π-Face Differentiation in Michael Reaction to the Enone Group adjacent to the (η-C_5H_5)Mo(CO)$_2$(π-Allyl) Fragment: a New Approach to the Stereoselective Synthesis of 2,3,4,5-Tetrasubstituted-tetrahydrofuran Compounds

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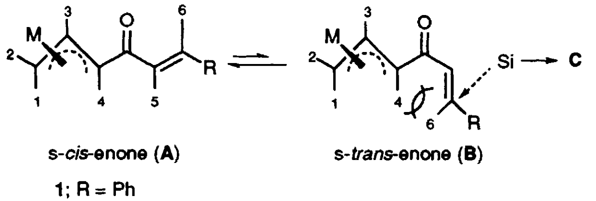
The stereochemical outcome of the 1,4-addition of organocopper reagents to (η-C_5H_5)Mo(CO)$_2$[η^3-1-(*E*)-$C_3H_4COCH{=}CHR$] compounds has been elucidated; utilization of this reaction for synthesis of 2,3,4,5-tetrasubstituted tetrahydrofuran is demonstrated.

Conjugated addition of organocopper reagents to an α,β-unsaturated enone had become a very useful tool in organic synthesis.[1,2] Stereocontrol of this carbon–carbon bond-forming reaction on an acyclic enone group is more challenging because of its more flexible conformation than its cyclic analogues. Utilization of an organometallic fragment as chiral auxiliary in Michael reaction proves effective, but only few cases are only known, *e.g.* (η-C_5H_5)FeCO(PPh$_3$)[η^1-(*E*)-enone][3] and (1-enone-2-OR-benzene)Cr(CO)$_3$.[4] Here we report the stereochemical course of the Michael reaction on (η-C_5H_5)Mo(CO)$_2$[η^3-1-(*E*)-$C_3H_4COCH{=}CHR$].



s-*cis*-enone (**A**) s-*trans*-enone (**B**)

1; R = Ph
2; R = 2-furyl
3; R = Me

Scheme 1 [M = (η-C_5H_5)Mo(CO)$_2$]

The starting (*E*)-enone compounds **1–3** were easily obtained from (η-C_5H_5)Mo(CO)$_2$(η^3-$C_3H_4COCH_2Li$)[5] *via* an aldol reaction, and subsequent dehydration with Ac_2O–Et_3N. An X-ray structure of **1**† reveals that the molecule adopts a sickle-shaped conformation in the allyl ketone moiety and a s-*cis* conformation in the enone moiety as represented by **A**. According to ^{1}H NOE (nuclear Overhauser effect)

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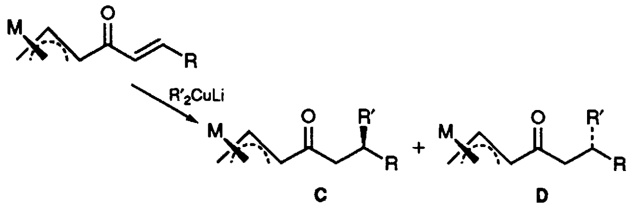
† *Crystal data* for **1**: crystallized in the monoclinic space group $P2_1/c$, a = 10.957(3), b = 12.8429(19), c = 12.758(4) Å, β = 111.26(3)°, V = 1673.1(8) Å^3, Z = 4, final R = 0.027 and R_w = 0.022 for 1788 reflections with $I > 2\sigma(I)$ out of 2180 unique reflections.

For **5C**: crystallizes in the monoclinic space group $C2/c$, a = 26.560(10), b = 7.195(3), c = 21.236(5) Å, β = 112.35(3)°, V = 3753.4(22) Å^3, Z = 8, final R = 0.032 and R_w = 0.022 for 1943 reflections with $I > 2\sigma(I)$ out of 2451 unique reflections.

For **10**: crystallizes in the monoclinic space group, $P2_1/c$, a = 24.059(5), b = 11.310(3), c = 15.877(3) Å, β = 108.85(2)°, V = 4088.5(14) Å^3, Z = 8. Each asymmetric unit contains two independent molecules; final R = 0.040 and R_w = 0.043 for 4217 reflections with I $>3\sigma(I)$ out of 7248 unique reflections.

Atomic coordinates, bond lengths and angles, and thermal parameters for these structures have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

Table 1



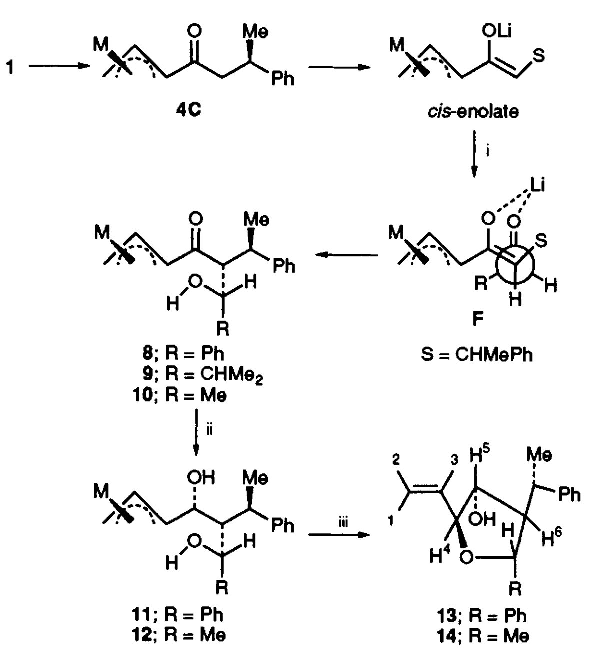
Entry	Enone	R'$_2$CuM	C/D (Yield %)[a]	C/D (Yield %)[b]	Product
1	**1**	Me$_2$CuLi	4/1(65)	14/1(90)	**4**
2	**1**	Et$_2$CuMgBr	6/1 (70)	>20/1 (88)	**5**
3	**2**	Me$_2$CuLi	3/1 (80)	16/1 (88)	**6**
4	**2**	Et$_2$CuMgBr	5/1 (74)	>20/1 (85)	**7**
5	**3**	Ph$_2$CuLi	2.5/1 (80)	14/1 (88)	**4***[c]

[a] These product ratios and yields are given in absence of Lewis acid.
[b] Products ratios and yields in presence of 1 equiv. of $BF_3.Et_2O$.
[c] See text for **4C***.

difference spectra,‡ the s-*trans* enone is the major solution species which however equilibrates with the s-*trans*-conformer **B**. Steric interactions between the 3-H and 6-H hydrogens would destabilize the corresponding s-*trans* isomer.[3]

The Michael reactions between **1–3** and various organocopper reagents R_2CuM were carried out in tetrahydrofuran (THF) (−40 °C, 6 h), and the results are given in Table 1. The reactions proceed with reasonable diastereoselectivities (**C**/**D** = 2.5–6), and in all cases the two diastereoisomers **C** and **D** were easily separated on a conventional SiO_2 column. Notably, the major isomers in entries 1 and 5 (Table 1) have reverse configurations, *i.e.* **4C** = **4D*** and **4D** = **4C***, providing stereocontrol of the desired structure. Clarification of the structures of the major isomer **C** relies on X-ray structural analysis of **5C** and an aldol derivatives of **4C** (compound **10**, Fig. 1).†

In connecting the stereochemical outcome with the two possible enone conformations, we conclude that the minor conformer **B** rather than **A** is responsible for the observed structure if Mo-π-allyl acts as chiral auxiliary to block the attack of organic copper reagents from the enone group of each conformer from the metal face. This result is in sharp contrast with other metal-η^1-enones [M = (η-C_5H_5Fe-CO(PPh_3))[3] and (2-X-C_6H_4)Cr$(CO)_3$[4]] systems, in which the s-*cis* enone **A** is both the X-ray structure and the active species in solution. Michael addition to **A** in our system is less sterically hindered because its vinyl group is further from the metal centre relative to **B**. The electronic effect must be favourable for **B** to account for its higher reactivities. In the presence of $BF_3{\cdot}Et_2O$, excellent selectivities for the product **C** (Table 1) were achieved. The coordinated $BF_3{\cdot}O{=}C$ fragment of conformer **A** is expected to exert more steric hinderance with its C=C bond, which tends to increase the concentration of **B**.



Scheme 2 *Reagents and conditions*: i, RCHO; ii, for **8** and **10**, DIBAL-H (2.5 equiv.), THF; iii, $NOBF_4$ (1 equiv.); [M = (η-C_5H_5)Mo(CO_2)]

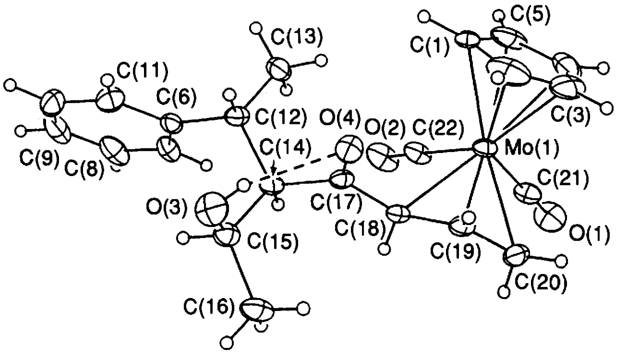


Fig. 1 Molecular structure of compound **10**. Pertinent bond distances (Å): Mo(1)–C(18) 2.342(6), Mo(1)–C(19) 2.209(7), Mo(1)–C(20) 2.340(7), C(17)–C(18) 1.485(7), C(17)–O(4) 1.218(7), C(15)–O(3) 1.424(9), O(3)–O(4) 2.82(1).

The ultimate aim of this Michael reaction is to explore its potential for organic synthesis. Toward this objective, we have generated the enolate of **4C** LiN$(SiMe_3)_2$ (1 equiv.) in THF at −78 °C, which subsequently condensed with RCHO (R = Me, Me_2CH, Ph) to give the aldol products **8–10**, in excellent selectivities (yields > 85%). From ORTEP drawings of **10**, the *cis*-enolate which was clearly generated selectively added to aldehyde with a possible lithium-chelated cyclized transition state[6] **F**. The evidence for the latter is inferred from the solid structure of **10**† (Fig. 1). According to a Fourier difference map, there exists an intramolecular hydrogen bond within O(3)H···O(4)=C(17), that locks the three carbons C(15)–C(14)–C(17) in a boat-like conformation. Once Li^+ replaces H^+, the transition-state **F** is generated, which has two mutually *trans* R and S (S = CHMePh) substituents to minimize steric hindrance. Although the *cis*-enolate and the s-*cis* enone conformer **A** have identical skeleton, interestingly their roles in the corresponding reactions are different. The compounds **8–10** can be utilized for stereoselective syntheses of highly substituted tetrahydrofurans. Reduction of **8** and **10** with diisobutylaluminium hydride (DIBAL-H) (2.5 equiv.) in THF gave the alcohols **11** and **12** as single diastereoisomers. Further treatment of **11** and **12** with $NOBF_4$ (1 equiv.) produced an allyl cation[7,8] which subsequently underwent Na_2CO_3-promoted intramolecular cyclization to liberate

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‡ In a ^{1}H NOE-difference experiment of **1** (−40 °C, $CDCl_3$), irradiation of the 4-H-signal (δ 2.25) causes an increase in the intensities of the 1-H (δ 1.41), 5-H (δ 6.85) and 6-H (δ 7.60) signals by 2.1, 5.2 and 2.2% respectively. In the s-*trans* enone conformer **B**, the 4-H is expected to exert more Overhauser effect on 6-H than 5-H-proton which is inconsistent with our observation.

2,3,4,5-tetrasubstituted tetrahydrofurans **13** and **14**§ in 69 and 50% yields, respectively. The specific proton positions of the ring were confirmed by ^{1}H NOE-difference spectra.

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§ Selected ^{1}H NMR data (CDCl$_3$, 300 MHz, coupling constants in Hz): For **13**: δ 7.24–7.00 (10H, Ph, m), 5.92 (1H, 3-H, ddd, *J* 17.1, 10.4, 6.0), 5.39 (1H, 1-H, d, *J* 17.1), 5.24 (1H, 2-H, d, *J* 10.4), 4.68 (1H, 7-H, d, *J* 7.3), 4.43 (1H, 4-H, t, *J* 6.0), 4.04 (1H, 5-H, dd, *J* 11.1, 6.0), 2.91 (1H, C*H* Me, dq, *J* 7.0, 6.5), 2.50 (1H, 6-H, ddd, *J* 11.1, 7.3, 7.0), 1.58(1H, OH, s), 1.37(3H, Me, d, J 6.5).

For **14**: δ. 7.36–7.21 (5H, Ph, m), 5.84 (1H, 3-H, ddd, *J* 17.2, 10.2, 6.6), 5.34 (1H, 1-H, d, *J* 17.2), 5.21 (1H, 2-H, d, *J* 10.3), 4.14 (1H, 4-H, t, *J* 6.6), 3.84 (1H, 5-H, dd, *J* 6.6, 6.0), 3.80 (1H, 7-H, m), 2.74 (1H, C*H* Me dq, *J* 9.6, 6.7), 1.94 (1H, H^6, ddd, *J* 9.6, 6.6, 6.0), 1.39 (3H, Me, d, *J* 6.7), 0.85 (3H, Me, d, *J* 6.6).