DOI: 10.1002/ejoc.200801029

Mapping the Mechanism of Nickel-Ferrophite Catalysed Methylation of Baylis–Hillman-Derived S_N2' Electrophiles

Andrew Novak,[a] Maria José Calhorda,[b] Paulo Jorge Costa,[c] and Simon Woodward*[a]

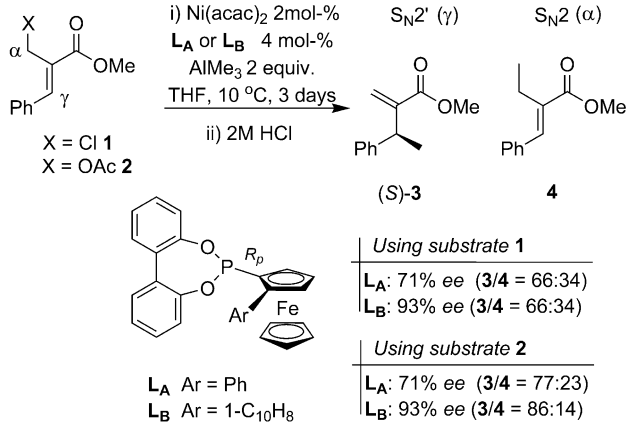
Keywords: Nickel / Aluminum / P ligands / Asymmetric catalysis / Alkylation / Density functional calculations

Enantioselective Ni-catalysed methylation of Baylis–Hillman-derived allylic electrophiles in the presence of ferrophite ligands has been investigated computationally and experimentally. The sense and degree of enantioselectivity attained is independent of both the leaving group and the isomeric structure of the initial allylic halide. DFT studies support the selective formation of a limited number of energetically favoured *anti* and *syn* π-allyl intermediates. The observed regio- and enantioselectivity can be rationalised based on the energetics of these structures.

Introduction

We briefly reported an enantioselective (49–94% *ee*) methylation of **1**–**2**[1] in the presence of the (R_p) planar chiral ferrophite ligands L_A-L_B (Scheme 1).[2] The allylic chloride **1** and acetate **2** were chosen as these substrates are readily available through Baylis–Hillman chemistry and lead to useful α-chiral methylene carboxylate products.[3] In comparison to our previously investigated copper chemistry, that afforded only γ-alkylated products,[3,4] the Ni-ferrophite system delivered mixtures of γ-methylated **3** and α-methylated **4** products (with [**4**]/[**3**] down to 0.16). Moderate to good levels of stereoinduction were also achieved (49–94% *ee*). Attempts to rationalise the observed trends in regio and stereochemistry of these reactions were hindered by lack of basic information on the behaviour of the nickel π-allyl species. Therefore theoretical calculations on the ferrophite bearing species that can be supposed to be key intermediates in these catalytic transformations were carried out.

Compared to their Pd^{II} analogues, $Ni^{II}(\eta^3$-allyl)(X)(L) species are much more stereochemically rigid.[5] Typically, the onset of η^3-η^1 allyl interconversion does not begin until ca. 80 °C and this is seldomly observed due to decomposition before this temperature is attained. Rotation of $Ni^{II}(\eta^3$-allyl) species typically demonstrate barriers of ca. 16–17 kcal mol^{-1} leading to minimal interconversion in these square-planar complexes below ambient temperature. If rapid exchange between the diastereomeric nickel π-allyl intermediates in an asymmetric process is *not* achieved then the relative populations of these species in asymmetric process could become highly important. We proposed to undertake further experiments supported by DFT calculations as means of attaining pointers towards improved regio- and stereoselectivity in the chemistry of Scheme 1.



Scheme 1. Preliminary methylation studies of allylic electrophiles **1**–**2**.

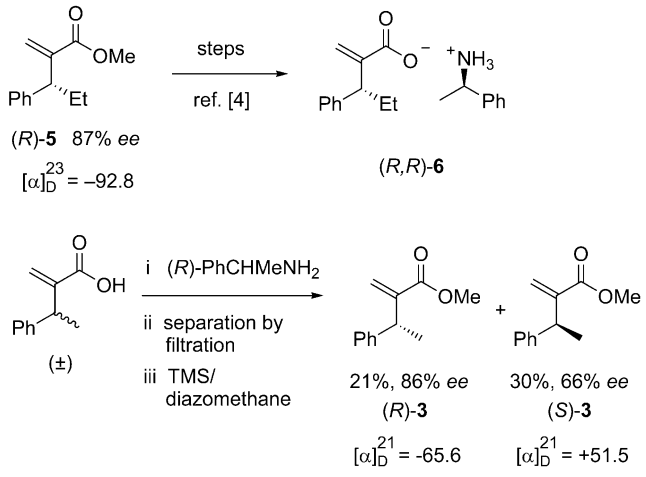
Results and Discussion

Structural Assignments

The $Ni(acac)_2$-L_A process of Scheme 1 provides a mixture of **3** and **4** whose chromatographic properties on silica gel are identical. To allow accurate quantification of their separate yields by quantitative GC access to pure (±)-**3** free

[a] School of Chemistry, University of Nottingham, Nottingham, NG7 2RD, UK
Fax: +44-115-9513564
E-mail: simon.woodward@nottingham.ac.uk
[b] Departamento de Química e Bioquímica, CQB, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal
Fax: +351-21-7500088
E-mail: mjc@fc.ul.pt
[c] Departamento de Química, CICECO, Universidade de Aveiro, 3810-193 Aveiro, Portugal
E-mail: pjcosta@ua.pt
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

of **4** (and vice versa) was required. The former was attained by γ-specific $ZnMe_2$-based methylation, using CuCN/NBu_4Br.[4] We found pure **4** was attained by $AlMe_3$ methylation of **1** in the presence of un-ligated $Ni(acac)_2$. The enantiomers of **3** were initially assigned[1] by assuming the second eluting species under GC octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin analysis corresponded to the (*R*) enantiomer as it had in the analogous ethyl addition product (–)-(*R*)-**5** (Scheme 2).[4] The assignment of the ethyl derivative is secured on the basis of ester hydrolysis and an X-ray structure of the insoluble (*R*)-$PhCHMeNH_2$ amine salt (*R*,*R*)-**6**.[4] To ensure the correctness of this assignment racemic **3** was hydrolysed and the derived acids exposed to (*R*)-phenylethylamine. In identical behaviour to that of (*R*)-**5** the less soluble amine salt afford (–)-**3** upon re-esterification with $TMSCHN_2$. The assignment of *R* stereochemistry to (–)-**3** is also in accord with the only other literature report on this compound: (–) equivalent to *R*, 69% *ee*, attained by oxidative degradation of asymmetric "Heck" products.[6] Our more soluble (*R*)-phenylethylamine salt yielded (+)-**3** with an equal and opposite rotation (allowing for the enantiopurity of the two samples). Thus, it was confirmed that (+)-(*S*)-**3** elutes first upon chiral GC on octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin (see Supporting Information).



Scheme 2. Partial resolution and stereochemical assignment of **3**. All optical rotations in $CHCl_3$: (*R*)-**5** *c* = 1.00; (*R*)-**3** *c* = 0.62; (*S*)-**3** *c* = 0.75.

Regioisomer Effects

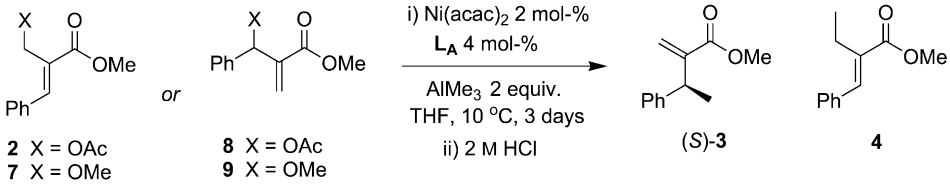
The reactivity of regioisomeric allylic halides starting materials was compared to the "linear" species **1**–**2** (Table 1). Ligand $\mathbf{L_A}$ was used throughout to allow direct comparison to be made. In all cases, where there is a reaction, only the **4**/**3** ratio is affected by the substrate choice with the enantioselectivity of the derived (*S*)-**3** being constant within the measurement error.

One explanation for these observations is that a mixture of non converting diastereoisomeric Ni(η^3-allyl) species is present in the reaction mixture leading to **3** and **4**. If the relative populations of these are defined at the moment of oxidative addition then the observed regiochemical behaviour might be accounted for. Direct observation of the actual catalytic reaction mixture described in Schemes 1 and 2 by ^{31}P NMR shows the presence of only four ferrophite coordinated species, one of significantly higher concentration, when substrate **1** is used (δ_P = 206.9, 205.1, 195.1, 194.0; ratio 1.6:1.0:0.9:7.7). As nothing was known about the structures of Ni-coordinated ferrophite complexes we turned our attention to a computational study of possible Ni(π-allyl) intermediates in this reaction.

Theoretical Studies

η^3-Coordination of the substituted allyl "CH_2=C(CO_2Me)CHPh" to a "$Ni^{II}Me(\mathbf{L_A})$ unit is expected to generate 16 possible intermediates due to: (i), the enantioface of the allyl selected; (ii), the presence of two rotamers per complex; and (iii), the placement of the phenyl substituent either *anti* or *syn* to the central CO_2Me. The factors that affect the relative energetics of these 16 possible combinations are not expected to be obvious as only small energy differences between the allyls are expected. This expectation

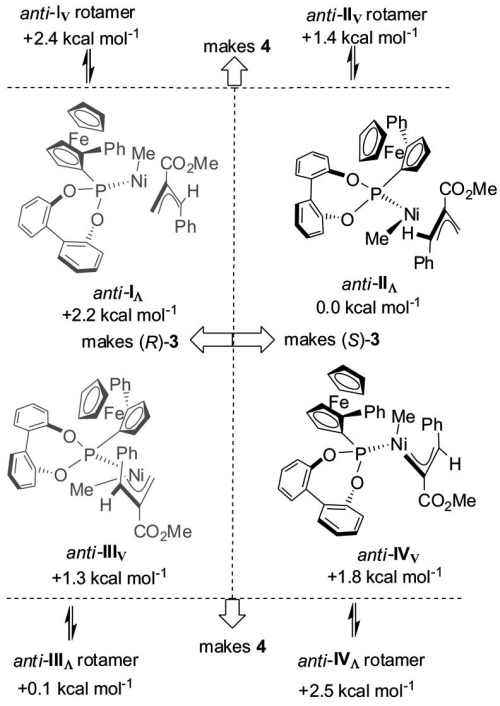
Table 1. Effect of varying the electrophile structure on selectivity.[a]



Entry	Allyl electrophile	% Conversion	% Yield of **3**+**4**	**4**:**3** ratio	% *ee*
1	**1**	82	73	0.52	71, *S*
2	**2**	50	26	0.30	71, *S*
3	**7**	31[b]	24	0.85	71, *S*
4	**8**	80[b]	71	0.49	70, *S*
5	**9**	<5[b]	–	–	–

[a] Reactions carried out on 0.25 mmol substrate with 0.02/0.04/2 equiv. $Ni(acac)_2$/$\mathbf{L_A}$/$AlMe_3$ in THF (3.0 mL), 10 °C, 3 d. Conversions, yields regio- and enantioselectivities by GC. [b] Determined by ^1H NMR spectroscopy.

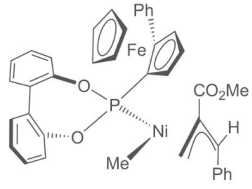
is not always apparently the case. In early work, $Ni(C_6Cl_5)(\eta^3\text{-}CH_2CHCHMe)(PMe_2Ph)$ was shown to exist as a single *syn* species by ^1H NMR spectroscopy.[7] Our own investigations of the $Ni^{II}/\mathbf{L_A}$ system were carried out by DFT methods[8] using a B3LYP/sdd,6-311G** approach. Because the pre-existing *anti* arrangement in the initial allylic electrophiles **1**–**2** and **7** is expected to favour formation of *anti* π-allyl species these were investigated first. In the nomenclature of Scheme 3 the "V" and "Λ" subscripts refer to the conformation of the allyl rotamer with respect to the ferrocenyl unit (always placed topmost in Scheme 3).



Scheme 3. Calculated (B3LYP/sdd,6-311G**) relative energies of *anti*-NiMe(η^3-allyl)$\mathbf{L_A}$ complexes.

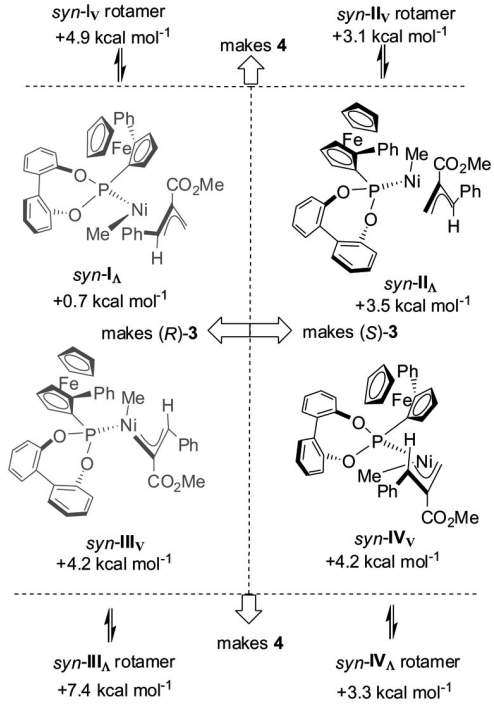
Rewardingly, the calculations indicate that the lowest energy π-allyl species *anti*-$\mathbf{II_Λ}$ correlates to the formation of a preponderance of (*S*)-**3** in the actual catalytic reaction. Not discounting the clear importance of transition state effects,[9] the energy differences between the calculated lowest energy (*S*)-**3** vs. (*R*)-**3** producing π complexes (*anti*-$\mathbf{II_Λ}$ vs. *anti*-$\mathbf{III_V}$) corresponds well with the enantioselectivity range observed for $\mathbf{L_{A,B}}$ [$\Delta G^o(283\ K) = 1.30$ kcal mol^{-1}, K = 0.0985 equiv. to 82% $ee_{calcd.}$]. The origin of the poorer regioselectivity in Scheme 1 is also clear. The presence of near iso-energetic *anti*-$\mathbf{III_Λ}$ leads to significant production of **4** upon reductive elimination.

We predict that to down weight the contribution of the *anti*-$\mathbf{III_Λ}$ component the steric profile of one or both Cp ferrocenyl ring should be further increased. However, such ligand modifications are non trivial synthetic exercises and were not pursued. It is also clear that in the absence of added $\mathbf{L_{A,B}}$ an *anti*-$\mathbf{III_Λ}$ related species becomes the major reaction manifold and this might be used for highly selective formation of the α homologation product **4**.



anti-$\mathbf{III_Λ}$ rotamer
+0.1 kcal mol^{-1}

The pre-existing *anti* arrangement of the leaving group and phenyl function in our allylic electrophiles means that the equivalent *syn* allyls to Scheme 3 can only be accessed by a *anti*-*syn* exchange process; predicted to be inefficient under our reaction conditions (10 °C). Nevertheless, for completness the equivalent *syn*-**I**–**IV** structures were calculated (Scheme 4).



Scheme 4. Calculated (B3LYP/sdd,6-311G**) relative energies of *syn*-NiMe(η^3-allyl)$\mathbf{L_A}$ complexes.

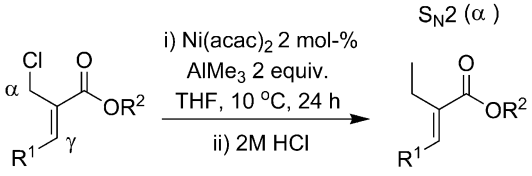
The lowest energy specie *syn*-$\mathbf{I_Λ}$ does not correlate with the observed stereochemistry of the final product (*S*)-**3** (see Scheme 1). Interestingly, however, the computational behaviour of the *syn*-**I**–**IV** group mirrors the behaviour of $Ni(C_6Cl_5)(\eta^3\text{-}CH_2CHCHMe)(PMe_2Ph)$ in that a single dominant *syn* isomer is predicted. In our case access to these species is prevented by the *anti* arrangement in the starting electrophiles and the nonconversion of the *anti*-*syn* allyl forms under the reaction conditions.

Generalised α-Homologation of Allyl Chlorides

In the absence of any added ligand, **4** was formed as essentially the sole $AlMe_3$ S_N2 displacement product (*α*/*γ*

attack >50:1). Prompted by the low energy of the *anti*-$\mathbf{III_A}$ π-allyl further investigation into this selective one carbon homologation reaction was undertaken. A range of aryl-substituted Baylis–Hillman-derived allylic chlorides **10**–**19**, attained by standard methods were trialled (Table 2). In all cases full conversion of the starting chloride was achieved. Moderate to good yields of the α-products were isolated with high to excellent *α*/*γ* selectivity being attained. Unfortunately, alkyl-substituted **19** gave an unclean reaction which contained only trace amounts of the desired product by ^{1}H NMR spectroscopy (Entry 11). Overall though this Ni chemistry is particularly useful as a complimentary method to the *γ*-selective copper-catalysed chemistry our group reported earlier.[3]

Table 2. Highly selective α-methylation of allylic chlorides under nickel catalysis.[a]



1, **10-19** **4**, **20-29**

Entry	R^1	R^2	α-Product	% Yield	α/γ[b]
1	Ph	Me	**4**	49	>50
2	Ph	Et	**20**	68	5.26
3	4-(OMe)C_6H_4	Me	**21**	77	>50
4	4-FC_6H_4	Me	**22**	71	>50
5	4-ClC_6H_4	Me	**23**	69	>50
6	4-MeC_6H_4	Me	**24**	76	6.67
7	4-*t*BuC_6H_4	Me	**25**	77	7.70
8	2-BrC_6H_4	Me	**26**	75	9.09
9	1-$C_{10}H_8$	Me	**27**	73	25
10	2-$C_{10}H_8$	Me	**28**	43	>50
11	*n*-C_7H_{15}	Me	**29**	<5	–

[a] Reactions carried out on 0.50 mmol substrate with 0.02/2 equiv. $Ni(acac)_2$/$AlMe_3$ in THF (5.0 mL), 10 °C, 24 h. Isolated yields. [b] Determined by ^{1}H NMR spectroscopy.

Conclusions

All experimental and computational data are consistent with Nickel-ferrophite methylation of allylic electrophiles **1** proceeding via formation of a somewhat favoured *anti*-allyl species, *anti*-$\mathbf{II_A}$. This intermediate is formed irrespective of the leaving group (starting materials **2** and **7**) or the regioisomer of the electrophile employed (**2** vs. **8**). The origin of the poorer regioselectivity has been traced to the presence of a near iso-energetic *anti*-allyl ($\mathbf{III_A}$) in which the Ni-Me and α-allyl termini are mutually *cis*. Rapid reductive elimination leads to the α-homologation product. In the absence of added ligand a related process dominates leading to the development of a synthetically useful process for α-methylation. Based on their calculated energies *syn* allyl species are not important in this chemistry. However, intriguingly one of *syn*-allyls ($\mathbf{I_A}$) is predicted to be of considerably lower energy than its seven partners. Thus, the possibility of accessing a *syn*-$\mathbf{I_A}$-based route to (*R*)-**3** should be viable. Overall, the study clearly points to three potential routes for improving the selectivity of the process: (i) additional groups placed on one or both cyclopentadienyl rings of $\mathbf{L_{A,B}}$ might be useful in destabilising *anti*-$\mathbf{III_A}$ improving the regiochemistry; (ii) using (*E*)-**1**, rather than (*Z*)-**1**, should allow the *syn* (rather than the *anti*) π-allyl manifold to be populated resulting in dramatically improved regio- and enantioselectivity due to the lower relative energy of *syn*-$\mathbf{I_A}$; (iii) identification of a different ligand type that allowed fast *anti*-*syn* interconversion and simultaneous stabilisation of *syn*-$\mathbf{I_A}$ would allow equivalent use of (*Z*)-**1** to good effect. In the cases of (ii) and (iii) formation of (*R*)-**3** is predicted. Investigation of these approaches is underway in our laboratory.

Experimental Section

General: Procedures were performed under atmospheres of argon or nitrogen using standard Schlenk techniques. Trimethylaluminium (2 M in heptane) and $ZnMe_2$ (2 M in toluene) were commercial products (Sigma–Aldrich) used as supplied. Column chromatography was performed using Fluorochem (35–70 micron) silica gel and TLC analysis using Merck Kieselgel 60 $F_{245+366}$. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker AV400, DRX500 or JEOL EX270 spectrometers, using tetramethylsilane as an internal standard. Chemical shifts are quoted in ppm and coupling constants (*J*) are given in Hz. Chiral GC analysis was performed on a Varian 3380 gas chromatograph using suitable cyclodextrin based stationary phases as indicated using low molecular weight alkanes, such as pentadecane, as internal standards. Allylic halides, acetates and methoxides were prepare by literature procedures: **1**, **2**, **7**, **8**, **9**–**19**.[10]

(±)-Methyl 2-Methylene-3-phenylbutanoate (3): Under an argon atmosphere a 2 M solution of $ZnMe_2$ in dry toluene (0.5 mL; 1.0 mmol) was added to a cooled (–20 °C) stirred solution of allylic chloride **1** (0.50 mmol), containing CuCN (9.0 mg; 0.10 mmol) and NBu_4Br (32.2 mg; 0.10 mmol) in dry THF (2 mL). The reaction mixtures were stirred for 1 h at –20 °C and then warmed to room temp. over 20 h. The reaction mixture was quenched by the slow addition of 2 M HCl (2 mL). The product was extracted with Et_2O (10 mL), the combined organic layers were dried with $MgSO_4$, concentrated and purified by flash column chromatography using mixtures of Et_2O/hexane as eluent to afford (±)-**3** as a colourless oil (81 mg; 85%); R_f = 0.32 (hexane/Et_2O, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.16 (m, 5 H, *Ar*), 6.28 (s, 1 H, =C$H_{2\alpha}$), 5.61 (s, 1 H, =C$H_{2\beta}$), 4.03 (q, *J* = 7.2 Hz, 1 H, C*H*Me), 3.67 (s, 3 H, O*Me*), 1.42 (d, *J* = 7.2 Hz, 3 H, *Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 145.0, 144.5, 128.6, 127.6, 126.5, 124.0, 52.0, 40.7, 20.9 ppm. IR (thin film): $\tilde{\nu}$ = 2969, 1721 (C=O), 1627, 1437, 1149, 947 cm^{-1}. EIMS: *m*/*z* (%) = 190 (92) [M$^+$], 158 (42), 130 (100). HR-EIMS: *m*/*z* 190.0998 calcd. for $C_{12}H_{14}O_2$; found 190.0998; elemental analysis: C 75.76, H 7.42 calcd. for $C_{12}H_{14}O_2$; found C 75.75, H 7.37. The GC assay: 25 m (2,6-*O*-dimethyl,3-*O*-pentyl)-γ-cyclodextrin silica column, 120 °C (30 min): 10 °C/min: 200 °C (20 min), He carrier gas, 12 psi, (*S*): 14.8 min. (*R*): 15.2 min.

(*E*)-Methyl 2-Benzylidenebutanoate (4): A flame-dried Schlenk tube under argon was charged with $Ni(acac)_2$ (2.4 mg, 4 mol-%) and anhydrous THF (5 mL) was stirred at –10 °C for 5 min. To this the neat allylic chloride **1** (0.50 mmol) was added and the mixture

stirred at –10 °C for 10 min. A solution of $AlMe_3$ (2 M solution in heptane, 0.5 mL; 1.0 mmol) was added dropwise to the reaction mixture, which was then warmed to 10 °C. After 24 h at 10 °C the black reaction mixture was quenched with 2 M HCl (2 mL). The product was extracted into Et_2O (2 × 5 mL), the combined organic layers were dried with $MgSO_4$. After removal of the solvent the crude product was purified by flash column chromatography using mixtures of Et_2O/hexane to yield **4**[11] as a olourless oil (47 mg; 49%) (63% by GC); R_f = 0.32 (hexane/Et_2O, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1 H, =C*H*), 7.40–7.35 (m, 5 H, *Ar*), 3.83 (s, 3 H, O*Me*), 2.57 (q, *J* = 7.6 Hz, 2 H, CH_2Me), 1.18 (t, *J* = 7.6 Hz, 3 H, *Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 138.6, 135.8, 134.8, 129.2, 128.3, 128.0, 51.9, 20.8, 13.9 ppm. IR ($CHCl_3$ solution): $\tilde{\nu}$ = 3027, 2952, 2877, 1698 (C=O), 1628, 1495, 1435, 1312, 1284, 1238, 1204, 1130, 1045, 810 cm^{-1}. EIMS: *m*/*z* (%) = 213 (26) [MNa^+], 191 (15) [MH^+]. HR-EIMS: *m*/*z*: calcd. for $C_{12}H_{14}O_2Na$: 213.0897; found 213.0898. The GC assay: 25 m (2,6-*O*-dimethyl,3-*O*-pentyl)-γ-cyclodextrin silica column, 120 °C (30 min): 10 °C/min: 200 °C (20 min), 24.9 min.

Partial Resolution of (±)-Methyl 2-Methylene-3-phenylbutanoate (3): A sample of (±)-**3** (192 g, 0.92 mmol) was dissolved in THF/water (3:1, 20 mL), treated with LiOH·H_2O (138 mg, 3.29 mmol) and stirred at ambient temperature (24 h) after which time the reaction mixture was diluted with water (10 mL) and THF was removed in vacuo. The aqueous phase was extracted with EtOAc in order to remove any residual starting material and neutralised with 2 M HCl (50 mL). The product was extracted with EtOAc, the combined organic layers were dried with Na_2SO_4 and solvent removed in vacuo to give a quantitative yield of the derived acid (162.0 mg, 0.92 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 2 H, *Ar*), 7.26–7.22 (m, 3 H, *Ar*), 6.48 (s, 1 H, =C$H_{2\alpha}$), 5.76 (s, 1 H, =C$H_{2\beta}$), 4.05 (q, *J* = 7.1 Hz, 1 H, C*H*Me), 1.47 (d, *J* = 7.1 Hz, 3 H, CH*Me*) ppm. The latter was dissolved in Et_2O (5 mL) and neat (*R*)-PhCHMeNH$_2$ (120 μL, 0.95 mmol) added. The resulting white amine salt was fractionated with CH_2Cl_2/Et_2O. After acidification (HCl, 2 M), re-extraction (Et_2O), drying (Na_2SO_4) and re-esterification (four fold excess $TMSCHN_2$, Et_2O, 30 min) the *less* soluble amine salt afforded (*R*)-**3** (36.5 mg, 0.19 mmol, 20.7% yield) with $[\alpha]_D^{21}$ = –65.6 (*c* = 0.62, $CHCl_3$) for an 86% *ee* sample (as determined by GC as above); ref.[6] $[\alpha]_D^{20}$ = –47.7 (*c* = 0.65, $CHCl_3$) for a 69% *ee* (*R*)-**3** sample. Similar treatment of the *more* soluble amine salt gave (*S*)-**3** (52.2 mg, 0.27 mmol, 30% yield) with $[\alpha]_D^{21}$ = +51.5 (*c* = 0.75, $CHCl_3$) for an 66% *ee* sample (as determined by GC as above).

(*E*)-Ethyl 2-Benzylidenebutanoate[12] **(20):** Prepared analogously to **4** using 0.50 mmol of **10**. Colourless oil (69 mg; 68%); R_f = 0.50 (pentane/EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 1 H, =C*H*), 7.39–7.37 (m, 5 H, *Ar*), 4.28 (q, *J* = 7.1 Hz, 2 H, CH_2Me), 2.55 (q, *J* = 7.4 Hz, 2 H, OCH_2Me), 1.36 (t, *J* = 7.1 Hz, 3 H, CH_2*Me*), 1.18 (t, *J* = 7.4 Hz, 3 H, OCH_2*Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 138.3, 135.9, 135.1, 129.2, 128.5, 128.3, 60.7, 20.8, 14.4, 13.9 ppm. IR ($CHCl_3$ solution): $\tilde{\nu}$ = 2970, 1698 (C=O), 1455, 1369, 1311, 1128, 1046 cm^{-1}. EIMS: *m*/*z* (%) = 204 (87) [M^+], 158 (52), 131 (100), 129 (42), 115 (37), 91 (42). HR-EIMS: *m*/*z*: calcd. for $C_{13}H_{16}O$: 204.1150; found 204.1163.

(*E*)-Methyl 2-(4-Methoxybenzylidene)butanoate (21): Prepared analogously to **4** using 0.50 mmol of **11**. Colourless oil (85 mg; 77%); R_f = 0.35 (pentane/EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (s, 1 H, =C*H*), 7.37–7.34 (m, 2 H, *Ar*), 6.94–6.90 (m, 2 H, *Ar*), 3.82 [s, 3 H, C(O)O*Me*], 3.80 (s, 3 H, ArO*Me*), 2.57 (q, *J* = 7.4 Hz, 2 H, CH_2Me), 1.18 (t, *J* = 7.4 Hz, 3 H, *Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 159.7, 138.2, 132.5, 131.0, 128.2, 113.9, 55.2, 51.8, 20.7, 13.7 ppm. IR ($CDCl_3$ solution): $\tilde{\nu}$ = 2952, 2839, 1694 (C=O), 1608, 1514, 1435, 1310, 1258, 1181, 1131, 1035, 833 cm^{-1}. EIMS: *m*/*z* (%) = 220 (100) [M^+], 189 (18), 160 (53), 145 (46), 115 (11). HR-EIMS: *m*/*z*: calcd. for $C_{13}H_{16}O_3$: 220.1099; found 220.1097; elemental analysis: C 70.89, H 7.32 calcd. for $C_{13}H_{16}O_3$; found C 70.73, H 7.37. The HPLC assay: Chiralcel OD-H, isocratic (*n*-hexane/*i*PrOH, 99.5:0.5, flow 0.5 mL min^{-1}), λ = 254 nm, 24.9 min.

(*E*)-Methyl 2-(4-Fluorobenzylidene)butanoate (22): Prepared analogously to **4** using 0.50 mmol of **12**. Colourless oil 74 mg; 71%; R_f = 0.70 (pentane/Et_2O, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (s, 1 H, =C*H*), 7.37–7.33 (m, 2 H, *Ar*), 7.10–7.06 (m, 2 H, *Ar*), 3.82 (s, 3 H, O*Me*), 2.52 (q, *J* = 7.4 Hz, 2 H, CH_2Me), 1.16 (t, *J* = 7.4 Hz, 3 H, CH_2*Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 162.5 (d, $^1J_{CF}$ = 249.0 Hz), 137.4, 134.5, 131.8 (d, $^4J_{CF}$ = 3.3 Hz), 131.0 (d, $^3J_{CF}$ = 8.0 Hz), 115.5 (d, $^2J_{CF}$ = 21.7 Hz), 51.9, 20.7, 13.7 ppm. IR ($CHCl_3$ solution): $\tilde{\nu}$ = 2952, 1609 (C=O), 1600, 1511, 1435, 1306, 1233, 1129, 1045, 836 cm^{-1}. EIMS: *m*/*z* (%) = 208 (100) [M^+], 176 (27), 148 (86), 133 (38). HR-EIMS; *m*/*z*: calcd. for $C_{12}H_{13}FO_2$: 208.0900; found 208.0899.

(*E*)-Methyl 2-(4-Chlorobenzylidene)butanoate (23): Prepared analogously to **4** using 0.50 mmol of **13**. Colourless oil (77 mg; 69%); R_f = 0.42 (pentane/EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.58 (s, 1 H, =C*H*), 7.36 (d, *J* = 8.5 Hz, 2 H, *Ar*), 7.29 (d, *J* = 8.5 Hz, 2 H, *Ar*), 3.82 (s, 3 H, O*Me*), 2.52 (q, *J* = 7.5 Hz, 2 H, CH_2Me), 1.16 (t, *J* = 7.5 Hz, 3 H, CH_2*Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 137.2, 135.3, 134.2, 134.2, 130.4, 128.7, 52.0, 20.8, 13.7 ppm. IR ($CHCl_3$ solution): $\tilde{\nu}$ = 2902, 1708 (C=O), 1243, 1130, 1014 cm^{-1}. EIMS: *m*/*z* (%) = 226 (27) [M^+, ^{37}Cl], 224 (95) [M^+, ^{35}Cl], 193 (32), 165 (56), 139 (100). HRMS: *m*/*z*: calcd. for $C_{12}H_{13}{}^{35}ClO_2$: 224.0604; found 224.0613.

(*E*)-Methyl 2-(4-Methylbenzylidene)butanoate (24): Prepared analogously to **4** using 0.50 mmol of **14**. Colourless oil (78 mg; 76%); R_f = 0.70 (pentane/EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1 H, =C*H*), 7.45 (d, *J* = 8.0 Hz, 2 H, *Ar*), 7.36 (d, *J* = 8.0 Hz, 2 H, *Ar*), 3.98 (s, 3 H, OMe), 2.73 (q, *J* = 7.4 Hz, 2 H, CH_2), 2.53 (s, 3 H, Ar*Me*), 1.34 (t, *J* = 7.4 Hz, 3 H, CH_2*Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 138.6, 138.4, 133.8, 132.8, 129.2, 129.1, 51.8, 21.3, 20.8, 13.8 ppm. IR ($CHCl_3$ solution): $\tilde{\nu}$ = 2951, 1694 (C=O), 1511, 1435, 1312, 1133, 1045 cm^{-1}. EIMS: *m*/*z* (%) = 204 (100) [M^+], 173 (21), 144 (57), 129 (50). HR-EIMS; *m*/*z*: calcd. for $C_{13}H_{16}O_2$: 204.1150; found 204.1147.

(*E*)-Methyl 2-(4-*tert*-Butylbenzylidene)butanoate (25): Prepared analogously to **4** using 0.50 mmol of **15**. Colourless oil (93 mg; 76%); R_f = 0.72 (pentane/EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (s, 1 H, =C*H*), 7.43 (d, *J* = 8.4 Hz, 2 H, *Ar*), 7.35 (d, *J* = 8.4 Hz, 2 H, *Ar*), 3.82 (s, 3 H, O*Me*), 2.59 (q, *J* = 7.4 Hz, 2 H, CH_2Me), 1.34 (s, 9 H, *tBu*), 1.20 (t, *J* = 7.4 Hz, 3 H, CH_2*Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 151.6, 138.5, 133.9, 132.8, 129.2, 125.4, 51.8, 34.7, 31.2, 20.9, 13.8 ppm. IR ($CHCl_3$ solution): $\tilde{\nu}$ = 2951, 1694 (C=O), 1626, 1510, 1435, 1314, 1269, 1192, 1132, 1045 cm^{-1}. EIMS: *m*/*z* (%) = 246 (39) [M^+], 231 (100). HR-EIMS: *m*/*z*: for $C_{16}H_{22}O_2$: 246.1620; found 246.1618.

(*E*)-Methyl 2-(2-Bromobenzylidene)butanoate (26): Prepared analogously to **4** using 0.50 mmol of **16**. Colourless oil determined to be a 9:1 mix of α/γ products (101 mg; 75%); R_f = 0.76 (pentane/EtOAc, 9:1). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.83 (s, 1 H, =C*H*), 7.82–7.79 (m, 3 H, *Ar*), 3.85 (s, 3 H, O*Me*), 2.54 (q, *J* = 8.1 Hz, 2 H, CH_2Me), 1.09 (t, *J* = 8.1 Hz, 3 H, CH_2*Me*) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 168.1, 137.9, 136.4, 136.2, 132.7, 129.9, 129.5, 127.1, 123.9, 52.0, 20.9, 13.8 ppm. EIMS: *m*/*z* (%) = 270 (41)

[M^+, ^{81}Br], 268 (38) [M^+, ^{79}Br], 238 (100). HR-EIMS: *m*/*z*: calcd. for $C_{12}H_{13}{}^{79}BrO_2$: 268.0099; found 268.0115.

(*E*)-Methyl 2-(Naphthalen-1-ylmethylene)butanoate (27): Prepared analogously to **4** using 0.50 mmol of **17**. Colourless oil (88 mg; 73%); R_f = 0.68 (pentane/EtOAc, 5:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1 H, =C*H*), 7.95–7.86 (m, 3 H, *Ar*), 7.54–7.47 (m, 4 H, *Ar*), 3.90 (s, 3 H, O*Me*), 2.43 (q, *J* = 7.4 Hz, 2 H, CH_2Me), 1.10 (t, *J* = 7.4 Hz, 3 H, CH_2*Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 137.3, 136.9, 133.4, 133.3, 131.5, 128.4, 126.3, 126.1, 125.9, 125.8, 125.2, 124.7, 51.9, 21.3, 14.2 ppm. IR ($CHCl_3$ solution): $\tilde{\nu}$ = 2952, 2877, 1698 (C=O), 1435, 1315, 1132, 1048 cm^{-1}. EIMS: *m*/*z* (%) = 240 (76) [M^+], 181 (100), 165 (92), 155 (70). HR-EIMS: *m*/*z*: calcd. for $C_{16}H_{16}O_2$: 240.1150; found 240.1143.

(*E*)-Methyl 2-(Naphthalen-2-ylmethylene)butanoate (28): Prepared analogously to **4** using 0.50 mmol of **18**. Colourless oil (52 mg; 43%); R_f = 0.36 (pentane/EtOAc, 9:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.78 (m, 5 H, *Ar* and = C*H*), 7.53–7.43 (m, 3 H, *Ar*), 3.85 (s, 3 H, O*Me*), 2.64 (q, *J* = 7.4 Hz, 2 H, CH_2Me), 1.23 (t, *J* = 7.4 Hz, 3 H, *Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 138.6, 135.0, 133.3, 133.1, 132.9, 128.8, 128.3, 128.0, 127.8, 127.6, 126.6, 126.4, 52.0, 20.9, 13.9 ppm. IR ($CHCl_3$ solution): $\tilde{\nu}$ = 2962, 1705 (C=O), 1600, 1436, 1285, 1242, 1125 cm^{-1}. EIMS: *m*/*z* (%) = 240 (84) [M^+], 209 (8), 180 (48), 166 (24), 155 (100). HR-EIMS: *m*/*z*: calcd. for $C_{16}H_{16}O_2$: 240.1150; found 240.1141.

Computational Studies: All DFT calculations were performed by using the Gaussian03 software package,[13] with the B3LYP functional. This functional includes a mixture of Hartree–Fock[14] exchange with DFT[8] exchange-correlation, given by Becke's three-parameter functional[15] with the Lee, Yang, and Parr correlation functional, which includes both local and nonlocal terms.[16,17] The geometries were optimized without any symmetry constraints using the Stuttgart/Dresden ECP (sdd) basis set and associated ECP[18] for Fe and Ni while a standard 6-311G** basis set was used for the other elements. The molecules with all the substituents were considered in the calculations.

Supporting Information (see also the footnote on the first page of this article): Summary data on the DFT calculated *syn* and *anti*-**I**–**IV** allyl complexes. Experimental procedures for the preparation of the allylic halide electrophiles.

Acknowledgments

Financial support from European Union (project FP6-NMP3-C-2003-505267 associated with Ligbank® and the COST D40 programme) is acknowledged. One of us (A. N.) is grateful to GlaxoSmithKline for the provision of a studentship. M. J. C. and P. J. C. thank Fundação do Ministério de Ciência e Tecnologia (FCT), Programa Operacional Ciência e Inovaçao (POCI) and Fundo Europeu de Desenvolvimento Regional (project POCI/QUI/58925/2004).

[1] A. Novak, R. Fryatt, S. Woodward, *C. R. Chim.* **2007**, *10*, 206.
[2] V. E. Albrow, A. J. Blake, R. Fryatt, C. Wilson, S. Woodward, *Eur. J. Org. Chem.* **2006**, 2549.
[3] K. Biswas, C. Börner, J. Gimeno, P. J. Goldsmith, D. Ramazzotti, A. L. K. So, S. Woodward, *Tetrahedron* **2005**, *61*, 1433.
[4] P. J. Goldsmith, S. Woodward, *Angew. Chem. Int. Ed.* **2005**, *44*, 2235.
[5] Review: a) H. Kurosawa, S. Ogoshi, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 973. Recent developments: b) M. Aresta, A. Dibenetto, E. Quaranta, M. Lanfranchi, A. Tiripicchio, *Organometallics* **2000**, *19*, 4199; c) L. C. Silva, P. T. Gomes, L. F. Veiros, S. I. Pascu, M. T. Duarte, S. Namorando, J. R. Ascenso, A. R. Dias, *Organometallics* **2006**, *25*, 4391; d) A. Bottoni, G. P. Miscione, M. A. Carvajal, J. J. Novoa, *J. Organomet. Chem.* **2006**, *691*, 4498. Histrorical cases: e) B. Bogdanovic, H. Bönnemann, G. Wilke, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 582; f) D. Walter, G. Wilke, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 897.
[6] K. S. Yoo, C. P. Park, C. H. Yoon, S. Sakaguchi, J. O'Nieill, K. W. Jung, *Org. Lett.* **2007**, *9*, 3933.
[7] M. Wada, T. Wakabayashi, *J. Organomet. Chem.* **1975**, *96*, 301.
[8] R. G. Parr, W. Yang, *Density Functional Theory of Atoms and Molecules*, Oxford University Press, New York, **1989**.
[9] The calculation of transition states featuring these heavy bimetallic Ni-ferrophite ligands proved highly challenging.
[10] See Supporting Information for preparation and data.
[11] P. Dauben, *Nouv. J. Chim.* **1977**, *1*, 243.
[12] J. Castells, F. Lopez-Calahorra, Z. Yu, *Tetrahedron* **1994**, *50*, 13765.
[13] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Revision C.02, Gaussian, Inc., Wallingford CT, **2004**.
[14] W. J. Hehre, L. Radom, P. von R. Schleyer, J. A. Pople, *Ab initio Molecular Orbital Theory*, Wiley, New York, **1986**.
[15] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.
[16] B. Miehlich, A. Savin, H. Stoll, H. Preuss, *Chem. Phys. Lett.* **1989**, *157*, 200.
[17] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785.
[18] a) U. Haeusermann, M. Dolg, H. Stoll, H. Preuss, *Mol. Phys.* **1993**, *78*, 1211; b) W. Kuechle, M. Dolg, H. Stoll, H. Preuss, *J. Chem. Phys.* **1994**, *100*, 7535; c) T. Leininger, A. Nicklass, H. Stoll, M. Dolg, P. Schwerdtfeger, *J. Chem. Phys.* **1996**, *105*, 1052.

Received: October 21, 2008
Published Online: January 12, 2009

