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Tetrahedron
Tetrahedron 61 (2005) 8677–8685

X=Y–ZH systems as potential 1,3-dipoles. Part 61: Metal exchanged zeolites, silver(I) oxide, Ni(II) and Cu(I) complexes as catalysts for 1,3-dipolar cycloaddition reactions of imines generating proline derivatives

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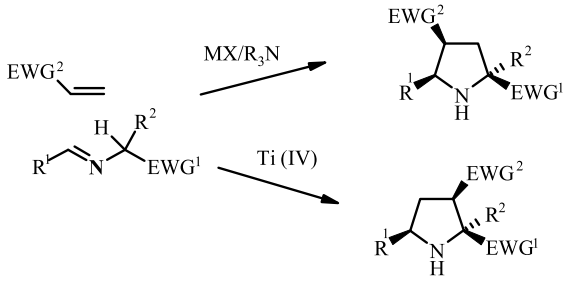
Received 11 April 2005; revised 16 June 2005; accepted 30 June 2005

Abstract—A range of regio- and stereo-selective 1,3-dipolar reactions of imines of α-amino esters, generating polysubstituted prolines, catalysed by silver(I) exchanged zeolites or silver(I) supported on titania, both in combination with DBU, are described. The use of a catalytic amount of silver(I) oxide, Ni(II) complexes and cuprous iodide as catalysts for the cycloaddition reactions are also disclosed.

1. Introduction

Metal exchanged zeolites are widely used for the catalysis of a variety of reactions.[1–9] For example, combination of Co(II), Mn(II) and Ni(II) with certain types of zeolites, for example, ZSM-5 and mordenite are active catalysts for the reduction of NO_X with methane in an oxidising atmosphere[1] and Ag-ZSM-5 catalyst, prepared by an ion exchange method, is an effective catalyst for the catalytic decomposition of NO_X in flue gases.[2] Multifunctional metal-exchanged zeolites are active catalysts for the conversion of methyl halides to ethylene[3] whilst complete catalytic oxidations of low molecular weight chlorinated hydrocarbons such as CH_2Cl_2, trichloroethane and CCl_4 in air over several cation-exchanged Y zeolites (Co–Y, Cr–Y and Mn–Y) have been reported.[4] Catalysts prepared by impregnating samples of neutral chabazite and mordenite zeolites with silver nitrate are active and selective for the epoxidation of ethane[5] whilst Cu(II) or Zn(II) exchanged zeolites catalyse the rearrangement[6] of (+)-pinene oxides. Silver(I) exchanged zeolite Y catalyses the dimerization of alkanes under UV–vis photochemical conditions at room temperature[7] and AgX and AgY are effective catalysts for the formation of glycosyl linkages.[8,9] However, to our knowledge, the use of silver exchanged zeolites as catalysts for 1,3-dipolar cycloaddition reactions has not been reported.

We introduced a facile and wide ranging Bronsted acid[10] or metal salt-tertiary amine catalysed 1,3-dipolar cycloaddition reaction of imines, activated by an appropriately located carbanion stabilising substituent, with electronegative alkenes. The reaction, which proceedes via in situ formation of metalloazomethine ylides, occurs at room temperature or below, is highly regio- and stereo-selective (Scheme 1) and furnishes polysubstituted pyrrolidines in excellent yield.[11]



Scheme 1.

In the case of Bronsted acids the rate in toluene correlates with p*K*a of a range of carboxilic acids.[10] The metal salt

Keywords: Metallo-azomethine ylides; Cycloaddition; Silver-exchanged zeolites; Silver oxide; Ni(II) catalysis; Cu(I) catalysis.
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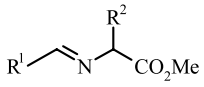
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.06.110

mediated process is compatible with a range of solvents (toluene, CH_2Cl_2, THF, MeCN, DMF, DMSO), metal salts [Ag, Li, Tl(I), Zn, Mg, Mn(II), Co(II), Ni(II)(vide infra), Cu(I)(vide infra)][11] and bases (tertiary amines, DBU, guanidines) and the regiochemistry is precisely reversed, for room temperature reactions, when Ti(IV) catalysts are employed[12] whilst maintaining the stereoselectivity (Scheme 1). The reaction tolerates a wide variation in EWG[1] [ester, nitrile, COR, $P(O)(OR)_2$, 2-pyridyl, 9-thiazolyl, 9-fluorenyl][11] and EWG[2]. Asymmetric versions of the reaction have been developed, which employ either a chiral catalyst[13] or a chiral auxiliary.[13b,14,15]

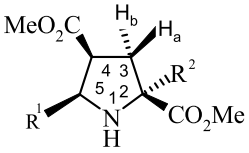
The mild reaction conditions, regio- and stereo-selectivity, simple experimental protocol and high yields ensured it was one of the first ring syntheses to be exploited by solid phase combinatorial chemistry.[16] Since then many further combinatorial chemistry applications have been developed[17] including combinations with other core reactions such as the Pictet–Spengler reaction and palladium catalysis.[18] Very large numbers of pyrrolidines have been made for biological screening by pharmaceutical and agrochemical companies using this chemistry. Recent applications in medicinal chemistry include inhibitions of hepatitis C virus RNA-dependent RNA polymerase[19] and inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma metastasis.[20]

An area experiencing rapid recent growth is the use of solid phase reagents,[21] which has many applications in solution phase combinatorial chemistry. This encouraged us to evaluate metal exchanged zeolites as potential heterogeneous catalysts for our pyrrolidine synthesis. This paper describes our studies in this area and also reports the first applications of Ni(II) and Cu(I) complexes/salts as catalysts for Scheme 1.

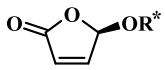
The 1,3-dipolar cycloaddition reaction of methyl (2-naphthylidene)alanate **3** and methyl acrylate, which is known to procede rapidly and in high yield with other Ag(I) salts, was chosen as the standard reaction. The first reaction (MeCN, DBU, 4 h, 25 °C) with a commercial 100-mesh silver exchanged zeolite[22] afforded only 12% of the cycloadduct **4**. When the reaction solvent was changed to dichloromethane the yield of the cycloadduct increased to 56% and when toluene was used as solvent, the product **4** was isolated in 82% yield (Scheme 2). Two further commercial silver exchanged zeolites (20-mesh and 1/16″ pellets) gave yields of 54 and 42%, respectively, under the optimised conditions.



5a-l



6a-l



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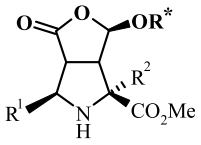


8a-c

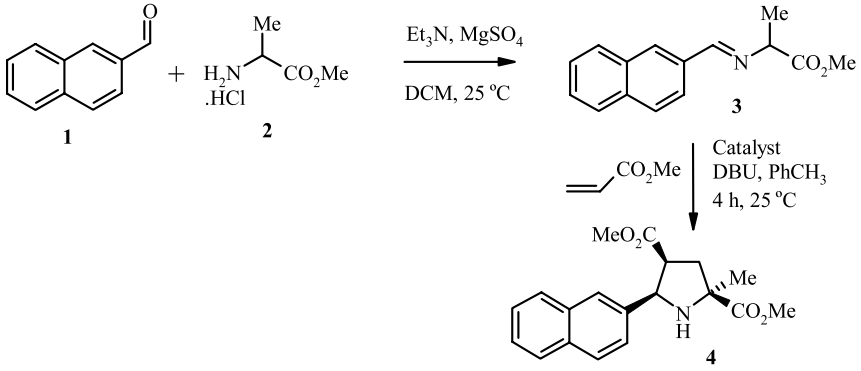
R* = menthyl

The applicability of the 100-mesh silver exchanged zeolite catalyst was demonstrated by using it in a number of other cycloaddition reactions involving imines **3** and **5a–i**. The cycloadditions proceeded regio- and stereo-specifically with methyl acrylate in toluene at room temperature in the presence of commercial silver exchanged zeolite and DBU to give single cycloadducts **6a–i** in 50–96% yield (Table 1). Cycloaddition of imines **3** and **5g** with the chiral dipolarophile (*R*)-5(1*R*)-menthyloxy-2-(5*H*)-furanone **7** resulted in cycloadducts in good yield and diastereoselectivity (Table 1, entries 10 and 11). The lower de in the case of the glycine imine **5g** reflects the well known sensitivity of azomethine ylides derived from glycine imines to stereomutation.[11]

The reaction of imine **3** with methyl acrylate was next investigated with a combination of 20% silver chloride on titania (donated by Johnson Matthey) and DBU in toluene (25 °C, 5 h), which furnished an 85% yield of **4**. Powdered silver chloride alone was then tested, to see whether it was effective in the absence of titania and was found to give a quantitative yield of cycloadduct **4** in a few minutes. Thus, the reaction was retarded by the titania support.

1.1. Silver oxide catalysis

Silver oxide (1 mol equiv) was examined as a potential heterogeneous catalyst in the standard imine cycloaddition reaction (Scheme 2) (toluene, DBU, 2 h, 25 °C). It was found that when 1 mol equiv of silver oxide was used, the



Scheme 2.

Table 1. Cycloaddition of imines **5a–i** using AgA[a] as catalyst[b]

Entry	Imine	Dipolarophile[c]	R^1	R^2	Cycloadduct	Yield (%)
1	**5a**	MA	2-Naphthyl	CH_2Ph	**6a**	96
2	**5b**	MA	2-Naphthyl	CH_2OH	**6b**	50
3	**5c**	MA	2-Naphthyl	CH_2-2-indolyl	**6c**	93
4	**5d**	MA	2-Pyridyl	Me	**6d**	50
5	**5e**	MA	*p*-$MeOC_6H_4$	CH_2Ph	**6e**	53
6	**5f**	MA	Phenyl	Me	**6f**	90
7	**5g**	MA	2-Naphthyl	H	**6g**	50
8	**5h**	MA	Cyclohexyl	Me	**6h**	68
9	**5i**	MA	Cyclohexyl	$CH_2CH_2SCH_3$	**6i**	92
10	**3**	7	2-Naphthyl	Me	**8a**	73 (100% de)[14b d]
11	**5g**	7	2-Naphthyl	H	**8b**	97 (90% de)[14b d]

[a] The amount of commercial zeolite (100 mesh, 20% Ag) used was equivalent to 1 mol equiv of silver.
[b] Reaction conditions: imine (1 equiv), dipolarophile (1 equiv), DBU (1 equiv), toluene, 25 °C, 5 h.
[c] MA = methyl acrylate.
[d] Determined by chiral HPLC—see Section 3.

reaction was over within 5 min and gave a quantitative yield of cycloadduct **4**. Moreover when 10 mol% silver oxide was employed, the reaction was over within 2 h, affording **4** in quantitative yield. Several reactions with different dipolarophiles were conducted to further test the efficacy of silver oxide as a catalyst. Imines **5g**,**h** and **5j–k** reacted with methyl acrylate in the presence of 10 mol% of Ag_2O to afford the corresponding cycloadducts in 92–100% yield. Reactions with chiral dipolarophile (*R*)-5(1*R*)-menthyloxy-2-(5*H*)-furanone **7** afforded the cycloadducts **8a–c** in excellent yield (95–100%) and diastereoselectivity (90–100% de) (Table 2).

1.2. Heterogeneous versus homogeneous nature of the catalysis

It was important to find out whether the silver zeolite and silver oxide were acting in a heterogeneous or a homogeneous manner. Calculations indicated the cycloadduct was larger than the pore size of the zeolite. Hence reactions inside the zeolite cavity would be non-productive. However, heterogeneous catalysis by silver might occur by coordination of the imine to silver ions located on the outer surface of the zeolite. Alternatively, the reactants might leach the silver from the zeolite affording a soluble silver species, which catalyses the cycloaddition in the usual way. It was observed that if the silver exchanged zeolite was filtered from the reaction mixture after the reaction was complete, then washed and reactivated by heating at 40 °C in a high vacuum (1 mmHg) for 24 h and reused, its catalytic activity was reduced. Thus, only 52% of **4** was obtained with recycled catalyst in the same reaction time. Deactivation of the zeolite might be due to reduction of silver (I) to silver metal during the reaction/regeneration cycle or it might arise from soluble silver species leaching from the zeolite. Leaching of silver species may originate in a number of ways, for example, in the preparation of the silver exchanged zeolite, some of the silver nitrate, used in the preparation of the silver exchanged zeolites will be sorbed onto the zeolite and hence more readily transferred to the bulk solution. Another possibility is that silver within the exchanged zeolite is released due to some kind of structural breakdown. For example, Kim and Seff[23] discovered that when Br_2 is sorbed onto zeolite AgA it interacts with the framework oxygen atoms and causes the decomposition of hexasilver clusters with the oxidised silver ion migrating out of the zeolite cavities.

It appeared likely that a leaching mechanism was responsible for the observed catalysis in both the Ag zeolite and Ag_2O cases. Silver oxide is prepared from silver nitrate and it generally contains traces of silver nitrate. We demonstrated that 10 mol% silver nitrate catalysed the 1, 3-dipolar cycloaddition reaction under the same conditions although the yields were lower and the time taken for the completion of the reaction was longer. Fortunately, we were able to obtain some silver oxide from Johnson Matthey, which contained only 5 ppm of silver nitrate. At this level, it was unlikely to be the major catalytic species when the silver oxide was used as a catalyst.

The standard imine cycloaddition reaction (Scheme 2) was carried out in toluene using 10 mol% silver oxide containing 5 ppm silver nitrate. The reaction was followed by thin-layer chromatography and was completed in 2 h. The reaction mixture was filtered through acid washed Celite to

Table 2. Cycloaddition of imines **3** and **5g–k** with dipolarophiles using Ag_2O as catalyst[a]

Entry	Imine	Dipolarophile[b]	R^1	R^2	Cycloadduct	Yield (%)
1	**3**	MA	2-Naphthyl	Me	**4**	100
2	**5g**	MA	2-Naphthyl	H	**6g**	100
3	**5h**	MA	Cyclohexyl	Me	**6h**	95
4	**5j**	MA	Cyclohexyl	H	**6j**	100
5	**5k**	MA	2-Naphthyl	$CH_2CH_2SCH_3$	**6k**	100
6	**3**	7	2-Naphthyl	Me	**8a**	100 (100% de)[14b c]
7	**5g**	7	2-Naphthyl	H	**8b**	97 (90% de)[14b c]
8	**5h**	7	Cyclohexyl	Me	**8c**	95 (99% de)[14b c]

[a] Reaction conditions: DBU/imine/dipolarophile = 1:1:2, Ag_2O (10 mol%), toluene, 25 °C, 2 h.
[b] MA = methyl acrylate.
[c] Determined by chiral HPLC—see Section 3.

Table 3. Filtration experiments for the reaction shown in Scheme 2

Reaction	Dipolarophile	DBU	Imine	Silver oxide	Time (h)	Conversion (%)
1	Yes	Yes	No	Yes	72	50
2	Yes	No	Yes	Yes	72	30
3	No	Yes	Yes	Yes	2	100
4[a]	Yes	Yes	Yes	Yes	2	100

[a] No filtration.

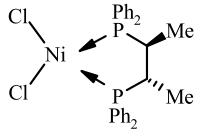
remove all the solids. If any silver was passed through the Celite, it was assumed to be a soluble silver species. The toluene filtrate was then evaporated to dryness under reduced pressure and the residue sent for accurate silver analysis. It was found that soluble silver had passed through the Celite filtration and that the amount (0.44% Ag) exceeded that attributable to silver nitrate alone (11×10^{-5} % Ag).

Using the same filtration technique the mode of solubilisation was examined in more detail. A series of reactions was carried out for 2 h omitting one of the reagents. The reaction mixture was then filtered through Celite and the reagent, which was left out in the first stage was added to the filtrate (Table 3). The reaction was then allowed to proceed for the time shown in Table 3 and progress was followed by thin layer chromatography.

The results in Table 3 demonstrate that both imine and DBU are required for any appreciable solubilisation of silver species from the silver oxide catalyst, and therefore rate enhancement (reactions 3 and 4). When either DBU or imine was omitted (reactions 1 and 2) the reaction was substantially retarded and DBU alone effected a greater solubilisation of Ag(I) than the imine alone. In conclusion, both DBU and imine are required for effective solubilisation of Ag(I) and catalysis.

1.3. Ni(II)–phosphine complexes as catalysts

Nickel(II) catalysed 1,3-dipolar cycloadditions of azomethine ylides were studied. It was found that both $NiCl_2$(dppe), or $NiCl_2(PPh_3)_2$, in combination with Et_3N (1.5 mol equiv) efficiently promoted the cycloaddition reactions of imine **3** with methyl acrylate to give the cycloadduct **4** in 97% yield over 3 h (Scheme 2). The reactions were performed in dichloromethane using equimolar amounts of the Ni(II) complex and imine.



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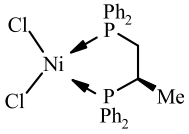


10

Previous success with chiral Co(II)[13] and Ag(I)[14] complexes as catalysts for Scheme 2 encouraged us to explore chiral Ni(II)–phosphine complexes. Such complexes have been widely used in a range of catalytic reactions.[24] Nickel(II) halides are known to form a large number of complexes with nitrogen or phosphorus donor ligands[25] and Ni(II) aldimine complexes are known.[26] The square planar chiral nickel(II) complexes **9** and **10** were prepared[27] and evaluated in Scheme 2. Reactions were carried out in dichloromethane using equimolar amounts of the chiral Ni(II) complexes **9** and **10** and imine. When **9** was employed racemic **4** was isolated in 49% yield after 27 h. The dramatic increase in the reaction time, the large reduction in yield of the cycloadduct and lack of enantioselectivity clearly relates to the coordination chemistry of Ni(II).[28] Octahedral and distorted octahedral complexes are the most common but numerous four-coordinate tetrahedral and square planar complexes of Ni(II) are known, together with five-coordinate square pyramidal and trigonal bipyramidal complexes.[29] Equilibria exist between the different structural types in solution and are frequently temperature and concentration dependent. The absence of enantioselectivity and the long reaction time indicates that the cycloaddition reaction is catalysed by 'free Ni(II)' ions resulting from equilibria involving dissociation of the chiral phosphine. Similarly when equimolar amounts of chiral Ni(II) complex **10** and imine were reacted under the same reaction conditions the product, isolated in 92% yield after 24 h, was essentially racemic (4% ee).

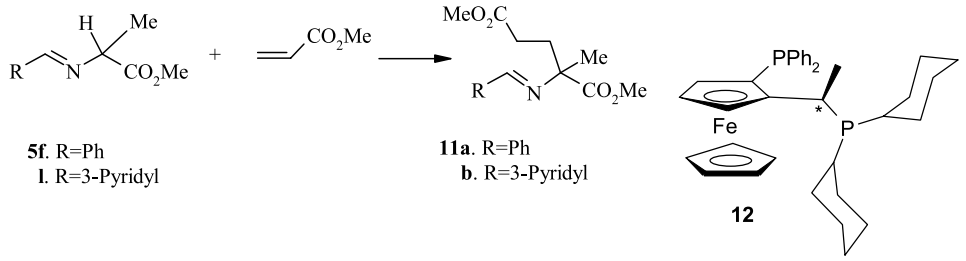
1.4. Cu(I) salts as catalysts

The success of the Ag_2O catalysed processes encouraged us to evaluate Cu_2O and other simple Cu(I) salts as catalysts for Scheme 2. When imines **5f** and **5l** were reacted separately with methyl acrylate in dichloromethane in the presence of Cu_2O (1 mol equiv) and DBU (1.12 mol equiv) the products were the Michael adducts **11a**[30] and **11b** (82–83%) (Scheme 3).

When the reaction was repeated with imine **5l** and a stoichiometric amount of CuCN replacing the Cu_2O the desired cycloadduct **6l**[31] was obtained in 72% yield. However, the same reaction with 10 mol% of CuCN afforded a 1:1 mixture of Michael adduct **11** and cycloadduct **6l**.

We then turned our attention to CuI as a possible catalyst. Cuprous iodide has found numerous applications in organic synthesis including asymmetric Kharasch reactions,[32] asymmetric conjugate addition of Grignard reagents,[33] enantioselective oxidative biaryl coupling,[34] and as an additive in many Pd(0) catalysed cross-coupling processes, for example, the Sonogashira rection.[35]

When Scheme 2 was carried out in dichloromethane with 10 mol% CuI in combination with DBU as base the desired cycloadduct **4** was isolated in 87% yield after 4 h. Analogous cycloadditions of imines **5a**, **5c**, and **5f** afforded the expected cycloadducts **6a**, **6c** and **6f** in 83–92% yield over 4–6 h. Repeating Scheme 2 with 10 mol% CuBr afforded **4** in 64% yield. The coordination chemistry of CuI with N-ligands is often complex[36] and frequently involve



Scheme 3.

aggregates.[37] However, in our studies up to 80% ee was achieved with CuI and ligand **12**.[38] Asymmetric versions of this process employing chiral $Cu(OTf)_2$[13d,e] complexes were reported after our own work was completed. Thus, it would appear that both Cu(I) and Cu(II) salts are effective catalysts with soft anions most effective for Cu(I) and hard anions for Cu(II).

2. Summary

Silver exchanged zeolites have been demonstrated to function as imine cycloaddition catalysts via leaching of silver species and are thus sources of of homogeneous catalytic silver salts. A leaching mechanism also operates in the case of 20% AgCl on titania. In this case, the titania support retards catalysis. The use of catalytic Ag_2O in toluene also involves soluble silver species and the solid→solution phase transfer involves both the imine and the amine base. Ni(II) complexes as shown to promote the imine cycloaddition for the first time. However, the use of chiral Ni(II)–phosphine complexes gives racemic cycloadducts. This together with the rate retarding effects of some chelating phosphines suggest the active Ni(II) catalyst is essentially phosphine free. Cu(I) salts are also shown, for the first time, to catalyse the imine cycloaddition. These salts show interesting selectivity with respect to their counterion. Thus, Cu_2O gives Michael addition products in good yield whilst CuCN gives either cycloadduct, when used in stoichiometric amount, or a 1:1 mixture of cycloadduct and Michael addition product when a substoichiometric amount (10 mol%) is employed. In contrast 10 mol% CuI proved an excellent catalyst whilst CuBr was somewhat less effective. The catalytic efficacy of Cu(I) salts of soft anions contrasts with that of the reported use of Cu(II) salts of hard anions as catalysts for analogous processes. The latter work[13d,e] appeared after completion of our own studies.

3. Experimental

General methods have been described previously.[39] Analytical grade anhydrous silver salts were used as purchased. Silver exchanged zeolites (20-mesh, 1/16″ pellets and 100-mesh) were purchased from Aldrich and were dried at 40 °C and 1 mmHg for 24 h before use. AgCl/TiO_2 (loading, 20% Ag) and Ag_2O containing 5 ppm $AgNO_3$ were supplied by Johnson Matthey. In all reactions involving silver(I) salts the reaction flask was covered with aluminium foil. Chiral HPLC was performed on a Chiralcel AD column (Daicel) eluting with 15% isopropanol in hexane, a flow rate of 1 mL/min and UV detection. All compounds were named using the ACD software version 8.0.

3.1. A. General procedure for preparation of imines

A mixture of amino acid methyl ester hydrochloride (22 mmol), aldehyde (20 mmol), triethylamine (20 mmol) and anhydrous magnesium sulfate (4 g) in dry DCM (50 mL) was stirred at room temperature for 16 h. On completion of the reaction (NMR monitoring), the mixture was diluted with DCM (100 mL), washed with water (2× 100 mL), dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo to give the imine. Solid imines were purified by crystallisation from ether–hexane, and liquid imines were used in the next step without further purification because attempted purification led to decomposition. Imines **3** and **5a**,**d**–**h**,**l** were prepared following the literature methods.[14c,30,31,40]

3.1.1. Methyl (2*E*)-3-hydroxy-2-[(2-naphthylmethyl) imino]propanoate 5b. Prepared by general procedure A from serine methyl ester hydrochloride (3.42 g, 22 mmol), 2-naphthaldehyde (3.10 g, 20 mmol) and triethylamine (2.8 mL, 20 mmol). Crystallisation from dichloromethane afforded **5b** (2.67 g, 52%) as colourless prisms, mp 79–80 °C. (Found: C, 70.05; H, 5.75; N, 5.60. $C_{15}H_{15}NO_3$ requires: C, 70.05; H, 5.85; N, 5.45%); δ ($CDCl_3$, 250 MHz): 8.39 (s, 1H, N=CH), 8.00–7.96 (m, 2H, Ar–H), 7.82–7.67 (m, 3H, Ar–H), 7.53–7.43 (m, 2H, Ar–H), 4.22–4.02 (m, 3H, C*H*CO_2Me and CH_2OH) and 3.73 (s, 3H, OMe); *m/z* (%): 257 (M^+, 30), 198(100), 167(12) and 103(20).

3.1.2. Methyl (2*E*)-3-(2,3-dihydro-1*H*-indol-2-yl)-2-[(2-naphthylmethyl)imino]propanoate 5c. Prepared by general procedure A from tryptophan methyl ester hydrochloride (5.60 g, 22 mmol), 2-naphthaldehyde (3.10 g, 20 mmol) and triethylamine (2.8 mL, 20 mmol). Crystallisation from ether–hexane afforded **5c** (5.41 g, 76%) as colourless plates, mp 155–157 °C. (Found: C, 77.30; H, 5.55; N, 7.65. $C_{23}H_{20}N_2O_2$ requires: C, 77.50; H, 5.60; N, 7.85%); δ ($CDCl_3$, 250 MHz): 7.93 (s, 1H, N=CH), 8.16–7.23 (m, 12H, ArH), 4.36 (dd, 1H, J=7.6, 4.7 Hz, C*H*CO_2Me), 3.81 (s, 3H, OMe), and 3.41 and 3.18 (2× dd, 2×1H, J=13.3, 4.7, 13.3, 7.6 Hz, CH_2); *m/z* (%): 356 (M^+, 48), 297(75), 202(24) and 130(100).

3.1.3. Methyl (2*E*)-*N*-(cyclohexylmethylene)methionate 5i. Prepared by general procedure A from methionine

methyl ester hydrochloride (4.39 g, 22 mmol), cyclohexyl carboxaldehyde (2.26 g, 20 mmol) and triethylamine (2.8 mL, 20 mmol). The product (2.83 g, 55%) was obtained as a colourless oil, which was used without further purification. Found (HRMS, $M^+ + H$): 258.1525. $C_{13}H_{23}O_2SN$ requires: 258.1528. δ ($CDCl_3$, 250 MHz): 7.55 (d, 1H, $J=5.6$ Hz, N=CH), 3.90 (dd, 1H, $J=8.6$, 5.0 Hz, C*H*CO_2Me), 3.74 (s, 3H, OMe), 2.63–2.32 (m, 2H, CH_2), 212–210 (m, 2H, CH_2), 2.08 (s, 3H, SMe) and 1.82–1.21 (m, 11H, cyclohexyl–H); *m/z* (ES, %): 258 ($M^+ + H$).

3.1.4. Methyl (2*E*)-*N*-(cyclohexylmethylene)glycinate 5j. Prepared by general procedure A from glycine methyl ester hydrochloride (3.07 g, 22 mmol), cyclohexyl carboxaldehyde (2.26 g, 20 mmol) and triethylamine (2.8 mL, 20 mmol). The product (2.27 g, 62%) was obtained as a colourless oil, which was used without further purification. Found (HRMS, $M^+ + H$): 184.1336. $C_{10}H_{17}O_2N$ requires: 184.1337. δ ($CDCl_3$, 250 MHz): 7.54 (d, 1H, $J=5.1$ Hz, N=CH), 4.16 (s, 2H, CH_2), 3.75 (s, 3H, OMe) and 2.35–1.21 (m, 11H, cyclohexyl–H); *m/z* (ES, %): 184 ($M^+ + H$).

3.1.5. Methyl (2*E*)-*N*-(2-naphthylmethylene)methionate 5k. Prepared by general procedure A from methionine methyl ester hydrochloride (4.39 g, 22 mmol), 2-naphthaldehyde (3.10 g, 20 mmol) and triethylamine (2.8 mL, 20 mmol). Crystallisation from dichloromethane afforded **5k** (5 g, 83%) as colourless prisms, mp 52–54 °C. (Found: C, 67.90; H, 6.05; N, 4.15; S, 10.90. $C_{17}H_{19}NO_2S$ requires: C, 67.75; H, 6.30; N, 4.65; S, 10.65%); δ ($CDCl_3$, 250 MHz): 8.47 (s, 1H, N=CH), 8.09–7.47 (m, 7H, ArH), 4.28 (dd, 1H, $J=7.9$, 5.4 Hz, C*H*CO_2Me), 3.76 (s, 3H, OMe), 2.39 (m, 2H, CH_2S), 2.31 (m, 2H, CH_2CH_2S) and 2.09 (s, 3H, SMe); *m/z* (%): 301 (M^+, 67), 242(100), 195(37) and 181(14).

3.2. B. General procedure for silver exchanged zeolite catalysed 1,3-dipolar cycloaddition reactions

Dried silver exchanged zeolite (9.72 g or 4.32 g based on 20 or 45% silver in partially and fully exchanged zeolite, respectively) was added to a solution of imine (12 mmol) in toluene (20 mL). The mixture was stirred for 5 min before the dipolarophile (24 mmol) and DBU (12 mmol) were added and stirring was continued until the starting materials had disappeared (TLC). The reaction mixture was quenched with saturated aqueous ammonium chloride, filtered and the filtrate extracted with dichloromethane (3×20 mL). The combined extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford the pyrrolidine.

3.3. C. General procedure for silver(I) oxide catalysed 1, 3-dipolar cycloaddition reactions

A mixture of imine (12 mmol) and silver oxide (0.28 g, 1.2 mmol, 10 mol%) in toluene (20 mL) was stirred for 5 min, dipolarophile (24 mmol) and DBU (12 mmol) added and stirring continued until TLC monitoring showed all the starting materials had disappeared. The reaction mixture was quenched with a saturated solution of ammonium chloride (20 mL) and extracted with dichloromethane (3× 20 mL). The combined extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford the pyrrolidine.

3.4. D. General procedure for cycloaddition reactions catalysed by Ni(II)–phosphine complexes

Ni(II)–phosphine complex (1 equiv) was stirred for 5 min in dichloromethane. Imine (1 equiv) was added and the reaction mixture was stirred for 15 min. Methyl acrylate (3 equiv) and triethylamine (1.5 equiv) were then added and the reaction was stirred at room temperature until the reaction was complete (TLC). The reaction mixture was washed with water, the aqueous layer extracted with dichloromethane and the combined fractions were dried ($MgSO_4$), filtered and evaporated under vacuum. Flash chromatography afforded the cycloadducts.

3.5. E. General procedure for copper(I) iodide catalysed 1,3-dipolar cycloaddition reactions

Cuprous iodide (0.112 mmol, 10 mol%) was added to a stirred solution of imine (1.12 mmol) in dichloromethane (15 mL). Methyl acrylate (1.68 mmol) and DBU (1.12 mmol) were then added dropwise over 5 min. The reaction was followed by TLC until the starting materials had disappeared (4–6 h), then quenched (saturated aqueous NH_4Cl) and extracted with dichloromethane (3×10 mL). The combined extracts were dried ($MgSO_4$), filtered and the solvent removed in vacuo. The crude pyrrolidine was purified by flash column chromatography.

3.5.1. Dimethyl 2-methyl-5-(2-naphthyl)pyrrolidine-2,4-dicarboxylate 4. Prepared by general procedure B from **3** (2.89 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded a colourless solid, which was purified by column chromatography eluting with 3:2 v/v ether–hexane to give **4** (3.73 g, 100%), which crystallised from dichloromethane–hexane as colourless needles, mp 83–85 °C. (Found: C, 69.50; H, 6.25; N, 4.55. $C_{19}H_{21}NO_4$ requires: C, 69.70; H, 6.45; N, 4.30%); δ ($CDCl_3$, 250 MHz): 7.84–7.76 (m, 4H, ArH), 7.48–7.37 (m, 3H, ArH), 4.81 (d, 1H, $J=7.3$ Hz, 5-H), 3.85 (s, 3H, OMe), 3.44 (ddd, 1H, $J=7.5$, 7.3, 4.8 Hz, 4-H), 3.12 (s, 3H, OMe), 2.79 (dd, 1H, $J=13.5$, 4.8 Hz, 3-H_a), 2.11 (dd, 1H, $J=13.5$, 7.5 Hz, 3-H_b) and 1.55 (s, 3H, Me); *m/z* (%): 327 (M^+, 61), 269(13), 268(62) and 209(100).

3.5.2. Dimethyl 2-benzyl-5-(2-naphthyl)pyrrolidine-2,4-dicarboxylate 6a. Prepared by general procedure B from **5a** (3.8 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded a colourless solid, which was purified by column chromatography eluting with 1:1 v/v ether–hexane to give **6a** (4.64 g, 96%), which crystallised from dichloromethane–hexane as colourless prisms, mp 108–109 °C. (Found: C, 74.50; H, 6.05; N, 3.55. $C_{25}H_{25}NO_4$ requires: C, 74.45; H, 6.20; N, 3.45%); δ ($CDCl_3$, 250 MHz): 7.81–7.22 (m, 13H, ArH), 4.64 (d, 1H, $J=$ 7.5 Hz, 5-H), 3.74 (s, 3H, OMe), 3.28 (m, 1H, 4-H), 3.16 (d, 1H, $J=13.1$ Hz, CH_2Ph), 3.09 (s, 3H, OMe), 2.95 (d, 1H, $J=13.1$ Hz, CH_2Ph), 2.79 (dd, 1H, $J=13.6$, 4.8 Hz, 3-H_a) and 2.25 (dd, 1H, $J=13.6$, 7.5 Hz, 3-H_b); *m/z* (%): 403 (M^+, 67), 344(100), 285(45) and 194(54).

3.5.3. Dimethyl 2-hydroxymethyl-5-(2-naphthyl)pyrrolidine-2,4-dicarboxylate 6b. Prepared by general procedure B from **5b** (3.08 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded a colourless solid, which was purified by column chromatography eluting with 4:1 v/v ether–hexane to give **6b** (2.06 g, 50%), which crystallised from ether as colourless needles, mp 117–119 °C. (Found: C, 66.30; H, 6.30; N, 3.90. $C_{19}H_{21}NO_5$ requires: C, 66.45; H, 6.10; N, 4.10%); δ ($CDCl_3$, 250 MHz): 7.82–7.75 (m, 4H, ArH), 7.50–7.33 (m, 3H, ArH), 5.29 (br, 1H, OH), 4.65 (d, 1H, $J=6.8$ Hz, 5-H), 3.87 (s, 3H, OMe), 3.79 and 3.54 (2×d, 2×1H, $J=10.7$ Hz, CH_2OH), 3.35 (m, 1H, 4-H), 3.14 (s, 3H, OMe), 2.62 (dd, 1H, $J=13.9$, 3.3 Hz, 3-H_a) and 2.09 (dd, 1H, $J=13.9$, 7.4 Hz, 3-H_b); *m/z* (%): 343 (M^+, 57), 284(100), 225(58) and 194(39).

3.5.4. Dimethyl 2-(1*H*-indol-2-ylmethyl)-5-(2-naphthyl) pyrrolidine-2,4-dicarboxylate 6c. Prepared by general procedure B from **5c** (3.85 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded a colourless solid, which was purified by column chromatography eluting with 3:2 v/v ether–hexane to give **6c** (5.05 g, 93%), which crystallised from dichloromethane–hexane as colourless prisms, mp 116–118 °C. (Found: C, 73.20; H, 5.70; N, 6.50. $C_{27}H_{26}N_2O_4$ requires: C, 73.30; H, 5.90; N, 6.35%); δ ($CDCl_3$, 250 MHz): 8.10 (br, 1H indole NH), 7.79–7.65 (m, 4H, ArH), 7.44–7.06 (m, 7H, ArH), 4.71 (d, 1H, $J=7.2$ Hz, 5-H), 3.70 (s, 3H, OMe), 3.47 (m, 1H, 4-H), 3.22 (s, 2H, CH_2), 3.09 (s, 3H, OMe), 2.78 (dd, 1H, $J=13.4$, 5.5 Hz, 3-H_a) and 2.28 (dd, 1H, $J=13.4$, 7.6 Hz, 3-H_b); *m/z* (%): 443 (M^+, 53), 383(100), 324(19) and 194(33).

3.5.5. Dimethyl 2-methyl-5-pyridin-2-ylpyrrolidine-2,4-dicarboxylate 6d. Prepared by general procedure B from **5d** (2.3 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded the crude product, which was purified by column chromatography eluting with ether to 10% methanol in ether to give **6d** (2.77 g, 80%) as a yellow oil. (Found: C, 60.30; H, 6.25; N, 10.30. $C_{14}H_{18}N_2O_4$ requires: C, 60.45; H, 6.45; N, 10.05%); δ ($CDCl_3$, 250 MHz): 8.52–5.16 (m, 4H, ArH), 4.68 (d, 1H, $J=7.6$ Hz, 5-H), 3.81 (s, 3H, OMe), 3.41 (m, 1H, 4-H), 3.27 (s, 3H, OMe), 2.70–2.75 (m, 2H, 3-H_a/H_b) and 1.51 (s, 3H, Me); *m/z* (%): 278 (M^+, 32), 219(100), 160(17) and 145(28).

3.5.6. Dimethyl 2-benzyl-5-(4-methoxyphenyl)pyrrolidine-2,4-dicarboxylate 6e. Prepared by general procedure B from **5e** (3.4 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded a colourless solid, which was purified by column chromatography eluting with 1:1 v/v ether–hexane to give **6e** (3.81 g, 86%) as a colourless viscous oil. (Found: C, 68.40; H, 6.35; N, 3.60. $C_{21}H_{23}NO_5$ requires: C, 68.30; H, 6.25; N, 3.80%); δ ($CDCl_3$, 250 MHz): 7.26–7.15 (m, 7H, ArH), 6.81 (m, 2H, ArH), 4.47 (d, 1H, $J=7.5$ Hz, 5-H), 3.77, 3.75 and 3.22 (3×s, 3×3H, 3×OMe), 3.15 (m, 1H, 4-H), 3.10 and 2.92 (2×d, 2×1H, $J=13.1$ Hz, $ArCH_2$), 2.74 (dd, 1H, $J=5.2$, 13.7 Hz, 3-H_a) and 2.18 (dd, 1H, $J=7.5$, 13.7 Hz, 3-H_b); *m/z* (%): 369 (M^+, 53), 310(100), 262(19) and 251(33).

3.5.7. Dimethyl 2-methyl-5-phenylpyrrolidine-2,-4-dicarboxylate 6f. Prepared by general procedure B from **5f** (2.29 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded a colourless solid, which was purified by column chromatography eluting with 1:2 v/v ether–hexane to give **6f** (2.99 g, 90%) as a colourless oil. (Found: C, 64.95; H, 6.90; N, 5.15. $C_{15}H_{19}NO_4$ requires: C, 65.00; H, 6.85; N, 5.05%); δ ($CDCl_3$, 250 MHz): 7.31–7.22 (m, 5H, ArH), 4.65 (d, 1H, $J=7.5$ Hz, 5-H), 3.82 (s, 3H, OMe), 3.52 (m, 1H, 4-H), 3.20 (s, 3H, OMe), 2.72 (dd, 1H, $J=13.6$, 5.3 Hz, 3-H_a), 2.05 (dd, 1H, $J=13.6$, 7.5 Hz, 3-H_b) and 1.50 (s, 3H, Me); *m/z* (%): 277 (M^+, 61), 269(13), 268(61) and 209(100).

3.5.8. Dimethyl 5-(2-naphthyl)pyrrolidine-2,4-dicarboxylate 6g. Prepared by general procedure C from **5g** (2.24 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded a colourless solid, which was purified by column chromatography eluting with 1:1 v/v ether–hexane to give **6f** (3.57 g, 100%) as colourless plates, mp 161–163 °C. (Found: C, 68.90; H, 6.20; N, 4.40. $C_{18}H_{19}NO_4$ requires: C, 69.00; H, 6.10; N, 4.45%); δ ($CDCl_3$, 250 MHz): 7.85–7.26 (m, 7H, ArH), 4.65 (d, 1H, $J=$ 8.1 Hz, 5-H), 4.04 (dd, 1H, $J=8.8$, 7.3 Hz, 2-H), 3.82 (s, 3H, OMe), 3.38 (m, 1H, 4-H), 3.12 (s, 3H, OMe) and 2.43–2.85 (m, 2H, 3-H_a/H_b); *m/z* (%): 313 (M^+, 60), 254(100), 240(62) and 195(10).

3.5.9. Dimethyl 5-cyclohexyl-2-methylpyrrolidine-2,4-dicarboxylate 6h. Prepared by general procedure C from **5h** (2.36 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded a colourless solid, which was purified by column chromatography eluting with 1:1 v/v ether–hexane to give **6h** (3.26 g, 95%) as colourless plates, mp 125–127 °C. (Found: C, 63.35; H, 9.00; N, 4.70. $C_{15}H_{25}NO_4$ requires: C, 63.60; H, 8.85; N, 4.95%); δ ($CDCl_3$, 250 MHz): 3.72 and 3.61 (2×s, 2×3H, 2×OMe), 2.90–2.96 (m, 2H, 5-H and 4-H), 2.68 (m, 1H, 3-H_a), 2.57 (m, 1H, 3-H_b), 1.40 (s, 3H, Me) and 2.05–0.90 (m, 11H, cyclohexyl-H); *m/z* (%): 283 (M^+, 21), 224(100), 165(47) and 150(17).

3.5.10. Dimethyl 5-cyclohexyl-2[2-(methylthioethyl]pyrrolidine-2,4-dicarboxylate 6i. Prepared by general procedure B from **5i** (3.08 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded a colourless solid, which was purified by column chromatography eluting with 3:2 v/v ether–hexane to give **6i** (3.79 g, 92%) as a colourless viscous oil. (Found: C, 59.50; H, 8.50; N, 4.15; S, 9.05. $C_{17}H_{29}NO_4S$ requires: C, 59.45; H, 8.45; N, 4.10; S, 9.350%); δ ($CDCl_3$, 250 MHz): 3.77 and 3.63 (2×s, 2×3H, OMe), 2.95–2.83 (m, 2H, 5-H and 4-H), 2.65–2.50 (m, 3H. SCH_2 and 3-H_a), 2.26 (m, 1H, 3-H_b), 2.07 (s, 3H, SMe), 2.04–0.84 (m, 13H, CH_2 and cyclohexyl-H); *m/z* (%): 343 (M^+, 16), 296(80), 284(100) and 225(21).

3.5.11. Dimethyl 5-cyclohexylpyrrolidine-2,4-dicarboxylate 6j. Prepared by general procedure C from **5j** (2.2 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded a colourless solid, which was purified by column chromatography eluting with 1:1 v/v ether–hexane to give **6j** (3.07 g, 95%) as colourless plates, mp 35–37 °C. (Found: C, 62.35; H, 8.75; N, 5.05. $C_{14}H_{23}NO_4$ requires: C, 62.45; H, 8.55; N, 5.20%); δ ($CDCl_3$+2 drops C_6D_6, 250 MHz): 3.83 (dd, 1H, $J=5.5$, 10.0 Hz, 2-H), 3.76 and 3.64 (2×s, 2×3H, 2×OMe), 2.94 (ddd, 1H, $J=1.7$, 5.8,

7.3 Hz, 4-H), 2.82 (dd, 1H, $J=5.8$, 9.5 Hz, 5-H), 2.39–2.15 (m, 2H, 3-H_a/H_b), and 2.20–1.15 (m, 11H, cyclohexyl-H); *m/z* (%): 269 (M^+, 21), 210(100), 186(47) and 150(17).

3.5.12. Dimethyl 2-(2-methylthioethyl)-5-(2-naphthyl) pyrrolidine-2,4-dicarboxylate 6k. Prepared by general procedure C from **5k** (3.61 g, 12 mmol) and methyl acrylate (2.24 g, 24 mmol). Work up afforded a colourless solid, which was purified by column chromatography eluting with 1:1 v/v ether–hexane to give **6h** (4.5 g, 100%) as colourless needles, mp 176–178 °C. (Found: C, 65.00; H, 6.50; N, 3.70; S, 8.35. $C_{21}H_{25}NO_4S$ requires: C, 65.10; H, 6.45; N, 3.60; S, 8.250%); δ ($CDCl_3$, 250 MHz): 7.75–7.68 (m, 4H, ArH), 7.39–7.27 (m, 3H, ArH), 4.63 (d, 1H, $J=6.9$ Hz, 5-H), 3.79 (s, 3H, OMe), 3.28 (ddd, 1H, $J=7.4$, 6.9, 3.9 Hz, 4-H), 3.04 (s, 3H, OMe), 2.71–2.60 (m, 2H, CH_2SMe and 3-H_a), 2.32 (m, 1H, CH_2SMe), 2.17–2.01 (m, 2H, CH_2CH_2SMe and 3-H_b), 2.03 (s, 3H, SMe) and 1.88 (m, 1H, CH_2CH_2SMe); *m/z* (%): 387 (M^+, 56), 328(100), 369(31) and 222(46).

3.5.13. Methyl (1*S*,2*R*,4*S*,5*R*,8*R*)-2-methyl-4-(2′-naphthyl)-3-aza-6-oxo-7-oxa-8-(1′*R*,2′*S*,5′*R*-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate 8a. Prepared by general procedure B and C. The product showed identical spectral data as described in literature.[14b]

3.5.14. Methyl (1*S*,2*R*,4*S*,5*R*,8*R*)-4-(2′-naphthyl)-3-aza-6-oxo-7-oxa-8-(1′*R*,2′*S*,5′*R*-menthyloxy)-bicyclo[3.3.0] octane-2-carboxylate 8b. Prepared by general procedure B and C. The product showed identical spectral data as described in literature.[14b]

3.5.15. Methyl (1*S*,2*R*,4*S*,5*R*,8*R*)-2-methyl-4-(cyclohexyl)-3-aza-6-oxo-7-oxa-8-(1′*R*,2′*S*,5′*R*-menthyloxy)-bicyclo[3.3.0]octane-2-carboxylate 8c. Prepared by general procedure B and C. The product showed identical spectral data as described in literature.[14b]

3.5.16. 2-Methyl-2-{[1-pyridin-3-yl-methylidene]-amino}-pentanedioic acid dimethyl ester 11b. Prepared by general procedure E from imine **5l** (215 mg, 1.12 mmol) and methyl acrylate (0.15 mL, 1.68 mmol). Purification by flash column chromatography (ether) afforded the product (21 mg, 82%) as a colourless gum. HRMS: $[M+H]^+C_{14}H_{19}N_2O_4$ requires 279.1345; found 279.1347. δ (500 MHz): 8.87 (br, m, 1H, PyH), 8.66 (br, s, 1H, PyH), 8.34 (s, 1H, N=CH), 8.15 (dt, 1H, $J=8.2$, 1.8 Hz, PyH), 7.37 (dd, 1H, $J=8.2$, 5.2 Hz, PyH), 3.76 (s, 3H, CO_2CH_3), 3.65 (s, 3H, CO_2CH_3), 2.54–2.34 (m, 3H, C$HCH_2CO_2CH_3$), 2.17 (ddd, 1H, $J=13.6$, 9.3, 6.6 Hz, C$HCH_2CO_2CH_3$) and 1.54 (s, 3H, CH_3). δ ^{13}C: 191.2 (C=N), 2×174.1 (C=O), 157.7, 152.2, 150.9, 135.0 and 124.0 (PyC), 68.1 (4 °C), 52.7 and 52.0 (CO_2CH_3), 35.4 and 29.8 (CH_2) and 23.7 (CH_3). ν (film, cm^{-1}): 3055 (C–$H_{stretch}$), 1732 (C=O_{ester}), 1647 (C=N) and 1591 (C=$C_{aromatic}$); *m/z* (ES^+, %): 279 ($[M+H]^+$, 100).

Acknowledgements

We thank the Mary and Alice Smith Memorial Fund (E.M.) and the Commonwealth Scholarship Commision in the UK (M.A.B.S.) for scholarships and Leeds University, GlaxoSmithKline and the EPSRC for support. We thank the EPSRC, Leeds University and the Royal Society for support.

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