Unprecedented Diastereoselective Addition Reactions of 6,6-Dimethylcyclohexadienyl Titanium Complexes to Aldehydes and Ketones

Anne M. Wilson, F. G. West,* Atta M. Arif, and Richard D. Ernst*

Department of Chemistry, University of Utah Salt Lake City, Utah 84112

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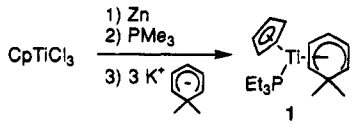
The selective construction of multiple chiral centers in organic molecules is an important challenge and continues to be a major area of focus in synthesis. To that end, extensive use has been made of stoichiometric reactions of π-complexes to give substituted cyclic and acyclic hydrocarbons.[1] Typically, such complexes undergo nucleophilic addition, with the generation of one or two new stereocenters. Reactions of the opposite polarity, in which the metal system behaves in a nucleophilic manner, have been of interest to this group for some time,[2] and the coupling chemistry of titanium−pentadienyl complexes in particular has been shown to be quite versatile. Herein we describe the coupling chemistry of a new half-open titanocene system, involving unprecedented regiochemistry and high or complete diastereoselectivity and resulting in the generation of up to five new stereocenters in a single reaction.

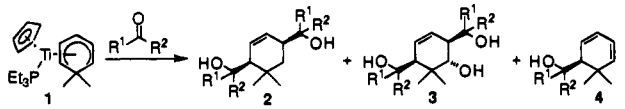
Acyclic pentadienyl systems have already been shown to readily undergo additions with unsaturated organic compounds such as ketones, imines, aryl isocyanides,[2a] acetylenes, diacetylenes,[2b] and nitriles,[2c] much like analogous butadiene complexes.[3] To test the viability of extending this sort of chemistry to cyclic dienyl systems, the 6,6-dimethylcyclohexadienyl (dmCh)[4] ligand was chosen. The new complex, Ti(C_5H_5)(dmCh)(PMe_3), could be synthesized using a procedure similar to that used for the acyclic systems.[2c] Cyclopentadienyltitanium trichloride was reduced with zinc, and the subsequent dichloride was treated with 3 equiv of the potassium dimethylcyclohexadienyl anion[4] in the presence of trimethylphosphine (eq 1). Complex **1** was isolated in 70% yield as moderately air stable red crystals and its structure confirmed by X-ray crystallography.



(1)

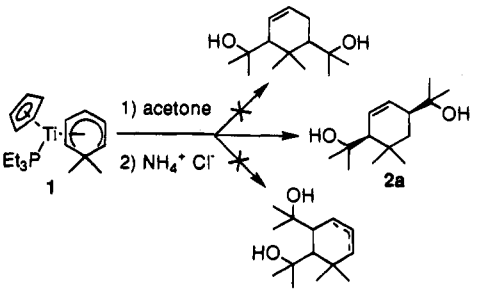
With **1** in hand, the coupling chemistry of this new complex was then explored. Upon treatment with excess acetone, a noncrystalline organometallic intermediate resulted. When the intermediate was subjected to saturated aqueous ammonium chloride, product **2a**, apparently incorporating 2 equiv of acetone, was isolated as a single diastereomer (eq 2). However, the spectral data for **2a** were not consistent with the 1,2- or 1,5-substitution patterns that would be expected in analogy to previously observed pentadienyl coupling chemistry.[2,5] Structure determination via X-ray crystallography was necessary to resolve this issue. To our surprise, **2a** was found to be the product of an unprecedented 1,4-syn addition of acetone to the dienyl ligand. As shown in Table 1, this diastereoselective coupling process appears to be general for ketones.

Table 1. Coupling Reactions of **1** with Aldehydes and Ketones[a]



entry	R^1	R^2	compd	yield,[b] %	**2:3:4**
1	Me	Me	**a**	85	100:0:0
2	Me	Me	**a**	43[c]	13:87:0
3	Et	Et	**b**	51	14:86:0
4	$-(CH_2)_5-$		**c**	57[d]	17:83:0
5	$-(CH_2)_4-$		**d**	44[d]	100:0:0
6	Ph	H	**e**	67	0:0:100[e]
7	*i*-Pr	H	**f**	43	75:0:25[f]
8	*t*-Bu	H	**g**	51	80:0:20[f]
9	*t*-Bu	H	**g**	57[c]	tr:100:0

[a] Standard procedure: Aldehyde or ketone trap (2.2 equiv) was added to an Et_2O solution of **1** and the reaction stirred at room temperature for 1 h. Saturated NH_4Cl was then added, and the reaction mixture was stirred for an additional 4 h, followed by standard aqueous workup and chromatography. All products were isolated as single diastereomers unless otherwise noted and were fully characterized by IR, ^1H and ^{13}C NMR, and combustion analysis. [b] Isolated yields. [c] Reaction mixture was stirred for 12 h open to air prior to NH_4Cl quench. [d] A 33−35% yield of the corresponding ketone pinacol coupling product was also obtained. [e] Product **4e** was isolated as an inseparable 5:1 mixture of diastereomers. [f] Aliphatic aldehydes gave partially hydrogenated monoaddition products derived from **4f,g**.



(2)

In addition to the 2:1 adduct **2**, a second product could be obtained by a slight variation in conditions (entry 2). Exposure to air after addition of the ketone or during the hydrolysis step led to the isolation of triol **3** as the major product. This product appears to arise from reaction of one of the organometallic intermediates with atmospheric oxygen. Notably, the third hydroxyl group was positioned on the side opposite the two acetones, indicating an unusual exo attack by oxygen. As with diol **2**, **3** was formed in all cases as a single diastereomer, and the regio- and stereochemistry were verified in the case of **3a** via X-ray crystallography.

Unlike acyclic titanium−pentadienyls, **1** was also found to react with aldehydes. In the case of benzaldehyde, only 1 equiv of aldehyde was incorporated (**4e**) as an inseparable 5:1 mixture of diastereomers, even in the presence of 5 equiv of aldehyde.

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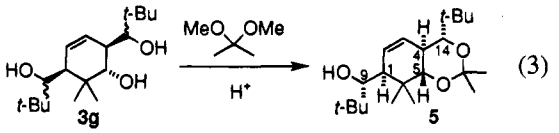
However, isobutyraldehyde and pivalaldehyde gave both mono- (**4f,g**) and diaddition (**2f,g**) products, with the latter isolated as single diastereomers. In contrast, other recently reported examples involving addition of acyclic metal–pentadienyl complexes to aldehydes proceeded with regioselective monoaddition at position 3 and little or no diastereoselectivity.[1a] In the present study, 1:1 adducts **4e–g** and 2:1 adducts **2f,g** were formed with complete regiocontrol for positions 1 and 4 and in high diastereoselectivity.

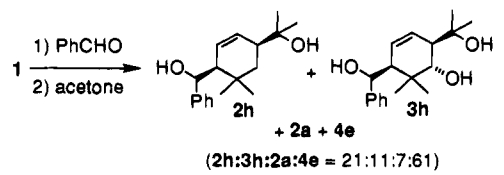
In the case of pivalaldehyde, it was again possible to generate the highly functionalized triol **3g** via the air oxidation protocol. This product was also obtained as a single isomer, and the relative stereochemistry was determined via a combination of chemical derivatization and X-ray crystallography (eq 3).



(3)

Conversion of **3g** to acetonide **5** permitted assignment of the relative stereochemistry at carbons 4, 5, and 14 via vicinal ^{1}H NMR coupling constants of the ring protons and ^{13}C chemical shifts of the acetonide methyl carbons and demonstrated that the aldehyde coupling at position 4 had its *t*-Bu group oriented toward the dmCh bridge.[6,7] A syn relationship between the two side chains was assumed by analogy to **3a**, but the stereochemistry of the final center at C-9 could not be determined. All efforts to generate cyclic derivatives (e.g., $NaH/CO_2/I_2$ or $O_3/NaBH_4$/acetonide formation) were unsuccessful, suggesting a configuration at C-9 that would destabilize six-membered rings. Fortunately, analysis of **5** via X-ray crystallography was possible, confirming the assignment of carbons 1, 4, 5 and 14, as well as verifying the stereochemistry at C-9 to be as deduced. This result revealed that the aldehyde coupling at position 1 had its *t*-Bu group oriented away from the nearby dmCh bridge. *Importantly, the construction of* **3g** *from* **1** *and pivalaldehyde entails the generation of five new stereocenters with complete stereocontrol in a single operation.* The regio- and stereoselective elaboration of the dmCh fragment into highly functionalized products **2–4** entails an unprecedented 1,4-diaddition to a carbocyclic skeleton and, together with the remarkable stereocontrol, provides a potentially important new tool for the synthesis of oxygenated carbocyclic targets.

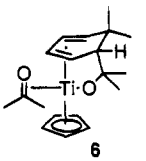
The formation of mixed 2:1 adducts incorporating two different carbonyl acceptors was also investigated. The challenge posed by such mixed couplings is minimization of competing formation of 2:1 adducts derived from the first electrophile. Use of benzaldehyde as the first acceptor was attractive, given its demonstrated reluctance to undergo a second coupling (entry 6), and acetone was chosen as the second electrophile. In the event, sequential treatment of **1** with benzaldehyde and acetone furnished two new mixed adducts **2h** and **3h**, along with previously isolated benzaldehyde and acetone adducts **4e** and **2a**, in a combined 89% yield (eq 4). Although unoptimized, this result establishes the potential applicability of dmCh couplings to two different electrophiles.



(4)

(6) (a) Rychnovsky, S. D. *J. Org. Chem.* **1989**, *54*, 4982. (b) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.

Given the understandable proclivity for the non-edge-bridged pentadienyl compounds to undergo preferential coupling with ketones at their terminal (1,5) carbons, the mechanism by which 1,4-regiochemistry occurs for the dmCh analog is clearly of interest. This may be simply explained through an intermediate such as **6**, in which there has been incorporation of 2 equiv of ketone. The first equivalent is presumed to undergo rapid



6

coupling with a terminal position, yielding an η^4-diene complex. The second ketone (or aldehyde) is presumed to coordinate initially without coupling. However, upon addition of a proton or O_2 at the other terminus of the former dienyl ligand, an allyl ligand spanning carbons 2–4 would ensue. Subsequent coupling between one of the allyl termini and the second ketone would lead to the observed regiochemistry. This mechanism is consistent with the 1,4-regiochemistry common to both **2** and **3**, as well as the anti relationship between the substituents at positions 4 and 5. Additional support has been obtained from related coupling reactions involving dienyl ligands and diones. In these cases, characterization of the hydrolyzed products revealed that coupling of only one of the dienyl termini to one carbonyl had occurred, while the other ketone was reduced to the secondary alcohol, as would be expected if simple coordination were involved. Furthermore, electron transfer processes do not appear likely, since coupling reactions employing methyl cyclopropyl ketone led cleanly to cyclopropyl-containing products, with no evidence of ring-opened species.[8]

In summary, we have reported a new class of coupling reactions of a cyclic (edge-bridged) titanium–pentadienyl complex with aldehydes and ketones. The transformation occurs with unusual 1,4-regiochemistry and establishes two to five new stereocenters with high or complete selectivity. In the process, a planar cyclohexadienyl moiety is functionalized at up to three positions, leaving an olefin in place for additional manipulation. The detailed mechanisms of these coupling reactions, the origins of the exceptional stereocontrol, and potential extensions to seven-membered and larger dienyl ligand systems will be reported in due course.

Acknowledgment. R.D.E. would like to thank the National Science Foundation for generous support of this work, and F.G.W. gratefully acknowledges the American Cancer Society for a Junior Faculty Research Award, Eli Lilly and Co. for a granteeship, and American Cyanamid for a Cyanamid Faculty Award.

Supporting Information Available: X-ray crystallographic details (ORTEPs, positional parameters, bond lengths, and bond angles) for compounds **2a**, **3a**, and **5** as well as representative experimental procedures and physical data for compounds **2–5** (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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