## Carbocycle Formation *via* Intramolecular Insertion of Alkynes into Titanium-Carbon Bonds

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Abstract: Treatment of alkyl titanocene chloride complexes with the Lewis acids EtAlCl<sub>2</sub> or Me<sub>2</sub>AlCl resulted in intramolecular insertion of a tethered alkyne into the Ti-C bond. Regioselective alkyne insertion produced exocyclic trisubstituted alkene products resulting from four-, five-, and six-membered ring formation. In the case of cyclohexane formation, the alkyne was found to insert with syn stereoselectivity.

Intramolecular addition of alkyl organometallic species (-CH2-M) to an alkyne has been of interest for many years, and the use of a variety of metals has been investigated for promotion of this transformation through non-radical intermediates. Initial work in this area revealed formation of five-membered rings from organolithium<sup>1</sup> and magnesium<sup>2</sup> intermediates tethered to alkynes. Interest in developing this methodology has led to a flurry of activity, including the investigation of stereoselective addition of alkylmagnesium species to more reactive MeaSi-substituted alkynes.<sup>3</sup> Similarly, alkyllithium species were later found to form cyclopentane rings from dialkyl alkynes,<sup>4</sup> and four- and six-membered rings were accessible using more reactive phenyl- or Me<sub>3</sub>Si-substituted alkyne.<sup>4c,5</sup> Modification of these species, through the use of Cu/Mg,<sup>6</sup> Cu/Li,<sup>7</sup> or Cu/Zn,<sup>8</sup> led to successful cyclopentane formation with phenyl- or Me<sub>3</sub>Si-substituted alkynes. Fivemembered ring formation resulting from alkyne insertion into alkyl-metal intermediates of Ni<sup>9</sup> and Pd<sup>10</sup> has also been reported. An early transition metal system, involving the cyclization of organoaluminum species promoted with a catalytic amount of zirconium, has shown a great deal of versatility in the formation of both five- and six-membered rings with Me<sub>3</sub>Si-substituted alkynes.<sup>11</sup> Recently, in a related stoichiometric Ti/Al system, we reported the aluminum-promoted regio-and stereoselective formation of five- and six-membered rings by intramolecular insertion of alkenes into titanium-carbon bonds.<sup>12</sup> Extention of our methodology to include the analogous insertion of alkynes led to efficient formation of four-, five-, and six-membered rings.

Formation of the organotitanium species 3 was readily accomplished in isolated yields of 50-67% in the same manner as that reported for the alkene substrates (eq. 1).<sup>12</sup> Treatment of 1 with 4.0 equiv. magnesium turnings in THF produced a solution of 2, which, when added to a suspension of Cp<sub>2</sub>TiCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>, resulted in formation of 3. Separate analysis of each step in this process revealed inefficient formation of  $2^{13}$  followed by essentially quantitative transmetallation to produce 3 in moderate yields.<sup>14</sup> These resulting organotitanium species were found to be much less sensitive toward hydrolysis or air oxidation than the corresponding Grignard complexes.

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Treatment of a toluene solution of 3 with either EtAlCl<sub>2</sub> or Me<sub>2</sub>AlCl resulted in intramolecular insertion of the alkyne into the activated Ti-C bond to give 5 (eq. 2). Optimum conditions for the formation of four- and five-membered rings were achieved by addition of EtAlCl<sub>2</sub> to the solution of 3 at -78 °C (see Table). Substrate 3a required the addition of 6 equiv. of EtAlCl<sub>2</sub> to give 96% ligand cyclization (6a:7a, 4:96),<sup>15</sup> while the same degree of ring formation could be achieved for 3b with as little as 0.5 equiv. of EtAlCl<sub>2</sub>. Cyclization of 3a and 3b occurred to give the corresponding product mixtures in 84% and 93% yields, respectively.<sup>16</sup>



Table. Cyclization Conditions and Yields for the Preparation and Intramolecular Insertion of 3.<sup>16</sup>

Cmpd	n_	R	Yield _(1_to_3)	<b>Cyclization</b> Conditions	Product Ratio (6:7)	Yield (3 to [6+7])
a	1	Ph	50%	6.0 eq. EtAlCl <sub>2</sub> , -78°C	4:96	84%
b	2	Et	67%	0.5 eq. EtAlCl <sub>2</sub> , -78°C	4:96	93%
с	3	Me	65%	2.0 eq. Me <sub>2</sub> AlCl, -30°C	4:96	75%
d	3	SiMe <sub>3</sub>	55%	3.6 eq. Me2AlCl, -30°C	3:97	72%
е	4	Me	62%	4.0 eq. Me <sub>2</sub> AlCl, 0°C	100:0	68%
f	4	SiMe <sub>3</sub>	79%	2.0 eq. Me <sub>2</sub> AlCl, 0°C	100:0	56%

Efficient formation of cyclohexane products from 3c and 3d required the use of a milder Lewis acid, Me<sub>2</sub>AlCl, which promoted cyclization at warmer reaction temperatures (-30 °C). Under these optimum conditions, 3c and 3d resulted in  $\geq$ 96% ring formation with yields of 75% and 72%, respectively. The corresponding seven-membered ring formation (n=4) was not observed under a variety of tested reaction conditions. Comparative rate studies of the relative cyclization of 3c and 3d were performed by placing equal amounts of the two substrates in the same reaction vessel, and treating the mixture with 1.5 equiv. of Me<sub>2</sub>AlCl. In a representative experiment, cyclization of 3c to 5c was 80% complete after 30 min. as compared to only 21% conversion of 3d to 5d. Typically, a SiMe<sub>3</sub> group will stabilize the transition state of the organometallic insertion process, 4, by stabilization of the positive charge developing  $\beta$  to the silicon. However, in this case the steric bulk of the Cp ligands apparently impedes the approach of the SiMe<sub>3</sub>-substituted alkyne (4d) relative to that substrate containing a methyl substituent (4c).



The stereoselectivity of the alkyne insertion during six-membered ring formation was determined through the use of substrate 8. Treatment of 8 with 5 equiv. of EtAlCl<sub>2</sub> for 19 hours at -78 °C, followed by warming to ambient temperature and subsequent protonolysis, produced 10 as the only cyclic product. The 5:95 mixture of 9:10 was produced in 83% yield. Removal of solvent from the mixture by preparative gas chromatography allowed confirmation of the olefin geometry of 10 through NMR analysis.<sup>17</sup> Based on the selective formation of 10 as the only olefin stereoisomer, the intramolecular syn insertion of 8 was shown to be >95% selective.<sup>18</sup> In contrast to what was observed in the catalytic Zr/Al cyclization of a Me<sub>3</sub>Si-substituted alkyne, ligand equilibration to a mixture of *E* and *Z* alkene isomers did not occur in the Ti/Al system.<sup>11</sup>



The titanium-mediated cyclization with acetylenes has led to a number of advances in the formation of carbocycles. The versatility of this ring forming method has been demonstrated in the regioselective formation of four-, five-, and six-membered ring systems. In the latter two cases, this methodology could even be used with dialkyl substituted alkynes and did not require the use of phenyl or Me<sub>3</sub>Si substitutents to activate the alkyne toward addition. In each case examined, regiospecific ring formation to exocyclic trisubstituted alkene products could be driven to at least 95% completion. This intramolecular alkyne insertion was found to stereoselectively proceed by syn insertion of the alkyne into Ti-C bond.

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- For an example of intramolecular alkyne insertion into a -CH<sub>2</sub>-Pd bond, see: Wu, G.; Lamaty, F.; Negishi, E. J. Org. Chem. 1989, 54, 2507. In this case, a benzylic -CH<sub>2</sub>-Pd bond was used in order to avoid the typically observed β-H elimination from the metal.
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- 13. Inefficient formation of Grignard complexes in the presence of alkyne functionality has also been reported by others.<sup>11</sup>
- 14. Product distribution and yields for these compounds were determined by capillary gas chromatographic analysis of the volatile products from the quenched reaction mixture (AcOH/H<sub>2</sub>O, 1:1) using internal standards and correcting for detector response (quantification by titration of the ligand).
- 15. Four-membered ring formation with this ligand has also been observed resulting from the lithium species<sup>5</sup> and through use of a Zn/Ti system similar to that reported here.<sup>8c</sup>
- 16. Product yields reported for the treatment of 3 with the Lewis acid represent the combined amounts for the product mixture of 6 and 7, which were the only volatile products present in the reaction mixture.<sup>14</sup> Yields less than quantitative resulted from intermolecular oligomerization of the alkyne ligand; these mixed metal systems are also very efficient carbometallation reagents and polymerization catalysts.<sup>12</sup>
- 17. Proton assignments were made from selective decoupling experiments, and olefin geometry was confirmed through the use of nuclear Overhauser enhancement NMR experiments.
- 18. For comparison, radical cyclization of 8-bromo-7-methyl-2-octyne, by treatment of a 0.01 M solution with Bu<sub>3</sub>SnH and AIBN at 80 C, produced a 73:13:14 mixture of 9:10:11 in 87 % yield.

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