Silver-Catalyzed [4+3] Cycloaddition of 1,3-Dienes with Vinyl-*N*-triftosylhydrazones: A Practical Approach to 1,4-Cycloheptadienes

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ABSTRACT: The first formal [4+3] cycloaddition of 1,3-dienes with vinyl-*N*-sulfonylhydrazones has been achieved by virtue of easily decomposable vinyl-*N*-triftosylhydrazones in the presence of silver catalysis. A series of acyclic and cyclic 1,3-dienes reacted effectively with silver(I) non-acceptor vinyl carbenes, including alkyl- and alkenyl-substituted carbenes, which are notoriously challenging, producing a broad spectrum of 1,4-cycloheptadienes with high yield and predictable stereochemistry. The products resulting from the herein described transformation include bridged and fused polycyclic systems, as well as the natural product dictyopterene C' and its isomer ectocarpene. The reaction mechanism and the origin of stereoselectivity were investigated via experimental work and density functional theory calculations.

INTRODUCTION

Cycloheptadienes, a class of functionalized seven-membered carbocycles, are present in many drug-like molecules and natural products (Scheme 1A).[1] Accordingly, considerable efforts have been devoted to the development of versatile synthetic methods suitable for assembling these system.[1a,b,2] Among them, [4+3] cycloaddition reactions of 1,3-dienes with vinyl carbenes are particularly attractive as a straightforward approach to the creation of the cycloheptadiene frameworks.[3-6] Since the pioneering work of Davies and coworkers[4], a number of examples of rhodium-catalyzed [4+3] reaction between 1,3-dienes and alkenyldiazoacetates have been reported.[5] This approach may provide a synthetic route to otherwise hardly accessible 1,4-cycloheptadienes, which may be achieved with predictable stereochemistry and in high stereomeric excess due to the requirement of a boat-like transition state for Cope rearrangement.[3] Although this strategy has been used in many instances for the synthesis of natural product,[6] it was reported that only complexes based on rhodium, known to be rare and expensive metal, would catalyse this type reaction.[3-7] Even more critically, these protocols are not suitable for unsubstituted and alkyl-substituted vinyldiazoacetates, due to the propensity of these substrates to undergo self-cyclization to yield pyrazoles.[8] In addition, diazo compounds-are often unstable and potentially explosive, which hampers the usefulness of these methodologies, especially for industrial-scale applications.[9] To address these limitations, an attractive option would be to use operationally safe alternatives to the diazo compounds, such as as vinyl carbene precursors.[10] For instance, 4-alkenyl-1-sulfonyl-1,2,3-triazoles[11] and 7-alkenyl cycloheptatrienes[12] have been shown to act as masked equivalents of vinyl carbenes and are capable of undergoing formal [4+3] cycloaddition with 1,3-dienes through rhodium catalysis. Despite these impressive advances, there are still numerous crucial limitations, including use of expensive metal catalysts[12] and sophisticated starting materials,[10] which can be time-consuming and tedious to prepare. Additional disadvantages of the known methods include lack of chemoselectivity,[10e] and the fact that the scope is mainly restricted to aryl-

substituted vinyl carbenes[12] and intramolecular reactions.[10a,b]

N-Sulfonylhydrazones are valuable *in situ* sources of diazo compounds for various carbene reactions.[13] Despite alkenyl units could provide new reactivity, catalytic carbene transfer reactions based on vinyl-*N*-sulfonylhydrazones, wherein the alkenyl units could provide additional opportunityies for functionalization, have drawn little interest, presumably because they tend to rearrange spontaneously to 3*H*-pyrazoles.[14] As part of our efforts toprovide new synthetic methods based on transformations of functionalized *N*-sulfonylhydrazones,[15] we herein report the first [4+3] cycloaddition of 1,3-dienes with vinyl-*N*-sulfonylhydrazones. The use of easily decomposable vinyl-*N*-triftosylhydrazones and weakly coordinating Tp$^{(CF3)2}$Ag catalyst[16] allows to suppress the undesired formation of pyrazoles (Figure 1C). This strategy is suitable for intermolecular reactions as well as for intramolecular additions, which provides a rapid access to synthetically important and pharmacologically privileged cycloheptadienes from acyclic simple starting materials with complete and predictable regio- and stereochemistry. Because stable and operationally safe vinyl-*N*-triftosylhydrazones are used as non-acceptor carbene surrogates, the method described here is substantially advantageous over the previous methods in terms of practicality, scalability, reaction scope and functional-group tolerance. We demonstrated these features in the late-stage modification and total synthesis of natural products.
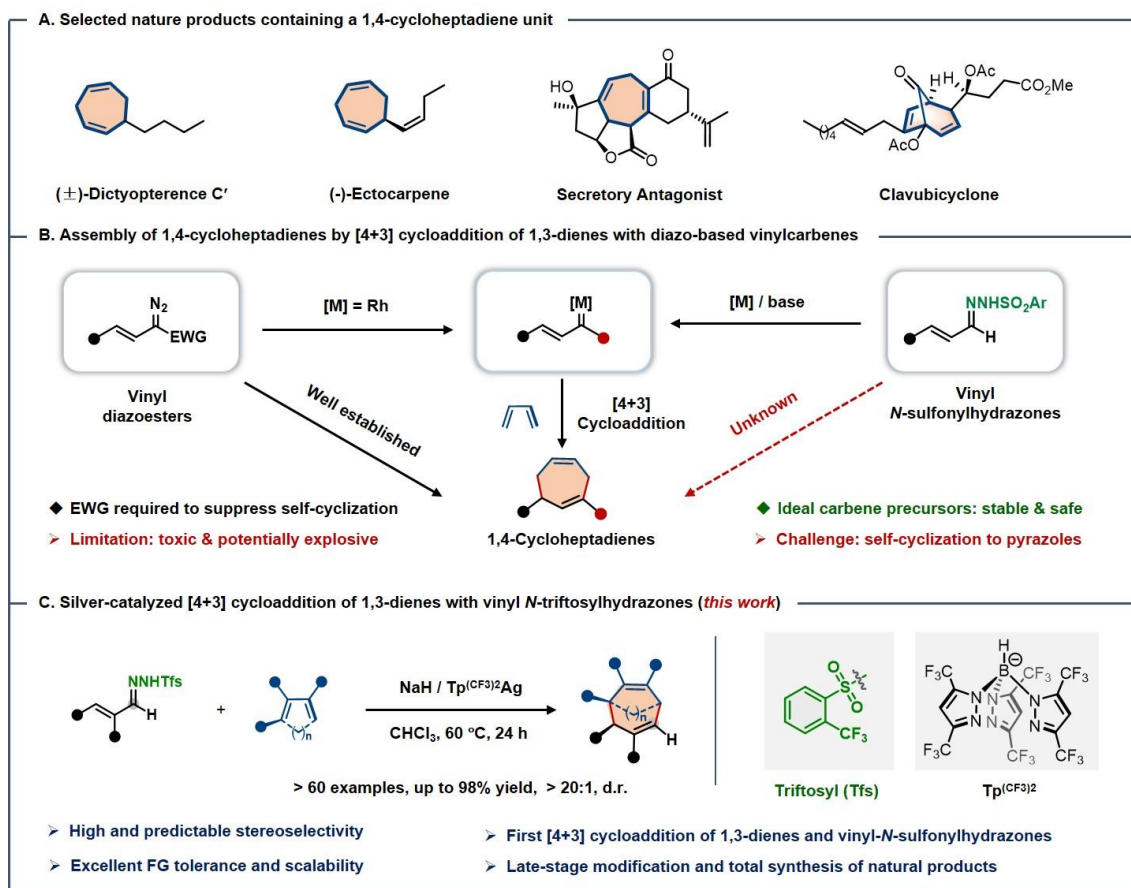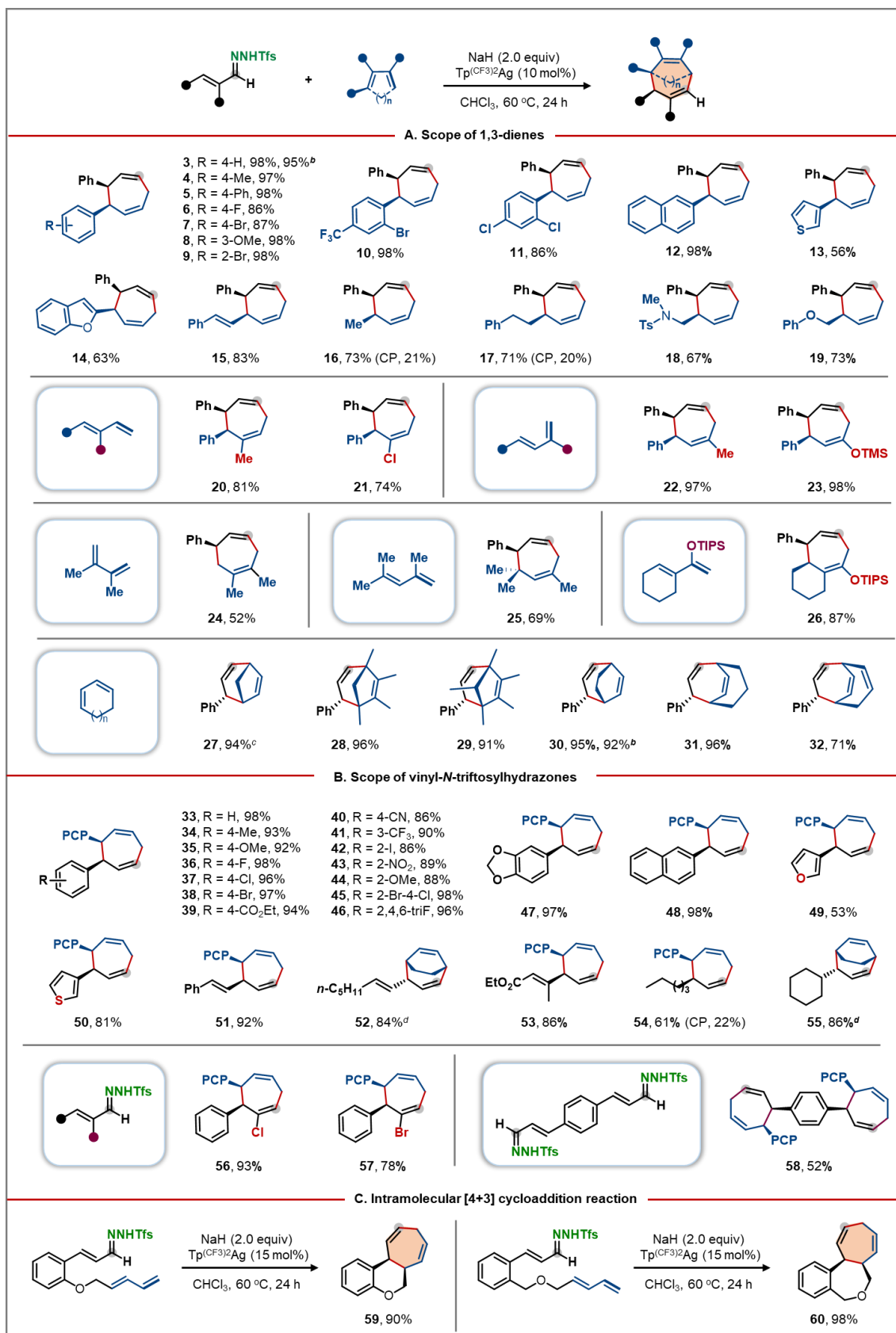

Figure 1. Assembly of seven-membered carbocycles by formal [4+3] cycloaddition of 1,3-dienes and vinyl carbenes. A. Representative natural products containing seven-membered ring. B. Traditional approach to 1,4-cycloheptadiene via [4+3] cycloaddition of 1,3-dienes with metal carbenes. C. This work: silver-catalyzed [4+3] cycloaddition of 1,3-dienes with vinyl-*N*-triftosylhydrazones.

RESULTS AND DISCUSSION

After extensive optmization work (for details see Table S1 in supporting information), we found that in the reaction of vinyl-*N*-triftosylhydrazone (**1**) and (*E*)-1-phenyl-1,3-butadiene (**2**) the best yield of the desired 1,4-cycloheptadiene (98%) is achieved in the presence of $Tp^{(CF3)2}Ag$ (10 mol%) and NaH (2.0 equiv) in $CHCl_3$ at 60 °C achieves (**3**). Notably, the use of easily decomposable vinyl-*N*-triftosylhydrazones and weakly coordinating $Tp^{(CF3)2}Ag$ catalyst plays a pivotal role in that the undesired cyclization of vinyl-*N*-sulfonylhydrazones is supressed and the desired [4+3] cycloaddition reaction with the vinylcarbene moiety is obtained. With the optimized conditions in hand, we initially investigated the scope of substrates in this reaction. As illustrated in Scheme 1A, a variety of 1,3-dienes reacted effectively with vinyl-*N*-triftosylhydrazone (**1a**) to provide the corresponding cycloheptadienes (**3-32**) in yields suitabel for preparative scale. For 1-aryl-1,3-butadienes, the electronic effects and steric hindrance of substituents on the aryl ring did not affect the outcome (**3-11**). Apolycyclic diene fused with 2-naphthy provided the expected product (**12**) in quantitative yield. However, heteroaromatic 1,3-dienes (e.g., 3-thienyl and benzofuranyl) afforded the target products (**13 and 14**) in moderate yield. The product (**15**) was obatined from 1-alkenyl-substituted 1,3-diene in 83% yield. For aliphatic 1,3-dienes, the yields were slightly lower. We speculated that this was due to the formation of *trans*-divinylcyclopropanes (about 20%), which failed to undergo the Cope rearrangement reaction under standard conditions (**16-19**). Furthermore, also 1,2-, 1,3-, 2,3-disubstituted and 1,1,3-, 1,2,3-trisubstituted 1,3-dinene proved to be suitable substrates (**20-26**). Notably, sensitive groups, such as sulfonamide, alkyl- and silyl ether, are compatible, which further demonstrates the potential for this reaction to provide substrates suitable for further synthetic elaborations.[17] Bridged bicyclo[3.2.n] frameworks are widely found in natural products and provide significant biological activity due to their conformationally restricted structures.[18] We were pleased to find that the extension of the method to cyclic dienes provided corresponding bridged seven-membered bicycles in excellent yields (**27-32**). Notably, we found that these reactions can be successfuly performed on a multigram scale. For instance, the reaction of vinyl-*N*-triftosylhydrazone (**1**) with (*E*)-1-phenyl-1,3-butadiene (**2**) or 1,3-cyclohexadiene was carried out on 10 mmol scale and the target products **3** and **30** were obtained in 95% and 92% yield, respectively. These results demonstrate that the yield is not affected by scaling-up the reaction, indicating the possibility for the industrial application of this transformation.

Next, we turned our attention to the vinyl-*N*-triftosylhydrazones reaction component (scheme 1B). A plethora of α,β-unsaturated *N*-triftosylhydrazones possessing electron-neutral, electron-donating (Me, OMe) and electron-withdrawing groups (F, Cl, Br, I, CN, CO_2Et, CF_3, NO_2) at either para-, meta- or *ortho*-position of the aromatic ring underwent the desired reaction smoothly to provide the corresponding products (**33-48**) in good-to-excellent yields. Likewise, the reaction of *N*-triftosylhydrazones with a heteroaromatic ring (**49 and 50**) and alkenyl (**51-53**) also proceeded smoothly, albeit, in the case of **53**, with lower yield. More importantly, alkyl-substituted vinyl-*N*-triftosylhydrazones reacted smoothly to give the corresponding 1,4-cycloheptadienes **54** and **55** in 61% and 86% yield, respectively. It is notable that 7-vinyl cycloheptatriene.based method does not appera to be suitable for alkyl-substituted vinyl carbenes.[12] The presence of chlorine and bromine substituent in vinyli position was found to be compatible with the reaction conditions, which allows for further orthogonal derivatization.[19] A double [4+3] cycloaddition was also observed, providing the expected product **58** in 52% yield, with formation of four new stereocenters in one step. Finally, we were pleased to find that this method could be further applied to the intramolecular mode. Vinyl-*N*-triftosylhydrazones bearing a tethered 1,3-diene at the *ortho*-position were elaborated and subjected to the reaction, providing fused ring systems (**59 and 60**) in high yield. Note that these fused ring systems are widely present in natural products, such as Enmein,[20a] Colchicine,[20b] and Aspergillin PZ,[20c] etc.

Scheme 1. Scope of reaction substrates[a]

A. Scope of 1,3-dienes

3, R = 4-H, 98%, 95%[b]
4, R = 4-Me, 97%
5, R = 4-Ph, 98%
6, R = 4-F, 86%
7, R = 4-Br, 87%
8, R = 3-OMe, 98%
9, R = 2-Br, 98%

10, 98%

11, 86%

12, 98%

13, 56%

14, 63%

15, 83%

16, 73% (CP, 21%)

17, 71% (CP, 20%)

18, 67%

19, 73%

20, 81%

21, 74%

22, 97%

23, 98%

24, 52%

25, 69%

26, 87%

27, 94%[c]

28, 96%

29, 91%

30, 95%, 92%[b]

31, 96%

32, 71%

B. Scope of vinyl-*N*-triftosylhydrazones

33, R = H, 98%
34, R = 4-Me, 93%
35, R = 4-OMe, 92%
36, R = 4-F, 98%
37, R = 4-Cl, 96%
38, R = 4-Br, 97%
39, R = 4-CO$_2$Et, 94%

40, R = 4-CN, 86%
41, R = 3-CF$_3$, 90%
42, R = 2-I, 86%
43, R = 2-NO$_2$, 89%
44, R = 2-OMe, 88%
45, R = 2-Br-4-Cl, 98%
46, R = 2,4,6-triF, 96%

47, 97%

48, 98%

49, 53%

50, 81%

51, 92%

52, 84%[d]

53, 86%

54, 61% (CP, 22%)

55, 86%[d]

56, 93%

57, 78%

58, 52%

C. Intramolecular [4+3] cycloaddition reaction

59, 90%

60, 98%

[a]Standard reaction conditions: vinyl-*N*-triftosylhydrazone (0.3 mmol), 1,3-diene (2.0 equiv), NaH (2.0 equiv) and Tp$^{(CF3)2}$Ag (10 mol%) in CHCl$_3$, 60 °C, 24 h. [b]10 mmol scale. [c]Cyclopentadiene (3.0 equiv), at 40 °C for 2 h. [d]Cyclohexa-1,3-diene was used. CP, Cyclopropane Product.

The practical utility of this method was further demonstrated by the selective late-stage modification

and and synthesis of natural products (Scheme 2). Ocimene, a natural perfume isolated from basil oil, reacted effectively to afford the desired 1,4-cycloheptadiene (**61**) in 58% yield. The derivatives of Vitamin D$_3$ and citral, containing conjugated 1,3-diene and isolated double bond, also selectively underwent [4+3] cycloaddition (**62** and **63**, 51% and 57% yield, respectively). Notably, compound **63** is the key intermediate for the synthesis of natural product (-)-5-*epi*-Vibsanin E.[6b] In addition, a key intermediate of Fluvastatin was converted to the corresponding vinyl-*N*-triftosylhydrazone and subjected to the standard reaction conditions, delivering the 1,4-cycloheptadiene (**64**) in 67% yield. Dictyopterene C′ (**66**),[21] a natural pheromone isolated from brown algae, was prepared in 56% yield by [4+3] cycloaddition reaction of 1,3-butadiene with vinyl-*N*-triftosylhydrazone (**65**). Finally, starting from vinyl-*N*-triftosylhydrazone **67** and 1,3-butadiene, we successfully synthesized (*E*) isomer of ectocarpene, a natural product with sperm-attracting activity.[22]

Scheme 2. Late-stage modification and total synthesis of natural products.
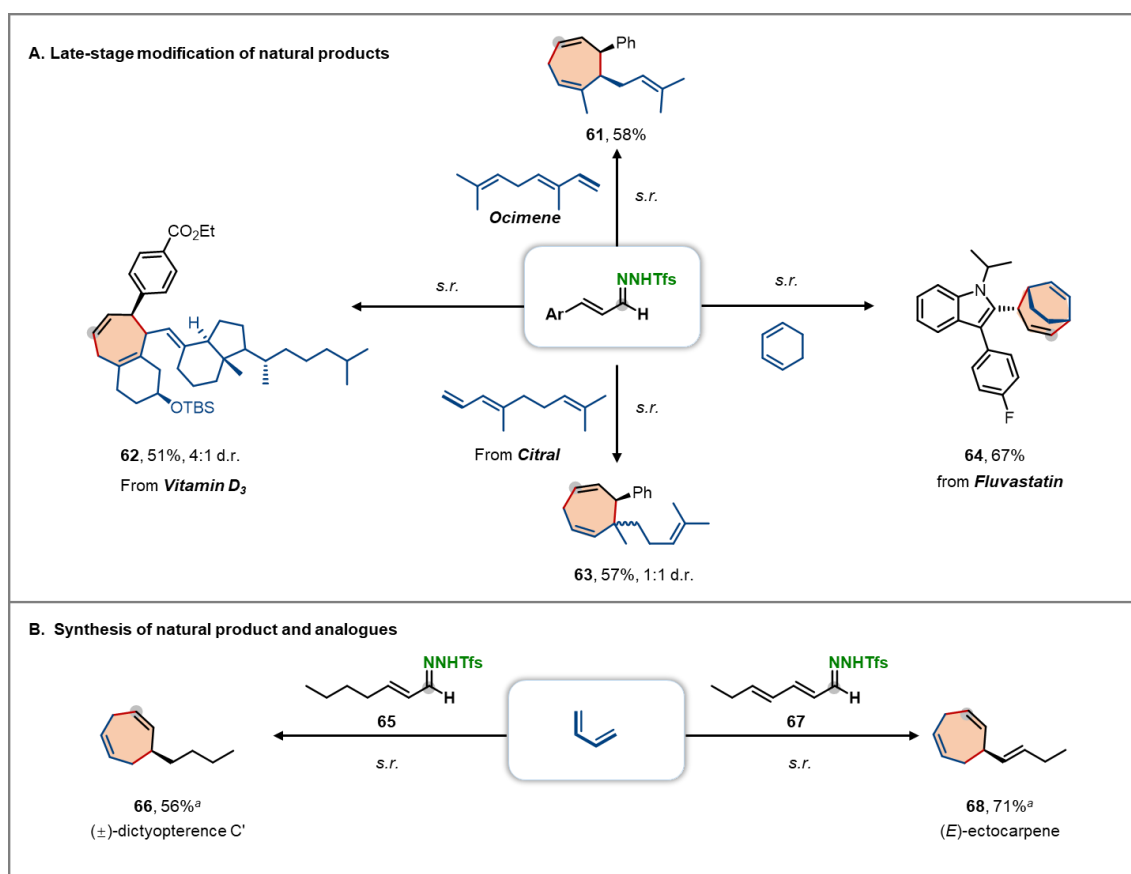
Standard reaction conditions (*s.r.*): vinyl-*N*-triftosylhydrazone (0.3 mmol), 1,3-diene (2.0 equiv), NaH (2.0 equiv) and Tp$^{(CF3)2}$Ag (10 mol%) in CHCl$_3$, 60 °C, 24 h. [a]1,3-Butadiene (5.0 equiv) was used.

Based on related precedents, this silver-catalyzed [4+3] cycloaddition reaction may proceed through a tandem cyclopropanation/Cope rearrangement. This mechanistic hypothesis was confirmed by obtaining 1,4-cycloheptadienes (**70**) by heating *cis*-divinylcyclopropane (**69**) at 160 °C for 24 h (Figure 2A).[12] Furthermore, the progress of the reaction depicted in Figure 2B was first examined by ^{1}H NMR. Initially, the formation of intermediate **30'** was observed, which reached maximum intensity within 30 min. **30'** then converted to the 1,4-cycloheptadiene **30**, which was found to be the nearly sole component of the reaction mixture by 120 min. These results suggest that *cis*-divinylcyclopropane is the key intermediate for the desired outcome of this reaction.

To gain deeper insight into the mechanism, we carried out density functional theory (DFT) calculation at the M06/6-31+G(d,p) level (SDD for Ag) with the SMD solvent model (CHCl3) on B3LYP optimized

geometries in gas phase (Figure 2C). The reaction starts by the silver-catalyzed decomposition of vinyl-*N*-triftosylhydrazone in the presense of NaH to form silver carbene **Int4** (For details see Figure S2 in supporting information).[23] The cyclopropanation of 1,3-diene **2** with silver carbene **Int4** proceeds through an asynchronous concerted mechanism. DFT calculations indicated that the formation of *cis*-divinylcyclopropane **Int6** via **TS4-*cis*** (0.1 kcal/mol) is kinetically more favored than the *trans* by 4.1 kcal/mol. According to TST calculator,[24] the calculated ratio of k(*cis*)/k(*trans*) is 489:1, which is in good agreement with experimental observation. To clarify the origin of the stereoselectivity, the color-filled reduced density gradient (RDG) isosurface analysis of **TS4-*cis*** and **TS4-*trans*** was performed.[25] As indicated by the facts that the distance between carbene carbon and olefin carbon in **TS4-*cis*** is shorter than that in **TS4-*trans*** (2.46 vs 2.62 Å, and 2.83 vs 2.95 Å, respectively), there is a clear non-covalent interaction in **TS4-*cis*** (green), which stabilizes configuration of **TS4-*cis***. This is also consistent with the experimental data that alkyl-substituted 1,3-dienes, in which such non-covalent interaction is absent, generated 20% *trans*-divinylcyclopropane. The single bond rotation of **Int6** leads to the intermediate **Int7**, which undergoes Cope rearrangement to provide the final product **3** with an energy barrier of 18.0 kcal/mol (**TS5**). Alternatively, after decoordination from Ag (I), free cyclopropane **Int6'** can undergo a thermal Cope rearrangement (**TS5'**, 20.4 kcal/mol), with only a slightly higher energy barrier ($\Delta\Delta G^{\neq} = 2.4$ kcal/mol). Therefore, the thermal Cope rearrangement can not be completely ruled out at this stage. In conclusion, we propose that this [4+3] cycloaddition reaction proceed through a cyclopropanation/Cope rearrangement pathway, wherein silver catalysis plays a crucial role in controlling the stereoselectivity of vinylcyclopropanation of alkenes to give the key *cis*-divinylcyclopropane.
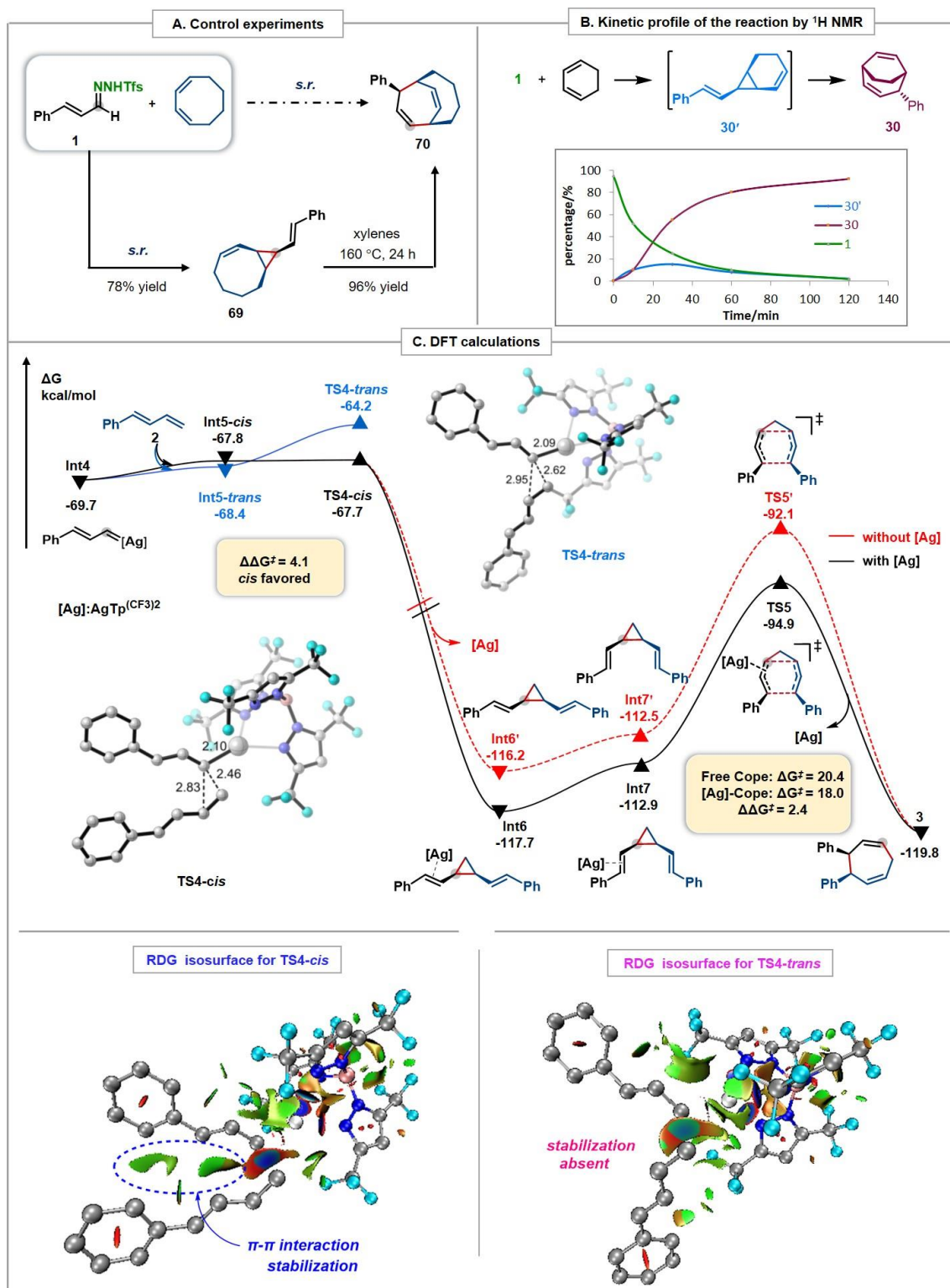
Figure 2. Mechanistic investigations. **A**. Control experiments. **B**. Kinetic profile of the reaction by ^{1}H NMR. **C**. Mechanistic investigations by DFT calculations. Color filled RDG isosurface for **TS4-*cis*** and **TS4-*trans*** (isovalue set to 0.5): (blue) areas of attraction (covalent bonding); (green) vdW interaction; (red) areas of repulsion (steric and ring effects). Calculations were performed at the M06/[6-31+G(d,p)/SDD(Ag)] level of theory in chloroform within the SMD model. Energies are given in kcal/mol and distances in angstroms.

CONCLUSIONS

In summary, we have demonstrated a practical and powerful method for rapid synthesis of complex 1,4-cycloheptadienes through a formal [4+3] cycloaddition of 1,3-dienes with non-acceptor vinyl silver carbenes, generated *in stiu* from vinyl-*N*-triftosylhydrazones. Silver catalysis plays a crucial role to give the key *cis*-divinylcyclopropane by suppressing the formation of pyrazoles and controlling the stereoselectivity of vinylcyclopropanation of alkenes. In view of the ready availability of the starting materials, the excellent functional-group compatibility, scalability, and the chemo-, regio- and stereoselectivity, we believe that this practical [4+3] cycloaddition reaction could become an attractive method for the straightforward synthesis of 1,4-cycloheptadienes, a privileged motif found in natural and synthetic compounds with interesting biological and pharmaceutical activities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, and copies of NMR spectra are available free of charge *via* the Internet at (http://pubs.acs.org/page/jacsat/submission/authors.html).

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Shaopeng Liu and Zhaohong Liu made equal contribution to this paper. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENT

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TOC

> 60 examples, up to 99% yield, > 20:1, d.r.

Triftosyl (Tfs)