Hydroxyl-Directed, Stereoselective Olefination of Ketones by Transition Metal Alkylidenes

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The construction of trisubstituted carbon–carbon double bonds by the stereoselective olefination of ketones represents a difficult challenge in organic synthesis.[2] A number of strategies have been pursued,[3] including the application of chiral olefinating agents.[4] As part of an ongoing program directed toward the development of transition metal alkylidenes as reagents for organic synthesis,[5] we are evaluating the viability of a new strategy for stereoselective ketone olefination based on "direction" by a remote substituent.[6–8]

Several transition metal alkylidenes had been shown to convert carbonyl derivatives to the corresponding olefins. In addition to the Tebbe complex[9] and Kauffmann's reagents,[10] substituted alkylidenes of tungsten and molybdenum have been shown to react with esters and ketones, opening the possibility of trisubstituted olefin synthesis. However, initial investigations of these latter complexes resulted in olefinic products which were of mixed stereochemistry,[11] suggesting that simple steric interactions were not sufficient to provide the required stereocontrol.

Scheme 1. Ligand-Directed, Stereoselective Olefination of Ketones

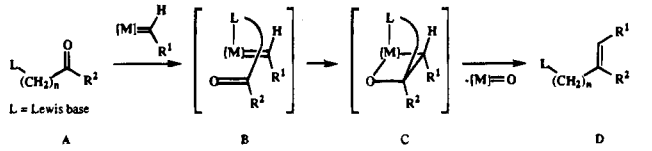
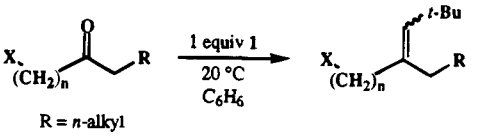


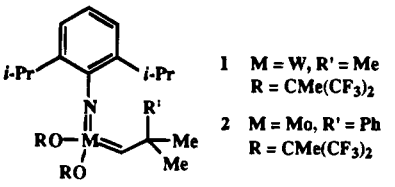
Table 1. Isomer Ratios for the Olefination of Functionalized Ketones by Tungsten Alkylidene 1



X	$n = 3$	$n = 2$	$n = 1$
BnO	<2:1	<2:1	<2:1
AcO	<2:1	<2:1	4:1
HO	<2:1	**9:1**	5:1

Our strategy for effecting ketone olefination with high stereoselectivity (Scheme 1) requires that the substrate bear a Lewis basic functional group, which serves to differentiate the two substituents of the ketone carbonyl (**A**). In the first step of the directed olefination process, the Lewis base complexes to the metal syn to the hydrogen as a consequence of steric considerations (**B**). [2 + 2] cyclization then produces an oxametallacycle (**C**) wherein R^1 and R^2 bear a syn relationship. Productive collapse of this intermediate affords the olefin (**D**).[12]

In the initial studies, the tungsten alkylidene W(CHCMe$_3$)(NAr)(OCMe(CF$_3$)$_2$)$_2$ (**1**; Ar = 2,6-(*i*-Pr)$_2$C$_6$H$_3$)[13] was chosen as the olefinating agent for several reasons: (1) it olefinates ketones at room temperature;[13] (2) it is coordinatively unsaturated and therefore can accommodate a Lewis basic directing group and the carbonyl;[14,15] (3) the alkylidene exists as a single stereoisomer;[13] and (4) derivatives can be prepared from phosphorus ylides.[16] Oxygen-based directing groups (ethers, esters, and hydroxyls) were chosen for initial study due to the well-established affinity of tungsten alkylidenes for oxygen[15] and the ubiquity of oxygen in natural products.



The stereoselectivities observed in the olefination of functionalized ketones by **1** are compiled in Table 1.[17] The olefinations of ketones bearing benzyloxy, acetoxy, and γ- and α-hydroxy groups are not highly stereoselective, but reaction

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(2) For comments regarding the challenges faced in synthesizing trisubstituted olefins stereoselectively, see: (a) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526. See page 2512. (b) Schreiber, S. L.; Ragan, J. A.; Standaert, R. F. *Strategies and Tactics in Organic Synthesis*; Academic: New York, 1991; Vol. 3, Chapter 11.

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(4) For leading references, see: (a) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7655–7658. (b) Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1992**, *114*, 10674–10676.

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(6) For a review of directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

(7) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260–4262. These workers have reported that the Wittig reaction of unstabilized ylides and acyclic α-alkoxyketones leads to protected trisubstituted allylic alcohols with high stereoselectivity. Although the origin of this stereoselectivity has not been elucidated, the reported dependence on solvent (reaction in THF is *more* selective than in Et$_2$O) appears to be inconsistent with a directed reaction. See also ref 3.

(8) Control of olefin stereochemistry through the use of a *covalently tethered* olefinating reagent has been demonstrated. For example, see: Evans, D. A.; Carreira, E. M. *Tetrahedron Lett.* **1990**, *31*, 4703–4706.

(9) (a) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270–3272. (b) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212–1216.

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(14) Complex **1** is four-coordinate, and tungsten alkylidenes are known to readily adopt six-coordinate geometries (ref 12).

(15) For example, see: Johnson, L. K.; Virgil, S. C.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 5384–5385.

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(17) Isomer ratios were determined by NMR. Yields are based on isolated products. Olefin stereochemical assignments were determined by NOE measurements. The γ-gauche effect also confirms the assignment made on the basis of the NOE experiments. See the supplementary material for additional details.

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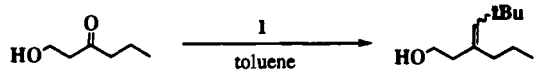
Table 2. Temperature Effect on the Stereoselectivity of Hydroxyl-Directed Olefination by **1**



entry	temp (°C)	time (h)	yield[a] (%)	E/Z[b,c]
1	20	0.5	70	89/11
2	0	3.0	68	95/5
3	−78	6.0	70	>99/1[d]

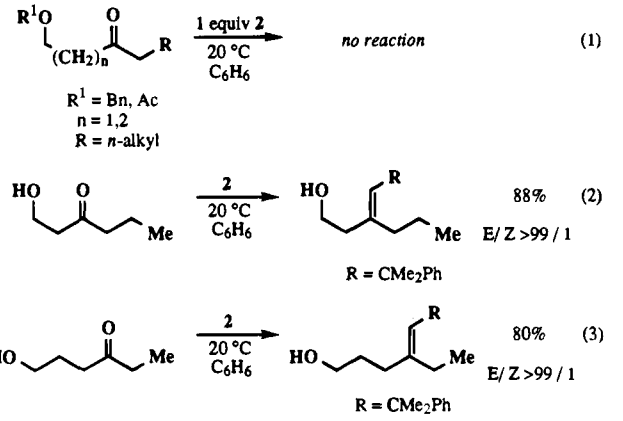
[a] Isolated yield. [b] Determined by ^{1}H NMR and GC. [c] NOE showed that the major isomer is the E isomer. [d] The minor isomer was not detected.

of the β-hydroxy ketone with **1** affords the E olefin with relatively high selectivity. These results suggest that the hydroxyl group is the only Lewis basic functionality that is small enough or basic enough to coordinate the highly sterically hindered metal center.

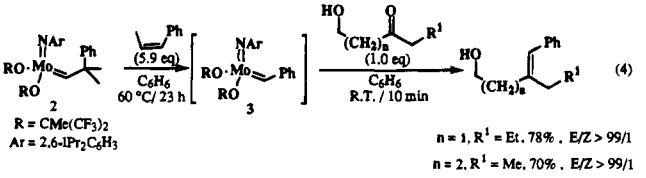
The stereoselectivity of this reaction is significantly improved by lowering the reaction temperature.[18] The results are shown in Table 2.

In contrast to tungsten alkylidene **1**, molybdenum alkylidene Mo(CHCMe$_2$Ph)(NAr)(OCMe(CF$_3$)$_2$)$_2$ (**2**, Ar = 2,6-(*i*-Pr)$_2$C$_6$H$_3$) typically does not olefinate ketones at room temperature (eq 1).[19] However, we have discovered that *γ- and β-hydroxy ketones undergo highly stereoselective E olefination within minutes when treated with 1 equivalent of* **2** (eqs 2, 3).[17] The tremendous rate acceleration and the stereochemistry of the products are consistent with the operation of a functional group directed process.

Finally, it has been shown that the nature of the alkylidene group which is transferred can be altered by a prior metathesis reaction. For example, complex **2** reacts with *cis*-β-methylstyrene to produce alkylidene **3**.[20] Introduction of the substrate then results in a directed olefination reaction to afford thephenyl-



substituted olefin in good yield and excellent selectivity (eq 4).[17,21]



These observations on the hydroxyl-directed carbonyl olefination provide a new strategy for the stereospecific construction of trisubstituted olefins. Future efforts will focus on further defining the scope of this process as well as on developing practical reagents for effecting this selective transformation.

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Supplementary Material Available: Experimental procedures and full characterization data for reaction products (14 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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(18) Olefination with the more reactive **1** can proceed by two competing pathways. The reaction which goes through the chelated intermediate gives products with high stereoselectivities while the nonchelating pathway gives mixtures of isomers. The temperature effect suggests that at lower temperatures the rate for the olefination by the nonchelating path is significantly slowed relative to that of the chelating path. The less reactive **2** can only react by the chelated pathway.

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(20) Only aryl-substituted alkylidenes were successfully transferred with this reaction.

(21) In the case of **1**, alkylidene transfer reached equilibrium in 3 h at 20 °C (benzylidene/neopentylidene = 90/10). Addition of β-hydroxy ketone to this reaction mixture produced the benzylidenated product, but in much lower stereoselectivity than in the case of **2** (at room temperature, E/Z = 75/25; at −78 °C, E/Z = 90/10).