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Authors: Verner A. Lofstrand; F. G. West

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Efficient Trapping of 1,2-Cyclohexadienes with 1,3-Dipoles

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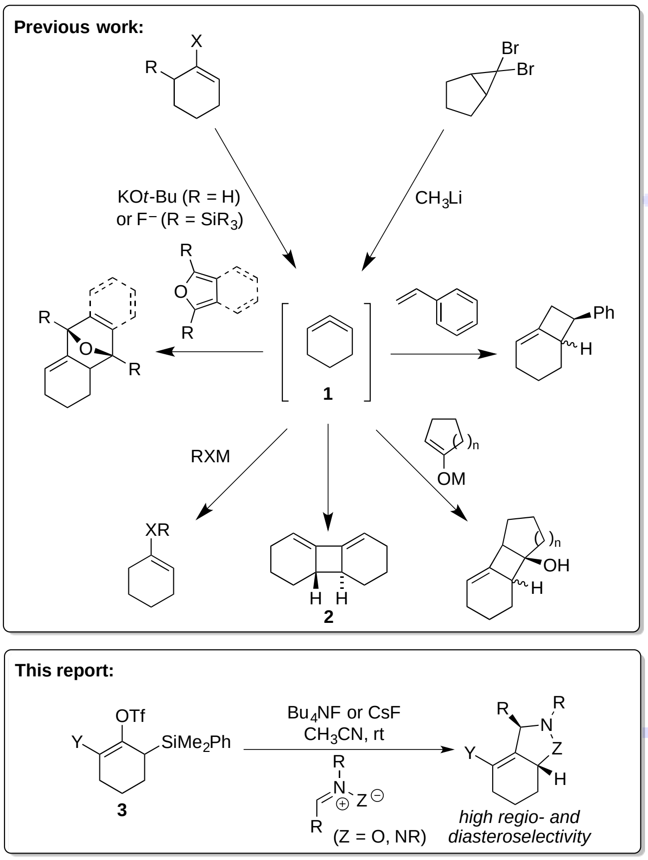
Dedication ((optional))

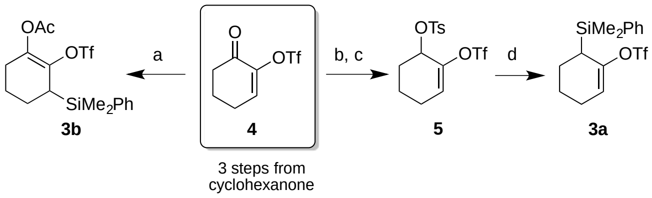
Abstract: 1,2-Cyclohexadienes are transient intermediates that undergo rapid dimerization and intermolecular trapping with activated olefins and heteroatomic nucleophiles. Fluoride-mediated desilylative elimination of readily accessible 6-silylcyclohexene-1-triflates allows the mild, chemoselective, and functional group tolerant generation of cyclic allene intermediates, which undergo efficient trapping reactions with stable 1,3-dipoles. The reactions proceed with high levels of both regio- and diastereoselectivity. The reaction of cyclic allenes with azides is accompanied by the facile loss of dinitrogen, resulting in the formation of tetrahydroindoles or polycyclic aziridines depending on the azide employed.



Scheme 1. Known generation and trapping processes of 1,2-cyclohexadiene.

Apart from the commonly encountered charged and radical species, transient molecules whose high reactivity derives from ring strain offer an attractive means for the rapid assembly of molecular complexity.[1][2] Cyclic alkynes have received considerable attention recently as strategic intermediates for bio-orthogonal tagging and synthetic methodology;[3] however, there have been comparatively few studies dedicated to the synthetic utility of the isomeric cyclic allenes. The generation and functionalization of 1,2-cyclohexadiene **1** eluded chemists until Wittig and Fritze reported the [4+2] cycloaddition of 1,3-diphenylisobenzofuran with 1,2-cyclohexadiene *via* an E2 elimination of HBr from 1-bromo-1-cyclohexene (Scheme 1).[4] Subsequent research in this area has principally focused on methods to generate these highly strained intermediates–studies which have historically relied upon large excesses of styrenes, furans, 1,3-dienes, alkoxides, and enolates as intermolecular traps of putatitve cyclic allene intermediates in order to avoid rapid dimerization to **2**.[5] These challenges have imposed limitations on the range of substrates and conditions available for broader study of cyclic allene reactivity and its exploitation in synthesis. Herein, we report the mild generation of 1,2-cyclohexadienes *via* the fluoride-mediated desilylative elimination of vinylic leaving groups (**3**), and their synthetically useful cycloaddition reactions with various 1,3-dipoles.

To circumvent the complicated elimination of vinylic leaving groups under strongly basic conditions previously investigated and the limited functional group tolerance of the Doering-Moore-Skattebøl reaction,[6] we chose to investigate the fluoride-mediated elimination conditions first reported by Johnson and Shakespeare.[7] Further, the use of a vinyl triflate leaving group as reported by Quintana *et al.* was seen as a logical improvement of the allene generation method and served as the starting point for our investigations.[8,9] The readily accessible enol triflate derivative (**4**)[10] of cyclohexane-1,2-dione was found to be a convenient starting material for the synthesis of cyclic allene precursors (Scheme 2). 1,2-Reduction of the enone,[11] derivatization to allylic tosylate **5** under modified conditions,[12] and copper-mediated allylic substitution with



Scheme 2. Reaction conditions: a) CuBr•SMe$_2$, PhMe$_2$Si-Cl, Li(0), THF, –78 °C; Ac$_2$O (86 %), b) CeCl$_3$•7H$_2$O, NaBH$_4$, MeOH, c) TsCl, NMe$_3$•HCl, NEt$_3$, PhCH$_3$, 0 °C, (75 % over two steps), d) CuCN, PPh$_3$, PhMe$_2$Si-Cl, Li(0), 0 °C (85 %).

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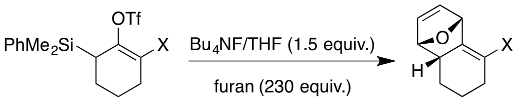
dimethylphenylsilyllithium provided an efficient and scalable synthesis of allylic silane **3a**,[13] equivalent to the previously described precursors.[8,9] Direct copper-mediated conjugate addition using dimethylphenylsilyllithium and capping of the enolate with acetic anhydride[14] afforded allylic silane **3b**, a potential precursor to an acetoxy-substituted 1,2-cyclohexadiene.

The suitability of allylic silanes **3a** and **3b** as precursors of the desired cyclic allenes was evaluated *via* treatment with a THF solution of tetrabutylammonium fluoride (TBAF) in the presence of furan (Scheme 3). Both precursors furnished the corresponding [4+2]-cycloadducts **6a** and **6b** as mixtures of diastereomers favoring the *endo* diastereomer (~11:1), in agreement with previously reported cycloadditions of 1,2-cyclohexadiene with furan.[15] The reaction of **3b** is notable: carbocyclic allenes bearing oxygen substituents have not previously been reported, and the complete selectivity for reaction *via* the non-oxygenated π bond leaves a synthetically useful enol acetate moiety intact in the cycloadduct **6b**.



3a/3b

6a (X = H; 80%; 11:1 *endo*:*exo*)
6b (X = OAc; 33%; 11.3:1 *endo*:*exo*)

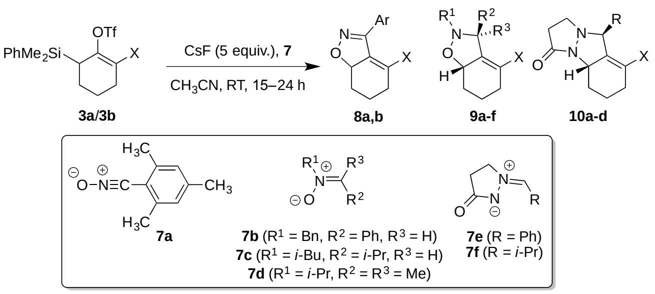
Scheme 3. [4+2] Cycloaddition of furan with unsubstituted and acetoxy-substituted cyclic allenes generated *in situ*.

With a convenient approach to the generation of cyclic allene intermediates in hand, their reactivity with 1,3-dipoles was examined. Upon addition of cesium fluoride to a solution of **3a** or **3b** and 2,4,6-trimethylbenzonitrile oxide **7a**,[16] the 4-alkylidene isooxazoline 1,3-dipolar cycloadducts **8a** and **8b** were isolated in good yields (Table 1, entry 1–2). Notably, each was obtained as a single regioisomer as determined by ^{1}H NMR analysis. As previously noted by Engels and Christl,[17] and Werstiuk[18] cyclic allenes can be viewed as weak nucleophiles at the central carbon of the allene; thus, preferential bonding of this carbon with the electrophilic carbon terminus of the 1,3-dipole is not surprising. Complete selectivity for reaction *via* the non-oxygenated alkene of the acetoxy-substituted allene derived from **3b** was a welcome observation, and the higher yield seen with this example indicates that polarizing substituents on the allene moiety may enhance reaction with 1,3-dipoles, in accord with the orbital considerations noted by Houk and coworkers.[19]

Remarkably low loadings of the nitrile oxide trap (5 equivalents) could be used, indicating the comparatively more effective reactivity match versus the conventionally employed dienes and alkenes. However, this approach was incompatible with *in situ* generated nitrile oxides only yielding material derived from the dimerization of the cyclic allenes.

The analogous nitrones also underwent 1,3-dipolar cycloaddition with cyclic allenes to produce alkylidene isoxazolidines **9a-f** in good yields, and with complete regiocontrol and excellent diastereoselectivity (Table 1, entry 3–8).[20] Given the greater bench stability of nitrones more variability in the 1,3-dipole structure was available for study. Only a single diastereomer was observed by analysis of the ^{1}H NMR spectral data regardless of the substituents on the nitrone, which was determined to be *anti*- *via* TROESY correlations.[21]

Table 1. Reaction of nitrile oxide, nitrone and azomethine imine 1,3-dipoles with cyclic allenes.[a]



Entry	X	1,3-dipolar trap	Product	Yield[e]	d.r.[a]
1	H	**7a**[b]	**8a**	43 %	n.a.
2	OAc	**7a**[b]	**8b**	69 %	n.a.
3	H	**7b**[c]	**9a** (R^1=Bn, R^2=Ph, R^3=H)	62 %	>20:1
4	OAc	**7b**[c]	**9b** (R^1=Bn, R^2=Ph, R^3=H)	34 %	>20:1
5	H	**7c**[c]	**9c** (R^1=*i*-Bu, R^2=*i*-Pr, R^3=H)	54 %	>20:1
6	OAc	**7c**[c]	**9d** (R^1=*i*-Bu, R^2=*i*-Pr, R^3=H)	40 %	>20:1
7	H	**7d**[c]	**9e** (R^1=*i*-Pr, R^2=R^3=Me)	58 %	n.a.
8	OAc	**7d**[c]	**9f** (R^1=*i*-Pr, R^2=R^3=Me)	–[f]	n.a.
9	H	**7e**[d]	**10a** (R=Ph)	46 %	11:1
10	OAc	**7e**[d]	**10b** (R=Ph)	51 %	>20:1
11	H	**7f**[d]	**10c** (R=*i*-Pr)	63 %	>20:1
12	OAc	**7f**[d]	**10d** (R=*i*-Pr)	44 %	>20:1

[a] In all cases d.r. was determined by comparison of the ^{1}H NMR signals of the isolated mixtures, [b] 5 equiv. of nitrile oxide were used, [c] 5 equiv. of nitrone were used, [d] 3 equiv. of azomethine imine were used, [e] All yields are for isolated products after purification, [f] only dimerization and decomposition were observed (see text).

In contrast to earlier trapping examples, reaction of cyclic allenes with nitrones and nitrile oxides affords new carbon-oxygen bonds along with the C–C bond generated at the central allene carbon, broadening the synthetic potential of these intermediates. In order to further expand the versatility of this approach, we also examined trapping of cyclic allenes with isolable azomethine imines as an entrée to strategic carbon-nitrogen bonds.[22] The reaction of 3-oxopyrazolidin-1-ium-2-ides with cyclic allenes generated *in situ* showed complete regioselectivity, olefin selectivity (in the case of the acetoxy-substituted cyclic allene) and only slight decreases in the diastereoselectivity relative to the nitrone examples to give tricyclic products **10a-d** (Table 1, entry 9–12). The relative configuration and regiochemistry were established by similar means to the nitrone adducts (*vide supra*) and further confirmed by single crystal X-ray diffraction analysis of pyrazolidino[1,2-a]indazol-3-one **10a**.[23]

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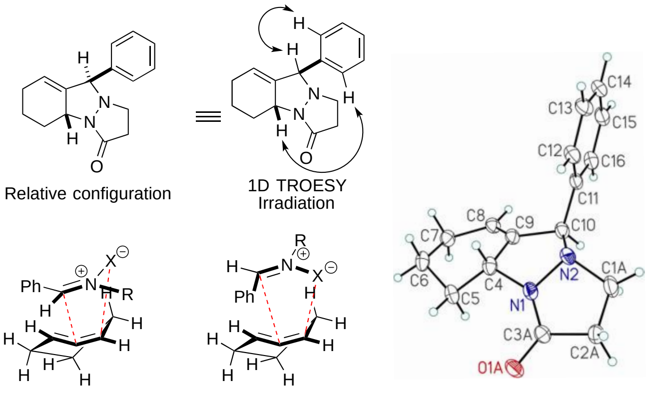
The high levels of stereoselectivity seen in these cycloadditions is consistent with a concerted pericyclic process, but the intervention of short-lived biradical or zwitterionic intermediates cannot be ruled out at this point, indicating fruitful future studies. Concerted reaction is also consistent with the high degree of stereochemical fidelity reported by Christl and Engels in the furan trapping of substituted 1,2-cyclohexadienes derived from enantioenriched precursors.[24] In analogy, we posit a concerted dipolar cycloaddition in these cases, with the observed diastereoselectivity arising from an *endo*-like transitions state (Figure 1, **TS 2**).



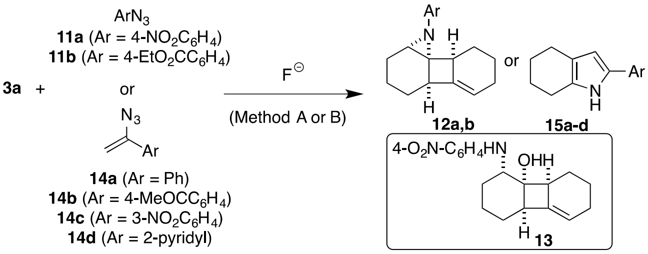
TS 1 (exo) **TS 2 (endo)** **10a**

Figure 1. TROESY correlations corroborated by X-ray crystal structure of azomethine imine adduct **10a**. The relative configuration of the cycloadducts is consistent with *endo* transition state, (TS 2).

Reaction of 1,2-cyclohexadienes with stable and readily accessible azide 1,3-dipolar partners was also of interest.[25] Initial studies indicated that only the electron-deficient aromatic azides **11a-b** furnished characterizable products (Table 2, entries 1–2). Treatment of **2a** with cesium fluoride in the presence of these traps afforded unexpected 2:1/cyclic allene:azide serial [2+1]/[2+2] cycloadducts **12a** and **12b**. The relative configuration of these structurally complex polycyclic products was determined by TROESY correlations of both the cycloadducts as well as the ring-opened amino alcohol **13**, which was obtained upon acidic workup. Unfortunately, reaction of acetoxy-substituted cyclic allene precursor **3b** and organic azides only gave complicated mixtures in the presence of fluoride.

Intramolecular cycloaddition of acyclic allenes with azides was studied extensively studied by Feldman and coworkers.[26] The initially formed 5-methylene-4,5-dihydro-1,2,3-triazole intermediates were found to be thermally unstable, undergoing a retro-[3+2] cycloaddition, extruding dinitrogen and furnishing an azatrimethylene methane intermediate, which could be intercepted with tethered olefins. The 2:1 adducts **12a,b** appear to result from a [2+2]-cycloaddition of alkylidene aziridine **B** with a second cyclic allene (Scheme 4). This aziridine may arise from an azatrimethylene methane (**A**) analogous to those postulated by Feldman and coworkers; however, it is not clear whether **A** would be formed *via* cycloreversion from an initial alkylidenetriazoline, since this process typically requires high reaction temperatures. A possible stepwise process involving biradical intermediates could intervene under these conditions,

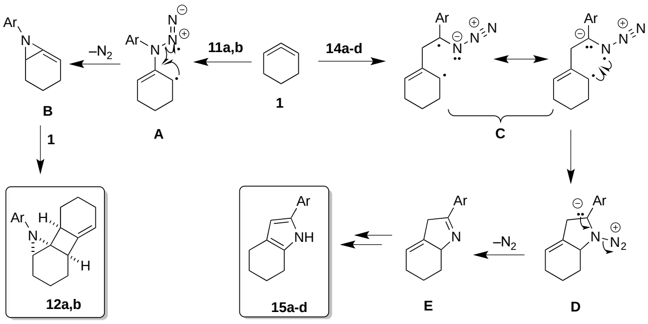
Table 2. Reaction of organoazide 1,3-dipolar compounds with cyclic allenes.[a]



Entry	Azide	Conditions[a]	Product	Yield[b]
1	**11a**	A	**12a**	52 %
2	**11b**	A	**12b**	51 %
3	**11a**	A	**13**	34 %[c]
4	**14a**	B	**15a**	47 %
5	**14b**	B	**15b**	66 %
6	**14c**	A/B	**15c**	34 %/43 %
7	**14d**	B	**15d**	15 %

[a] Conditions: A: Azide (5 equiv.) and **3a** (1 equiv.) were dissolved in dry MeCN and CsF (5 equiv.) was added as a granular solid. The reaction was stirred for 18–24 h; B: Azide (5 equiv.) and **3a** (1 equiv.) were dissolved in dry THF (0.2 M) and TBAF solution (0.1 in THF) was added via syringe pump (2mL/h). Reaction was stirred for 2 h, [b] all yields are for isolated product after purification, [c] product was only obtained after an acidic aqueous workup.

given the proposed accessibility of open-shell electronic states in the case of strained cyclic allenes.[27] Regardless of their provenance, the formation of **12a,b** is notable given the presumed combination of two short-lived reactants (cyclic allene + alkylidene aziridine) and the introduction of amine functionality at a synthetically challenging angular position.



Scheme 4. Proposed mechanism for the formation of 2:1 adducts **12** and 2-aryltetrahydroindoles **15** via reaction with azide traps.

The intermediacy of aza-trimethylenene methane intermediate **A** was investigated *via* reaction of **3a** with **11a** and CsF in the presence of excess styrene (Scheme 5). However, only known [2+2]-cycloadduct **16** was observed.[28] This result indicated that reaction of styrene with the cyclic allene is kinetically favored over that of the aryl azide. With this in mind, we then examined allene trapping with styryl azides **14a-d** (Table 2, entry 3–6). These traps, combining styrene and azide functionalities, afforded 2-aryl-4,5,6,7-tetrahydroindoles **15a-d**.[28] The reaction tolerated a range of electronic environments;

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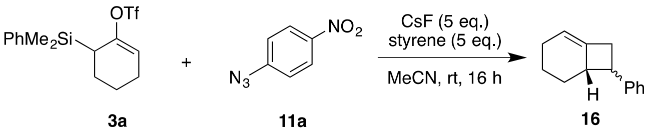
however, incorporation of methyl substituent at the β-styryl position completely extinguished any reaction between the trap and the cyclic allene, indicating a high sensitivity to steric demand.



Scheme 5. Attempted interception of the allene/azide [2+1+2] cycloaddition with styrene.

Previously studied reactions of substituted styrenes with cyclic allenes strongly suggest the reactions involve diradical intermediates.[28,30,31] In analogy, the present reaction likely occurs *via* the radical addition of the central cyclic allene carbon atom into the styrene to generate a new biradical intermediate **C** (Scheme 4). Upon ring closure, spontaneous extrusion of dinitrogen would occur furnishing tetrahydroindole **E** which could rearrange to the aromatic product **15** *via* a series of proton transfers.

We have described a succinct, convenient and scalable route to highly reactive 1,2-cyclohexadienes, exemplified here by the parent compound and the 1-acetoxy derivative. In addition to well-established [4+2] reaction with furan, we have shown that nitrile oxide, nitrone and azomethine imine 1,3-dipoles can serve as efficient traps to furnish polycyclic heterocyclic products with high regio- and stereoselectivity. In contrast, azide traps afford unique reactivity, involving formation of unusual 2:1 adducts in the case of aryl azides, and tetrahydroindoles in the case of styryl azides. Further efforts to intercept these fascinating intermediates in synthetically useful transformations and attempts to elucidate reactions mechanisms and the origins of the high selectivities are ongoing and will be described elsewhere.

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Keywords: Cyclic Allene • Dipolar Cycloaddition • Heterocycles • Reactive Intermediate

[1] *Reactive Intermediate Chemistry,* (Eds.: R. A. Moss, M. S. Platz, M. Jones Jr.); John Wiley & Sons, **2004**.

[2] *Strained Hydrocarbons*, (Eds.: H. Dodziuk); John Wiley & Sons, **2009**.

[3] a) C. M. Gampe, E. M. Carreira, *Angew. Chem. Int. Ed.* **2012**, *51,* 3766–3778; b) C. M. Gampe, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50,* 2962–2965; c) K. Lang, J. W. Chin, *Chem. Rev.* **2014**, *114,* 4764–4806; d) N. J. Agard, J. A. Prescher, C. R. Bertozzi, *J. Am. Chem. Soc.* **2004**, *126,* 15046–15047.

[4] a) G. Wittig, P. Fritze, *Angew. Chem. Int. Ed.* **1966**, *5,* 846; b) G. Wittig, P. Fritze, *Liebigs Ann Chem.* **1968**, *711,* 82–87.

[5] a) R. P. Johnson, *Chem. Rev.* **1989**, 89, 1111–1124; b) M. Balci, Y. Taskesenligil, In *Advances in Strained and Interesting Organic Molecules, Vol. 8* (Ed.; B. Halton), JAI Press: Stamford, Connecticut, **1999**, pp. 43–82; c) M. Christl, in *Modern Allene Chemistry*, (Eds.: N. Krause, A. S. K. Hashmi) Wiley-VCH, Weinheim, **2005**, pp 243–357.

[6] a) W. V. E. Doering, A. K. Hoffman, *J. Am. Chem. Soc.* **1954**, *76,* 6162–6165; b) W. R. Moore, H. R. Ward, *J. Org. Chem.* **1960**, *25,* 2073; c) L. Skattebol, *Tetrahedron Lett.* **1961**, 167–172; d) L. Skattebol, S. Solomon, *Organic Syntheses*. **1969**, *49,* 35–38.

[7] W. C. Shakespeare, R. P. Johnson, *J. Am. Chem. Soc.* **1990**, *112,* 8578–8579.

[8] I. Quintana, D. Peña, D. Pérez, E. Guitián, *E. J. Org. Chem.* **2009**, 5519–5524.

[9] During preparation of this manuscript a similar study concerning nitrone trapping of the parent 1,2-cyclohexadine was reported: J. S. Barber, E. D. Styduhar, H. V. Pham, T. C. McMahon, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2016**, *138*, 2512–2515.

[10] Accessible via a three step procedure from cyclohexanone; a) M. Utaka, S. Matsushita, A. Takeda, *Chem. Lett.* **1980**, 779–780; b) M. G. Saulnier, J. F. Kadow, M. M. Tun, D. R. Langley, D. M. Vyas, *J. Am. Chem. Soc.* **1989**, *111,* 8320–8321.

[11] J. L. Luche, A. L. Gemal, *J. Am. Chem. Soc.* **1979**, *101*, 5848–5849.

[12] Y. Yoshida, Y. Sakakura, N. Aso, S. Okada, Y. Tanabe, *Tetrahedron* **1999**, *55,* 2183–2192.

[13] a) I. Fleming, in *e-EROS Encyclopedia Of Reagents for Organic Synthesis*. **2009**, 1–3; b) J. T. B. H. Jastrzebski, G. van Koten, In *Modern Organocopper Chemistry*, (Ed.; N. Krause), Wiley-VCH, Wienheim, **2002**; pp 1–44.

[14] P. L. Stotter, K. A. Hill, *J. Org. Chem.* **1973**, *38,* 2576–2578.

[15] A. T. Bottini, L. L. Hilton, J. Plott, *Tetrahedron*. **1975**, 1997–2001.

[16] P. Beltrame, P. L. Beltrame, A. Filippi, G. Zecchi, *J. Chem. Soc. Perkin Trans. 2*, **1972**, 1914–1919.

[17] B. Engels, J. C. Schöneboom, A. F. Münster, S. Groetsch, M. Christl, *J. Am. Chem. Soc*. **2002**, *124,* 287–297

[18] N. H. Werstiuk, C. D. Roy, J. Ma, *Can. J. Chem.* **1996**, *74*, 1903–1905.

[19] a) K. N. Houk, J. Sims, C. R. Watts, L. J. Luskus, *J. Am. Chem. Soc.* **1973**, *95,* 7301–7315; b) K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier, J. K. George, *J. Am. Chem. Soc*. **1973**, *95,* 7287–7301.

[20] a) N. A. LeBel, E. Banucci, E. *J. Am. Chem. Soc.* **1970**, *92,* 5278–5280; b) G. B. Blackwell, R. N. Haszeldine, D. R. Taylor, *J. Chem. Soc. Perkin Trans. 1,* **1983**, 1–5.

[21] See supporting information for full characterization.

[22] Only catalyzed reactions have been reported for azomethine imine/ allene cycloadditions. C. Nájera, J. M. Sansano, M. Yus, *Org. Biomol. Chem*. **2015**, *13,* 8596–8636.

[23] CCDC 1457161 (**10a**) contains the supplementary crystallographic data for this paper. These data may be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[24] M. Christl, H. Fischer, M. Arnone, B. Engels, *Chem. Eur. J.* **2009**, *15,* 11266–11272.

[25] For earlier examples of 1,3-dipolar cycloadditions of azides with acyclic and cyclic allenes, see: a) W. Ried, H. Mengler, *Liebig Ann. Chem.* **1964**, *678,* 95–113; b) D. K. Wedegaertner, R. K. Kattak, I. Harrison, S. K. Cristie, *J. Org. Chem.* **1991**, *56,* 4463–4467.

[26] a) K. S. Feldman, M. R. Iyer, *J. Am. Chem. Soc.* **2005**, *127,* 4590–4591; b) C. S. López, O. N. Faza, K. S. Feldman, M. R. Iyer, D. K. Hester, *J. Am. Chem. Soc.* **2007**,*129,* 7638–7646.

[27] R. O. Angus, Jr, M. W. Schmidt, R. P. Johnson, *J. Am. Chem. Soc.* **1985**, *107*, 532–537.

[28] W. R. Moore, W. R. Moser, *J. Org. Chem.* **1970**, *35,* 908–912.

[29] a) Z. Wang, In *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, **2010**, *475,* 2107–2110; b) P. K. Chiu, M. P. Sammes, *Tetrahedron,* **1988**, 3531–3538.

[30] S. Harnos, S. Tivakornpannarai, E. E. Waali, *Tetrahedron Lett.* **1986**, *27*, 3701–3704.

[31] M. Christl, M. Schreck, *Chem. Ber.* **1987**, *120*, 915–920.

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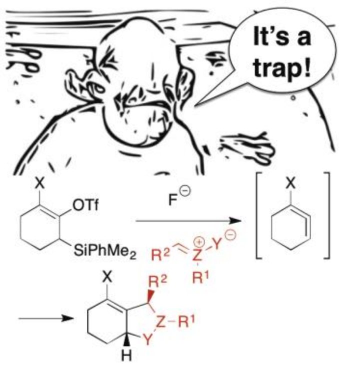
Layout 1:

COMMUNICATION

1,2-Cyclohexadienes–strained, highly reactive, short-lived intermediates–are readily generated from silyl triflate precursors. These species undergo efficient reaction with several classes of 1,3-dipole to afford polycyclic products with high regio- and stereoselectivity. In the case of azide traps, unusual new products are formed via loss of dinitrogen.



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Page No. – Page No.

Efficient Trapping of 1,2-Cyclohexadienes with 1,3-Dipoles

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