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Tetrahedron: *Asymmetry* 19 (2008) 391–396

New chiral diamide ligands: synthesis and application in allylic alkylation

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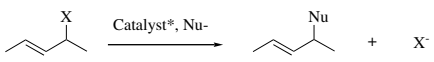
Received 13 December 2007; accepted 14 January 2008

Abstract—A new family of chiral diamide ligands has been designed and synthesised. These ligands have been successfully applied to an asymmetric allylic substitution reaction. A palladium complex of one of the diamide ligands achieved enantioselectivities of up to 93% in the allylic alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene.

1. Introduction

The formation of a new asymmetric carbon–carbon or carbon–heteroatom bond is of great synthetic value; hence, the transition-metal-catalysed asymmetric allylic substitution (AAS) reaction is a very important synthetic organic tool (Scheme 1).[1] It uses milder conditions than normal substitution reactions and involves varying degrees of chemo-, enantio- and regioselectivity.

In 1977, Trost and Strege developed a catalytic version of the reaction with the ligand, DIOP.[2] Since then, the transformation has been developed to achieve high selectivities with a range of substrates.[1] Typically, acetates and carbonates are used as leaving groups.[3] A wide variety of transition metals have been used but palladium continues to be the most common, closely followed by molybdenum.[4] The AAS reaction has been exploited as a key enantioselective step in the synthesis of many complex molecular targets.[5] Its use has been reported in over 50 total synthesis of a wide array of natural products.[6]



Scheme 1. Asymmetric allylic substitution.

The AAS reaction is a versatile asymmetric transformation since the same chiral catalyst can form several types of bonds, for example, C–H, C–C, C–N, C–O, C–S, etc., by varying either the substrate or the nucleophile.[7]

The bis(picolinamide) ligand **1** reported by Trost[8,9] (Fig. 1) has been employed successfully with catalytic molybdenum complexes used in AAS reactions. Numerous derivatives of **1** have been synthesised to probe its structure–behaviour relationship, and it has been shown that only one pyridine ring or even a picolinamide unit is required for the formation of an active catalytic complex.[10] Similarly, further studies demonstrated that a symmetric scaffold, as well as two stereogenic centres were not necessary.[11] Inspired by the success of bis(picolinamide) ligand **1** in molybdenum-catalysed asymmetric allylic substitution reactions, we have developed a novel set of structurally related chiral diamide ligands **2** and **3** (Fig. 1). Ligand **1** has been shown, during

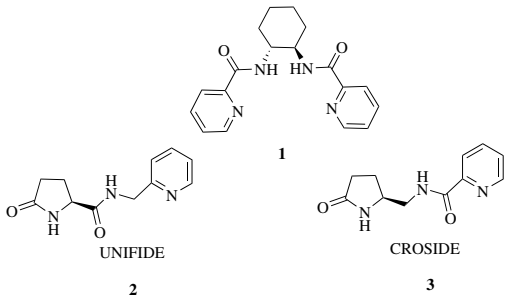


Figure 1. Novel pyridylamide ligands **2** and **3**, and known bis(pyridyl)-amide ligand **1**.

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doi:10.1016/j.tetasy.2008.01.018

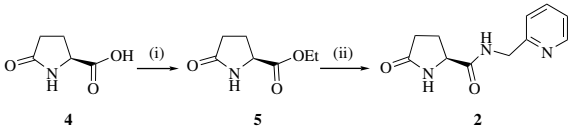
its catalytic cycle, to coordinate to molybdenum using both nitrogens of one pyridylamide unit as well as binding to the remote carbonyl oxygen of the second pyridylamide unit when the allyl substrate is present.[12] We envisaged our ligands **2** and **3** showing similar behaviour.

While our novel diamide ligands have been modelled upon those which form effective molybdenum allylation catalysts, we herein report on the reactivity of their palladium complexes. Palladium pre-catalysts have traditionally been applied to phosphorus-containing ligands[13] and the present study presents the novel application of chiral diamide Pd complexes forming effective asymmetric allylation catalysts with chiral diamide ligands. To the best of our knowledge, there has been no report of asymmetric allylic alkylations involving such simple chiral diamide–palladium complexes.

2. Results and discussion

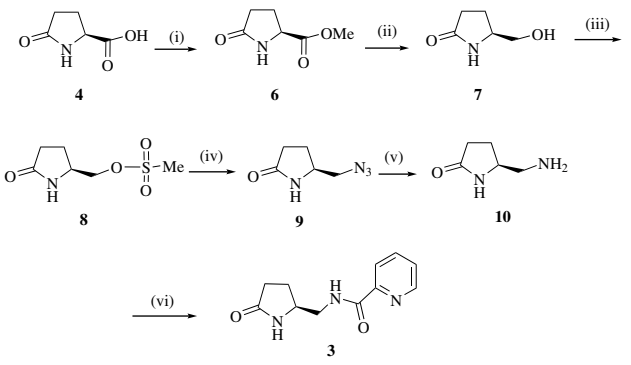
2.1. Synthesis of ligands

Ligands **2** and **3** were synthesised starting with (*S*)-(−)-pyrrolidone-5-carboxylic acid **4**. Esterification of **4**, and subsequent condensation with commercially available 2-pyridylamine, led to the formation of UNIFIDE **2** in 61% overall yield (Scheme 2).



Scheme 2. Reagents and conditions: (i) EtOH, H_2SO_4, $PhCH_3$, 72%; (ii) 2-pyridylamine, EtOAc, 85%.

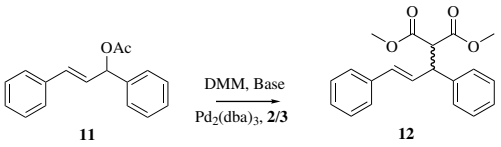
In the case of **3**, a longer synthetic pathway is necessary (Scheme 3). Following quantitative esterification of **4** the resulting methyl ester **6** was reduced to the amido alcohol, with no reduction of the amide being observed. The best synthetic approach was found to be the isolation and purification of mesylate **8** before reaction with sodium azide to form **9**. The corresponding amine **10** was obtained by the hydrogenation of **9** before performing a DCC-mediated coupling with 2-picolinic acid to afford **3** in 53% overall yield.



Scheme 3. Reagents and conditions: (i) Amberlyst 15$^+$, MeOH, 99%; (ii) $NaBH_4$, EtOH, 99%; (iii) MsCl, TEA, DCM, 99%; (iv) NaN_3, DMF, 71%; (v) 10%Pd/C, EtOH, 30 psi, 98%; (vi) 2-pyridylamine, DCC, DCM, 78%.

2.2. Allylic alkylation of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene

Preliminary screening of these ligands led us to test their palladium complexes in the allylic alkylation of (*rac*)-1,3-diphenyl-3-acetoxyprop-1-ene **11** (Scheme 4).



Scheme 4. Asymmetric allylic alkylation of **11**.

In all cases, the catalysts were generated in situ using $Pd_2(dba)_3$ dimer as the metal source. Complexation was carried out in toluene or THF, using 15 mol % ligand and 10 mol % palladium. Separately, the nucleophile was prepared from dimethyl malonate and base in the chosen solvent. On formation of the nucleophile, substrate **11** was added followed by the active catalyst and the reaction was carried out and monitored at intervals over of 48 h (Table 1).

Table 1. Pd-catalysed allylic alkylation of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene using ligands **2** and **3**, as outlined in Scheme 2

Entry	Ligand	Solvent	Temp (°C)	% Conv.	% ee (*S*)[e]
1[a]	**3**	$PhCH_3$	85	52	22
2[a]	**3**	THF	60	22	21
3[a]	**2**	$PhCH_3$	85	72	93
4[b]	**2**	$PhCH_3$	85	44	49
5[a]	**2**	THF	60	56	90
6[a,c]	**2**	$PhCH_3$	85 and rt	13	57
7[a]	**2**	$PhCH_3$	rt	0	—
8[a,d]	**2**	$PhCH_3$	85	100	78

[a] Nucleophile generated using NaH as base.
[b] Nucleophile generated using BSA/NaOAc as base.
[c] Catalyst formation occurred at 85 °C, reaction at rt.
[d] Reaction carried out in round-bottomed flask instead of Schlenk tube.
[e] % ee determined by chiral HPLC analysis; Chiralcel OD column, 254 nm, hexane (0.1% diethylamine)/isopropyl alcohol, 99:1, 0.5 ml/min, $t(R) = 19.3$ min, $t(S) = 21.2$ min.

Initially, a brief study was conducted using ligand **3** to generate the catalyst. The product was formed in 47% conversion and 22% ee (Table 1) when toluene was used as the solvent and the nucleophile was generated using sodium hydride. On changing the reaction solvent to tetrahydrofuran, the conversion to product more than halved to 22%. The enantioselectivity of the reaction system was not altered with the product being isolated in 21% ee. Overall the catalyst derived from ligand **3** gave poor yields and enantioselectivities, so we then focused on ligand **2**.

The study conducted on the reactions using ligand **2** was more extensive. Performing the entire reaction in toluene at 85 °C led to the formation of the desired product **12** in 93% ee. The fact that such a high degree of stereocontrol is observed for a structurally simple ligand with a single stereogenic centre is intriguing. It was noted during the reaction that the gelatinous nature of the nucleophile was hindering the rapid formation of a uniform reaction mixture. It took almost 24 h for this 'biphasic' mixture to appear consistent/uniform. To test if the lack of homogeneity was affecting the overall conversion, we conducted the reaction in a round-bottomed flask rather than a narrow Schlenk tube improve mixing (Table 1, entry 8). The product was formed in 100% conversion, but the enantioselectivity had dropped to 78% ee. Without uniformity, we postulate that the reaction was behaving more like a heterogeneous system and the concentration of 'available' nucleophile, allylic acetate or catalyst was lower than in the latter reaction. It is therefore plausible that this had a bearing on the enantioselectivity of the reaction.

When tetrahydrofuran was used as the solvent, the most striking difference from the toluene reaction was the consistency of the nucleophile solution (Table 1, entries 2 and 5). A clear solution was observed unlike the gelatinous mixture in toluene. It was anticipated that this solubility would lead to a faster reacting system and in turn a higher conversion. To our surprise, the conversion was lower than in toluene at 56% but a high enantioselectivity of 90% was achieved. The tetrahydrofuran reactions are run at 60 °C, as opposed to 85 °C for toluene. While this decrease in temperature did not seem to improve enantioselectivity, as one might expect, it did influence the reactivity of the system. To probe the effect of temperature on the catalytic system, we performed the toluene reaction at room temperature instead of 85 °C (Table 1, entries 6 and 7). Initially, the entire reaction was carried out at rt. No product could be detected after 48 h. No product formed likely due to the inadequate formation of an active catalyst. Subsequently, a reaction was performed, where the catalyst preparation was conducted at 85 °C, for 2 h before being cooled and the rest of the reaction carried out at rt. After 48 h, only 13% conversion to the desired product was obtained in 57% ee. This represents a TON of ~1 indicating that the active catalyst is not reformed at lower temperature. Lowering the reaction temperature decreased the enantioselectivity and significantly reduced conversion. It appears that elevated temperatures are critical to the efficiency and enantioselectivity of the reactions, presumably due to the inherent lack of reactivity of amides in comparison to other metal complex ligands. In the case of **2**, an alternative method of nucleophile generation was also investigated, that is, from dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[14] and a catalytic amount of sodium acetate (Table 1, entry 4). The BSA/dimethyl malonate system has been reported to yield products with higher enantioselectivities in shorter reaction times. It is reported that BSA works as a silylating agent for the dimethyl malonate anion, forming a ketene silyl acetal.[15] However, (entries 3 and 4) the effectiveness of a particular counterion is specific to the reacting system, and in this case it appears that the NaH/dimethyl malonate system works best.

3. Conclusion

We have succeeded in creating simple chiral diamide ligands, which contain only one stereocentre. In the case of one ligand, the palladium complex is an active catalyst and gives good enantiocontrol in asymmetric allylic alkylation reactions. This work has been innovative in its application of such small diamide ligands to palladium complex-catalysed alkylation of diphenyl allyl acetate. We are hopeful that further development of these ligand systems will lead to highly selective catalyst systems and work is currently underway to extend the use of these ligands to other metals and reactions.

4. Experimental

4.1. General information

All chemicals were purchased from Aldrich Chemical Company and generally used without further purification. Any necessary reagent purification, along with the drying and distillation of solvents, was carried out according to the literature procedures.[16] Melting points were measured on a Stuart Scientific SMP3 apparatus. IR spectra were measured on a Perkin Elmer Spectrum 1000 FT-IR, or a Perkin Elmer Spectrum One FT-IR. Optical rotations were measured on a Perkin Elmer 241 polarimeter at 589 nm (Na) in a 10 cm cell. Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 F254); column chromatography was conducted using Merck silica gel 60 or Apollo Scientific silica gel 40–63 μm or alumina (activated, neutral, Brockmann I, ca. 150 mesh). Elemental analysis was performed on a Perkin Elmer 2400 analyser. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{31}P NMR (162 MHz) and ^{15}N NMR (40.5 MHz) were recorded on a JEOL ECX-400 NMR spectrometer. ^{15}N NMR spectra were externally referenced to nitromethane. All spectra were recorded at probe temperatures (~20 °C) using tetramethylsilane as an internal standard. All chiral liquid–liquid chromatography (HPLC) was carried out on a Varian instrument, with an UV/vis detector at the specified wavelength, with a Daicel CHIRALCEL OD 0.46 cm × 25 cm column, using isopropanol/hexane (0.1% diethylamine) as the solvent, under conditions described for each experiment.

4.1.1. (1*R*,2*R*)-*N*,*N*′-Bis(2-pyridine carboxamide)-1,2-cyclohexane 1. Oxalyl chloride (6.5 g, 51.2 mmol) and dimethylformamide (5 drops) were added to a suspension of picolinic acid (4.73 g, 38.4 mmol) in dichloromethane (55 ml) at 0 °C. The resulting buff-coloured suspension was warmed to room temperature and stirred for 5 h before removing volatiles, including excess oxalyl chloride, in vacuo. This acid chloride was resuspended in dichloromethane (73 ml) and cooled to 0 °C before the addition of (−)-(1*R*,2*R*)-*trans*-1,2-diaminocyclohexane (1.46 g, 12.8 mmol) and triethylamine (17 ml, 12.3 g, 121.6 mmol). The reaction mixture was stirred at 0 °C for 4 h and then quenched by the addition of water (20 ml). The organic layer was isolated and washed successively with water (2 × 20 ml), saturated sodium hydrogen carbonate

(25 ml), water (20 ml) and brine (25 ml), dried and concentrated in vacuo. Recrystallisation from hot ethanol (~20 ml) afforded product **7** as a colourless crystalline solid (7.84 g, 63%); mp 172–173 °C (lit.,[17] 172–175 °C); ^{1}H NMR ($CDCl_3$): 1.41–1.46 (m, 4H), 1.82 (m,2H), 2.15–2.20 (m, 2H), 4.04 (br s, 2H), 7.30–7.33 (m, 2H), 7.69–7.73 (m, 2H), 8.03–8.05 (m, 2H), 8.21 (br s, 2H), 8.48–8.50 (m, 2H); ^{13}C NMR ($CDCl_3$) 24.9, 32.7, 53.3, 122.1, 126.0, 137.1, 148.2, 149.8, 164.6.[18] IR (solid): 3345, 2151, 1650, 1513, 1154, 750, 689 cm^{-1}.

4.1.2. (*S*)-5-Oxopyrrolidine-2-carboxylic acid ethyl ester 5. (*S*)-(−)-2-Pyrrolidone-5-carboxylic acid **4** (8.33 g, 64.5 mmol), concentrated sulfuric acid (0.16 ml), ethanol (20 ml) and toluene (6.4 ml) were combined and the mixture was refluxed for 2.5 h in a flask fitted with a Dean–Stark apparatus to collect water formed in situ.The mixture was cooled, carbon tetrachloride (65 ml) and potassium carbonate (2.3 g, 16.7 mmol) were added and stirring was continued for 30 min before filtering and removing the solvent in vacuo. The crude product was purified by Kügelrøhr distillation (oven temp 206 °C; 0.1 mmHg) (lit.,[19] 180 °C, 0.1 Torr), giving a clear oil which solidified to a colourless solid on standing (7.23 g, 72%); mp 51–52 °C (lit.,[19] 49–50 °C); $[\alpha]_D^{20} = +2.4$ (*c* 10, ethanol) {lit.,[20] $[\alpha]_D^{20} = +2.4$ (*c* 10, ethanol)}; ^{1}H NMR ($CDCl_3$): 1.29 (t, *J* 4.8, 3H), 2.17–2.32 (m, 1H), 2.34–2.52 (m, 3H), 4.22 (m, 3H), 6.75 (br s, 1H); ^{13}C NMR (100 MHz) 14.0, 24.7, 29.2, 55.4, 61.6, 172.0, 178.0.[21] IR (solid): 2983, 1732, 1684, 1198 cm^{-1}.

4.1.3. (2*S*)-5-Oxo-*N*-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide (UNIFIDE) 2. 2-(Aminomethyl)pyridine (2.50 ml, 2.62 g, 24.25 mmol) was slowly added to a solution of (*S*)-5-oxopyrrolidine-2-carboxylic acid ethyl ester **5** (3.81 g, 24.25 mmol) in ethyl acetate (20 ml). The solution was stirred at room temperature for 48 h before filtering and concentrating in vacuo. The crude solid obtained was triturated with acetone to give a creamy white solid, which upon drying gave a colourless solid (4.50 g, 85%); mp 93–95 °C; $[\alpha]_D^{20} = -22.2$ (*c* 0.5, chloroform); ^{1}H NMR ($CDCl_3$) 2.13–2.28 (m, 2H), 2.32–2.48 (m, 2H), 4.22 (dd, *J* 8.7, 5.0, 1H), 4.40 (dd, *J* 15.6, 5.5, 1H), 4.54 (dd, *J* 15.6, 5.5, 1H), 7.06 (dd, *J* 7.3, 5.5, 1H), 7.23 (d, *J* 7.8, 1H), 7.57 (dt, *J* 7.8, 1.8, 1H), 8.04 (br s, 1H), 8.16 (t, *J* 5.5, 1H), 8.27 (d, *J* 4.1, 1H); ^{15}N NMR (40 MHz, $CDCl_3$) −75.6, −255.8, −269.1; ^{13}C NMR ($CDCl_3$) 25.6, 29.4, 44.2, 57.4, 122.3, 122.6, 136.8, 148.7, 156.4, 172.7, 179.6; IR (film) 3681, 3665, 2943, 1702, 1655, 1054 cm^{-1}; *m*/*z* [EI]; found (HRMS, EI): *m*/*z* 219.1014 (<1%), R_t 10.27 min. $C_{11}H_{13}N_3O_2$ (M^+) requires 219.1008; 135 (88%), 93 [$CH_2(C_5H_4)NH^+$, 100%], 92 (57%), 84 (43%). Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 59.85; H, 5.92; N, 18.87.

4.1.4. Methyl-(*S*)-2-pyrrolidinone-5-carboxylate 6. Amberlyst 15 resin (5.0 g wet) was added to a solution of (*S*)-(−)-2-pyrrolidone-5-carboxylic acid **4** (12.92 g, 0.1 mol) in methanol (50 ml). The mixture was refluxed for 24 h, cooled, filtered and concentrated in vacuo affording the product as a yellow oil (14.22 g, 99%); no further purification was necessary (>99% pure by GC); $[\alpha]_D^{20} = -8.4$ (*c* 1.0, dichloromethane) {lit.,[22] $[\alpha]_D^{20} = -8.2$ (*c* 1.0, dichloromethane)}; ^{1}H NMR ($CDCl_3$) 2.18–2.48 (m, 4H), 3.73 (s, 3H), 4.23 (dd, *J* 9.1, 5.5, 1H), 7.25 (br s, 1H); ^{13}C NMR ($CDCl_3$) 24.8, 29.4, 52.7, 55.6, 172.6, 178.5;[23] IR (film) 3369, 1748, 1699, 1220 cm^{-1}.

4.1.5. (*S*)-5-(Hydroxymethyl)-2-pyrrolidone 7. Sodium borohydride (3.78 g, 100 mmol) was added portionwise, over 15 min, to a solution of methyl-(*S*)-2-pyrrolidinone-5-carboxylate **6** (14.22 g, 99.4 mmol) in ethanol (130 ml) and the mixture stirred overnight. The reaction was quenched with dilute hydrochloric acid (10%, 20 ml) and concentrated in vacuo. The residue was dissolved in distilled water (60 ml) and the solution passed down an ion exchange column (Amberlite IR 120$^+$, strong cation exchange). The water was removed in vacuo and the remaining solid azeotropically dried with methanol affording **7** as a colourless gum (11.43 g, 99%); no further purification was necessary (>98% pure by GC); $[\alpha]_D^{20} = +29.2$ (*c* 5.0, ethanol) {lit.,[24] $[\alpha]_D^{20} = +28.0$ (*c* 5.0, ethanol)}; ^{1}H NMR ($CDCl_3$) 1.75–1.83 (m, 1H), 2.10–2.21 (m, 1H), 2.31–2.44 (m, 2H), 3.45 (dd, *J* 11.0, 6.8, 1H), 3.73 (dd, *J* 11.0, 3.1, 1H), 3.80 (m, 1H), 4.56 (br s, 1H), 7.60 (br s, 1H); ^{13}C NMR ($CDCl_3$) 22.6, 30.4, 56.9, 65.6, 179.7;[23] IR (film) 3318, 1676, 1419, 1047 cm^{-1}.

4.1.6. (2*S*)-5-Oxopyrrolidin-2-yl methyl methanesulfonate 8. Methanesulfonyl chloride (6.60 ml, 9.78 g, 85.40 mmol) and triethylamine (15.7 ml, 11.38 g, 112.5 mmol) were added to a suspension of (*S*)-5-(hydroxymethyl)-2-pyrrolidone, **7** (6.47 g, 56.26 mmol) in dichloromethane (30 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h at which stage water (1.5 ml) was added and the mixture concentrated in vacuo. The crude product was purified by flash column chromatography (ethyl acetate/methanol, 10:1), affording the desired product **8** as a colourless solid (9.99 g, 92%); mp 75–77 °C (lit.,[24] 75.5–77.5 °C); $[\alpha]_D^{20} = +15.8$ (*c* 1, ethanol) {lit.,[24] $[\alpha]_D^{20} = +16.2$ (*c* 1.02, ethanol)}; ^{1}H NMR ($CDCl_3$) 1.84–1.95 (m, 1H), 2.25–2.49 (m, 3H); 3.07 (br s, 3H), 4.03–4.28 (m, 3H), 7.34 (br s, 1H); ^{13}C NMR ($CDCl_3$) 22.6, 29.7, 37.6, 53.5, 71.1, 178.9;[24] IR (film) 3227, 2937, 1686, 1347, 1168, 944 cm^{-1}.

4.1.7. (*S*)-5-(Azidomethyl)-2-pyrrolidone 9. A solution of (2*S*)-5-oxopyrrolidin-2-yl methyl methanesulfonate **8** (9.92 g, 51.39 mmol) in dimethylformamide (100 ml) was stirred for 15 min before the portionwise addition of sodium azide (16.84 g, 259.1 mmol). The reaction mixture was heated to 80 °C and stirred for 36 h, during which time it was monitored through IR assays. On completion of the reaction, it was cooled and concentrated in vacuo. The resulting residue was resuspended in chloroform (250 ml), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (chloroform/methanol, 19:5), affording the desired product **9** as a colourless solid (5.18 g, 71%); mp 62–63 °C (lit.,[25] 62–63 °C); $[\alpha]_D^{20} = +72.8$ (*c* 5.0, ethanol) {lit.,[25] $[\alpha]_D^{30} = +72.0$ (*c* 5.0, ethanol)}; ^{1}H NMR ($CDCl_3$) 1.74–1.82 (m, 1H), 2.16–2.42 (m, 3H), 3.26 (dd, *J* 12.4, 6.5, 1H), 3.41 (dd, *J* 12.4, 4.8, 1H), 3.79 (m, 1H), 7.28 (br s, 1H); ^{13}C NMR

($CDCl_3$) 24.0, 29.9, 53.7, 55.9, 178.8; IR (film) 3226, 2932, 2096, 1672 cm^{-1}.

4.1.8. (*S*)-5-(Aminomethyl)-2-pyrrolidone 10. Ten percent palladium on carbon (899 mg) was added, to a solution of (*S*)-5-(azidomethyl)-2-pyrrolidone **11** (6.29 g, 43.6 mmol) in ethanol (200 ml). The mixture was agitated under hydrogen (30 psi) in a Parr apparatus, which had been purged with air, for 6 h. The crude reaction mixture was filtered through a short column of Celite using ethanol (30 ml) as eluant, to remove the hydrogenation catalyst, and the volatiles were removed in vacuo. The crude product was purified by column chromatography (chloroform/methanol, 19:5) to give the product **10** as a yellow oil (4.92 g, 98%); $[\alpha]_D^{21} = +33.4$ (*c* 5.0, ethanol) {lit.,[26] $[\alpha]_D^{25} = +37.2$ (*c* 2.0, ethanol)}; ^1H NMR ($CDCl_3$) 1.66–1.75 (m, 1H), 1.78 (br s, 2H), 2.15 (m, 1H), 2.29–2.33 (m, 2H), 2.61 (dd, *J* 12.8, 7.6, 1H), 2.80 (dd, *J* 12.8, 4.4, 1H), 3.63 (m, 1H), 7.41 (br s, 1H); ^{13}C NMR ($CDCl_3$) 24.2, 30.3, 47.4, 57.0, 179.0.[26] IR (film) 3238 br, 2926 w, 1667 s cm^{-1}.

4.1.9. *N*-{[(2*S*)-5-Oxopyrrolidin-2-yl]methyl}pyridine-2-carboxamide CROSIDE 3. (*S*)-5-(Aminomethyl)-2-pyrrolidone **10** (1.64 g, 14.39 mmol) and 2-picolinic acid (1.77 g, 14.39 mmol) were suspended in dichloromethane (18 ml) and cooled to 0 °C before the slow addition of a dicyclohexylcarbodiimide (2.97 g, 14.39 mmol) solution in dichloromethane (18 ml). The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature and stirred overnight before filtering through Celite and washing with dichloromethane (10 ml). The combined organics were concentrated in vacuo. The crude product was purified by column chromatography using gradient elution (ethyl acetate–methanol; R_f 0.31 (silica) ethyl acetate/methanol, 10:1) affording **3** as a colourless solid (3.08 g, 78%); mp 140–141 °C; $[\alpha]_D^{20} = +41.1$ (*c* 5.0, ethanol); ^1H NMR ($CDCl_3$) 1.80–1.89 (m, 1H), 2.17–2.36 (m, 3H), 3.46–3.62 (m, 2H), 3.89–3.95 (m, 1H), 7.08 (br s, 1H), 7.34 (ddd, *J* 7.6, 4.8, 1.4, 1H), 7.76 (dt, *J* 7.8, 1.4, 1H), 8.08 (d, *J* 7.8, 1H), 8.40 (t, *J* 5.5, 1H), 8.44 (d, *J* 4.6, 1H); ^{15}N NMR (40 MHz, $CDCl_3$) −76.6, −253.3, −276.1; ^{13}C NMR ($CDCl_3$) 24.3, 29.8, 43.9, 54.2, 122.2, 126.2, 137.2, 148.0, 149.4, 165.0, 178.6; IR (film) 3346, 3218, 2967, 1665, 1645, 1537, 1286, 1253 cm^{-1}. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 59.85; H, 6.06; N, 18.84.

4.2. Typical procedure for Pd(0)-catalysed asymmetric allylic alkylation of 11

A flame-dried Schlenk tube was charged with UNIFIDE, **2** (32.8 mg, 0.15 mmol, 15 mol %) and tris(dibenzylideneacetone)dipalladium (45.5 mg, 0.05 mmol, 10 mol % Pd) before being degassed. Toluene (3 ml) was added to this and the resulting mixture heated to 85 °C for 2 h. Separately, a flame-dried Schlenk tube was charged with sodium hydride (60% dispersion in mineral oil, 80.0 mg, 2.0 mmol) and was degassed before toluene (8 ml) and dimethyl malonate (0.25 ml, 291 mg, 2.2 mmol) were added. The resulting gel was stirred at 85 °C for 15 min, before the addition of (±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene, **11**,[27] (252.0 mg, 1.0 mmol), in toluene (1 ml), and was stirred for a further 15 min. The catalyst solution was transferred to the substrate–nucleophile mixture via a gas-tight syringe, along with a toluene rinse (1 ml). The resulting mixture was stirred at 85 °C for 48 h. Saturated ammonium chloride solution (10 ml) was added, the organic layer separated and the aqueous layer extracted with diethyl ether (3 × 10 ml). The combined organics were washed with brine (10 ml), dried, filtered and concentrated in vacuo, affording the crude product. The conversion to product was indicated by ^1H NMR spectral analysis of this material. The crude product was then purified by flash column chromatography (silica gel; petrol/ethyl acetate, 19:1) yielding the product **12** as pale yellow oil, which solidified on standing (210.6 mg, 65% yield). The enantiomeric excess was established by HPLC analysis [Daicel Chiralcel OD, 254 nm, hexane (0.1% diethylamine)/isopropyl alcohol, 99:1, 0.5 ml/min], $t(R) = 19.3$ min, $t(S) = 21.2$ min, and confirmed by chiral shift NMR. ^1H NMR ($CDCl_3$) 3.52 (s, 3H), 3.70 (s, 3H), 3.96 (d, *J* 11.0, 1H), 4.27 (dd, *J* 11.0, 8.7, 1H), 6.33 (dd, *J* 15.6, 8.7, 1H), 6.48 (d, *J* 15.6, 1H), 7.20–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) 49.2, 52.5, 52.6, 57.7, 126.4, 126.6, 127.2, 127.6, 127.9, 128.5, 129.1, 131.9, 136.8, 140.2, 167.8, 168.2. The product **12** was formed in 72% conversion and was found to have 93% ee (*S*).

4.3. Alternative nucleophile generation

The reaction was carried out according to Section 4.2, except that the dimethyl malonate nucleophile species was generated as follows: a flame-dried Schlenk tube was charged with dimethyl malonate (0.25 ml, 291 mg, 2.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (0.55 ml, 447 mg, 2.2 mmol), and sodium acetate (2.5 mg) in toluene (8 ml). The resulting solution was stirred at 85 °C for 15 min and the rest of the reaction was performed as described. Product **12** was formed in 44% conversion and was found to have 49% ee (*S*).

4.4. Determination of enantiomeric excess by chiral shift ^1H NMR

The purified reaction product, **12** (7 mg, 0.024 mmol) was dissolved in chloroform-*D* (0.8 ml) before the addition of (+)-Eu(hfc)$_3$ (13 mg, 0.0106 mmol). The resulting solution was then transferred to an NMR tube. The ^1H NMR spectrum displayed two singlets and a doublet in the region of 4 ppm. Each antipode of one of the methyl groups causes the singlets, while the doublet arises from the non-baseline resolved signal for the other methyl group. The integration of the doublet is equivalent to the sum of the integrations of both singlets. The relative integrals of the singlets are used to give the enantiomeric excess. The singlet, which appears furthest downfield, corresponds to the (*R*)-enantiomer, when the (+)-antipode is used.[27]

Acknowledgements

We thank Enterprise Ireland, Limerick County Council and Science Faculty, NUI, Galway for supporting this work.

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