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The first examples of ester enolate addition across a chiral (alkoxybenzene)–chromium complex π-bond with a remarkable degree of 1,5-asymmetric induction

James D. Dudones and Anthony J. Pearson*

Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106, USA

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Abstract

The first examples are described wherein addition of an ester enolate to an alkoxy-substituted arene–chromium tricarbonyl complex, to afford a substituted cyclohexenone in high enantiomeric excess.

The scope of nucleophile addition reactions to substituted (arene)$Cr(CO)_3$ complexes to give dearomatized cyclohexadienyl products is somewhat limited.[1] This is a direct consequence of the electron accepting ability of the $Cr(CO)_3$ subunit which has two separate effects on the arene ligand. The first is that it increases the Brønsted acidity of the arene protons (by 6–9 pK_a units) so that hard nucleophiles prefer to deprotonate the arene ligand. Secondly, the $Cr(CO)_3$ subunit only modestly activates the arene ligand towards nucleophilic attack, so that often there is an unfavorable equilibrium between the starting complex (e.g. **1**, Eq. (1)) and the anionic intermediate **4**, such that only very reactive nucleophiles (p$K_a \geq 23$) undergo successful addition. The Kündig group has demonstrated that these problems can be partially ameliorated by using electron withdrawing substituents on the arene ligand (R = oxazolidine, hydrazones, etc.)[2] and/or by using various additives in the reaction mixture that serve to drive the initial equilibrium to the right (K^+ instead of Li^+ counterions, use of crown ethers or HMPA, etc.).[3] Nonetheless, arene ligands with electron donating substituents, such as substituted (alkoxyarene)$Cr(CO)_3$ complexes (e.g. **1**–**3**, Eq. (1)) are generally compatible with only a much narrower range of nucleophiles.

* Corresponding author.

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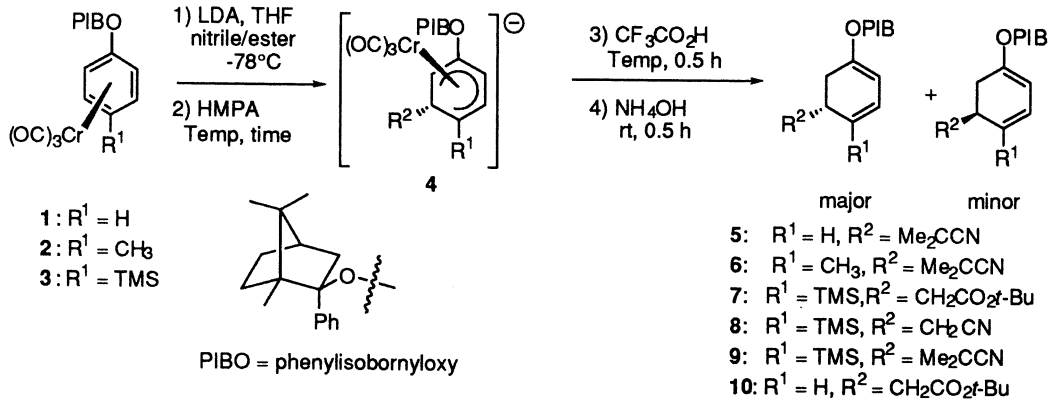


(1)

Previously we have demonstrated that the anion of isobutyronitrile can be added to chiral (alkoxyarene)$Cr(CO)_3$ complexes **1** and **2** in good yields with moderate to excellent diastereoselectivity (Eq. (1), Table 1, entries 1 and 2).[4,5] Although a remarkable example of efficient 1,5-asymmetric induction, the isobutyronitrile substituent is clearly of limited synthetic utility. We now report that excellent stereocontrol can be achieved during unprecedented ester enolate addition reactions.[6]

Our first attempts towards realizing this goal utilized the enolate of *t*-butyl acetate (Rathke's salt[7]) along with the TMS substituted Cr(arene) complex **3**. Unfortunately, the lithium ester enolate did not add to the Cr(arene) complex, even upon prolonged reaction times (4–18 h) up to −40°C (e.g. Table 1, entry 3). It appears that the equilibrium in the initial nucleophile

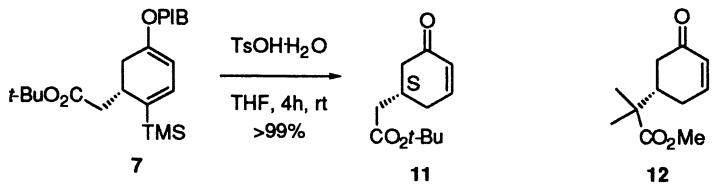
Table 1
Results of nucleophile addition/electrophile addition/demetallation reactions with Cr(arene) complexes **1**, **2**, and **3**

Entry	Cr(arene) complex	Ester/nitrile[a]	HMPA (equiv.)	Temp. (°C)	Time (h)	Method[b]	Yield (%)[c]	Diastereomer ratio (% de)
1	**1**	Me_2CHCN		−78	2	A	**5**:95	4:1 (60)
2	**2**	Me_2CHCN		−78	2	A	**6**:63	24:1 (92)
3	**3**	*t*-BuOAc		−60	18	A	**7**:0	
4	**3**	*t*-BuOAc	19.6	−60	8	A	**7**:(86)	11:1 (84)
5	**3**	*t*-BuOAc	6.5	−60	8	A	**7**:(30)[d]	>50:1 (>99)
6	**3**	*t*-BuOAc	12.5	−60	4	A	**7**:60 (60)	20–38:1 (90–94)
7	**3**	*t*-BuOAc	19	−60	8	B	**7**:60 (60)	20:1 (90)
8	**3**	CH_3CN	25	−60	18	B	**8**:79	2.6:1 (47)
9	**3**	Me_2CHCN	25	−60	20	B	**9**:(66)[e]	>50:1 (>99)
10	**1**	*t*-BuOAC	19	−60	16	B	**10**:(54)	5:1 (66)

[a] Five equiv. of ester/nitrile were used relative to 1 equiv. of Cr(arene) complex in all reactions.
[b] Method A: Final THF reaction concentration was 0.10 M. Method B: Final THF reaction concentration was 0.05 M.
[c] Yield in parentheses determined by ^1H NMR analysis of the crude reaction mixture using pyridine as an internal standard.
[d] Reaction only proceeded to about 50% completion as determined by ^1H NMR analysis of the crude product.
[e] ^1H NMR analysis of the crude product indicated that 10% of the starting complex **3** remained unreacted.

addition reaction (**3**/**4**, R^1 = TMS, Eq. (1)) lies unfavorably towards the starting complex **3**. In an attempt to increase the reactivity of the ester enolate ion and thus drive this equilibrium towards the desired product, a crown ether was employed (12-crown-4) as well as the use of a K^+ instead of a Li^+ counterion (KHMDS instead of LDA). In every case the unreacted starting Cr(arene) complex **3** was recovered quantitatively. We next examined the use of HMPA as an additive; when 19.6 equiv. was employed and the reaction was warmed to −60°C (to maintain homogeneity), the cyclohexadiene **7** was indeed produced (entry 4) in a promising 84% de.[8–10] By utilizing 6.5 equiv. of HMPA (entry 5), it was found that the reaction only proceeded to about 50% consumption of complex **3**, but **7** (NMR yield 30%) was produced as a single diastereomer! Eventually, it was found that an acceptable balance could be struck between reaction yield and diastereoselectivity by employing 12.5 equiv. of HMPA (entry 6), whereupon **7** was afforded in 60% isolated yield with a remarkable 90–94% de! *To our knowledge this is the first successful example of the addition of an ester enolate across a Cr(arene) double bond to give a cyclohexadiene product.*[11,12]

Hydrolysis of **7** ($TsOH{\cdot}H_2O$, THF) proceeded with concomitant removal of the TMS group, to afford enone **11** in quantitative yield (Eq. (2)). The absolute configuration of **11** was established as *S* by comparison of its CD spectrum with the previously published CD spectrum of the related enone **12** (negative n–π* Cotton effect at λ_{max} 338 nm).[13]



(2)

The steric bulk of the nucleophile and the *para* substituent on the Cr(alkoxybenzene) complex play a critical role in controlling the 1,5-asymmetric induction. Thus, reaction of the anion of acetonitrile with complex **3** gave a modest 2.6:1 ratio of diastereomers **8** (Table 1, entry 8), while essentially complete diastereoselectivity was obtained using the more bulky isobutyronitrile anion (entry 9; it should be noted that this reaction does not proceed at all in the absence of HMPA[4]). In addition, reaction of the enolate of *t*-butyl acetate with complex **1** (entry 10) proceeded with much poorer stereoselectivity (reaction with **2** was capricious and is not reported here). This data is consistent with the previous hypothesis put forth by our group,[4] wherein a larger *para* substituent forces the nucleophile to take an approach trajectory at the reaction center that is closer to the influence of the chiral auxiliary.

It is clear that the electron accepting TMS group does indeed have an activating influence on the addition reactions (Table 1, entries 6 and 10) due to its ability to stabilize the intermediate anionic Cr(dienyl) species (**4**, R^1 = TMS). The reaction with complex **1** required longer times for completion, and the yield of diene product was observably lower than with **3**. Apart from some demetallated and rearomatized arene byproducts (less than 10% by NMR), it is not clear at this point what has happened to the mass balance in this reaction.

In conclusion, we have demonstrated that the ester enolate of *t*-butyl acetate can be efficiently added across a π-bond of Cr(alkoxybenzene) complex **3** with a high degree of 1,5-asymmetric induction. To our knowledge this is the first documented example of such an overall addition reaction to a Cr(arene) complex and may considerably broaden the scope of the nucleophile addition/electrophile addition/demetallation reaction sequence. Current studies are ongoing in

our laboratory to determine the generality and range of this important extension of useful synthetic methodology, the results of which will be reported in due course.

Acknowledgements

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5. PIBOH was prepared in one step from (+)-camphor and phenylmagnesium chloride according to the procedure found in: Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* **1994**, *35*, 6713.
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7. Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050.
8. The diastereomer ratio was determined by the direct comparison of the integrations corresponding to the vinyl protons for each isomer at 5.91 ppm (major) and 5.84 ppm (minor) in the ^{1}H NMR spectrum of the crude product.
9. The cyclohexadiene products described herein are generally unstable and difficult to isolate in analytically pure form. Chromatography using silica gel as the stationary phase has proven unsatisfactory due to the lability of the PIB group to even mildly acidic conditions. However it has proven possible to isolate pure dienes **7** and **8** by chromatography on basic alumina. Due to this inherent instability the yields from many of the reactions described herein were established by analysis of the ^{1}H NMR spectra of the crude diene products using pyridine as an internal standard. For synthetic application, this lability is not problematic, as the dienol ethers are readliy hydrolyzed to enones (e.g. **11**).
10. Use of DMPU instead of HMPA did not prove to be advantageous. Use of 11 equiv. of DMPU according to method A gave none of the diene product **7** and led only to the recovery of starting material. The use of 70 equiv. of DMPU did give the desired product but the de was below 80% and the reaction only proceeded to about 40% completion.
11. For an example of a silyl ketene acetal reacting with a Cr(alkoxybenzene) complex to give as a minor byproduct an overall addition adduct see: Bellassoued, M.; Chelain, E.; Collot, J.; Rudler, H.; Vaissermann, J. *J. Chem. Soc., Chem. Commun.* **1999**, 187.
12. The purity of **3** has a marked effect on the outcome of this reaction. Although the diastereoselectivity remained constant ($\sim$20:1 in all cases) the degree to which the reaction proceeded to completion (amount of **3** consumed) varied widely from case to case if the starting complex **3** was not absolutely pure. A second set of conditions (Method B, Table 1, entry 7) were also developed that are more forgiving of reactant purity.
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