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How Tethers Control the Chemo- and Regioselectivities of Intramolecular Cycloadditions between Aryl-1-aza-2-azoniaallenes and Alkenes

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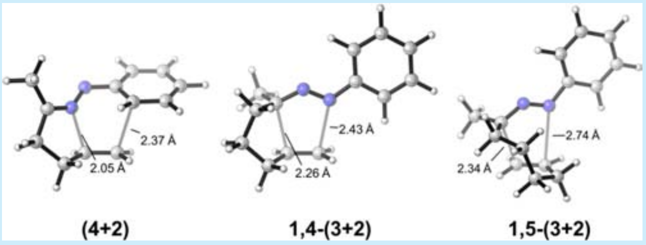
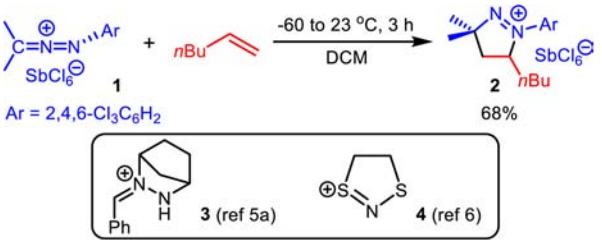
Ⓢ *Supporting Information*

ABSTRACT: Cationic 1-aza-2-azoniaallenes react intermolecularly with terminal alkenes to give 1,5-substituted (3 + 2)-cycloadducts, but intramolecular reactions lead to either 1,5- or 1,4-substituted (3 + 2)-cycloadducts or (4 + 2)-cycloadducts, depending on the tether length. DFT calculations and distortion/interaction analyses show that the $(CH_2)_3$ tether prevents the reacting partners from aligning efficiently to give 1,5-substituted (3 + 2)-cycloadducts, and the 1,4-regioselectivity dominates. With the $(CH_2)_2$ tether, the (3 + 2) cycloaddition is disfavored due to the forming four-membered ring in the transition state, and the (4 + 2) cycloaddition prevails.



The 1,3-dipolar cycloaddition reactions involve formally dipolar or zwitterionic molecules that add 1,3 to alkenes or alkynes to form five-membered heterocycles.[1] The identification and development of novel cycloaddition partners that lead to new heterocyclic scaffolds is an important area of ongoing research.[2] Jochims and co-workers reported that cationic aryl-1-aza-2-azoniaallenes can undergo intermolecular (3 + 2) cycloaddition reactions with alkenes to provide cationic diazenium products (Scheme 1).[3,4] This transformation has hitherto been described as a polar 1,3-dipolar cycloaddition,[3,4] but we now suggest that these heteroallene salts are more accurately described as 1,3-monopoles, since they are cations and add 1,3 to alkenes.

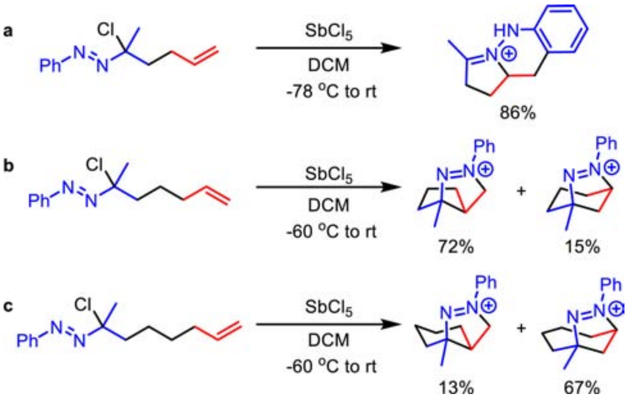
Scheme 1. Intermolecular (3 + 2) Cycloaddition between 1-Aza-2-azoniaallene Salt 1 and 1-Hexene and Examples of Other Experimentally Reported 1,3-Monopoles, Protonated Azomethine Imine 3 and Dithionitronium Cation 4



Other 1,3-monopoles that participate in cycloaddition reactions include protonated azomethine imines[5] and dithionitronium cations[6] (Scheme 1). Reactions of these species with alkenes represent an unrecognized class of cycloadditions, which we term 1,3-monopolar cycloadditions.

Recently, Brewer and co-workers studied the intramolecular reactions between aryl-1-aza-2-azoniaallene cations and alkenes (Scheme 2), which lead to either normal (3 + 2) cycloadditions[7] or (4 + 2) cycloadditions[8] using the azo bond and one aromatic π-bond of a 1-aryl substituent. All of these cycloadditions proceed efficiently and selectively at low temperature with unactivated alkenes (Scheme 2). The only factor that controls chemo- and regioselectivities is the length of the tether that connects the reacting partners.[9] To determine origins of the tether-controlled reaction selectivity, we have undertaken a

Scheme 2. Chemo- and Regioselectivities of Intramolecular Cycloadditions between Aryl-1-aza-2-azoniaallenes and Alkenes



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computational study at the B3LYP-D3/6-311+G(d,p)//B3LYP/6-31G(d) level of theory.[10,11]

We first studied the reactions of a simple 1,3-monopole **5**,[12] the result of hydride abstraction from the phenylhydrazone of acetone. Both (3 + 2) and (4 + 2) cycloadditions of **5** and propene were investigated. As shown in Figure 1, the concerted (3 + 2) cycloaddition can occur with the methyl group of propene proximal to the forming C−N bond (via **TS6**) or distal to the C−N bond (via **TS8**). The free energy barrier for (3 + 2) cycloaddition via **TS6** is only 16.3 kcal/mol, and this reaction leads to a very stable five-membered ring product **7**. The alternative (3 + 2) transition state **TS8** is calculated to be 4.9 kcal/mol higher in free energy than **TS6**. The carbon terminus of **5** is highly electrophilic, and the LUMO+1 orbital coefficient of C3 in phenyl-1-aza-2-azoniaallene is much larger than that of N1.[13] This indicates that C3 reacts with the nucleophilic terminal carbon of propene, which has the larger HOMO orbital coefficient. The (3 + 2) cycloaddition via **TS6** (Figure 1) is the most favorable, consistent with the exclusive 1,5-regioselectivity reported for intermolecular reactions (Scheme 1).[3] The competing (4 + 2) cycloaddition via **TS10** leading to the bicyclic product **11** has a barrier of 26.4 kcal/mol. The (4 + 2) cycloaddition barrier is significantly higher than that of the (3 + 2) cycloaddition; the (4 + 2) cycloaddition pathway involves breaking the aromaticity of the phenyl ring in **5**.[14] Indeed, the (4 + 2) cycloadditions have not been observed in any intermolecular reactions of aryl-1-aza-2-azoniaallenes. While each of these cycloadditions is concerted, with a single transition state, the most favorable pathway is highly asynchronous, dominated by the C−C bond formation.

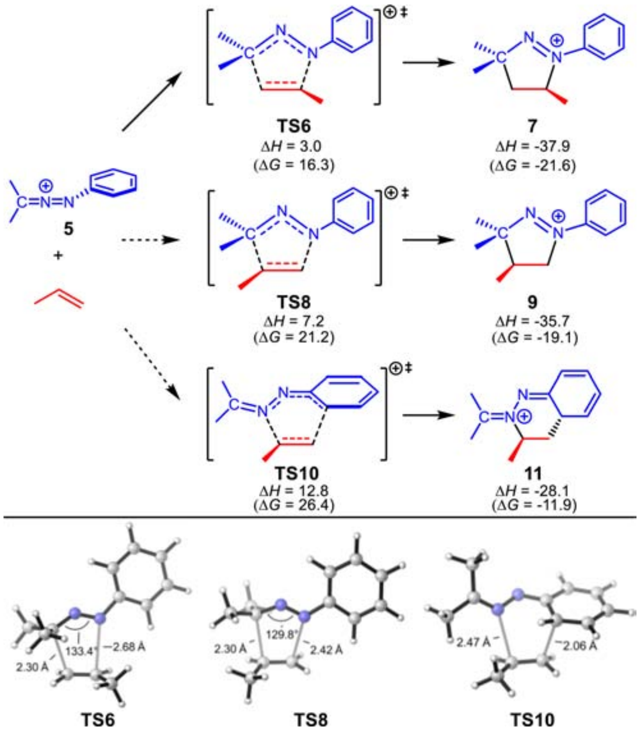
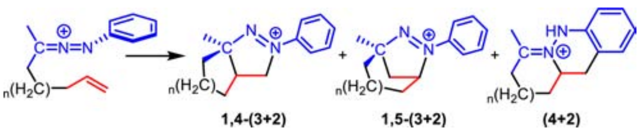


Figure 1. DFT-computed energetics (in kcal/mol) and transition-state structures for the (3 + 2) and (4 + 2) cycloadditions between 1-aza-2-azoniaallene **5** and propene.

We also studied the intramolecular cycloadditions between aryl-1-aza-2-azoniaallenes and alkenes with tether lengths of n = 0−2 (Scheme 3). The barriers computed for various processes are shown in Figure 2. When n = 0, only (3 + 2) cycloaddition transition state **TS13** can be located. The regioisomeric (3 + 2) transition state could not be located, because the tether is too short. The barrier for the (3 + 2) cycloaddition (ΔG = 19.8 kcal/mol) is much higher than that for the alternative (4 + 2) cycloaddition via **TS14** (ΔG = 13.0 kcal/mol), in line with the experimental finding that only (4 + 2) cycloadditions occur for this system (Scheme 2a).[8] The tether introduces minimal strain to the (4 + 2) transition state, and the entropy penalty is small for this intramolecular process. When n = 1, one (4 + 2) and two regioisomeric (3 + 2) transition states were located. The activation free energy required for the (4 + 2) cycloaddition via **TS18** is about 5 kcal/mol higher than those for the (3 + 2) cycloadditions. These results align well with the experimental finding that only (3 + 2) products are formed in this reaction.[7] Comparing the two regioisomeric (3 + 2) cycloaddition transition states **TS16** and **TS17**, there is a 0.3 kcal/mol advantage for the formation of the 1,4-substituted (3 + 2)-cycloadduct via **TS16**, which is consistent with the experimental observation of a mixture of products (Scheme 2b). When n = 2, the (4 + 2) cycloaddition is even less favorable. The regioselectivity of the (3 + 2) cycloaddition, which prefers the 1,5-substituted (3 + 2)-cycloadduct via **TS21**, is like the selectivity observed in intermolecular reactions.

Scheme 3. Possible Intramolecular (3 + 2) and (4 + 2) Cycloadditions between Aryl-1-aza-2-azoniaallenes and Alkenes



To understand the role of the tether on the reaction barriers, we have separated the electronic energy barrier (ΔE) into two terms (Scheme 4): (1) a term ($\Delta E'$) representing energy contributions stemming from the structurally distorted reacting fragments (in this case a cationic 1-aza-2-azoniaallene [blue] and ethylene [red] fragment) amd (2) a term (ΔE_{tether}) representing energy contributions stemming from the tether. We previously applied this type of distortion/interaction analysis to other intramolecular cycloadditions.[9,15] To obtain the contribution of the reacting fragments, the optimized transition structure for the intramolecular reaction of interest was modified by replacing the tether with hydrogen atoms appended at a C−H distance of 1.09 Å. This provides a distorted version of an intermolecular TS for the reaction of a model 1-aza-2-azoniaallene cation with ethylene. The $\Delta E'$ term represents the difference in energy between this distorted intermolecular TS and the separated reactants. The energy associated with distorting the 1-aza-2-azoniaallene cation and ethylene to their transition-state geometries is the distortion energy (ΔE_{dist}), and the energy stemming from interactions between the two fragments is the interaction energy

Scheme 4. Representative Distortion/Interaction Model for the Transition State of an Intramolecular Cycloaddition

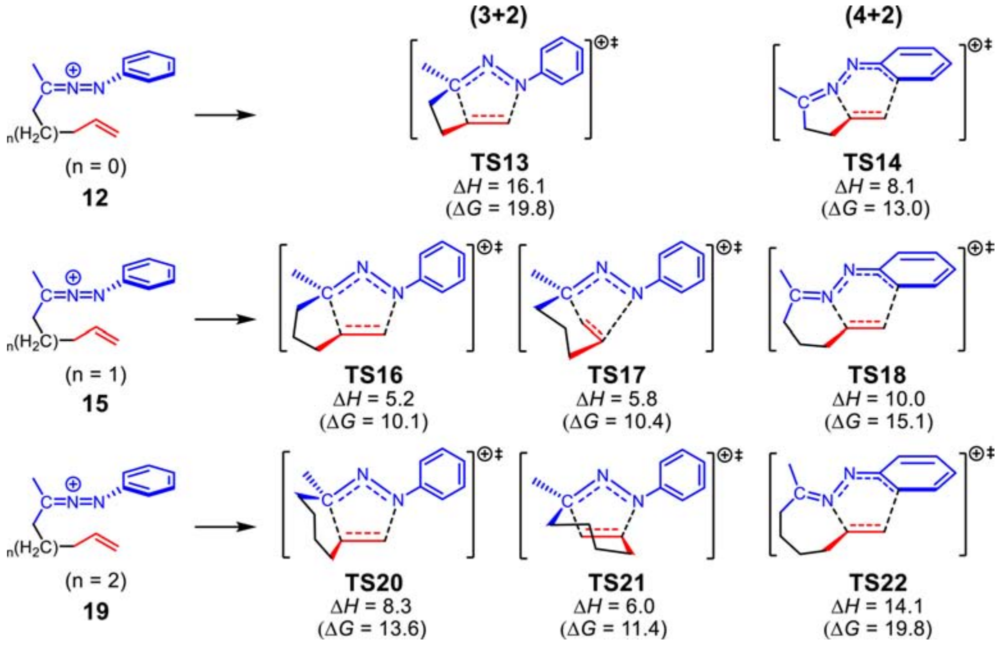


Figure 2. DFT-computed activation enthalpies and free energies (in kcal/mol) for the intramolecular (3 + 2) and (4 + 2) cycloadditions between 1-aza-2-azoniaallenes and alkenes with different tether lengths.

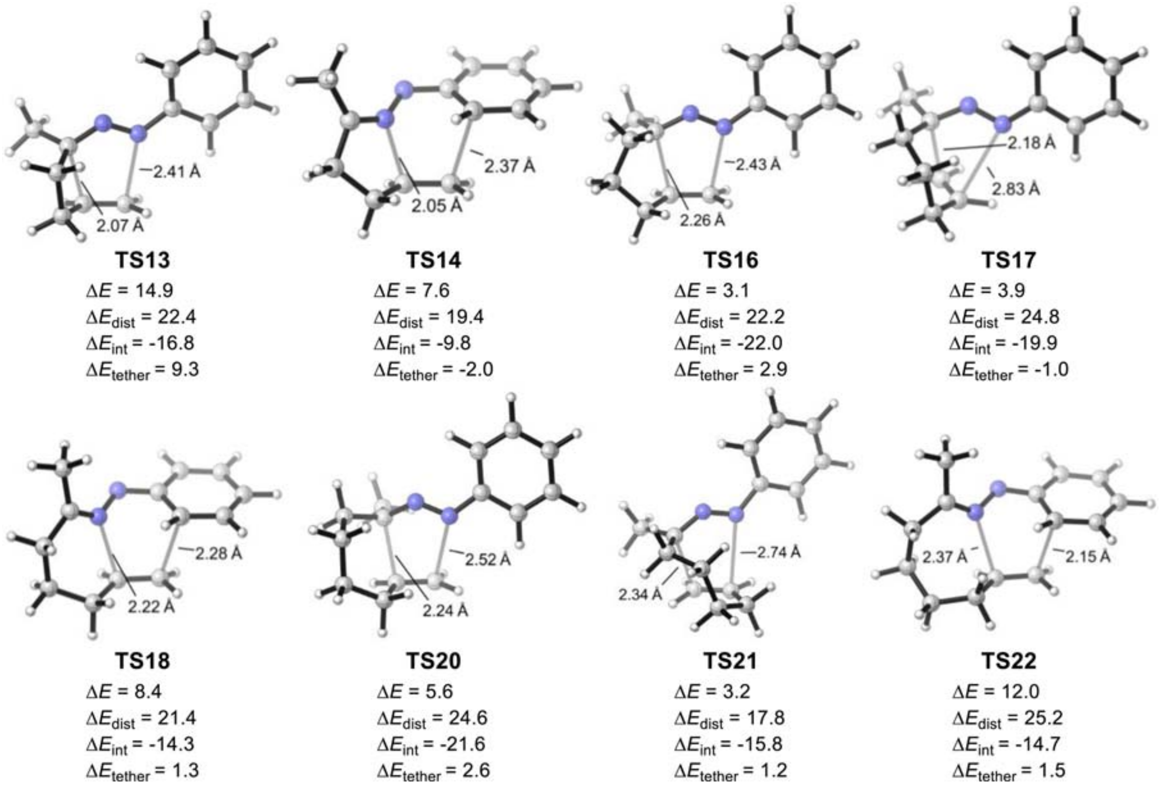


Figure 3. DFT-optimized transition structures, electronic energy barriers, distortion and interaction energies, and energy contributions from the tether for the intramolecular (3 + 2) and (4 + 2) cycloadditions with different tethers. Energies are in kcal/mol.

(ΔE_{int}).[16−18] Because $\Delta E'$ represents the reaction barrier for the two fragments to undergo an "intramolecular reaction" without the tether, the difference between ΔE and $\Delta E'$ quantitatively shows how the tether affects the energetics of the reaction ($\Delta E_{\text{tether}} = \Delta E - \Delta E'$).

We first analyzed the effects of the shortest tether in the (3 + 2) transition state **TS13** and the (4 + 2) transition state **TS14** (Figure 3). The tether in **TS13** significantly increases the barrier (ΔE_{tether} = 9.3 kcal/mol) due to the partial formation of a strained four-membered ring. By contrast, the tether stabilizes the (4 + 2) transition state **TS14** by 2.0 kcal/mol.[19] The difference in energy imparted by the tether for these two reactions prevents the intrinsically more favorable (3 + 2) cycloaddition from occurring, and the unique (4 + 2) cycloaddition is realized. When a longer tether ($n = 1$) is applied, the longer tether imparts similarly small energies to the (3 + 2) and (4 + 2) transition states **TS16** and **TS18** (2.9 and 1.3 kcal/mol, respectively), and thus the innate (3 + 2) chemoselectivity is observed in this case. In considering the regioselectivity of the (3 + 2) cycloaddition, we note that it is opposite to the intrinsic 1,5-regioselectivity observed for the intermolecular (3 + 2) cycloaddition (Scheme 1). This is attributable to the fact that while the reacting partners in **TS16** have similar geometries and orientations as the intermolecular reaction (**TS8**, Figure 1), the reacting partners in **TS17** must distort more severely than in **TS6** (Figure 1) to achieve C−C and C−N bond formation. In this case, the tether controls the regioselectivity by dictating how the reacting partners can align. Lengthening the tether by one more methylene unit ($n = 2$), the computed tether effects are all small and similar. Therefore, this intramolecular cycloaddition has very similar chemo- and regioselectivities as compared to the intermolecular reaction.

These calculations have identified the origins of tether control of the chemo- and regioselectivities of intramolecular cycloadditions between aryl-1-aza-2-azoniaallenes and alkenes. The (3 + 2) cycloaddition is intrinsically more favorable than the competing (4 + 2) cycloaddition because it maintains the aromaticity of the aryl substituent. The high regioselectivity of intermolecular (3 + 2) cycloadditions is due to the better orbital interactions between the C3 in aryl-1-aza-2-azoniaallene and the terminal olefinic carbon. The chemo- and regioselectivities of intramolecular reactions depend on the length of the tether connecting the reacting partners. When the tether is sufficiently long ($n = 2$), the chemo- and regioselectivities of intramolecular reactions are similar to the selectivities observed for intermolecular reactions. Shortening the tether by one methylene unit ($n = 1$) prevents the reacting partners from aligning efficiently in the normally preferred orientation of the (3 + 2) cycloaddition, and thus the regioselectivity of the process changes. Finally, the shortest tether ($n = 0$) significantly destabilizes the (3 + 2) cycloaddition transition state because of unfavorable interactions within the forming four-membered ring; the (4 + 2) transition state is stabilized by the same tether and becomes preferred, leading to a reversal in chemoselectivity as compared to the intermolecular reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Computational details and complete ref 10. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51. (b) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018. (c) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235. (d) Sletten, E. M.; Bertozzi, C. R. *Acc. Chem. Res.* **2011**, *44*, 666. (e) Debets, M. F.; Van Berkel, S. S.; Dommerholt, J.; Dirks, A. J.; Rutjels, F. P. J. T.; van Delft, F. L. *Acc. Chem. Res.* **2011**, *44*, 805. (f) Ganesh, V.; Sudhir, V. S.; Kundu, T.; Chandrasekaran, S. *Chem.—Asian J.* **2011**, *6*, 2670. (g) Majumdar, K. C.; Ray, K. *Synthesis* **2011**, 3767. (h) Heaney, F. *Eur. J. Org. Chem.* **2012**, 3043. (i) Zhang, W. *Chem. Lett.* **2013**, *42*, 676. (j) Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296.

(2) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784.

(3) Wirschun, W. G.; Al-Soud, Y. A.; Nusser, K. A.; Orama, O.; Maier, G.-M.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4356.

(4) Wang, Q. R.; Amer, A.; Mohr, S.; Ertel, E.; Jochims, J. C. *Tetrahedron* **1993**, *49*, 9973.

(5) (a) Griffith, A. K.; Vanos, C. M.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 18581. (b) Rueping, M.; Maji, M. S.; Kucuk, H. B.; Atodiresei, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 12864. (c) Le Fevre, G.; Sinbandhit, S.; Hamelin, J. *Tetrahedron* **1979**, *35*, 1821. (d) Hesse, K.-D. *Justus Liebigs Ann. Chem.* **1971**, *743*, 50.

(6) Burford, N.; Johnson, J. P.; Passmore, J.; Schriver, M. J.; White, P. S. *J. Chem. Soc., Chem. Commun.* **1986**, 966.

(7) (a) Javed, M. I.; Wyman, J. M.; Brewer, M. *Org. Lett.* **2009**, *11*, 2189. (b) Wyman, J.; Javed, M. I.; Al-Bataineh, N.; Brewer, M. *J. Org. Chem.* **2010**, *75*, 8078.

(8) Bercovici, D. A.; Ogilvie, J. M.; Tsvetkov, N.; Brewer, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 13338.

(9) For a related theoretical study of tether length effects, see: Krenske, E. H.; Davison, E. C.; Forbes, I. T.; Warner, J. A.; Smith, A. L.; Holmes, A. B.; Houk, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 2434.

(10) Frisch, M. J. et al. *Gaussian 09*, revision D.01; Gaussian Inc.: Wallingford, CT, 2013.

(11) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104.

(12) For related DFT studies of cationic 1-aza-2-azoniaallenes, see: Wang, J.; Li, Z.; Wang, Q.; Tao, F. *J. Mol. Model.* **2013**, *19*, 83 and references therein.

(13) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. For the frontier molecular orbital (FMO) analysis, see the Supporting Information.

(14) Liang, Y.; Jiang, X.; Yu, Z.-X. *Org. Lett.* **2009**, *11*, 5302.

(15) (a) Krenske, E. H.; Houk, K. N.; Holmes, A. B.; Thompson, J. *Tetrahedron Lett.* **2011**, *52*, 2181. (b) Krenske, E. H.; Perry, E. W.; Jerome, S. V.; Maimone, T. J.; Baran, P. S.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3016.

(16) (a) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646. (b) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187.

(17) For reviews, see: (a) van Zeist, W.-J.; Bickelhaupt, F. M. *Org. Biomol. Chem.* **2010**, *8*, 3118. (b) Fernández, I. *Phys. Chem. Chem. Phys.* **2014**, *16*, 7662.

(18) For selected recent examples, see: (a) Lopez, S. A.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 1778. (b) Fernández, I.; Sola, M.; Bickelhaupt, F. M. *Chem.—Eur. J.* **2013**, *19*, 7416. (c) Kamber, D. N.; Nazarova, L. A.; Liang, Y.; Lopez, S. A.; Patterson, D. M.; Shih, H.-W.; Houk, K. N.; Prescher, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 13680. (d) Liu, F.; Paton, R. S.; Kim, S.; Liang, Y.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 15642. (e) Morin, M. S. T.; St-Cyr, D. J.; Arndtsen, B. A.; Krenske, E. H.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 17349. (f) Hong, X.; Liang, Y.; Griffith, A. K.; Lambert, T. H.; Houk, K. N. *Chem. Sci.* **2014**, *5*, 471. (g) Yang, J.; Liang, Y.; Seckute, J.; Houk, K. N.; Devaraj, N. K. *Chem.—Eur. J.* **2014**, *20*, 3365. (h) Fernández, I.; Bickelhaupt, F. M. *J. Comput. Chem.* **2014**, *35*, 371. (i) Liu, S.; Lei, Y.; Qi, X.; Lan, Y. *J. Phys. Chem. A* **2014**, *118*, 2638.

(19) Alkyl-substituted alkenes are more reactive than ethylene in cycloadditions with the electrophilic aryl-1-aza-2-azoniaallene. Therefore, the negative ΔE_{tether} values are observed in transition states **TS14** and **TS17**.