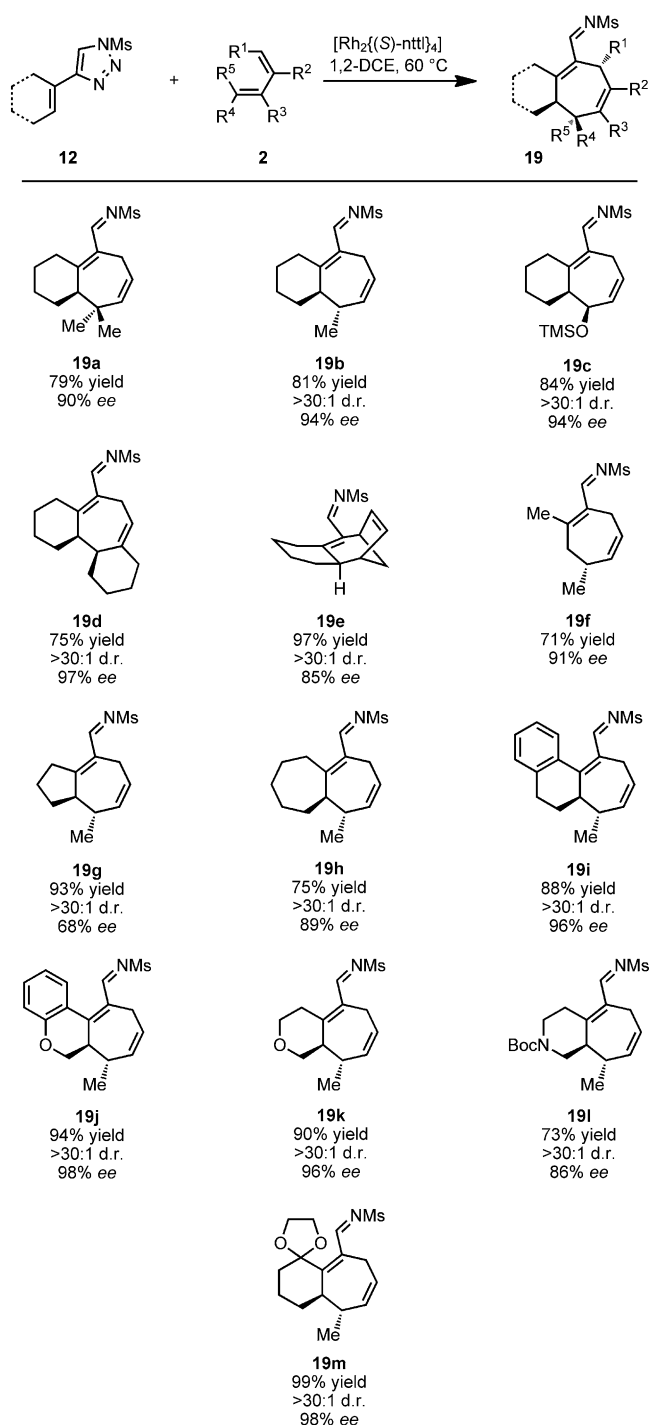


Scheme 4. Synthesis of 4-alkenyl-1-sulfonyl-1,2,3-triazoles. CuTC = copper thiophene carboxylate.

as illustrated in Scheme 4. Enynes **17** were prepared in a single step through a number of well-established cross-coupling reactions with an organometallic acetylide. Specifically, we found that both the Stille coupling of stannane **14**^[16] and the Kumada coupling of Grignard reagent **15**^[17] were both general and high yielding (75–95 % yield) procedures for the synthesis of **17**. The subsequent copper-catalyzed azide/alkyne cycloaddition of **17** with mesyl azide provided access to the 4-alkenyl-1,2,3-triazole **18**, and was compatible with a range of functional groups (Scheme 4).^[18] As the triazole is thermodynamically favored over the diazo imine isomer (Scheme 3), the undesirable rearrangement of the triazole to a pyrazole was not observed.

Following the optimization studies of the [4+3] cycloaddition, we were interested in determining whether the reaction would prove general for both the alkenylcarbene and diene partners. The results of these studies are reported in Scheme 5. Reaction of **12a** with 4,4'-disubstituted (**2b**), (*Z*)-4-substituted (**2c**) and (*E*)-4-substituted (**2d**) 1,3-dienes provided the corresponding cycloheptadienes (**19a–c**) in uniformly high yield and enantioselectivity (79–84 % yield, 90–94 % ee). When vinylcyclohexene (**2e**) was used, the semi-symmetric tricyclic [4.4.3.0] product **19d** was isolated in good yield and excellent stereoselectivity (75 % yield, > 30:1 d.r., 97 % ee). Moreover, bridged tricyclic products could be prepared from reaction with cyclopentadiene (**2f**). Indeed, the cyclic diene provided the cycloadduct (**19e**) in very high yield and good enantioselectivity (98 % yield, 85 % ee).

Proceeding with *cis*-1,3-pentadiene (**2c**) as the nucleophile, we then investigated the scope of the alkenylcarbene precursor (**12b–i**). Another triazole readily available from a commercial enyne, **12b** was first tested in the cycloaddition chemistry. The cycloheptadiene **19f** was formed in good yield and enantioselectivity (Scheme 5). We were more interested, however, in implementing this chemistry as a means to generate a variety of bicyclic [5.*n*.0] products. Thus, we moved forward with the study of varying ring sizes and substitution patterns for various 4-alkenyl-1,2,3-triazoles. A decrease in enantioselectivity was observed when the cyclopentenyl-substituted triazole **12c** was the carbene precursor (**19g**, 93 % yield, 68 % ee). Interestingly, the cycloheptenyl derivative **12d**, performed comparably to **12a**, affording the bicyclo[5.5.0]dodecane (**19h**) skeleton in 75 % yield and 89 % ee. Triazoles bearing an α -fused arene substituent (**12e** and **12f**) were particularly effective substrates, generating the corresponding angular tricyclic products (**19i** and **19j**) in excellent yield and stereoselectivity. The absolute configura-

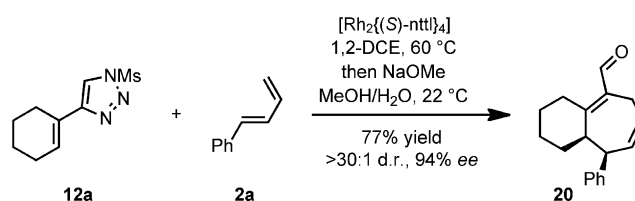


Scheme 5. Scope of the formal [4+3] cycloaddition. Yields shown are of isolated products. Diastereoselectivity determined by ^1H NMR analysis of the crude residue. Enantioselectivity determined by HPLC analysis on a chiral stationary phase. Boc = *tert*-butoxycarbonyl.

tion of the latter compound was established by single-crystal X-ray crystallographic analysis and the stereochemistry of the series of products was assigned by analogy.^[19] Heterocyclic alkenyl donor-groups were also well tolerated, as demonstrated in the syntheses of **19k** and **19l**. Thus, the fused pyranil and piperidinyl ring systems were generated in high

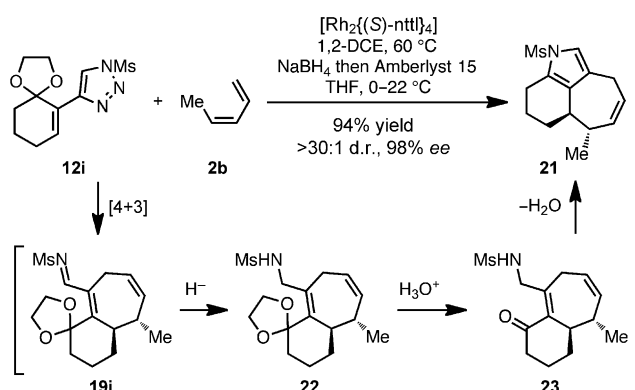
enantioselectivity (96% and 86% ee, respectively). The more hindered diazo precursor **12i**, which bears an α -quaternary carbon, was in fact the most efficient substrate overall. The ketal-bearing product **19m** was isolated in 99% yield and 98% ee.

As the products of the formal [4+3] cycloaddition contain a synthetically useful α,β -unsaturated imine moiety, we sought to demonstrate sequential one-pot manipulations could be conducted without epimerization of the γ -chiral center. Indeed, formal [4+3] cycloaddition of **12a** and **2a** followed by basic hydrolysis afforded the α,β -unsaturated aldehyde **20** in high yield with no observable epimerization (Scheme 6). The absolute configuration of **20** was further verified by X-ray crystallographic analysis.^[19]



Scheme 6. One-pot synthesis of α,β -unsaturated aldehyde **20**.

The combined utility of an appropriately chosen donor group and the readily functionalized imine group are exemplified in Scheme 7. Following the cycloaddition reaction with triazole **12i**, reduction of the imine was achieved



Scheme 7. One-pot synthesis of tetrahydroindole **21**.

with sodium borohydride to provide **22**. Subsequent acid-catalyzed opening of the ketal was induced by Amberlyst 15 resin, with the effect of concomitant cyclodehydration, through the intermediacy of **23**, to generate the tetrahydroindole **21** in 94% yield for the one-pot process.

In conclusion, we have developed a practical method for the synthesis of structurally diverse rhodium alkenylcarbenes from bench-top-stable 1-sulfonyl-1,2,3-triazole precursors. The reaction is general for a broad range of 4-alkenyl-1,2,3-triazoles and dienes, enabling the stereoselective synthesis of a variety of polycyclic imines, which are readily converted into amines or aldehydes in a one-pot process. The new entry into alkenylcarbenes enables the engineering of complex sub-

strates capable of subsequent transformations, which will likely be of value for expedited syntheses of natural products.

Experimental Section

Representative procedure for the synthesis of **13**: A 1,2-dichloroethane (1.5 mL) solution of 1,3-phenylbutadiene (**2a**) (130 mg, 1.0 mmol) was added to an Ar-purged culture tube containing **12a** (114 mg, 0.50 mmol) and $[\text{Rh}_2\{(\text{S})\text{-nttl}\}_4]$ (7 mg, 0.005 mmol). The reaction vessel was immersed in an oil bath heated to 60 °C and stirred for 6 h. The product was then purified directly by flash chromatography (SiO_2 , hexanes/EtOAc 80:20) to give a white solid (132 mg, 82 % yield).

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- [19] CCDC 938813 (**19j**) and 938623 (**20**) contain 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.