A New Synthesis of Cyclobutanones: Highly Selective Carbonylation of Titanacyclobutane Complexes Prepared by Free Radical Alkylation

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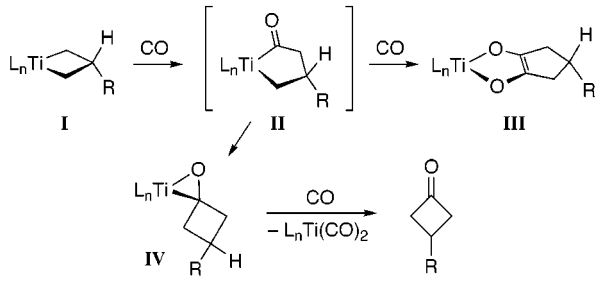
Cyclobutanones and related carbocyclic four-membered ring compounds constitute an important class of synthetic intermediates[1] and polymer precursors.[2] More recently, cyclobutane derivatives have emerged as significant in terms of biological and pharmaceutical activity.[3]

In this communication, we report general new methodology for the synthesis of substituted cyclobutanones, based on the highly selective *mono*-carbonylation of titanacyclobutane complexes, a new reactivity pattern for metallacyclobutane complexes of the early transition metals. In conjunction with the recent development of titanacyclobutane synthesis by free radical alkylation of η^3-allyltitanium(III) complexes,[4] this carbonylation constitutes a convergent and stereoselective new approach to the construction of cyclobutanones.

Carbonylation converts metallacyclopentane, metallacyclopentene, and related early transition metal complexes into synthetically valuable five-membered ring compounds via the insertion of one equivalent of carbon monoxide and subsequent reductive elimination.[5−7] In contrast, metallacyclobutane complexes of the early transition metals instead undergo the Bercaw carbonylation, incorporating *two equivalents* of carbon monoxide to give cyclopentendiolate complexes (e.g., **III**, Scheme 1).[8] Here we report that the carbonylation of titanacyclobutane complexes can, under appropriate conditions, be controlled to incorporate a single equivalent of CO, producing cyclobutanones exclusively.

Scheme 1



As anticipated, permethyltitanacyclobutane complexes **1** undergo the Bercaw carbonylation at low temperature under CO pressure (−78 °C, 60 psi).[9] Conducting the carbonylation at higher temperature and low pressure, however, promotes the intramolecular migration (**II** → **IV**) over the intermolecular carbonylation (**II** → **III**) and leads to the formation of organic cyclobutanones exclusively in high yield (Table **1**).[10,11] The organometallic product of the reaction, $(C_5Me_5)_2Ti(CO)_2$,[12] is recovered in high yield by precipitation from the nonpolar reaction medium. The low yield obtained for carbonylation of β-allyltitanacyclobutane complex **2e** arises from the thermal instability of this compound above room temperature.[13]

For synthetic applications, titanacyclobutane complexes **1** can be prepared without isolation of the η^3-allyltitanium intermediate, using SmI_2•THF to mediate both the reductive allylation and generation of the alkyl radical (eq 1). In contrast to the reactions of isolated η^3-allyltitanium complexes with unstabilized organic radicals generated by using SmI_2,[4a] the one-pot preparation does

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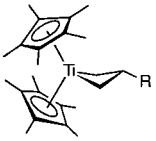
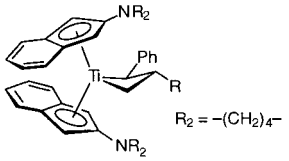
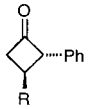
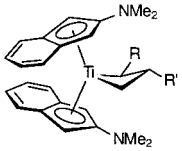
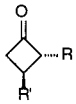
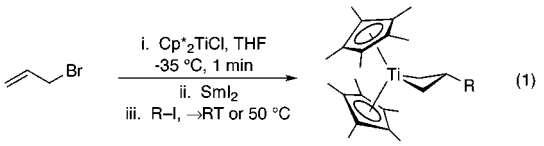
Table 1. Carbonylation of Titanacyclobutanes to Give Cyclobutanones[10]

Complex	Substituent(s)	Conditions[a]	Product	Yield[b] (%)
				
1a	^{i}Pr	A	**2a**	>95[c]
1b	^{t}Bu	A	**2b**	>95[c]
1c	CH_2Ph	A	**2c**	85
1d	$CHPh_2$	A	**2d**	91
1e	$CH_2CH{=}CH_2$	A	**2e**	45[c]
				
3a	^{i}Pr	B	**4a**	95
3b	^{t}Bu	B	**4b**	quant.
3c	cyclohexyl	B	**4c**	97
				
5a	R = Ph, R' = ^{i}Pr	C	**4a**	92
5b	R = Ph, R' = CH_2Ph	D	**4d**	86
5c	R = Me, R' = ^{i}Pr	E	**4e**	84[d]
5d	R = Me, R' = CH_2Ph	E	**4f**	82

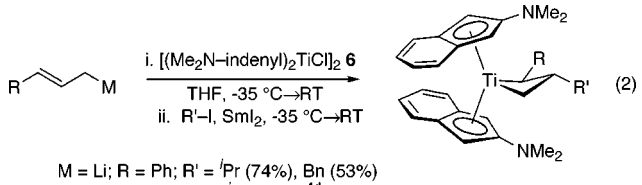
[a] Reaction conditions. A: 45 °C, 10 psig CO, pentane, 12 h; B: as in A, but in toluene, 6 h; C: rt, 1 atm CO, THF, 5−15 min; then air; D: 45 °C, 10 psig CO, THF, 15 min; then HCl; E: as in C, but with HCl quench. [b] Isolated yield after purification by chromatography. [c] Yield of volatile cyclobutanone determined by GC (calibrated against 2-butanone as internal standard). [d] Volatile cyclobutanone isolated and purified as the 2,4-dinitrophenylhydrazone.

not require elevated temperatures.[14] The titanacyclobutane complexes thus formed can be carbonylated directly without isolation or purification.[10]



R = ^{i}Pr (96%), cyclohexyl (95%) **1a,e**

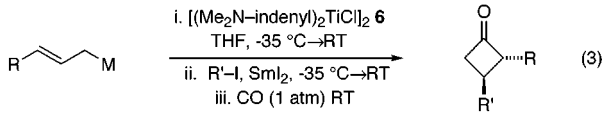
The synthesis of more highly substituted cyclobutanones requires the use of alternative titanocene templates based on 2-*N*,*N*-dialkylaminoindenyl ligand systems.[4c,d] Titanacyclobutane complexes **3** and **5** derived from 2-piperidinoindenyl[4c] and 2-*N*,*N*-dimethylaminoindenyl[4d] titanocenes, respectively, undergo highly selective carbonylation, providing *trans*-2,3-disubstituted cyclobutanones **4a**−**f** exclusively in high yield (Table **1**).[10] Although the carbonylation reaction proceeds cleanly in both systems, the use of the 2-*N*,*N*-dimethylaminoindenyl system provides significant advantages over the 2-piperidinoindenyl template. The substituted allyl complexes in the bis(2-*N*,*N*-dimethylaminoindenyl)titanium series can be prepared in situ from allylic Grignard or lithium reagents and alkylated without isolation (eq 2).[15] More importantly, the 2-methyl- and 3-benzyl-substituted titanacyclobutane complexes **5b**−**d** are thermally more stable than the corresponding bis(2-piperidinoindenyl)titanacyclobutane complexes, which do not undergo clean carbonylation.[16]



M = Li; R = Ph; R' = ^{i}Pr (74%), Bn (53%)
M = MgCl; R = Me, R' = ^{i}Pr (68%),[4d] Bn (75%) **5a-d**

In contrast to the carbonylations of bis(2-piperidinoindenyl)-titanacyclobutane complexes, however, the corresponding bis(2-*N*,*N*-dimethylaminoindenyl)titanacyclobutane complexes do not directly liberate cyclobutanone under standard carbonylation conditions. Although the crude reaction mixture contains the expected byproduct, (2-*N*,*N*-dimethylaminoindenyl)$_2$Ti(CO)$_2$ **7**, this complex is isolated in only about 50% yield.[10] The rest of the metal *and all of the organic fragment* are obtained in the form of an as yet uncharacterized paramagnetic intermediate. Release of the cyclobutanone is obtained upon air oxidation or hydrolytic workup.[10]

Finally, in a preliminary investigation, we have established that the cyclobutanone synthesis can be carried out in a single operation starting from bis(2-*N*,*N*-dimethylaminoindenyl)titanium chloride **6** (eq 3). As illustrated for cyclobutanones **4a** and **4f**,[10] this as yet unoptimized one-pot procedure delivers only moderate yields but avoids the isolation and manipulation of air- and moisture-sensitive intermediates.



M = Li; R = Ph; R' = ^{i}Pr (48%)
M = MgCl; R = Me, R' = Bn (44%) **4a,f**

The carbonylation of titanacyclobutane complexes can thus be controlled to produce strained cyclobutanones rather than the expected cyclopentenediolate complexes. Combined with the regioselective radical alkylation of allyltitanium complexes, the carbonylation provides a unique, convergent, three-component strategy for the stereocontrolled synthesis of substituted cyclobutanones. Development of improved titanocene templates and extension of titanacyclobutane synthesis to accommodate additional substitution, richer functionality, and intramolecular variants is currently under investigation.

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Supporting Information Available: Text providing full experimental details and complete spectroscopic and analytical characterization for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We tentatively attribute this observation to the intervention of an unidentified Ti(III) species, which catalyzes the generation of unstabilized radicals at a rate significantly greater than obtained from SmI_2 alone, as previously noted.[4b]

(15) The use of SmI_2·THF for both allyl complex generation and subsequent radical alkylation, analogous to the permethyltitanocene procedure (eq 1), returns high yields for the unsubstituted allyl ligand and moderate yields for the crotyl ligand, but fails for the cinnamyl ligand.

(16) 2-Methyltitanacyclobutanes decompose by β-hydride elimination from the methyl substitutent;[4c] 3-benzyltitanacyclobutanes undergo slow homolytic scission of the β-benzyl substituent at room temperature.[13]