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Journal of Organometallic Chemistry 498 (1995) C17–C19

Journal of Organometallic Chemistry

Preliminary communication

Regiocontrol switching in C–C bond formation during decomplexation of a tricarbonyl(η^4-cyclohexadiene)iron complex

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Received 24 February 1995

Abstract

A study has been made of additions of nucleophiles to the tricarbonyl(η^4-cyclohexadiene)iron complex **1** and subsequent reaction of the resulting anions with several electrophiles in the presence of added ligands. Carbonyl insertion to form a functionalised cyclohexene ring is assisted by the addition of phosphines. Depending on the electrophilic reagent, an unusual phosphine-controlled switch in regiochemistry ($PhCH_2Br$), and interruption of the process prior to loss of the metal ($CH_2{=}CHCH_2Br$), have been observed.

Keywords: Iron; Cyclohexadiene; Carbonyl; C–C bond formation

When employed in organic synthesis, tricarbonyliron complexes offer powerful control effects in which a substrate, attached to the iron as a π-bound ligand (the "working ligand" [1]) is converted in a series of steps into an elaborated product. As the synthesis progresses, key bond-formations ("working steps" [1]) are often completely stereocontrolled. However, in addition to these valuable working steps, other unproductive reactions (complexation and decomplexation of the working ligand) are needed. This reduces the efficiency of the synthesis, increasing the number of steps to reach the target molecule. If the complexation and decomplexation stages were also working steps, efficiency would be improved. There have been examples of significant C–C bond formations during complexation reactions [2] leading to π-bound ligands, and in the case of decomplexation, a number of procedures are available to elaborate the working ligand during detachment from the metal [3–6], but compared with the wealth of information about tricarbonyliron-mediated nucleophile addition to dienyl ligands, relatively little is known about the scope and limitations of the strategically important reactions that could effect decomplexation in a working step in synthesis of a target molecule.

The work of the Semmelhack [3] and Yeh [4,5] groups has shown that nucleophile addition to simple neutral η^4-tricarbonyliron complexes can be combined with carbonyl insertion and interception of the anion with an electrophile when performed under an atmosphere of carbon monoxide. The reaction is promising for use in the closing stages of an iron-mediated target molecule synthesis, because two C–C bonds are formed in a stereoselective manner. The nature of the electrophile is known to influence the efficiency of the decomplexation reaction, so offering access to high yielding processes. However, in synthesis of a target molecule, the choice of electrophile is dictated by the target structure, so an alternative strategy for fine-tuning is needed. Phosphine ligands promote alkyl migration to carbonylmetal units; we report here the effect of added phosphines on the nucleophile/CO/electrophile addition process. The efficiency of the reaction was found to vary with the nature of the phosphine, and selectivity between routes to different products was possible, pointing to potential advantages of the phosphine modification when employed in target molecule synthesis.

At first we chose a relatively simple nucleophile, benzyllithium, for use in these investigations. This reagent cannot be generated in the ordinary way (from a benzyl halide by BuLi), but can be made only by treatment of toluene with BuLi in the presence of 1,4-diazabicyclo[2.2.2]octane [7]. Attempted reaction of this nucleophile with tricarbonyl(η^4-cyclohexadiene)iron(0) was carried out in the presence of triphenylphos-

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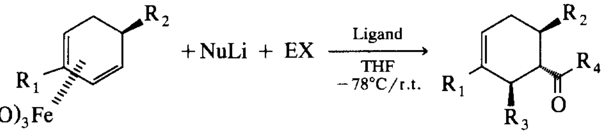
SSDI 0022-328X(95)05599-1

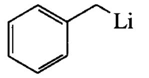
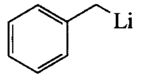
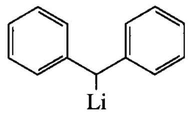
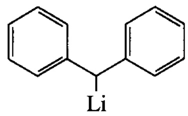
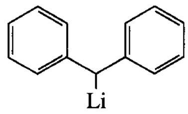
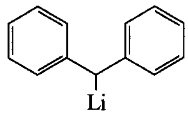
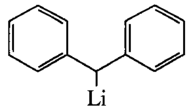
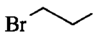
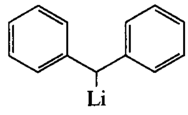
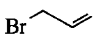
phine, and with methyl iodide or allyl bromide as the electrophile. Only in the case of methyl iodide was the expected product isolated, and then in low yield (Table 1, entry 1). Switching to trimethylphosphine (entry 2) improved the yield, but overall, the process still lacked the efficiency needed for use in organic synthesis. Furthermore, when this procedure was carried out with more highly substituted dienes (R_1 = OMe or R_2 = Ph, Me), either products were obtained in even lower yields or there was no reaction at all. Since the choice of nucleophile is likely to be an important factor, we repeated the experiment, using diphenylmethyllithium, which is commonly employed to good effect in the literature version of the reaction [4]. In this case, nucleophile addition, carbonyl insertion and anion trapping proved possible for a range of electrophiles (methyl iodide, benzyl bromide and allyl bromide), allowing more complete examination of the influence of the added phosphine ligands.

Table 1 (entries 3–8) shows the outcome of these experiments. Methyl iodide proved to be the best electrophile (entry 4), and the expected product was isolated in 40% yield. Trimethylphosphine was better than triphenylphosphine in promoting ligand migration. Trimethyl phosphite, on the other hand, was less effective, and there was no reaction at all in the case of ^{t}Bu–NC. With the more bulky electrophile, benzyl bromide, switching between products **II** and **III** [8] was observed (Scheme 1). This was controlled by the nature of the added phosphine. With triphenylphosphine (entry

Table 1



I **II**

Entry		NuLi	EX	Ligand	Product	Yield
1	$R_1 = H, R_2 = H$		MeI	Ph_3P	II: $R_1 = H, R_2 = H$ R_3 = Bn, R_4 = Me	20%
2	$R_1 = H, R_2 = H$		MeI	Me_3P	II: $R_1 = H, R_2 = H$ R_3 = Bn, R_4 = Me	34%
3	$R_1 = H, R_2 = H$		MeI	Ph_3P	II: $R_1 = H, R_2 = H$ $R_3 = CH(Ph)_2$, R_4 = Me	25%
4	$R_1 = H, R_2 = H$		MeI	Me_3P	II: $R_1 = H, R_2 = H$ $R_3 = CH(Ph)_2$, R_4 = Me	40%
5	$R_1 = H, R_2 = H$		BnBr	Ph_3P	II: $R_1 = H, R_2 = H$ $R_3 = CH(Ph)_2$, R_4 = Bn	23%
6	$R_1 = H, R_2 = H$		BnBr	Me_3P	III	33%
7	$R_1 = H, R_2 = H$			Me_3P	II: $R_1 = H, R_2 = H$ $R_3 = CH(Ph)_2$, $R_4 = CH_2CH = CH_2$	17%
8	$R_1 = H, R_2 = H$			Ph_3P Et_3OPF_6 [a]	II: $R_1 = H, R_2 = H$ $R_3 = CH(Ph)_2$, $R_4 = CH{=}CHCH_3$	24%

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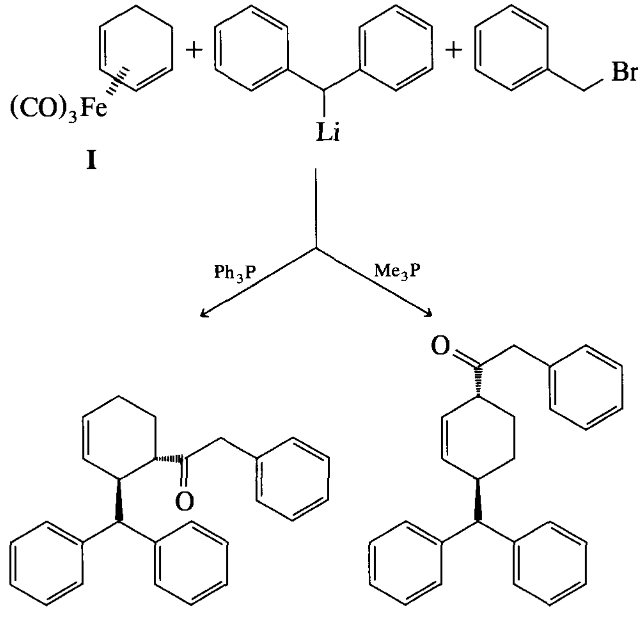
[a] In addition to a trace of a product of type II ($R_4 = CH_2CH{=}CH_2$), an organoiron complex was isolated in this experiment (see text) and was converted into an isomerised metal-free product ($R_4 = CH{=}CHCH_3$) by reaction with Et_3OPF_6.



II: $R_1 = H$, $R_2 = H$
$R_3 = CH(Ph)_2$, $R_4 = Bn$

III

Scheme 1.

5), normal 1,2-difunctionalisation afforded **II** ($R_1 = R_2 = H$), but use of trimethylphosphine gave the alternative 1,4-regioisomer **III**.

When allyl bromide was used as the electrophile for anion trapping, it was possible to isolate in 24% yield an organometallic intermediate (ν(CO) 2002, 1936 cm^{-1}) which was unstable, affording a second organoiron complex (ν(CO) 1994, 1931 cm^{-1}). The incorporation of the allyl ligand in this intermediate was supported by FAB mass spectrometry which showed the presence of an M + H ion (691$^+$) and fragmentation with two losses of carbonyl groups, and by conversion into **II** (entry 8). In this reaction, the expected product **II** (entry 7) was also isolated in 7% yield. The organoiron product was treated with Meerwein's reagent (Et_3OPF_6) to afford not **II** ($R_4 = CH_2CH{=}CH_2$), but the isomerised structure with $R_4 = CH{=}CHCH_3$ (entry 8), in almost quantitative yield. When the reaction was performed with trimethylphosphine as the added ligand only the product with $R_4 = CH_2CH{=}CH_2$ was isolated (17% yield), and none of the organoiron intermediate was observed.

This work has demonstrated the validity of the principle that inclusion of phosphines offers opportunities for fine-tuning the ligand displacement/C–C bond formation process, not only influencing the efficiency of the reaction but also, in the case of suitable electrophiles, promoting switching between regioisomer series, or allowing the reaction to be stopped before detachment of the metal. This indicates new possibilities for synthetic applications. In the course of these investigations a selection of solvents, temperature ranges and additional reactants have been examined without significantly influencing the yield of the reactions. Access to higher yielding processes for use in synthesis must await a full investigation of a wider variety of phosphine ligands.

Acknowledgement

MB thanks the Hungarian Scientific Research Fund (OTKA) and World Bank for a Research Fellowship. We are grateful to Dr. A.V. Malkov for discussions concerning this work. We thank the EPSRC Mass Spectrometry Service for FAB MS and high resolution mass measurements.

References and notes

[1] When a ligand from a stoichiometric π-complex is incorporated into an organic target through a series of metal mediated steps, this ligand can be regarded as the "working ligand" in the concept of synthesis plan, to distinguish it from other ligands at the metal ("auxiliary ligands") which can be varied to fine-tune reactivity: G.R. Stephenson, H. Finch, D.A. Owen and S. Swanson, *Tetrahedron*, *49* (1993) 5649. In a similar way, when synthesis design is discussed, "working steps" directly advance the synthesis by skeletal bond formation, G.R. Stephenson, review article in preparation.

[2] For examples of the preparation of η^4 Fe(CO)$_3$ complexes with concurrent C–C bond formation, see: K. Kafuku, K. Nakatsu, T.A. Mitsudo, H. Watanabe, T. Sasaki, Y. Takegami and Y. Watanabe, *Organometallics*, *8* (1989) 368; M.F. Semmelhack and J. Park, *J. Am. Chem. Soc.*, *109* (1987) 935; A.J. Pearson, R.J. Shively, Jr. and R.A. Dubbart, *Organometallics*, *11* (1992) 4096; A.J. Pearson and R.J. Shively, Jr., *Organometallics*, *13* (1994) 578; H.-J. Knolker, J. Heber and C.H. Mahlev, *Synlett*, (1992) 1002. In the case of η^6 Cr(CO)$_3$ complexes, construction of the η^6 ligand has been combined with later metal mediated reactions utilize the arene complex: S. Chamberlin and W.D. Wulff, *J. Am. Chem. Soc.*, *114* (1992) 10667.

[3] For examples in which an η^4 Fe(CO)$_3$ complex is demetallated with concurrent C–C bond formation, see: M.F. Semmelhack and J.W. Herndon, *Organometallics*, *2* (1983) 363; M.F. Semmelhack, J.W. Herndon and J.P. Springer; *J. Am. Chem. Soc.*, *105* (1983) 2497; see also Refs. [4] and [5].

[4] M.-C.P. Yeh, C.-C. Hwu, *J. Organomet. Chem.*, *419* (1991) 341.

[5] M.-C.P. Yeh, B.-A. Sheu, H.-W. Fu, S.-I. Tau, L.-W. Chuang; *J. Am. Chem. Soc.*, *115* (1993) 5941.

[6] The best example of a working decomplexation step of value in target molecule synthesis is provided by the replacement of an η^2 alkyne dicobalt complex by a cyclopentenone in the Pauson-Khand cyclisation. This decomplexation step can be combined with cobalt-mediated functionalization of propargyl cation complexes, as illustrated in a cobalt-mediated total synthesis of (t)-epoxydictymene: T.F. Jamison, S. Shambayati, W.E. Crowe and S.L. Schreiber, *J. Am. Chem. Soc.*, *116* (1994) 5505.

[7] B.J. Wakefield, *Organolithium Methods*, Academic Press, London (1988) p. 38.

[8] Mass spectrometric characterisation of products **II** and **III** was prevented by the ease of fragmentation of these compounds even under FAB ionisation conditions, so 2D NMR (COSY) spectroscopy was used to prove the structures shown in Table 1.