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An Enantiomerically Pure Tricyclic Isoindoline System by Cyclisation of Tricarbonyl[η^6-(*R*)-*N*-cyanomethyl-4-phenyloxazolidine]chromium

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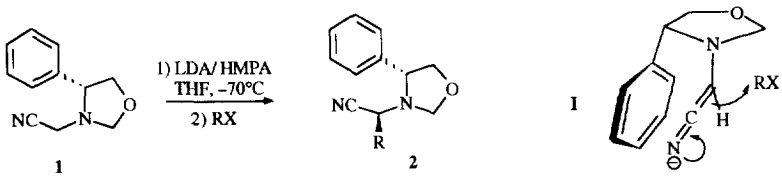
Abstract: The isolation of isoindoline **4** by oxidative trapping indicates that a tricyclic η^5 complex is a contributing form of the anion derived from the title compound **3**.

Over the past ten years, we have studied the asymmetric alkylation and the 1,3-dipolar cycloadditions of the chiral synthon (*R*)-*N*-cyanomethyl-4-phenyloxazolidine **1**.[1] In general, the stereochemical induction in alkylation reactions is modest (20-60% d.e. for **2**),[2] probably due to a lack of structural rigidity in the intermediate carbanion, whose reactive centre is located on a poorly-restrained side-chain of the rigid ring system. To explain the preponderant *S* absolute configuration at the new chiral centre, a preferred reactive conformer **I** (*cis* relative configuration, *exo* cyanomethyl anion) was invoked for the intermediate carbanion.[2a]



1 **2** **I**

Herein we report our first observations on the corresponding tricarbonylchromium(0) complex **3**. Our interest in this compound arose from the knowledge that (η^6-arene)chromium compounds react with carbanions derived from alkyl nitriles to give negatively-charged η^5 intermediates.[3] Some intramolecular examples are known, for which the bicyclic intermediates have been trapped,[4] but no simple cases have been described for γ-cyanoarenes, nor for heterocyclic systems. Furthermore, in simple intermolecular cases, the subsequent addition of an electrophile to the η^5 adduct results in alkylation of the nitrile α-carbon with concomitant cleavage and regeneration of the neutral (η^6-arene)chromium system.[3] If such phenomena could be induced for **3**, the highly-original intermediate **II** should allow much better stereochemical control during alkylation: temporary formation of a sigma bond effectively rigidifies the anion and completely blocks one side of the reactive centre. Thus **3** was prepared from **1** using standard procedures[5] (49% yield) in order to address two questions: does a tricyclic anionic η^5 complex **II** form on deprotonation? And, if so, does it allow improved stereoselectivity during alkylation?

Efficient deprotonation of **3** was achieved at –70 °C with LDA (2 equiv) in HMPA/THF or *n*-BuLi (2 equiv) in THF, as evidenced by quantitative incorporation of deuterium in recovered **3** upon treatment with excess D_2O. Oxidative trapping–decomplexation of **3** anion solutions generated in this way was carried out with an excess of iodine, and standard work up gave compound **4** as a single stereomer in about 20% yield. 2D NOESY NMR experiments showed correlations which suggested an *R* configuration at the new chiral centre, precisely as would be expected from the cyclisation of a *cis-exo* conformer of **3** anion.

Under the present reaction conditions, the isolated yield of **4** remains low, which we interpret as an indication of a low concentration of **II** in the anion solution. In consequence, **3** has no greater ability than **1** for stereochemical control during alkylation. Indeed, as shown in the Table, yields and diastereomeric excesses of alkylation products are more or less comparable for the two compounds.

Nonetheless, intermediate **II** is clearly accessible, apparently with total stereochemical control, *via* an unprecedented intramolecular *ortho*-directed cyclisation of a (γ-cyanoarene)chromium complex. The potential of this structure for asymmetric alkylation, and the novelty of the chiral isoindoline derivatives such as **4** which can be derived therefrom, justify continuing efforts towards the optimisation of its formation.[6]

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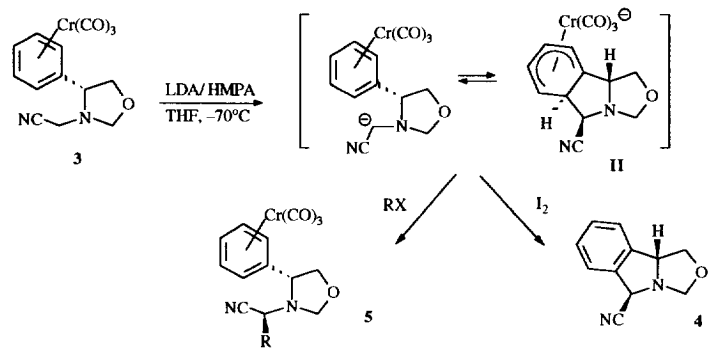

Table

RX	1 → 2 Yield (%)§	1 → 2 d.e. (%)*	3 → 5 Yield (%)§	3 → 5 d.e. (%)*
MeI	70	36	68	40
EtI	91	58	61	30
$PhCH_2Br$	67	44	52	43
Allyl Br	63	26	64	36

* In all cases the major diastereomer has an *S* configuration at the new chiral centre

§ Isolated pure after chromatography

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6. All new products showed satisfactory spectral and/or analytical data.

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