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Regioselective Cyclopentane Ring Formation Mediated by Titanocene Chloride[†]

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The formation of carbon–carbon bonds by addition of activated carbons to alkenes has been an intensely studied subject for many years. One focus of these studies has been on intramolecular carbon–carbon bond formation to produce five-membered rings through radical,[1] cationic,[2] and anionic[3] cyclization with alkenes. In addition, several reports have appeared that describe the intramolecular insertion of a single alkene into early transition metal–carbon bonds also known to catalyze olefin polymerization (Sc,[4] Zr,[5] Ti[6]).[7] A reaction involving titanium, the cyclization of **3a** to **4a**, was an elegant mechanistic probe that allowed the study of the Ziegler-Natta polymerization process (Scheme I).[6] The general efficiency and selectivity demonstrated by Ziegler-Natta polymerization catalysts[8] initiated our use of the $Cp_2TiCl_2/EtAlCl_2$ catalyst system[6,9] as a method for regioselective ring formation with unactivated alkenes.

Our preparation of **3a** followed established procedures involving formation of **2a** followed by reaction with Cp_2TiCl_2 (Scheme I).[6,10] Grignard complex **2a** was added to Cp_2TiCl_2 in CH_2Cl_2 at −40 °C, and after 30 min, the solution was warmed to 23 °C for 2 h. Quenching (HCl/MeOH) samples of both **2a** and **3a** generated the same 96:4 ratio of 1-hexene to methylcyclopentane; thus, the transmetalation process did not result in further ligand cyclization.[11] The titanium complex was purified by evaporation of solvents in vacuo, extraction of the solids with toluene/hexane (1:1), and then solvent removal to produce **3a** as a red oil.

Scheme I. Lewis Acid Promoted Intramolecular Alkene Insertion

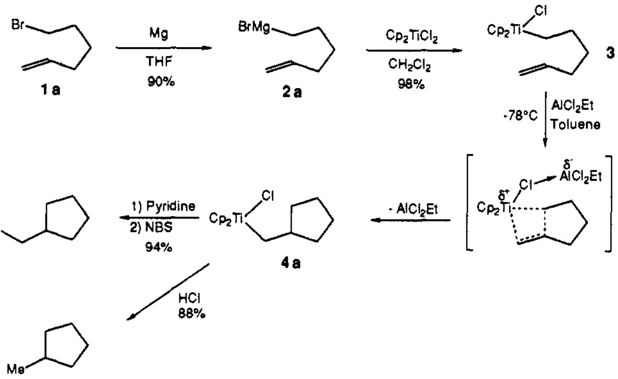
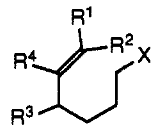
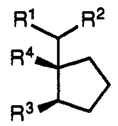
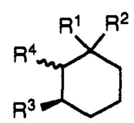
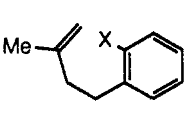
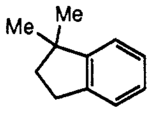
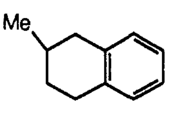


Table I. Product Distribution from Intramolecular Insertion of Disubstituted Alkenes

Substrate[a]					Product Mixture[b]	
					Exo	*Endo*
						
	R^1	R^2	R^3	R^4		
3a	H	H	H	H	100 (88%)	0
3b	H	Me	H	H	98 (79%)	1
3c	Me	H	H	H	98	2
3d	H	$-(CH_2)_2-$		H	97 (83%)	0
3e	H	$-(CH_2)_3-$		H	0	0
1e					0	0
3f	H	H	H	Me	98 (93%)	1
1f					40	60
3g	H	H	$-(CH_2)_3-$		99 (84%)	0
1g					15	22:51[d]
3h	H	H	$-(CH_2)_4-$		100 (74%)	0
1h[c]					15	25:4[d]
						
3i					100 (80%)	0
1i					39	52

[a] Method for cyclization of **3** (X = $TiClCp_2$): $EtAlCl_2$, toluene, −78 °C. Method for cyclization of **1** (X = Br): Bu_3SnH, AIBN, C_6H_6, 80 °C. [b] Numbers represent the percentage of each product in the reaction mixture. The balance of the product mixture, in each case, was the reduced substrate (X = H). Cyclization yield of major product is in parentheses (ref 12). [c] See ref 18. [d] Ratio of trans- to cis-fused endo cyclization products.

Cyclization of **3a** to **4a** (0.2 M toluene) was induced by the addition of 0.50 equiv of $EtAlCl_2$ at −78 °C. After 30 min, protonolysis of the reaction mixture produced methylcyclopentane, the product of exo cyclization, in 88% yield from **3a**.[12] Cyclo-

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[†] Dedicated to the memory of John K. Stille, Distinguished Professor of Chemistry (Colorado State University). Deceased July 19, 1989.

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hexane, the result of endo cyclization, was not observed. An alternate method of ligand removal involved the treatment of the reaction mixture with 1.5 equiv of pyridine, to neutralize the $EtAlCl_2$, followed by addition of 3.0 equiv of *N*-bromosuccinimide. Formation of (bromomethyl)cyclopentane in 94% yield demonstrated the efficient functionalization of the organic ligand following ring formation.

This investigation was extended to the study of vicinally and geminally disubstituted alkenes tethered to titanium (Table I). In general, these complexes were prepared with less than 1% ligand cyclization, and 2 equiv of $EtAlCl_2$ with longer reaction times than those necessary for **3a** was required to obtain >97% ring formation. Although cyclization of **3b** was 99% complete after 2 h at −78 °C, **3c** had progressed to only 65% cyclization under these conditions and required an additional 2.5 h at 23 °C to reach completion.[13] Insertion of a cyclopentene ring into the Ti–C bond proceeded well (**3d** to **4d**), but the tethered cyclohexene substrate **3e** failed to cyclize. In each case, the product ratios obtained for activation of substrates **3a**–**3e** were the same as those observed for free-radical intermediates generated from **1a**–**1e**. Substrates containing geminally disubstituted olefins resulted in selective formation of quaternary carbon centers. The methyl-substituted substrates **3f** and **3i** resulted in the formation of geminal dimethylcyclopentanes following protonolysis,[14] while the exo methylene ring substrates **3g** and **3h** selectively produced cis-fused ring systems with an angular methyl group.[15]

A notable feature of this titanium-mediated cyclization was the selective cyclopentane ring formation, especially in the generation of quaternary centers. These selectivities were similar to those produced by anionic cyclization, in which substrates **g** and **h** (X = Li) produced only exo cyclization products in 80% and 95% conversion, respectively.[16] On the other hand, the significant preference for five-membered-ring products under the titanium/aluminum Ziegler-Natta conditions was opposite those observed for the relatively nonselective free-radical cyclization of substrates **f**–**i**.[17] The high regioselectivities of these metal-mediated cyclizations are due to conformational restrictions on the intramolecular syn coplanar addition of the metal–carbon bond to the olefin.

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(12) Yields for these volatile compounds were determined by capillary GLC analysis of the quenched reaction mixture (HCl/MeOH) using internal standards and correction for detector response. Product confirmation was made by comparison with commercial or independently prepared samples.

(13) These observations were in accord with *Z* and *E* olefin reactivity with zirconocene chloride hydride.[5]

(14) Cyclization of **3i** required a reaction temperature of 80 °C to give optimum results.

(15) In each case, formation of the trans-fused product was not observed for the titanium-mediated or radical cyclization reactions of **3h** or **1h**, respectively.

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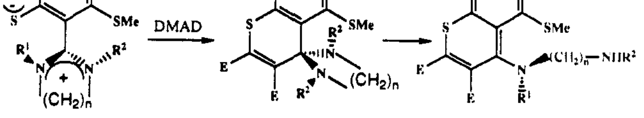
Additions and Corrections

The Chemistry of Enones. Parts 1 and 2. Book Review. [*J. Am. Chem. Soc.* **1990**, *112*, 4095]. SAUL PATAI and ZVI RAPPOPORT

The indexes are in Part 2, not in Part 1 as stated.

From Twisted to Folded Ethylenes [*J. Am. Chem. Soc.* **1988**, *110*, 4843–4844]. AGHA ZUL-QARNAIN KHAN and JAN SANDSTRÖM*

The compounds formed on addition of the 1-thioacyl-2,2-diaminoethylenes **4** to DMAD and claimed to be "folded" ethylenes with pyramidal carbon atoms (**6**) have been shown to be instead 4-aminothiopyrans **9**, formed by ring-opening on workup of the initially formed thiopyran-4-spiro-2′-1′,3′-diazacyclanes **8**.[1]



4 **8** **9**

Compounds **8** were not observed in the initial experiments, since they are transformed to **9** on TLC analysis and chromatographic workup. The structures of analogues of **8** have been determined by X-ray crystallography.[2]

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