Phenyl vs. Ferrocenyl Cyclometallation Selectivity: Diastereoselective Synthesis of an Enantiopure Iridacycle

Ross A. Arthurs,[a] Peter N. Horton,[b] Simon J. Coles[b] and Christopher J. Richards*[a]

This paper is dedicated to the memory of Sarah R. Delf. Friend, colleague and chemist.

Abstract: Ferrocenyl (Fc) and phenyl (Ph) containing imines FcCH=NCH(R)Ph and FcCH(N)=CPh (R = H and Me) were cycloaromatized using \([\text{Cp}^*\text{IrCl}_3]\) with NaOAc in CH\(_2\)Cl\(_2\). All resulted in the formation of neutral chloride ligated half-sandwich iridacyles as a result of ortho-phenyl and not alpha-ferrocenyl C-H activation. The complexes derived from FcCH=NCH(R)Ph (R = H, Me) were obtained as a mixture of \(E\) and \(Z\) imine isomers, and with R = Me the product obtained from the (S)-imine was isolated by recrystallisation as a single diastereoisomer. The configuration was determined by an X-ray crystal structure analysis as \(S\)-E.

Introduction

Several recent publications have described the synthesis of neutral or cationic iridium(III) half-sandwich mettallacycles of general structure 1 (Figure 1), with many of these investigations being directed towards application of the resulting complexes in catalysed organic transformations.\(^4\) In addition, a number of chiral non-racemic examples are known for which a key issue is configurational control of the iridium-based stereogenic centre.\(^3\) To this end we recently reported the synthesis of ferrocene-based planar-chiral iridacycle 2, synthesised as a single diastereoisomer from a precursor ferrocenylimine by alpha C-H bond activation. Extension of this reaction to a chiral non-racemic ferrocenylloxazoline substrate resulted in highly diastereoselective alpha C-H bond activation and isolation of iridacycle 3. In both 2 and 3 the iridium-centred chirality is controlled by the planar chirality via Fe-Ir mediated stereoelectronic control of ligand substitution.\(^4\)

In a related approach to obtain imine-based complexes we chose to investigate the cycloaromatization of N-benzylimines 4 and isomeric N-ferrocenylimethymines 5. These substrates, in addition to being readily accessible, are set up to determine the exo vs. endo or phenyl vs. ferrocenyl selectivity arising from alpha or ortho C-H bond activation. Furthermore, with substrates 4b and 5b there is the potential for the carbon-based stereogenic centre to control the iridium-based stereogenic centre of the resulting mettallacycle, either with or without the generation of a new element of planar chirality.

Results and Discussion

Imines 4a (81%), (S)-4b (93%), 5a (74%) and 5b (74%) were synthesised from the corresponding aldehyde and amine by heating these at reflux in toluene in the presence of a catalytic quantity of potassium carbonate. Water was removed from the reaction by use of a Dean and Stark apparatus and 4 Å molecular sieves. Cycloaromatization of phenyl compounds containing an ortho directing group with \([\text{Cp}^*\text{IrCl}_3]\) and NaOAc in CH\(_2\)Cl\(_2\) has resulted in a number of neutral half-sandwich iridacyles of general structure 1a.\(^3\) This cycloaromatization method was also used for the synthesis of complexes 2 and 3.\(^4\) Application of these conditions to 4a resulted in the isolation of an inseparable mixture of two iridacyles in a 1 : 0.45 ratio (Scheme 1). That both had arisen from phenyl ortho C-H activation was apparent from the two sets of four aromatic proton signals in the \(\text{H}^1\) NMR spectrum. This, together with there being two corresponding sets of nine ferrocenyl proton signals, led to the identification of these complexes as \((Z)-6a\) and \((E)-6a.\) The latter was assigned on the basis of the high chemical shift of one of the two diastereotopic \(\alpha\)-proton signals observed at 6.23 ppm due to the proximity of this hydrogen to the iridium-chlorine bond (vide infra). Following isolation, no change was observed in the solution ratio of \((Z)-6a\) to \((E)-6a \) over a period of 24 hours suggesting that following isolation imine isomerisation does not occur.\(^5\)

This observed preference for cycloaromatization of the phenyl group, and thus exo over endo selectivity, is in marked contrast

[a] R. A. Arthurs, Dr C. J. Richards
School of Chemistry
University of East Anglia
Norwich Research Park, Norwich, NR4 7TJ, U.K.
E-mail: Chris.Richards@uea.ac.uk
www.uea.ac.uk/chemistry/people/profile/chris-richards

[b] Dr. P. N. Horton, Dr. S. J. Coles
EPSRC National Crystallography Service, School of Chemistry,
University of Southampton,
Highfield, Southampton, SO17 1BJ, U.K.

Supporting information for this article is given via a link at the end of the document.
to the outcome of palladation of 4a which results exclusively in ferrocenyl alpha C-H activation and formation of an endo palladacycle. The preference for endo selective cyclopalladation has been noted elsewhere, including the cyclopalladation of 5a which results in a 3:2 ratio of endo:exo palladacycles. In this example endo selectivity partly overcomes the preference for ferrocenyl over phenyl cyclopalladation, an outcome rationalised by the significantly greater susceptibility of the former moiety to electrophilic aromatic substitution. In contrast, cyclodisation of 5a resulted only in phenyl C-H activation and formation of 7a, the 1H NMR spectrum of the product again containing four distinct aromatic proton signals (Scheme 2). In this instance the endocyclic imine functionality dictates a single double bond configuration.

Scheme 1. Phenyl (exo) selective cyclodiration of imine 4a.

The participation of an iridium-coordinated acetate in a concerted metatllation deprotonation pathway has been studied in depth, and compared to cyclopalladation, DFT calculations point to there being stronger electrophilic character in C-H bond activation with Ir(III) complexes. In agreement with this, a cyclodiration study with a series of meta-substituted phenylamines using [Cp*IrCl2] and NaOAc revealed that substrates with electron donating substituents reacted significantly faster than those with electron withdrawing substituents. In contrast, the exclusivity of phenyl over ferrocenyl C-H activation does not result from the relative susceptibility of these moieties to electrophilic substitution, assuming that the reactions are under kinetic control. Examination by 1H NMR spectroscopy of the cyclodiration reaction mixtures in the early stages of the reaction revealed no evidence of initial ferrocenyl C-H activation. Extension of cyclodiration to substrate 5b, containing a carbon-based stereogenic centre, also resulted exclusively in phenyl C-H activation and formation of a predominant diastereoisomer for which the percentage of the minor isomer (6%) did not change on standing in CDCl3 for 24 hours. After 1 week the percentage of the minor isomer had increased to 12% (Scheme 2). For the major isomer an NOE interaction is observed between the imine C-H and the methyl group (Figure 2). Based on this conformational preference, with respect to C-N bond rotation, the largest group attached to the stereogenic centre, i.e. the ferrocenyl moiety, is oriented towards the bulky Cp* group in the Rc*,Rd*-diastereoisomer. That this is avoided in the Rc*,Sc*-isomer is the basis of this relative configuration being assigned tentatively to 7b, this being supported by an NOE interaction between the methine of the carbon-based stereogenic centre and the Cp* group.

Scheme 2. Phenyl (endo) selective cyclodiration of imines 5a,b and suggested relative configuration of iridacycle 7b.

In contrast to imine 5b, enantiopure imine 4b is readily synthesised due to the commercial availability of both enantiomers of the precursor, α-methylbenzylamine. In addition to this impetus, it was reasoned that phenyl-selective C-H activation would place the carbon-based stereogenic centre within the resultant iridacycle, possibly leading to control of the iridium-based stereogenic centre. Reaction of (S)-4b with [Cp*IrCl2] and NaOAc in CH2Cl2 and analysis of the reaction mixture after 48 h, revealed the formation of two major iridacycles in a 1:0.4 ratio. Following filtration through Celite and precipitation with hexane this ratio had changed to 1:0.07 (Scheme 3). Recrystallisation from CH2Cl2/hexane enabled confirmation of the identity of the complex as an Iridacycle by an X-ray crystal structure analysis, which also revealed the configuration as Sc,Rd,E (Figure 3). That this is also the configuration of the major isomer found in solution was confirmed by the NOE interaction between Cp*/Me and also between Cp*/Fc-H (Figure 2). For the latter pair, the chemical shift of this ferrocenyl hydrogen which is proximate to the iridium-chlorine bond is 6.23 ppm. By comparison this confirms the identity of (E)-6a (vide supra). The similarity of the spectral data of (Z)-6a to that of the other cyclodiration product confirms it to be imine stereoisomer (S,Z)-6b (for which the Ir configuration was not determined).
As a preliminary investigation into the substitution sequentially with aqueous solutions of NaBr, Nal and KF, and the $^1$H NMR spectrum recorded after each cycle. These showed the formation of the halide substitution products for which the imine C-H signal changes as F (8.51), Cl (8.48), Br (8.42) and I (8.34 ppm). The iridium centre undergoing substitution is gamma to the ferrocenyl group and is connected by the unsaturated C=N bond. This connectivity may facilitate halide ligand substitution by a dissociative mechanism, and explain the greater configurational lability of ($S$, $R$, $E$)-6b compared to ($R^*$, $S^*$)-7b.

Very few half-sandwich iridacycles derived from α-methylbenzylamine, $N,N$-dimethyl-α-methylbenzylamine and related compounds have been reported. In contrast much more work has appeared on the synthesis and characterisation of corresponding half-sandwich rhodacycles and ruthenacycles which are generally obtained as a mixture of configurationally labile diastereoisomers. In common with a detailed analysis of some of these complexes, the X-ray structure of ($S$, $R$, $E$)-6b reveals that the cyclorolated five-membered ring displays an envelope conformation containing an out of plane nitrogen and a pseudodiagonal methyl substituent ($\delta$ conformation). That this arises from the ($S$, $R$) stereogenic centres is in agreement with the usual $R$, $S$-$\delta$ (or $S$, $R$-$\delta$) association found with metallacycles derived from primary and secondary α-methylbenzylamines.

The success of imine cyclorolation prompted an attempt to perform the same reaction on a corresponding amine. Reduction of ($S$)-4b gave ($S$)-8 with which cyclorolation was attempted by reaction with [Cp*IrCl$_2$]$_2$ and NaOAc in MeCN (Scheme 3). The main iridacycles in the initial product mixture were identified as imine derivatives ($S$, $S$, $E$)-6b and ($S$, $Z$)-6b and in a 1 : 0.2 ratio. Following a second cycle of precipitation from CH$_2$Cl$_2$/hexane this ratio increased to 1 : 0.05, the product also containing approximately 10% of the minor ($S$, $S$, $E$) isomer of 6b. That this outcome is very similar to that obtained with imine ($S$)-4b points to amine oxidation occurring prior to cycloroliation. Concomitant secondary amine oxidation/cycloroliation has been observed previously, and this result reinforces our previous observations that ferrocenylmethylamines, due to their propensity for oxidation, are unsuitable substrates for cycloroliation.

Conclusions

Cycloroliation with [Cp*IrCl$_2$]$_2$ and NaOAc in CH$_2$Cl$_2$ is selective for a phenyl group given the choice between this and a ferrocenyl group as the moiety undergoing C-H activation. Substrates FeCH($R$)=CHPh are endo selective, whereas substrates FeCH=N($CH$($R$))Ph are exo selective, and also result in imine E and Z diastereoisomers. Both types of substrate, with $R = \text{Me}$, result in the isolation of predominantly one chiral-at-iridium diastereoisomer, the configuration of the major iridacycle derived from ($S$)-FeCH=N($CH$($\text{Me}$))Ph being determined as ($S$, $R$, $E$)-6b by an X-ray crystal structure analysis.
Experimental Section

Synthesis of (*S₁, R₁-E)-6b. Imine (S₁)-4b (0.080 g, 0.25 mmol), (pentamethylcyclopentadienyli)iridium(III) chloride dimer (0.100 g, 0.13 mmol) and sodium acetate (0.023 g, 0.28 mmol) were added to a flame dried Schlenk tube under an inert atmosphere. Dry dichloromethane (8 mL) was added and the resulting solution stirred at room temperature for 48 h. Upon completion (reaction progress monitored by ¹H NMR), the reaction mixture was filtered through Celite® using dichloromethane as the eluent, collecting a deep orange solution. The solvent was reduced in vacuo and hexane added to afford precipitation. The solid was collected by filtration to give an orange powder containing predominantly (*S₁, R₁-E)-6b with (*S₂, R₂)-6b and (*S₂, S₂)-6b (1: 0.07: 0.05 ratio, 0.14 g, 80%). Pure (*S₂, S₂)-6b was obtained by recrystallisation from CH₂Cl₂/hexane. mp 210 -211°C (decomp.). [δ]c²⁵, -167 (c 0.12, CHCl₃).

Acknowledgements

The Al-Chem Channel (RAA) is thanked for financial support. We also thank the EPSRC National Mass Spectrometry Centre (University of Wales, Swansea).

Keywords: iridacycle • ferrocene • regioselectivity • diastereoselectivity • enantiopure

References

Imines containing both ferrocenyl and phenyl groups undergo selective phenyl C-H activation on cycloiridation with [Cp*IrCl₂] and NaOAc in CH₂Cl₂. This was applied to the diastereoselective synthesis of an enantiopure iridacycle of configuration Sₘ, Rₐ, E.