IN SEARCH OF NEW APPROACHES TO ASYMMETRIC CONJUGATE ADDITION: SCREENING STUDIES ON THE USE OF [Zn(bpy*)X(R)] REAGENTS AND α,β-UNSATURATED AMIDE MICHAEL ACCEPTORS

Alexander J. BLAKE[1], Daniela GIUNTA[2], Jonathan SHANNON[3], Maurizio SOLINAS[4], Francesca WALZER[5] and Simon WOODWARD[6,*]

School of Chemistry, The University of Nottingham, University Park, Nottingham NG7 2RD, United Kingdom; e-mail: [1] a.j.blake@nottingham.ac.uk, [2] daniela.giunta@icb.cnr.it, [3] pcxjms@nottingham.ac.uk, [4] maurizio.solinas@icb.cnr.it, [5] pcyxfw@nottingham.ac.uk, [6] simon.woodward@nottingham.ac.uk

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Dedicated to Professor Štefan Toma on the occasion of his 70th birthday.

Conjugate additions of [Zn(bpy*)Cl(Et)] (bpy* = 4,4′-di-*tert*-butyl-2,2′-bipyridine) to cyclohex-2-en-1-one are promoted by $ZnMe_2$ in 88% ee but in moderate yield under Cu^I phosphoramidite catalysis. In the absence of $ZnMe_2$ the [Zn(bpy*)Cl(Et)] is inactive indicating a Schlenk-type equilibrium. Other derivatives of [Zn(bpy*)Cl(R)] (R = Bu, 4-methylbenzyl), prepared in situ from [ZnCl(R)] and the bipyridine give low yields due to competing chloride abstraction. ^{13}C NMR studies indicate facile organo-ligand exchange between [Zn(bpy*)$(Et)_2$] and [Zn(bpy*)Cl_2] complexes. In the presence of the bipyridine, [ZnBr(allyl)] disproportionates into [Zn(bpy*)Br_2] and [Zn(bpy*)$(allyl)_2$] species. In separate studies, simple (*E*)-MeCH=CHCONMeR (R = Me, OMe) α,β-unsaturated amides undergo asymmetric 1,4-addition of EtMgBr in 75–99% yield and 48–79% ee in the presence of the diphosphines *JosiPhos* or *MeDuPhos* and copper(I) sources.

Keywords: Bipyridyl complexes; Zinc; Enamides; Copper catalysis; Grignard reagents; Asymmetric conjugate additions; 1,4-Additions; Phosphoramidite ligands; X-ray diffraction.

The field of copper-catalysed asymmetric conjugate addition (ACA) in the period 1997–2007 has seen the attainment of many remarkable catalytic systems giving stereoselectivities above 90% [1]. However, close inspection of the available literature indicates that many of these studies employ the use of $ZnEt_2$ as the organometallic and α,β-unsaturated enones as the Michael acceptors. Other copper-based systems operating outside this mainstream activity might conceivably offer complementary advantages, but have been much less investigated. Changing either the organometallic nucleophage or

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the Michael acceptor substrate are two clear possibilities for modification that we decided to screen some atypical choices for.

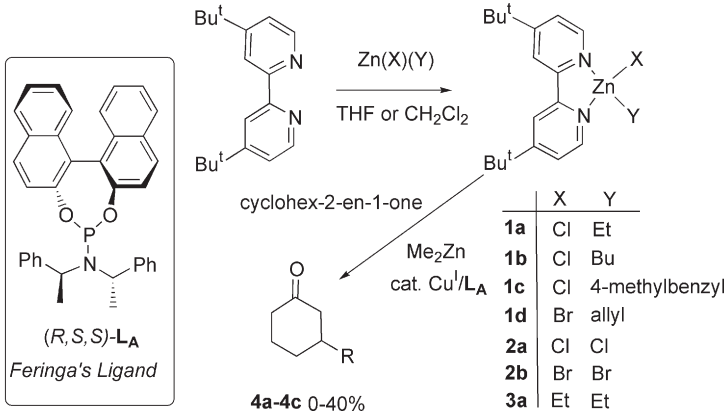
While many different terminal organometallics (RM; for example: M = Li, MgX, MnX)[2] have been trialled in copper-catalysed (asymmetric) 1,4-addition chemistry it occurred to us that organozinc complexes of 4,4′-di-*tert*-butyl-2,2′-bipyridine (bpy*) complexes had not been subjected to ACA investigations. The species [Zn(bpy*)$(R)_2$] are interesting for two reasons. Firstly, known bipy-analogues are somewhat air-stable[3], an area that is attractive to us[4]. Secondly, they afford an opportunity to further study the zinc Schlenk equilibrium[5]; an area where we were recently able to report the first measurement of the derived equilibrium constants[6]. Finally, from the Michael acceptor prospective, while many types of α,β-unsaturated systems participate in conjugate additions[1], copper-based organometallic ACA reactions on simple enamides were unknown. In addition we chose to investigate the potential of these for ACA electrophiles.

RESULTS AND DISCUSSION

Trials of [Zn(bpy)Cl(R)] and [Zn(bpy*)$(Et)_2$] (R = Et, Bu, 4-Methylbenzyl)*

While a number of 2,2-bipyridine derivatives of organozinc species are known we chose to focus on the use of 4,4′-di-*tert*-butyl-2,2′-bipyridine (bpy*) in order to attain more soluble complexes. These orange or yellow complexes were prepared by direct reaction of the ZnClEt or R_2Zn in THF or dichloromethane (Scheme 1). The species **1a**–**1d** were non-pyrophoric and easily isolated as powders by addition of toluene or pentane. However, they showed greater than expected sensitivity, decomposing very readily in air. This is in contrast to the reported behaviour of some other [Zn(bpy)$(R)_2$] species[3]. Due to these properties **1a**–**1d** were either characterised in solution by ^{1}H and ^{13}C NMR spectroscopy (**1a**) or simply used directly as in situ prepared reagents (**1b**–**1d**). For comparison the colourless dichloro (**2a**) and dibromo (**2b**) and the orange diethyl (**3a**) species were prepared by similar methods.

Based on our previous experience with the zinc Schlenk equilibrium[6] we attempted to promote the formation of mixed, bpy* free, diorganozincs RMeZn through the addition of Me_2Zn. The presence of any mixed diorganozinc was detected by its capture with cyclohex-2-en-1-one (Scheme 1, Table I). Copper(I) precursors and Feringa's phosphoramidite[7] were selected as a suitable catalyst system as these are known to provide the conjugate



	X	Y
1a	Cl	Et
1b	Cl	Bu
1c	Cl	4-methylbenzyl
1d	Br	allyl
2a	Cl	Cl
2b	Br	Br
3a	Et	Et

SCHEME 1

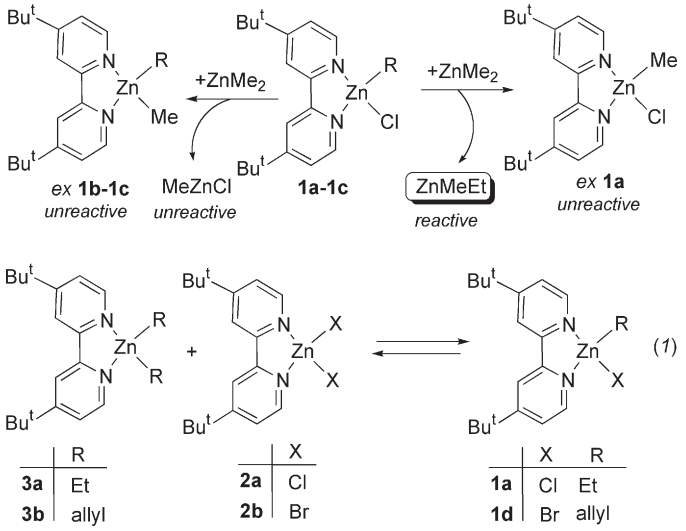
TABLE I
Copper-phosphoramidite catalysed 1,4-additions to cyclohex-2-en-1-one[a]

Run	Organozinc	Me_2Zn equiv.	Temp. °C	Solvent	Conversion %	Yield **4** %	ee %
1	Et_2Zn	0	–30	toluene	>99	92	97
2	MeEtZn[b]	–	–30	toluene–THF	>99	60	92
3	[Zn(bpy*)Cl(Et)] (**1a**)	0	–30	toluene	28	2	<2
4	[Zn(bpy*)Cl(Et)] (**1a**)	2	–30	toluene	67	30	88
5	[Zn(bpy*)$(Et)_2$] (**3a**)	0	–30	toluene	60	15	7
6	[Zn(bpy*)$(Et)_2$] (**3a**)	2	–30	toluene	80	40	26
7	[Zn(bpy*)Cl(Bu)] (**1b**)	2	–30	toluene	80	0	–
8	[Zn(bpy*)Cl(Bu)] (**1b**)	2	–30	THF	61	13	n.d.[c]
9	[Zn(bpy*)Cl(4-methylbenzyl)] (**1c**)	2	–30	THF	81	2	n.d.[c]

[a] Addition of cyclohex-2-en-1-one (0.5 mmol) to organozinc reagent (1.0 mmol, 0.5 M solution) in dry solvent (1 ml) at –30 °C in the presence of (R_a,*S*,*S*)-$\mathbf{L_A}$ (4 mole %; ref.[7]), and $Cu(OTf)_2$ or Cu(thiophene-2-carboxylate) (2 mole %). Yields and ee values determined by chiral GC analysis. [b] Data taken from ref.[6]; toluene–THF 98:2. [c] Could not be determined accurately due to low yield.

addition product **4a** (R = Et) with very high enantioselectivities when Et_2Zn or EtMeZn are present in toluene-based solvent systems (runs 1 and 2). Complex **1a** on its own was essentially inactive in conjugate addition (run 3). It could be activated by promotion with Me_2Zn (run 4) leading to a high-ee (88%) product. However, the chemoselectivity of the reaction was rather poor with the mass balance being accounted for by oligomerisation[6] (major) and competing 1,4-methyl to cyclohex-2-en-1-one transfer (minor). Unfortunately, other organohalide analogues (as represented here by **1b**, **1c**) were inactive towards conjugate addition in toluene solutions, even in the presence of Me_2Zn (run 7). In THF low yields of **4b**, **4c** could be attained but oligomerisation was the major reaction path (runs 8 and 9) as we have noted before[6].

The unexpected poor reactivity of **1b**, **1c** and the diethyl compound **3a** compared to [Zn(bpy*)ZnCl(Et)] (**1a**) in the presence of Me_2Zn requires rationalisation. The Zn–C bond in Et_2Zn is known to be one of the weakest in organozinc chemistry (44–52 kcal mol^{-1} as opposed to 68 kcal mol^{-1} for Me_2Zn)[8]. We believe that interaction of **1a** with Me_2Zn leads to the formation of ZnMeEt and [Zn(bpy*)Cl(Me)] (Scheme 2) while the stronger Zn–C bonds in **1b**, **1c** lead to competing chloride abstraction generating unreactive and unselective [Zn(bpy*)(Me)(R)] species (Scheme 2). The stereoselectivity realised by **1a** is, however, still somewhat lower than that which



SCHEME 2

should be expected from ZnMeEt (88 vs 92%, Table I) and we wondered if an additional zinc Schlenk equilibrium might be leading to the generation of unselective [Zn(bpy*)$(R)_2$] species whose presence would further degrade the enantioselectivity. Evidence for the viability of such a Schlenk exchange was gathered by ^{13}C NMR monitoring of mixtures of **2a** and **3a**. Under these conditions rapid ligand exchange took place leading to spectroscopically observed **1a** (equilibrium (*1*), Scheme 2).

Evidence for the reversibility of the equilibrium (*1*) was attained by the use of allylZnBr, prepared from CH_2=$CHCH_2Br$ and zinc powder. On addition of bpy* to allylZnBr the immediate formation of a bright orange colour is observed indicative of bpy* coordination to form **1d**. Two CH_2 signals are observed in the solution ^1H and ^{13}C NMR of the reaction mixture consistent with the rapid formation of a new allyl species of formula **1d**. However, on standing the reaction mixture produces two solids. An initial crop

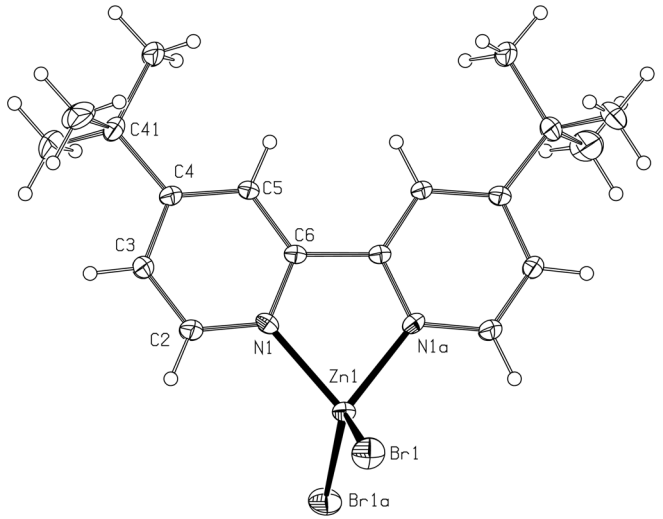


FIG. 1

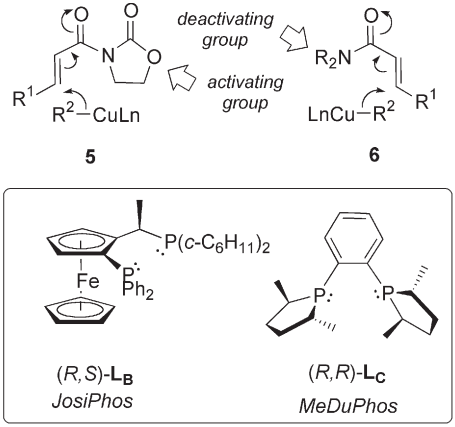
A view of one of the two crystallographically unique molecules of [Zn(bpy*)Br_2] (**2b**) showing the atom numbering scheme and with displacement ellipsoids drawn at the 20% probability level. Each molecule occupies a site of *mm*2 (C_{2v}) symmetry. Atoms carrying the suffix "a" are related to their unsuffixed equivalents by the symmetry operation (1/2 – *x*, 1/2 – *y*, *z*). Selected molecular geometry (Å; °): Zn1–Br1 2.3303(10), Zn1–N1 2.034(7); Br1–Zn1–Br1a 119.98(7), N1–Zn1–N1a 79.2(4), N1–Zn1–Br1 112.67(6). Corresponding parameters (Å; °) for the other molecule: Zn2–Br2 2.3349(11), Zn2–N11 2.064(7); Br2–Zn2–Br2b 117.95(7), N11–Zn2–N11b 78.9(4), N11–Zn2–Br2 113.46(7); with the suffix "b" are indicating the symmetry operation (1/2 – *x*, 3/2 – *y*, *z*)

of colourless crystals was shown reproducibly to be [Zn(bpy*)Br_2] (**2b**) both by X-ray crystallography and by comparison with an authentic sample. After crystallisation of **2b** the precipitation of a fine yellow powder occurs from which no single allyl species could be isolated due to its extreme reactivity. However, consistent with the presence of equilibrium (*1*), addition of cyclohex-2-en-1-one to the mixture did lead to the formation of the 1,2-addition product consistent with the presence of reactive **3b**. The molecular structure of [Zn(bpy*)Br_2] is shown in Fig. 1 together with selected bond angles and distances. As might be anticipated the structure of **2b** is essentially isostructural with that of [Zn(bpy)Br_2] [9].

In conclusion, while [Zn(bpy*)X(R)] species are potentially useful organometallics for selective 1,4-addition reactions their air sensitivity and reactivity presently compromises their practical use. Only the most reactive of the species (R = Et, allyl) are competent at transfer of organo-fragments and the attainment of selective systems is complicated by the presence of surprisingly efficient zinc Schlenk redistribution processes.

Trials of Simple α,β-Enamides as Michael Acceptors in Asymmetric Conjugate Addition Reactions

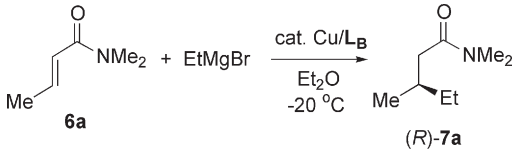
Compared to the many papers dealing with copper-catalysed 1,4-additions to enones[1] equivalent studies of enamides are limited to a handful of examples. Of principal note are the additions to the oxazolidinone structures **5** reported by Hoveyda and Nakamura (Scheme 3)[10]. However, the oxazolidinone is a special case because the substrate has far greater reactivity than a typical α,β-unsaturated amide (**5** vs **6** in Scheme 3)[11,12]. Recent advances



SCHEME 3

in the asymmetric conjugate addition reactions of Grignard reagents to enones and esters using (*R*,*S*)-**L$_B$**-*JosiPhos* and other ferrocenylphosphanes[1], led us to consider if enamides **6** might participate in related 1,4-reactions. Of especial interest was the idea that non-ferrrocenyl diphosphanes, such as (*R*,*R*)-**L$_C$**-*DuPhos*, might be active in this chemistry. We were encouraged by undercited reports in the early literature showing the viability of uncatalysed Grignard additions to α,β-enamides **6** under appropriate conditions[13].

Initial investigations have concentrated on the 1,4-addition of EtMgBr to the model α,β-enamide **6a** (Scheme 4, Table II). A reliable chiral GC assay could be determined and additionally, as the *R*-enantiomer of **7a** has already been described in the literature[14], identification of the enantioface attacked by the catalyst was possible via polarimetric studies of the product.



SCHEME 4

TABLE II
Copper-catalysed EtMgBr addition to α,β-enamide **6a**[a]

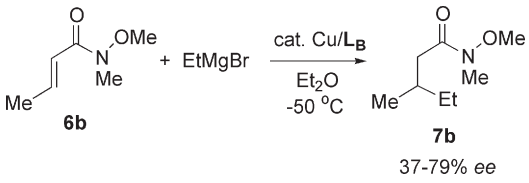
Run	Cu source	Ligand	Conversion **6a** %	ee **7a** %
1	–	–	23	–
2	$Cu(OTf)_2$	–	54	–
3	$CuBr{\cdot}SMe_2$	–	44	–
4	Cu(TC)	–	35	–
5	$[Cu(MeCN)_4]BF_4$	–	34	–
6	$Cu(OTf)_2$	PPh_3	31	–
7	$Cu(OTf)_2$	(*R*,*R*)-**L$_C$**-*MeDuPhos*	75	48 (*R*)
8	$Cu(OTf)_2$	(*R*,*R*)-**L$_C$**-*MeDuPhos*	81	19 (*R*)[b]
9	$Cu(OTf)_2$	(*R*,*R*)-**L$_C$**-*MeDuPhos*	61	35 (*R*)[c]
10	$Cu(OTf)_2$	(*R*,*R*)-**L$_C$**-*MeDuPhos*	>99	57 (*R*)[d]

[a] Reaction conditions: Et_2O, copper source (2 mole %), ligand (4 mole %), 1.5 equiv. EtMgBr, –20 °C, 15 min, all chemical yields are within 5% of conversion values as measured by GC using dodecane as internal standard. [b] Run at 0 °C. [c] Run at –60 °C. [d] 2.0 equiv. EtMgBr, 18 h.

In the absence of catalytic promotion only low yields of racemic product were attained (run 1). Significant acceleration of the reaction was realised in the presence of Cu^{I} and Cu^{II} pre-catalysts, suggesting copper(I)-based promotion of this reaction (runs 2–5). Among the copper sources tested, $Cu(OTf)_2$ and $CuBr{\cdot}SMe_2$ appeared to be the most promising for a stereoselective approach. A preliminary screening of chiral ligands showed 'ligand accelerated catalysis' effects[15] for diphosphane complexes formed in situ, the highest stereoselectivity being obtained with (*R*,*R*)-*MeDuPhos* (runs 7–10). Under our reaction conditions (5 mole % $Cu(OTf)_2$, 10 mole % (*R*,*R*)-$\mathbf{L_C}$, 2 equivalents of EtMgBr) **6a** could be quantitatively converted into its 1,4-addition product (**7a**) with a promising ee value (57%). Surprisingly, neither (*R*,*S*)-$\mathbf{L_B}$-*JosiPhos* nor other 'Solvias kit'[16] ligands proved effective in similar trials despite their known efficacy in related additions to ketones and esters (from –78 to 25 °C; complete conversion, but ee values <10%).

The observed stereoselectivity of addition to **6a** was highly sensitive to the reaction conditions. Increasing the amount of ligand from the initial 1:1.2 Cu:$\mathbf{L_C}$ stoichiometry favoured higher ee values (for copper:ligand ratios up to 1:2). Higher ligand loadings led to a catastrophic collapse in ee (6%, with Cu:$\mathbf{L_C}$ = 1:3). The formation of an inactive coordinatively saturated species and a competing background reaction are the likely causes. The observed ee of **7a** was also a function of the quantity of EtMgBr used in the reaction. Maximum stereoselectivity was observed at **6a**:EtMgBr ratios of 1:2.8 for a Cu:$\mathbf{L_C}$:ratio of 1:1.5. Similar behaviour has been noted recently in TolBINAP-Cu^{I} catalysed Grignard additions to esters[17].

We were interested to know if the presence of a second binding point on the unsaturated amide would result in improved stereoselectivity via a more rigid transition state. The reaction of the Weinreb amide **6b** with EtMgBr (Scheme 5) was an attractive model for such behaviour as this motif is known to favour chelate coordination to magnesium.



SCHEME 5

For reactions of **6b** it was necessary to cool the reaction to –50 °C to attain significant chemoselectivities[18] and in this case (*R*,*S*)-$\mathbf{L_A}$-*JosiPhos* proved to be a much more effective ligand than (*R*,*R*)-$\mathbf{L_B}$-*MeDuPhos* (Table III, runs 1 and 2). In the absence of added diphosphines none of the desired **7b** was observed. The by-products were MeCH=CHCOEt, resulting from addition-elimination chemistry and other high-molecular-weight species most probably due to enamide oligomerisation. However, in the presence of diphosphines the chemoselectivity was greatly improved with byproduct formation accounting for no more than 5% of the conversion. As for **6a**, use of a 2:1 or 3:1 excess of ligand $\mathbf{L_B}$ over copper maximised the ee obtained. The reaction of **6b** with EtMgBr is significantly slower than that of **6a** (whose reaction with EtMgBr is complete within 60 min at –50 °C in the presence of the catalyst). We believe that this behaviour is indicative of slow release of the kinetic enolate from the catalyst due to strong two-point binding of the species ultimately. Because of the improvement in stereoselectivity substrate **6a** had shown in the presence of excess EtMgBr, we were encouraged to try a similar study using **6b**. In this case the results were not as dramatic. However, increasing the quantity of Grignard reagent to 3.0 equivalents did allow the attainment of complete conversion in the reaction, after 72 h, while retaining a high stereoselectivity (79% ee).

TABLE III
Copper-catalysed EtMgBr addition to α,β-enamide **6b**[a]

Run	Cu source	Ligand	Cu:**L** ratio	Conversion **6b** %	ee **7b** %
1	$Cu(OTf)_2$	(*R*,*R*)-$\mathbf{L_B}$-*MeDuPhos*	1:1.5	54	37[b]
2	$CuBr{\cdot}SMe_2$	(*R*,*S*)-$\mathbf{L_A}$-*JosiPhos*	1:1	84	51
3	$CuBr{\cdot}SMe_2$	(*R*,*S*)-$\mathbf{L_A}$-*JosiPhos*	1:1.5	98	69
4	$CuBr{\cdot}SMe_2$	(*R*,*S*)-$\mathbf{L_A}$-*JosiPhos*	1:1.5	85	75[c]
5	$CuBr{\cdot}SMe_2$	(*R*,*S*)-$\mathbf{L_A}$-*JosiPhos*	1:2	91	77
6	$CuBr{\cdot}SMe_2$	(*R*,*S*)-$\mathbf{L_A}$-*JosiPhos*	1:3	88	78
7	$[Cu(MeCN)_4]BF_4$	(*R*,*S*)-$\mathbf{L_A}$-*JosiPhos*	1:1.5	89	74
8	Cu(TC)[d]	(*R*,*S*)-$\mathbf{L_A}$-*JosiPhos*	1:1.5	84	56

[a] Reaction conditions: Et_2O, copper source (5 mole %), ligand (4.4–15 mole %), 1.5 equiv. EtMgBr, –50 °C, 15 min, all chemical yields are within 5% of conversion values as measured by GC using dodecane as internal standard. [b] Run for 17 h. [c] Run using CuI (2 mole %) for 17 h. [d] Cu(TC) is Cu(thiophene-2-carboxylate).

In conclusion we have demonstrated that α,β-unsaturated amides can be effective substrates for prototypical asymmetric conjugate addition reactions of aliphatic Grignard reagents. Significant potential exists for this new reaction and current efforts are directed towards the identification of improved systems.

EXPERIMENTAL

General

Standard experimental conditions, solvent purifications and instrumentation were identical to those described previously[19]. The organozinc species EtZnCl, (4-methylbenzyl)ZnCl and allylZnBr were prepared as described previously[6,20] using 99.999% zinc powder 40 mesh (Acros catalogue No. 367260500) as the zinc dust source for all insertions. Solid zinc chloride was stored under argon and fused under vacuum immediately prior to use in organometallic reactions. Alternatively, commercial anhydrous solutions of $ZnCl_2$ in THF (Acros catalogue No. 370061000) were used. The compound 4,4′-di-*tert*-butyl-2,2′-bipyridine was commercial (Sigma–Aldrich) and dried under vacuum before use. Copper(I) thiophene-2-carboxylate, Cu(TC), and $[Cu(MeCN)_4]BF_4$ were prepared by literature methods[21,22]; $Cu(OTf)_2$, $CuBr{\cdot}SMe_2$ and CuI were commercial (Sigma–Aldrich). Spectroscopic data for the organozinc complexes were collected in undeuterated THF or dichloromethane containing ca. 5% C_6D_6 to provide a lock or in CD_2Cl_2. All other compounds were recorded in $CDCl_3$.

Representative Example Preparation of [Zn(bpy*)Cl(Et)] (**1a**)

To a flame-dried Schlenk tube containing zinc chloride (2.0 ml of 0.5 M THF solution, 1.0 mmol) in THF was added dropwise diethylzinc (0.9 ml of 1.1 M toluene solution, 1.0 mmol) followed by stirring (1 h, 25 °C). Under a buffer of argon, solid bpy* (0.54 g, 2.00 mmol) was added. The solution turned bright orange instantaneously, becoming pale and more yellow as the product precipitated. The solvent was removed by cannula and the orange product dried under vacuum. Handling the compound in air led to rapid deterioration so the compound was characterised in solution. ^{1}H NMR (270 MHz, CD_2Cl_2, 25 °C): 8.65 d, 2 H, *J*(5,6) = 5.3 (H-6); 8.30 s, 2 H (H-3); 7.59 d, 2 H, *J*(5,6) = 5.3 (H-5); 1.12 t, 3 H, *J*(ethyl) = 8.0 (CH_3); 0.86 s, 18 H ($C(CH_3)_3$); 0.19 q, 2 H, *J*(ethyl) = 8.0 (CH_2). ^{13}C NMR (125.1 MHz, CD_2Cl_2, 25 °C): 164.4 (2 C), 148.8 (4 C), 123.1 (2 C), 118.3 (2 C), 35.4 (2 C), 30.2 (6 C), 12.7, –1.1. Two *ipso* carbons overlap at 148.8 ppm.

Preparation of Other [Zn (bpy*)X(R)] (**1b**–**1d**) and [Zn(bpy*)$(Et)_2$] (**3a**) Complexes

In a similar manner to **1a**, a dried Schlenk tube under an argon atmosphere containing RZnX or Et_2Zn (0.5 M in either THF, dichloromethane or DME) were treated with bpy* (1 equiv.). The resulting orange or yellow suspensions were stirred for 1 h and then used directly. Alternatively, an equal volume of dry deoxygenated pentane was added and the supernatant solvent removed by cannula filtration to give bright coloured solids. The precipitates were redissolved in THF for the reactions in Table I or for spectroscopic characterisation.

[Zn(bpy)Cl(Bu)]* (**1b**). Used directly without further characterisation.

[Zn(bpy)Cl(4-methylbenzyl)]* (**1c**). Used directly without further characterisation.

[Zn(bpy)Br(allyl)]* (**1d**). ^{1}H NMR (500 MHz, CD_2Cl_2, 25 °C): 8.62 br, 2 H (=CH); 8.39 br, 2 H (H-3); 7.59 br, 2 H, 6.14 q, 1 H, *J* = 11.0 (CH); 4.42 (broad doublet), 2 H, *J*(vic) = 12.0 (CH_2); 4.17 br, 2 H (CH_2); 1.48 s, 18 H ($C(CH_3)_3$). ^{13}C NMR (125.8 MHz, CD_2Cl_2, 25 °C): 164.61 br (2 C), 150.6 (2 C), 148.6 (2 C), 145.2 (1 C), 123.3 br (2 C), 118.4 (2 C), 100.4 (CH_2), 35.5 (2 C), 30.2 (6 C), 18.8 (1 C).

[Zn(bpy)(Et)$_2$]* (**3a**). ^{1}H NMR (270 MHz, CH_2Cl_2 containing 5% v/v C_6D_6, 25 °C): 8.42 d, 2 H, *J*(5,6) = 5.4 (H-6); 8.16 br, 2 H (H-3); 7.11 dd, 2 H, *J*(5,6) = 5.4, *J*(3,5) = 1.9 (H-5); 1.19 s, 18 H ($C(CH_3)_3$); 0.94 t, 6 H, *J*(ethyl) = 8.0 (CH_3); –0.03 q, 4 H, *J*(ethyl) = 8.0 (CH_2). ^{13}C NMR (67.9 MHz, C_6D_6, CH_2Cl_2, 25 °C): 161.4 (2 C), 153.8 (2 C), 148.5 (2 C), 121.3 (2 C), 117.6 (2 C), 34.8 (2 C), 30.1 (6 C), 13.6 (2 C), 1.5 (2 C).

Preparation of [Zn(bpy*)X$_2$] (**2a**, X = Cl; **2b**, X = Br)

Anhydrous $ZnCl_2$ or $ZnBr_2$ (5.0 ml of 0.5 M THF solution, 2.5 mmol) was placed in a flame-dried Schlenk tube containing a stirrer bar. Solid bpy* (0.67 g, 2.5 mmol) was added against a buffer of argon. A white suspension was formed instantly which was allowed to stir vigorously (1 h). Stirring was stopped, the white powder allowed to settle and the solvent removed by canula and the solid dried under vacuum. Recrystallisation from dichloromethane–Et_2O gave the final products as colourless needles or tablets.

[Zn(bpy)Cl$_2$]* (**2a**). Yield 0.85 g (93%). M.p. 149–150 °C (decomp.). For $C_{18}H_{24}Cl_2N_2Zn$ (404.7) calculated: 53.42% C, 5.98% H, 6.92% N; found: 53.39% C, 5.93% H, 6.89% N. ^{1}H NMR (270 MHz, CD_2Cl_2, 25 °C): 8.69 d, 2 H, *J*(5,6) = 5.6 (H-6); 8.22 d, 2 H, *J*(3,5) = 1.5 (H-3); 7.75 dd, 2 H, *J*(5,6) = 5.6, *J*(3,5) = 1.5 (H-5); 1.46 s, 18 H ($C(CH_3)_3$). ^{13}C NMR (67.9 MHz, CD_2Cl_2, 25 °C): 166.7 (2 C), 149.2 (2 C), 148.7 (2 C), 124.7 (2 C), 118.6 (2 C), 35.8 (2 C), 30.1 (6 C). IR (thin film): 2962 (m), 1614 (s), 1466 (m), 1412 (s), 1250 (m), 1025 (m), 895 (m), 849 (m). MS (FAB), *m/z* (M^+): calculated for $C_{18}H_2ClN_2Zn$ 367.1, found 367.1. A representative colourless needle gave *a* = 16.696(4) Å, *b* = 16.414(4) Å, *c* = 8.542(2) Å, *V* = 2340.9 Å^3. The compound was isomorphous with **2b** but the X-ray data did not allow final refinement.

[Zn(bpy)Br$_2$]* (**2b**). Yield 0.92 g (90%). M.p. 150–152 °C (decomp.). For $C_{18}H_{24}Br_2N_2Zn$ (493.6) calculated: 43.80% C, 4.90% H, 5.68% N; found: 43.80% C, 4.84% H, 5.60% N. ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): 8.73 d, 2 H, *J*(5,6) = 5.7 (H-6); 8.15 br, 2 H (H-3); 7.71 dd, 2 H, *J*(5,6) = 5.7, *J*(3,5) = 1.7 (H-5); 1.66 s, 18 H ($C(CH_3)_3$). ^{13}C NMR (270 MHz, $CDCl_3$, 25 °C): 166.5 (2 C), 149.0 (2 C), 124.6 (2 C), 118.3 (2 C), 36.0 (2 C), 30.4 (6 C). IR (thin film): 2967 (w), 1612 (m), 1486 (m), 1411 (m), 1247 (m), 1023 (m), 896 (m), 844 (s). MS (FAB), *m/z*: calculated for $C_{18}H_2BrN_2Zn$ 411.0, found 411.0.

1,4-Additions of Organozinc Species (**1a**–**1c**, **3a**) to Cyclohex-2-en-1-one. General Procedure

A dried Schlenk tube was charged with Cu^I catalyst precursor (0.01 mmol, 2 mole %) and (*R*,*S*,*S*)-**L$_A$** (10.8 mg, 0.02 mmol, 4 mole %) under argon. Dry Et_2O (1.0 ml) was introduced and the stirred mixture cooled (–30 °C) for 30 min. A solution of the organozinc (typically 2.0 ml of 0.5 M THF or CH_2Cl_2 solutions, 1.0 mmol) was added. The resulting yellow-orange reaction mixture was stirred (30 min) and cyclohex-2-en-1-one (48.5 µl, 0.50 mmol) was added dropwise. Stirring was continued at –30 °C for 1 h upon which time the reaction was quenched by cautious addition of 2 M HCl (2 ml). Tridecane (25 µl) was added and the or-

ganic layer was passed through a plug of silica. The reaction mixture was analysed by GC with Lipodex-A and BP-20 columns; yields and ee values reported in Table I. In duplicate runs the organic components were isolated in comparable yields.

3-Ethylcyclohexan-1-one (**4a**). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): 2.48–2.25 m, 3 H ($COCH_2$); 2.11–1.92 m, 3 H ($COCH_2$ and ring-CH_2); 1.79–1.62 m, 2 H (ring-CH_2); 1.49–1.29 m, 3 H (ring-CH_2 and C**H**$_2$CH$_3$); 0.94 t, 3 H, *J*(ethyl) = 7.6 (CH_2C**H**$_3$). ^{13}C NMR (100.0 MHz, $CDCl_3$, 25 °C): 212.2 (1 C), 47.9 (1 C), 41.5 (1 C), 40.6 (1 C), 30.9 (1 C), 29.3 (1 C), 25.3 (1 C), 11.2 (1 C). These data were identical to an authentic sample[23]. The enantiomeric excesses were determined by chiral GC (Lipodex A, isothermal 75 °C): (*R*)-antipode 9.9 min; (*S*)-antipode 10.2 min.

3-Butylcyclohexan-1-one (**4b**). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): 2.47–2.22 m, 3 H ($COCH_2$); 2.10–2.01 m, 1 H ($COCH_2$); 2.02 td, 1 H, *J*(*anti*) = 12.0, *J*(*syn*) = 1.2 (H-3 CH); 1.95–1.88 m, 1 H (CH_2); 1.83–1.73 m, 1 H (CH_2); 1.72–1.62 m, 1 H (CH_2); 1.40–1.26 m, 7 H (CH_2); 0.90 t, 3 H, *J* = 6.9 (Me). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): 212.2 (1 C), 48.3 (1 C), 41.6 (1 C), 39.1 (1 C), 36.3 (1 C), 31.4 (1 C), 28.9 (1 C), 25.3 (1 C), 22.7 (1 C), 14.0 (1 C). HRMS (EI): calculated for $C_{10}H_{18}O^+$, [M^+] 154.1358, found 154.1358. The yield was determined by GC (BP20, isothermal 120 °C), retention time 9.6 min. All data were identical to an authentic sample[24].

3-(4-Methylbenzyl)cyclohexan-1-one (**4c**). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): 7.11 d, 2 H, *J*(2,3) = 8.9 (H-2 or 3 of Tol); 7.03 d, 2 H, *J*(2,3) = 8.9 (H-2 or 3 of Tol); 2.60 app. d, 2 H, *J*($ArCH_2$) = 6.8 ($COCH_2$); 2.34 s, 3 H ($TolCH_3$); 2.42–2.26 m, 3 H (ring-CH_2); 2.11–2.02 m, 3 H (ring-CH_2 and H-3 CH); 1.92–1.88 m, 1 H (ring-CH_2); 1.70–1.64 m, 1 H (ring-CH_2); 1.48–1.42 m, 1 H (ring-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 211.7 (1 C), 136.3 (1 C), 135.7 (1 C), 129.1 (2 C), 129.0 (2 C), 47.9 (1 C), 42.5 (1 C), 41.4 (1 C), 41.0 (1 C), 30.9 (1 C), 25.1 (1 C), 21.0 (1 C). IR ($CHCl_3$ solution): 2926, 2863, 1706, 1603, 1448, 1347, 1314. HRMS (EI): calculated for $C_{14}H_{18}ONa^+$, [M + Na^+] 225.1255, found 225.1236. All data were identical to an authentic sample[6].

Schlenk Equilibrium Studies of [Zn(bpy*)Cl(Et)] (**1a**)

The reaction of 0.5 M THF or dichloromethane solutions of [Zn(bpy*)$(Et)_2$] (**3a**) and [Zn(bpy*)Cl_2] (**2a**) was monitored by ^{13}C NMR spectroscopy (100.1 MHz). On mixture of the two solutions at ambient temperature immediate formation of [Zn(bpy*)Cl(Et)] (**1a**) was noted by comparison with an authentic sample of **1a**.

Schlenk Equilibrium Studies of [Zn(bpy*)Br(allyl)] (**1d**)

A Schlenk tube, containing a stirrer bar and zinc powder (0.20 g, 3.00 mmol), was twice heated (>100 °C) under vacuum and backfilled with argon. Anhydrous THF (3.8 ml) and TMSCl (10 µl, 0.08 mmol) were added, and the mixture left stirring (25 min). Dry allyl bromide (200 µl, 2.00 mmol) was added at ambient temperature to form a suspension that was vigorously stirred (1 h). The stirring was stopped, residual zinc allowed to settle, and the [ZnBr(allyl)] solution (shown to be 0.5 M solution in THF by titration) removed by syringe. The resultant [ZnBr(allyl)] solution (4.0 ml of 0.5 M THF solution, 2.0 mmol) was treated with solid bpy* (0.54 g, 2.00 mmol) under an argon atmosphere and the resultant orange mixture stirred (1 h). If stirring is stopped the solution deposits two different compounds: an initial crop of colourless tablets of [Zn(bpy*)Br_2] (**2b**) (0.20 to 1.0 mmol) followed by a yellow powder containing traces of [Zn(bpy*)Br(allyl)] (**1d**) and another highly reactive allyl

species. Addition of cyclohex-2-en-1-one (2.00 mmol) to the reaction mixture led to formation of 1-allylcyclohex-2-en-1-ol identified by comparison against an authentic sample (89.3 mg, 72% based on 1.00 mmol of **3b** formed).

1-Allylcyclohex-2-en-1-ol. Colourless oil. ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): 5.96–5.80 m, 2 H (=CH_2); 5.62 d, 1 H, *J*(cis) = 10.1 (=CH); 5.13 m, 2 H (=CH and =CH_2); 2.30 d, 2 H, *J*(1,2-allyl) = 7.3 (=CHC**H**$_2$); 2.11–1.89 m, 2 H (ring-CH_2); 1.79–1.60 m, 3 H (ring-CH_2); 1.34–1.18 m, 1 H (ring-CH_2). ^{13}C NMR (67.9 MHz, $CDCl_3$): 133.8 (1 C), 132.3 (1 C), 130.3 (1 C), 118.7 (1 C), 69.2 (1 C), 46.8 (1 C), 35.6 (1 C), 25.3 (1 C), 19.0 (1 C). HRMS (EI): calculated for $C_9H_{14}O^+$, [M^+] 138.1035, found 138.1044. The data were concordant with published values and the spectrum was identical to an authentic sample[25].

Representative Example of Conjugate Addition of EtMgBr to α,β-Enamides

Solid $Cu(OTf)_2$ (6.3 mg, 0.017 mmol) and (*R,R*)-**L$_C$**-*MeDuPhos* (8.0 mg, 0.026 mmol) were dissolved in 8 ml of freshly distilled Et_2O (other ligands were trialled analogously). The solution was stirred at room temperature for 30 min and cooled to –20 °C. A solution of EtMgBr (0.59 ml, 3.0 M in Et_2O, 1.76 mmol) was added dropwise and the resulting pale yellow solution was stirred for further 5 min before a solution of **6a** (0.1 g, 0.88 mmol, in 1 ml of Et_2O) was added. The reaction was allowed to proceed for 15 min and quenched with 0.5 ml of a 1 M solution of HCl. The organic layer was washed with water, dried (anhydrous $MgSO_4$), filtered and the solvent removed under vacuum. The crude reaction mixture was analysed by a Varian-GC equipped with octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin, 0.25 μm i.d. (50% in OV1701, w/w) using the programme: 50 °C (3 min), ramp to 100 °C (1 °C min^{-1}) ramp to 150 °C (25 °C min^{-1}). Retention times: **6a** 34.2, *R*-**7a** 38.8, *S*-**7a** 39.4 min. Dodecane was used as an internal standard; isolated yields in duplicate reactions were within 5–7% of the GC yields.

N,N-3-Triethylpentanamide (**7a**). Colourless oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): 2.98 s, broad, 6 H (NCH_3); 2.31 dd, 1 H, *J*(gem) = 14.7, *J*(vic) = 5.9 (H-2); 2.12 dd, 1 H, *J*(gem) = 14.7, *J*(vic) = 8.1 (H-2); 1.92 m, 1 H (H-3); 1.39 m, 1 H (H-4); 1.20 m, 1 H (H-4); 0.92 d, 3 H, *J*(CH_3,3) = 6.7 (3-CH_3); 0.89 t, 3 H, *J*(CH_3,4) = 7.4 (4-CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): 172.9 (C-1), 40.2 (C-2), 37.8 (broad NCH_3), 35.5 (broad NCH_3), 31.9 (C-3), 29.7 (C-4), 19.4 and 11.4 (3-CH_3 and C-5). IR: 2860, 2800, 2775, 1640, 1490, 1380, 1350, 1180, 1100, 1075, 1045, 1025, 935, 845. HRMS (EI), *m/z* ($C_8H_{17}NO$): found 144.1398, required 143.1310. The data were concordant with published values[14].

N-Methoxy-N-3-dimethylpentanamide (**7b**) Prepared in an identical manner to **7a** using **6b** (0.88 mmol). ^{1}H NMR (400.1 MHz, $CDCl_3$): 3.68 s, 3 H (OCH_3); 3.18 s, 3 H (NCH_3); 2.40 dd, 1 H, *J*(gem) = 15.0, *J*(vic) = 6.0, (H-2); 2.24 dd, 1 H, *J*(gem) = 15.0, *J*(vic) = 8.0, (H-2); 1.95 m, 1 H (H-3); 1.39 m, 1 H (H-4); 1.23 m, 1 H, (H-4); 0.93 d, 3 H, *J*(CH_3,3) = 6.5 (3-CH_3); 0.91 t, 3 H, *J*(CH_3,4) = 7.2 (4-CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): 174.3 (C-1), 61.1 (OCH_3), 41.0, br, (NCH_3), 32.1, br, (C-2), 31.4 (C-3), 29.4 (C-4), 19.4 and 11.4 (3-CH_3 and C-5). HRMS (EI), *m/z*: found 158.1536, required 159.1259.

X-Ray Crystal Structure Determination

A small colourless tabular crystal of **2b** was mounted in a thin perfluoropolyether film (Fomblin Y1800, Lancaster Synthesis) and mounted on a dual-stage glass fibre. Diffraction data were collected on a Bruker SMART1000 CCD area detector diffractometer[26] and the resulting frames integrated using SAINT[27]. The structure was solved by direct methods using

SIR92 [28] followed by iterative cycles of Fourier syntheses and full-matrix least-squares refinement on F^2 using SHELX97 [29]. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms were placed in geometrically calculated positions and refined using a riding model.

Areas of diffuse electron density were identified. These could not be modelled in terms of discrete atomic sites, but were allowed for by using PLATON SQUEEZE [30] which identified a total of 178 electrons in 668 Å^2 per unit cell. This electron density was assigned to four molecules of THF per unit cell. The crystal was found to be twinned by 180° rotation about [001] and the twin fraction was 0.339(2).

Relevant crystal and refinement data: $C_{18}H_{24}Br_2N_2Zn{\cdot}C_4H_{10}O$, FW = 567.70, orthorhombic, space group *Pmmn* (No. 59), a = 16.758(2) Å, b = 16.787(2) Å, c = 8.7293(12) Å, V = 2455.7(10) Å^3, Z = 4, D_{calc} = 1.536 g cm^{-3}, μ = 4.269 mm^{-1}, colourless tablet 0.18 × 0.11 × 0.04 mm, T = 150(2) K, $F(000)$ = 1152. For data collection, θ = 1.2–27.5°, 15 455 reflections measured, 3005 unique (R_{int} = 0.045 following absorption correction) and 2484 with $F \geq 4\sigma(F)$. For refinement, 137 parameters, $R_1[F \geq 4\sigma(F)]$ = 0.0505, wR_2[all F^2] = 0.146, GOOF(F^2) = 1.07, Δρ = –0.68–1.63 e Å^{-3}.

CCDC 641474 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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