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Addition reactions of *O*-bound cyclic nickel enolates to α,β-unsaturated ketones†

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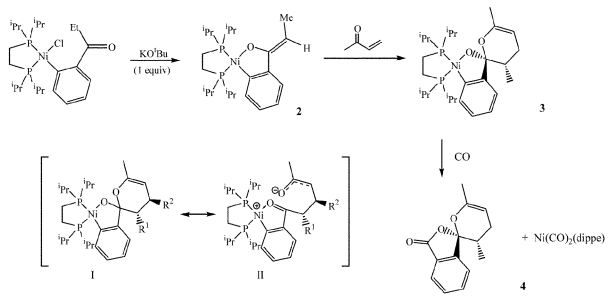
Received (in Cambridge, UK) 19th March 2003, Accepted 29th May 2003
First published as an Advance Article on the web 16th June 2003

The addition of the *O*-bound nickel enolates Ni(C$_6$H$_4$-*o*-C(=CHR)O)(dippe) (R = H, 1; R = Me, 2) to α,β-unsaturated ketones proceeds with complete stereoselectivity giving rise to [2 + 4] cycloadducts that can further evolve to generate open-chain, Michael-like products. The stereoselectivity of these reactions suggests a concerted mechanism, through an *exo* transition state.

The conjugate addition of enolates to α,β-unsaturated carbonyl compounds, or Michael addition, is one of the classical methods for the formation of carbon–carbon bonds.[1] Several variants of this methodology have been developed that improve its selectivity and the tolerance to sensitive functionalities,[2] often under conditions of catalysis. In some instances, the stereochemical outcome of the reactions has been explained by invoking the intermediacy of putative transition metal enolates,[3] which could undergo a [2 + 4] Diels–Alder cycloaddition of inverse electronic demand to the unsaturated carbonyl compound, followed by ring opening.

Despite the increasing applications of transition metal enolates in organic synthesis,[4] very little attention has been devoted to their conjugate additions.[5] One of the reasons for this is the acid–base exchange that may ensue between the metal enolate and the acidic α,β-unsaturated ketone, leading to a mixture of enolate complexes.[6] As this acid–base process is disfavoured for the metallacyclic, *O*-bound enolate Ni(C$_6$H$_4$-*o*-C(=CHR)O)(dippe), **1**, which has been shown to add cleanly to enolizable aldehydes like MeC(O)H,[7] we have considered this compound as a suitable candidate for conjugate additions to α,β-unsaturated ketones. In this contribution we show that enolate **1**, and its methylated analog **2** (Scheme 1) react with methylvinylketone (MVK) and *trans*-methylpropenylketone (MPK) in a highly stereoselective manner to give [2 + 4] cycloadducts, that can evolve to open chain enolate products.



Scheme 1

As represented in Scheme 1, compound **2** can be readily obtained following the methodology previously used for the synthesis of **1**. Interestingly **2** is produced as a single stereoisomer that displays a *Z* configuration at the double bond. This preference has also been observed in other related complexes[7] and is probably due to unfavorable interactions between the double bond substituents and the aromatic ring in the *E* isomer. Both nickel enolates react with MVK at room temperature, albeit **1** gives a complex mixture of compounds that are presently being investigated. For **2**, however, a single complex, **3**, is obtained whose carbonylation (Scheme 1) yields Ni(CO)$_2$(dippe) and the organic product **4**. The NMR spectra of **3** and **4** are consistent with a spirocyclic structure, that may be envisaged to result from a [2 + 4] addition of the enolate double bond to MVK. The NOESY spectra of **3** and **4** reveal an NOE crosspeak between the C*H*Me unique hydrogen and one of the aromatic resonances. Therefore the accompanying Me substituent and the phenylene unit maintain the relative *trans* configuration they possess in **2**. This observation is in agreement with a concerted cycloaddition, also hinted by the formation of a single diastereomer. The latter observation is probably a consequence of the synchronous generation of the two chiral centers.

Conclusive evidence for the structure of **3** was obtained from an X-ray analysis (Fig. 1),‡ which confirms the presence of a spirocyclic unit, with the expected *trans* disposition of C2 and C12. The terminal alkoxide ligand is a relevant structural feature, since only a few monomeric alkoxides of group 10 elements have been structurally characterized.[8] The Ni–O(1) bond length, 1.846(1) Å, is comparable to that found in the enolate complex **1**[8] and in nickel aryloxide complexes.[9] Bond lengths within the O1–C7–O2–C11 fragment display a remarkable alternation, with C(7)–O(1) (1.365(2) Å) and C(11)–O(2) (1.377(2) Å) being significantly shorter than C(7)–O(2) (1.469(2) Å), the latter being somewhat longer than the standard single C–O bond (1.43 Å). The variation of the three C–O bonds

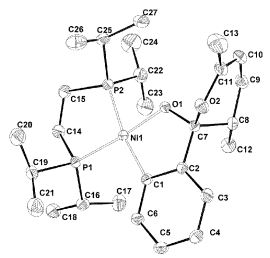


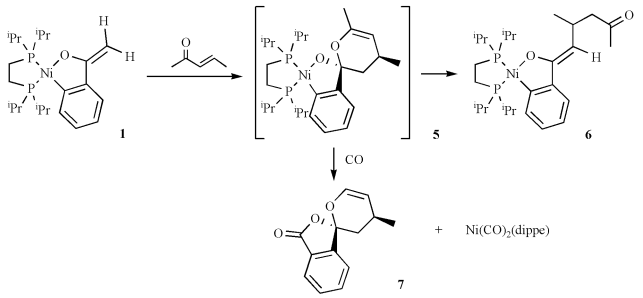
Fig. 1 View of the molecular structure of complex **3** together with the atomic numbering system. Selected bond distances (Å) and angles (°): Ni–O(1) 1.846(1), Ni–C(1) 1.932(2), Ni–P(1) 2.158(1), Ni–P(2) 2.207(1), O(1)–C(7) 1.365(2), O(2)–C(11) 1.377(2), O(2)–C(7) 1.469(2), C(10)–C(11) 1.317(3); O(1)–Ni–C(1) 86.16(7), O(1)–Ni–P(2) 84.84(5), P(1)–Ni–P(2) 88.56(3), C(7)–O(1)–Ni 117.7(1), O(1)–C(7)–O(2) 109.4(1).

† Electronic supplementary information (ESI) available: Further experimental and crystallographic details. See http://www.rsc.org/suppdata/cc/b3/b303062h/

DOI: 10.1039/b303062h

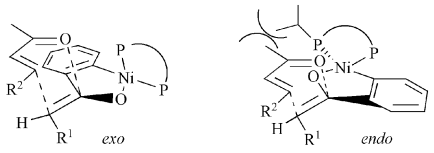
in **3** suggests an electronic distribution as that represented by the resonance forms I and II (Scheme 1). This situation is reminiscent of the well-known anomeric effect, observed in cyclic acetals and ethers.[10] Accordingly, the favored conformation for the six-membered ring of **3** is the one that keeps O(1) in an axial position.

With the aim of ascertaining the stereoselectivity of the addition process, we have studied the analogous reactions of MPK, whose terminal methyl group provides a stereochemical handle on the enone unit. Interestingly, there is no reaction with **2**, whereas, in contrast, complex **1** cleanly furnishes a single product, **6** (Scheme 2). The $^{13}C\{^1H\}$ NMR spectrum of this compound shows resonances at δ 208.4 and 22.9 ppm, attributable to the carbonyl and methyl groups of a pending acetyl functionality, and a doublet at 168.5 ppm (J_{CP} = 12 Hz), strikingly similar to that of the α-quaternary carbon of the Ni–O–*C*(=CHR) moiety of **1** (R = H) and **2** (R = Me), which appears in the same region (δ 176.1 and 169.9 ppm, respectively) as a doublet, with J_{CP} = 13 Hz. These and other spectroscopic considerations lead to an open-chain structure for **6** as shown in Scheme 2. Monitoring of the reaction by $^{31}P\{^1H\}$ spectroscopy reveals the intermediacy of a product, **5**, that proves to be too unstable for isolation. Notwithstanding this, optimization of the reaction time and the reagent ratio allowed accumulation of a sufficient concentration of **5**, which was then reacted with CO to give the corresponding cyclic lactone, **7**. Separation by standard chromatographic techniques gives **7** in 53% isolated yield. Comparison of its IR and NMR spectra with those of its isomer, **4**, unequivocally demonstrates the structural analogy that exists between these two compounds. As the carbonylation reaction preserves the structure of the organic fragment, this result demonstrates that **5** is a [2 + 4] cycloadduct analogous to **3**, whose formation precedes that of the open chain, "Michael-type" product **6**.



Scheme 2

Similarly to **3**, compound **5** is generated as a single stereomeric pair, whose stereochemistry has been ascertained with the aid of its 2D ^1H NOESY spectrum (see ESI†). The high diastereoselectivity of the reactions of Schemes 1 and 2, along with the observed rearrangement of the spirocyclic intermediate **5** into the open-chain enolate **6**, strongly suggests a concerted, inverse electronic demand, Diels–Alder mechanism for these reactions. Whereas [2 + 4] cycloadditions of enol ethers and enamines to unsaturated ketones are well-known,[11] to the best of our knowledge the analogous reactions of transition metal enolates have never been observed. Moreover the high *exo* selectivity of the reaction leading to **5** contrasts with the usual Diels–Alder *endo* preference determined by the secondary orbital interactions that involve the heteroatom substituent of the dienophile.[12] As shown in Scheme 3, this could be due to unfavourable steric interactions between the diene methyl substituent and the bulky isopropyl groups of the diphosphine ligand in the *endo* transition state.



Scheme 3

In conclusion, we have uncovered two examples of the very unusual additions of a transition metal enolate to an α,β-unsaturated ketone. The reactions investigated proceed with complete stereoselectivity and give rise to [2 + 4] cycloadducts that can further evolve to generate the more common, open-chain, Michael-like products. The analysis of the stereoselectivity of these reactions strongly suggests that they take place *via* a concerted mechanism, through an *exo* transition state. Continuing investigations in our laboratories to extend these results to other stoichiometric and catalytic processes, as well as to gain additional evidence in favour of this mechanistic proposal are currently under way.

Financial support from DGESIC (Project BQU2000-1169) is gratefully acknowledged. CMM thanks the Dirección General de Enseñanza Superior for a PFPI studentship.

Notes and references

‡ Crystal data for **3**: $C_{27}H_{46}NiO_2P_2$, M = 523.29, monoclinic, space group $P2_1/c$, a = 10.364(4), b = 14.185(4), c = 19.437(5) Å, β = 98.64(3)°, V = 2825.1(15) Å^3, Z = 4, D_c = 1.230 g cm^{-3} μ(MoKα) = 8.20 cm^{-1}, T = 293(2) K. 8633 reflections were measured (with θ in the range 3.04–30.01°), 8236 independent. The refinement converged at $wR2$ = 0.0959 for all data and 304 variables [$R1$ = 0.0371 for 5381 reflections with $I > 2\sigma(I)$. The SHELX-97 system of computer programs was used. CCDC 206759. See http://www.rsc.org/suppdata/cc/b3/b303062h/ for crystallographic data in .cif or other electronic format.

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