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Synthetic Studies and Mechanistic Insight in Nickel-Catalyzed [4+2+1] Cycloadditions

Yike Ni and John Montgomery*

Contribution from the Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489, and Department of Chemistry, University of Michigan, 930 North University, Ann Arbor, Michigan 48109-1055

Received November 14, 2005; E-mail: jmontg@umich.edu

Abstract: A new nickel-catalyzed procedure for the [4+2+1] cycloaddition of (trimethylsilyl)diazomethane with alkynes tethered to dienes has been developed. A broad range of unsaturated substrates participate in the sequence, and stereoselectivities are generally excellent. Stereochemical studies provided evidence for a mechanism that involves the [3,3] sigmatropic rearrangement of divinylcyclopropanes.

Introduction

Transition-metal-catalyzed multicomponent cycloadditions have emerged as a powerful strategy for preparing complex ring systems. Particular utility in the construction of medium rings has been demonstrated because the corresponding thermal counterparts are often either inaccessible or inefficient. In recent years, the repertoire of available metal-catalyzed cycloaddition entries to medium rings has grown to include [4+4], [5+2], [6+2], [6+4], [4+2+2], [5+2+1], [2+2+2+1], and [5+1+2+1] processes.[1] The development of an efficient [4+2+1] process has been the focus of a number of studies. In early work from Harvey, a molybdenum carbene-mediated process was developed in which dienynes underwent addition to the carbene unit in a [4+2+1] sense to afford seven-membered ring products.[2] The mechanism for that class of reactions was proposed to involve an alkyne metathesis cascade to generate a divinylcyclopropane, which then underwent facile Cope rearrangement to afford the seven-membered ring adduct. Although those studies were limited to stoichiometric processes, a related [4+3] cycloaddition process was extensively developed by Davies involving the rhodium-catalyzed addition of unsaturated diazo species with dienes.[3] Two isolated examples of the corresponding fully intramolecular [4+2+1] cycloaddition of a diazoalkane/alkyne/diene cycloaddition were also reported in studies from Padwa.[4] Although the developments involving rhodium catalysis provided elegant access to structurally complex seven-membered rings, access to simpler seven-membered ring systems by catalytic, partially intermolecular [4+2+1] processes had remained elusive. Prior to our original report in the area,[5] the only examples of partially intermolecular, catalytic [4+2+1] cycloadditions were from Wender.[6] In their studies of [2+2+1] carbonylative cycloadditions of dienynes, the [4+2+1] cycloaddition product was observed as a minor component of the reaction mixture.

In surveying the literature on nickel carbene complexes, it became apparent that the involvement of nickel carbene species in synthetic applications was considerably underdeveloped. Although a number of nickel carbene species had been characterized[7] and nickel complexes of N-heterocyclic carbenes had been widely used in catalytic applications,[8] the development of procedures in which the carbene unit was incorporated into an organic product structure had been little studied.[9] An interesting report from Barluenga suggested that nickel catalyzes carbene transfer from a chromium carbene complex to an

(1) (a) For [4+4] reactions: Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. (b) For [5+2] reactions: Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. (c) For [6+2] reactions: Rigby, J. H.; Henshilwood, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 5122. (d) For [6+4] reactions: Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 1382. (e) For [4+2+2] reactions: Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, *124*, 8782. (f) Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784. (g) For [5+2+1] reactions: Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876. (h) For [2+2+2+1] reactions: Ojima, I.; Lee, S.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 2385. (i) For [5+1+2+1] reactions: Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 2836.

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(5) For a preliminary communication of this work, see: Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 11162.

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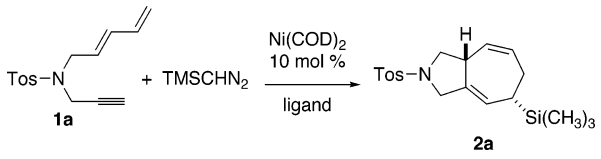
(8) (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (b) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698. (c) Zuo, G.; Louie, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2277. (d) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188. (e) Sato, Y.; Sawaki, R.; Mori, M. *Organometallics* **2001**, *20*, 5510. (f) Dible, B. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 872. (g) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046.

10.1021/ja057741q CCC: $33.50

Table 1. Reaction Optimization[a]



entry	ligand	solvent	temp (°C)	time (min)	% yield (dr)
1	dppe	THF	60	30	42
2	PCy_3	THF	60	30	20
3	$P(t\text{-}Bu)_3$	THF	25	10	35
4	none	THF	0	10	64 (4.8:1)
5	none	dioxane	90	30	54 (3.5:1)
6	none	toluene	60	5	45 (>19:1)
7	none	THF	25	5	72 (5.3:1)
8	none	THF	60	5	68 (>19:1)

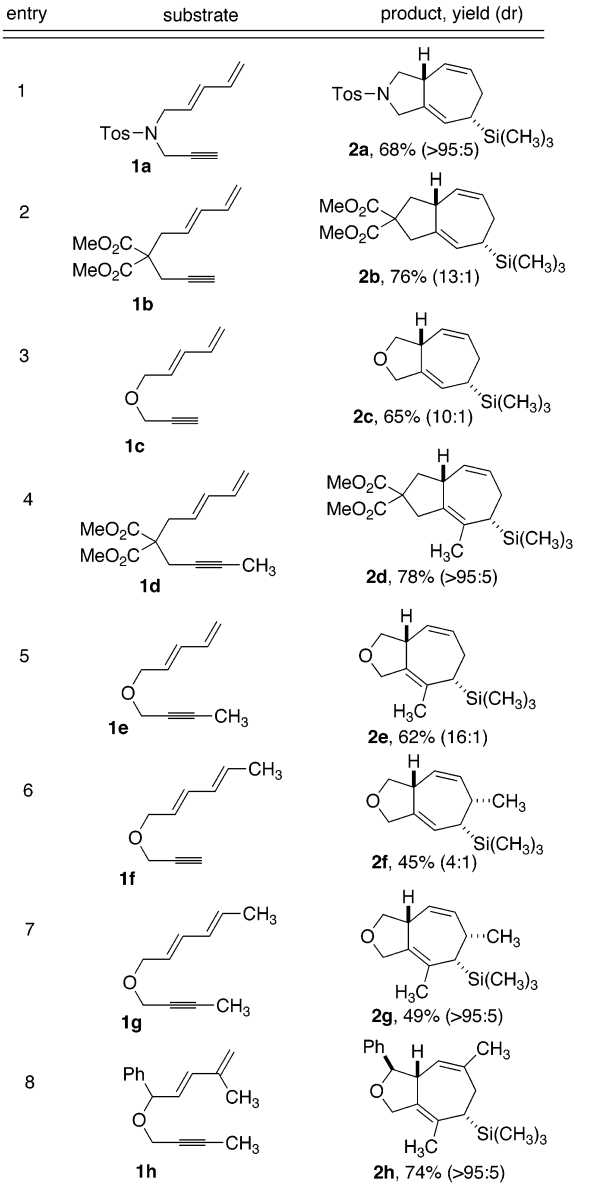
[a] Entries 1−4: **1a** (1.0 equiv) was added to a premixed solution of $TMSCHN_2$ (2.0 equiv) and $Ni(COD)_2$ (10 mol %). Entries 5−8: $Ni(COD)_2$ (10 mol %) was added to a premixed solution of **1a** (1.0 equiv) and $TMSCHN_2$ (2.0 equiv).

organic substrate,[9a] and a few studies involving olefin cyclopropanation with lithiated sulfones or diazoalkanes as the carbene precursor had appeared.[9b−d] Studies from Hillhouse had elegantly illustrated that reactive nickel carbene species could be generated from diazoalkanes by a pathway involving η^2 coordination of the diazo unit prior to the extrusion of dinitrogen in the presence of $Sm(OTf)_3$.[7a,9d] With this backdrop, it appeared to us that the development of new synthetic procedures involving the catalytic generation of nickel carbene intermediates from diazoalkane precursors was an area worthy of study. Considering the void in catalytic [4+2+1] cycloadditions and the void in synthetic applications of nickel carbene species, we chose the nickel-catalyzed [4+2+1] cycloaddition of (trimethylsilyl)-diazomethane with dienynes as the initial target of our studies. Herein, we report a full account of our work including the reaction scope and mechanistic insight.

Results and Discussion

Development of a Catalytic [4+2+1] Cycloaddition Process. Our initial studies focused on the [4+2+1] cycloaddition of nitrogen-tethered substrate **1a** (Table 1). A brief screen of conditions using $Ni(COD)_2$ as the catalyst and a 2:1 stoichiometry of (trimethylsilyl)diazomethane/substrate **1a** illustrated that the desired cycloaddition was most effective in the absence of phosphine ligands. Both reaction rates and overall yields were lower in the presence of either monodentate or bidentate ligands (Table 1, entries 1−4). Variations in order of reagent addition were tolerated, and yields were highest in THF, although dioxane and toluene were also effective solvents (entries 5 and 6). Interestingly, diastereoselectivities improved as temperatures increased, with 60 °C being the optimum temperature to maximize both yield and diastereoselectivity (entries 7 and 8). The optimized procedure used throughout most of this study involved premixing the diazoalkane and dienyne (2:1) in THF, followed by addition of 10 mol % $Ni(COD)_2$, and stirring at 60 °C for 10−30 min (entry 8).

Table 2. Reaction Scope



Following the optimized general procedure, a number of examples were carried out to illustrate the reaction scope (Table 2). In addition to the nitrogen-tethered substrate described previously in our optimization studies (entry 1), we examined the preparation of carbocyclic and oxacyclic structures. Malonate-derived substrate **1b** generated product **2b** in 76% yield in 13:1 dr (entry 2), and oxygen-containing substrate **1c** generated product **2c** in 65% yield as a 10:1 ratio of diastereomers (entry 3). Internal alkynes were also effective participants, as evidenced by the generation of products **2d**, **2e**, **2g**, and **2h** (entries 4, 5, 7, and 8). Substitution on either the diene terminus (entries 6 and 7) or an internal position of the diene (entry 8) was acceptable. Substitution within the tether chain was also tolerated with excellent resulting diastereoselectivity (entry 8). Notably, this latter example allowed the rapid preparation of densely functionalized product **2h** with two rings, two sites of unsaturation, and three chiral centers in a 1,2,5 relationship in excellent yield and diastereoselectivity from relatively simple precursor **1h**.

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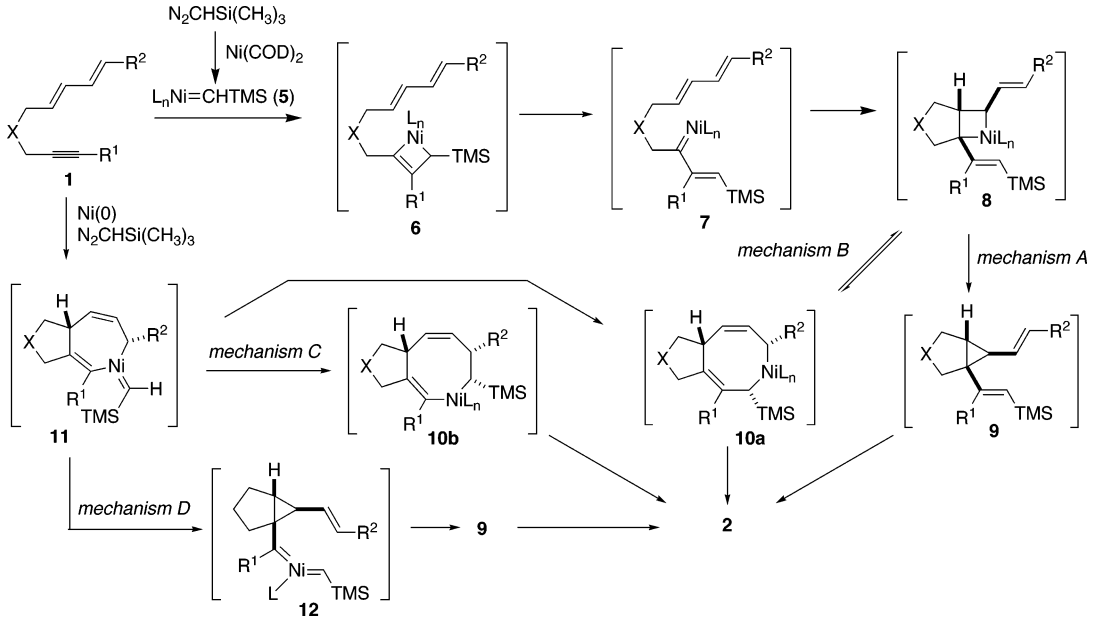
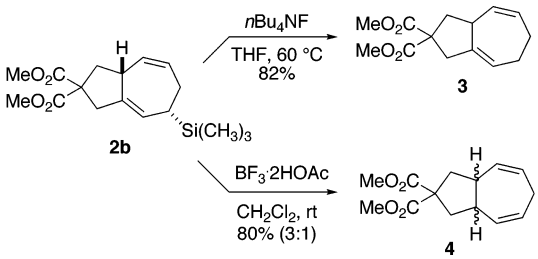
Scheme 1. Possible Mechanisms



The allyl silane handle installed in the cycloaddition process is potentially useful in a variety of post-cycloaddition manipulations. However, in this study, we only examined simple desilylation. Interestingly, *n*-Bu_4NF-mediated desilylation of **2b** proceeds without alkene migration to generate product **3**,[10a] whereas protodesilylation of **2b** with BF_3/HOAc proceeds with allylic transposition to generate product **4** (eq 1).[10b] Thus,



(1)

desilylated products **3** and **4** may be selectively prepared according to the reaction conditions chosen, although product **4** was prepared as a 3:1 ratio of isomers favoring the cis isomer. Unfortunately, readily available alkyl diazoacetates are unreactive in the protocol optimized for TMS diazomethane, although our studies to expand the scope of diazoacetates that participate are ongoing.

Possible Mechanisms. On the basis of a simple product analysis, we envisioned several mechanisms that may be operative in this new catalytic cycloaddition process (Scheme 1). As noted above, the stoichiometric behavior of molybdenum carbene complexes in [4+2+1] cycloadditions[2] as well as the related rhodium-catalyzed [4+2+1] processes[3,4] were proposed to follow an alkyne metathesis/cyclopropanation/[3,3] rearrangement sequence. In analogy to these proposals, the nickel-catalyzed process, via mechanism A (Scheme 1), could involve formation of a nickel carbene intermediate **5**, followed by alkyne metathesis to generate α,β-unsaturated carbene **7**. Conversion of **7** to **8** and reductive elimination of **8** to produce **9**, followed by [3,3] rearrangement, would afford product **2**.[11] As a second alternative (mechanism B, Scheme 1), ring expansion of **8** to **10a** would allow direct production of **2** upon reductive elimination.[12] In completely distinct mechanism C (Scheme 1), oxidative cyclization of nickel(0) with dienyne **1** could allow production of metallacycloheptadiene **11**.[13] Carbene insertion into either metal carbon bond of **11** to generate metallacycle **10a** or **10b**, followed by reductive elimination, would afford product **2**. This type of oxidative cyclization, migratory insertion sequence is commonly invoked in carbonylative cycloadditions, and the insertion of a metal carbene ligand into a metal−carbon bond is well precedented in other contexts.[14] Finally, a fourth alternative (mechanism D, Scheme 1) could involve ring contraction of metallacycle **11** to nickel biscarbene **12**. Carbene−carbene coupling of **12** could then generate divinylcyclopropane **9**, which rearranges to **2** as previously described. The ring contraction of a metallacycle to a cyclopropane has been demonstrated in a number of contexts.[15] Although mechanisms C and D have been depicted with the trimethylsilyl carbene unit present in the intermediate structures **11** and **12**, the analogous structures that lack the trimethylsilyl carbene unit could also be involved, with diazoalkane incorporation occurring at a late stage of the reaction pathway. In this study, we have focused largely on the key question of involvement of divinylcyclopropanes (mechanisms A or D) vs the direct kinetic production of a seven-membered ring (mechanisms B or C). A systematic examination of chemical reactivity and stereochem-

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(11) For a discussion of cyclopropanation and metathesis pathways of enynes, see: Peppers, B. P.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *126*, 9524.

(12) Involvement of ring-expanded nickel metallacycles in medium ring synthesis has precedent in Wender's [4+4] cycloaddition reactions. See ref 1a.

(13) Structure **11** has direct precedent in Wender's [4+2] alkyne/diene cycloadditions. See references: (a) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. (b) Wender, P. A.; Smith, T. E. *Tetrahedron* **1998**, *54*, 1255.

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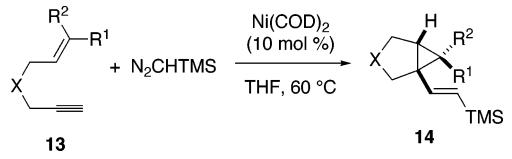
Table 3. Enyne Cyclizations



13 14

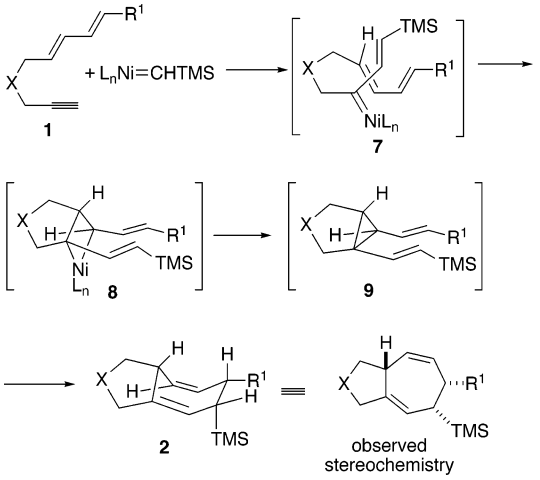
entry (substrate)	X	R^1	R^2	product, % yield (dr, *E*/*Z*)
1 (**13a**)	$C(CO_2Me)_2$	H	H	**14a**, 70 (*E* only)
2 (**13b**)	NTs	H	H	**14b**, 60 (10:1 *E*/*Z*)
3 (**13c**)	O	Et	H	**14c**, 36 (>95:5 dr, *E* only)
4 (**13d**)	O	H	Et	**14d**, 25 (>95:5 dr, 9:1 *E*/*Z*)

istry and a qualitative comparison of relative rates have provided significant insight into these intriguing mechanistic questions, as described below.

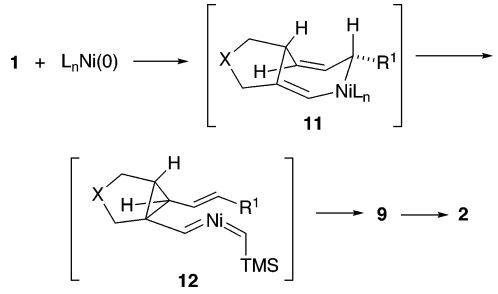
Evidence for the Involvement of Cyclopropane Intermediates. A key feature of mechanisms A and D is the formation of divinylcyclopropane **9** followed by its thermal conversion to **2**. To gain evidence for the involvement of structures such as **9**, we sought evidence that the nickel adduct generated from Ni(COD)$_2$ and TMS diazomethane could directly add to a simple enyne. This observation would serve as a direct model for the portions of mechanisms A and D that correspond to the **1** to **9** conversion while avoiding the subsequent sigmatropic rearrangement. Notably, Hoye had previously demonstrated this mode of reactivity upon treatment of enynes to molybdenum carbene species,[16] and the corresponding catalytic reaction was recently developed by Dixneuf upon exposure of enynes and TMS diazomethane to Cp*RuCl(COD).[17] Both malonate-derived substrate **13a** and nitrogen-tethered substrate **13b** were examined in the catalytic reaction with TMS diazomethane and Ni(COD)$_2$ (Table 3, entries 1 and 2). In both cases, the reactions proceeded smoothly at 60 °C to afford [3.1.0]-bicyclohexane ring systems **14a**,**b** in analogy to the studies from Hoye and Dixneuf. An important observation is that the *E*-vinyl silane was preferentially generated in both cases. In contrast, the ruthenium-catalyzed method of Dixneuf, involving the same diazoalkane, favored the *Z*-isomer.[17] Examination of substrates **13c** and **13d** clearly illustrated that this addition step is stereospecific (Table 3, entries 3 and 4). Although the chemical yields were low with 1,2-disubstituted alkenes, substrate **13c** afforded the cyclopropane **14c**, whereas **13d** afforded cyclopropane **14d**. Diastereoselectivities were excellent and opposite for these two cases, and the *E*-vinyl silane was produced in both instances with high selectivity. Knowledge about the stereochemistry of the vinyl silane produced and about the relationship of starting material olefin stereochemistry to product cyclopropane stereochemistry proved to be important features in our stereochemical analysis of the [4+2+1] process (vide infra).

Further Evidence for the Involvement of a [3,3] Rearrangement of Divinylcyclopropanes. A considerable amount is known about the mechanism of [3,3] rearrangements of divinylcyclopropanes. The reaction proceeds through a boat transition state, and the alkene stereochemistry controls both the relative stereochemistry of the newly formed chiral centers

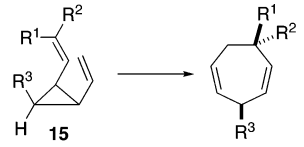
Scheme 2. Stereochemical Analysis: Mechanism A



Scheme 3. Stereochemical Analysis: Mechanism D



and the reaction rate.[18] In particular, the development of A^{1,3} strain in conformation **15** (eq 2), via substitution of R^1 or R^3, results in a significant retardation of reaction rates.[18f,g]



(2)

R^1,R^3 = H, R^2 = alkyl: proceeds at < 0 °C
R^1 or R^3 = alkyl: proceeds at >75 °C

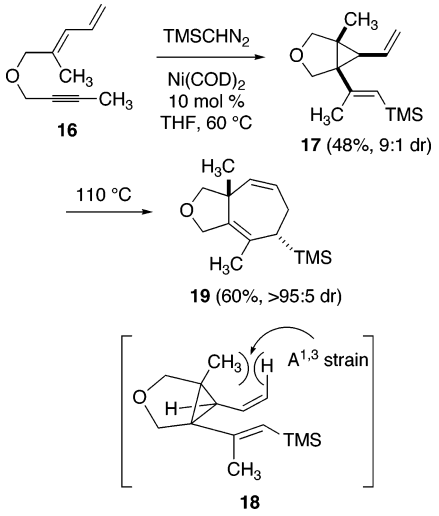
Because the enyne cyclizations described above (Table 3) provide a clear predictor of the stereochemistry of the vinyl silane and cyclopropane stereocenters, it is useful to consider how these stereochemical features would be expected to impact the stereoselectivity and reaction rates of dienyne cyclizations. Accordingly, if dienyne **1** participates in mechanism A described above (Scheme 1), then the initially formed intermediate **7** should possess the *E*-vinyl silane configuration (Scheme 2). Addition of the nickel carbene of **7** to the proximal *E*-alkene of the tethered diene should proceed in a stereospecific sense to afford compound **9** with the stereochemistry shown (Scheme 2). A similar analysis of mechanism D also predicts the observed stereochemistry of product **2** if one assumes that the *E*-vinyl silane of **9** is generated from **12** (Scheme 3). The key features of **9** to note are the *E*-stereochemistry of the vinyl silane, the

(16) (a) Korkowski, P. F.; Hoye, T. R.; Rydberg, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 2676. (b) Hoye, T. R.; Rehberg, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 2841.

(17) Monnier, F.; Castillo, D.; Dérien, S.; Toupet, L.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5474.

(18) (a) Wender, P. A.; Filosa, M. P. *J. Org. Chem.* **1976**, *41*, 3490. (b) Marino, J. P.; Browne, L. J. *Tetrahedron Lett.* **1976**, 3245. (c) Piers, E.; Nagakura, I. *Tetrahedron Lett.* **1976**, 3237. (d) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919. (e) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamesetti, K. G. *Org. React.* **1992**, *41*, 1. (f) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. (g) Ohloff, G.; Pickenhagen, W. *Helv. Chim. Acta* **1969**, *52*, 880.

Scheme 4. Isolation of a Divinylcyclopropane via Quaternization

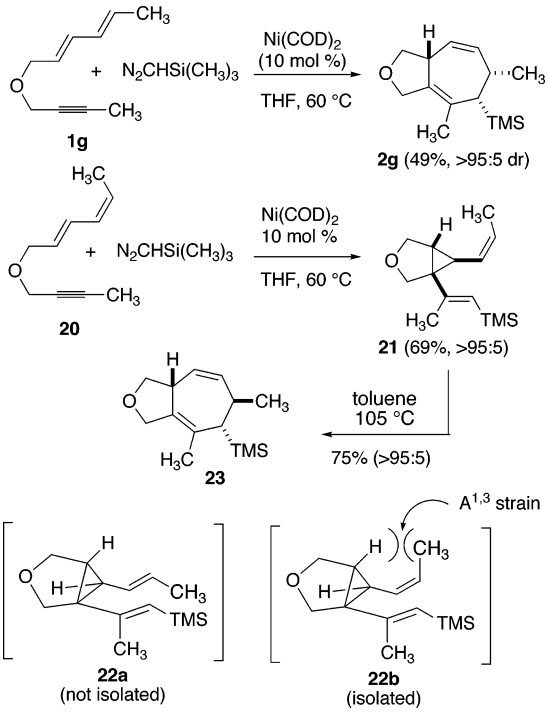


cis orientation of the two alkenes with respect to the cyclopropane, and the lack of a bridgehead substituent. All three of these features combine to provide a divinylcyclopropane structure that would be expected to undergo rapid [3,3] rearrangement to product **2**, which is exactly the product stereochemistry observed in catalytic [4+2+1] cycloadditions. Failure to detect the unrearranged divinylcyclopropane in cyclizations of dienynes and observation of the stereochemical outcome predicted by the above analysis are thus consistent with mechanism A or D.

To further probe the mechanistic features following this stereochemical analysis, we next installed functional groups into the starting dienyne that would introduce $A^{1,3}$ strain in the intermediate divinylcyclopropanes produced via mechanism A or D. We reasoned that mechanisms B and C would not be selectively and significantly impacted by these precise structural modifications. Installation of a bridgehead methyl in the intermediate divinylcyclopropane required the use of substrate **16** (Scheme 4). Treatment of **16** to the standard conditions at 60 °C in THF led to the selective formation of divinylcyclopropane **17** with the expected stereochemistry as shown. Significantly, the introduction of a bridgehead methyl substituent prevents the direct formation of a cycloheptadiene and instead allows divinylcyclopropane **17** to be isolated. Heating **17** to 110 °C in toluene led to a slow rearrangement of **17** to product **19**, and conformation **18** depicts the $A^{1,3}$ strain that slows the rate of this [3,3] sigmatropic rearrangement. Alternatively, carrying out the nickel-catalyzed reaction of **16** in toluene at 110 °C provided direct access to **19** in 50% yield without requiring isolation of cyclopropane **17**. The rate of [3,3] rearrangement of **17** was unaffected by the presence of $Ni(COD)_2$, suggesting that the rearrangement is a purely thermal, uncatalyzed process. On the basis of this experiment, the suggested involvement of mechanism A or D via a divinylcyclopropane rearrangement appears to be more secure.

A caveat in the above analysis is that installation of a quaternary center could potentially result in a change of mechanism. To avoid this significant structural change, we prepared both *E,E*-diene **1g** and *E,Z*-diene **20** (Scheme 5). This comparison now allows two stereoisomers to be directly analyzed. By the proposed mechanism A, *E,E*-diene **1g** will generate a divinylcyclopropane that lacks the $A^{1,3}$ strain that will slow the [3,3] rearrangement as depicted in conformation

Scheme 5. Isolation of a Divinylcyclopropane without Quaternization



22a, whereas *E,Z*-diene **20** will generate divinylcyclopropane **21**, which possesses the $A^{1,3}$ strain that will slow the [3,3] rearrangement as depicted in confomation **22b**. Indeed, these two stereoisomers **1g** and **20** afforded completely different reaction outcomes at 60 °C in THF, with **1g** exclusively producing rearrangement product **2g** and **20** exclusively producing divinylcyclopropane **21**. Heating compound **21** at 105 °C in toluene resulted in the smooth conversion to cycloheptadiene **23**, whereas carrying out the nickel-catalyzed reaction of substrate **20** in toluene at 110 °C provided direct access to **23** in 60% yield without requiring isolation of cyclopropane **21**. The divergent behavior of these two stereoisomeric starting materials provides compelling evidence that a mechanism involving divinylcyclopropane formation and rearrangement is the operative pathway in [4+2+1] cycloadditions.

Mechanisms A and D (Scheme 1) cannot be distinguished by the above experiments. However, failure to observe [4+2] cycloaddition products seems unlikely if a structure related to **11** is involved in the reaction pathway.[13] Furthermore, Wender has previously demonstrated that phosphine promotion is required to induce nickel-catalyzed [4+2] cycloadditions of dienyne substrates. Additionally, 1,1-disubstituted dienes with an *E*-internal alkene (related to structure **16**, Scheme 4) failed to undergo cyclization in the Wender study. These observations suggest that fundamental differences exist between the [4+2] and [4+2+1] cycloaddition pathways. Finally, our prior demonstrations of ring contractions of nickel metallacycles related to the **11** to **12** conversion (Scheme 1) required oxidative promotion with molecular oxygen.[15a] On the basis of these issues, mechanism A (alkyne metathesis, divinylcyclopropane formation, [3,3] rearrangement) is perhaps most consistent with the reactivity trends noted. The current study strongly suggests that divinylcyclopropanes, irrespective of the precise mechanism by which they are formed, are key intermediates in the nickel-catalyzed [4+2+1] reaction.

Conclusions

In summary, a new catalytic [4+2+1] cycloaddition of dienynes and (trimethylsilyl)diazomethane has been developed. A variety of carbocyclic and heterocyclic bicycles may be produced in a stereospecific fashion. Through a stereochemical analysis, strong evidence in favor of a mechanism involving formation and [3,3] rearrangement of divinylcyclopropanes was presented.

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Supporting Information Available: Full experimental details and copies of ^{1}H NMR spectra of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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