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PAPER

1,3-Dipolar cycloaddition of unstabilised azomethine ylides by Lewis base catalysis†

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Lewis base catalysed 1,3-dipolar cycloaddition between α,β-unsaturated acyl fluorides and *N*-[(trimethylsilyl)methyl]amino ethers has been achieved using 1 mol% DMAP. Competition experiments and ^{19}F-NMR studies indicate that the cycloaddition occurs preferentially between the α,β-unsaturated acyl fluoride and the unstabilised azomethine ylide. In addition, an enantioselective variant, using chiral isothiourea catalysts, has been achieved with 14% ee.

Introduction

The 1,3-dipolar cycloaddition of unstabilised azomethine ylides (*i.e.* **1**) with electron poor dipolarophiles is a useful approach to the stereoselective synthesis of pyrrolidines **2**.[1] While generation of the unstabilised azomethine ylide can be achieved using a number of methods, the desilylation of *N*-[(trimethylsilyl)-methyl]amino ethers (*i.e.* **3**) with metal fluorides,[2] or trifluoracetic acid,[3] remains a common strategy.[4] Despite on-going application of this reaction, realisation of a catalytic enantioselective variant has received little attention. This is in contrast to stabilized azomethine ylides, whose application in catalytic enantioselective transformations is well documented.[5,6] From our reading the only studies towards a catalytic enantioselective 1,3-dipolar cycloaddition of unstabilised azomethine ylides have been attempted using chiral Lewis acids, and unfortunately gave only 2% ee.[6,7] Presumably this lack of selectivity arose due to unselective 1,3-dipolar cycloaddition of stoichiometrically generated azomethine ylide **1** and the dipolarophile, in the absence of the chiral Lewis acid.

To address this limitation we envisaged an orthogonal approach to enantioselectivity, through the use of chiral Lewis base catalysis.[8] We postulated that by exploiting an α,β-unsaturated acid fluoride such as **4**,[9,10] and an appropriate chiral Lewis base, homochiral **5** could be generated, with concomitant formation of the unstabilised azomethine ylide **1**. Such a strategy would ensure that ylide **1** was maintained at substoichiometric levels and, provided the rate of cycloaddition between **5** and **1** is more rapid than with **4**, this should allow the development of an enantioselective pyrrolidine synthesis (Scheme 1). To trial this concept we recently commenced studies focused on establishing the viability of Lewis base catalysis of the 1,3-dipolar cycloaddition of unstabilised azomethine ylides. Herein, we report the first example of Lewis base catalysis of the 1,3-dipolar cycloaddition of unstabilised azomethine ylides.

Results and discussion

Studies commenced with the identification of Lewis base catalysts for the cycloaddition between cinnamoyl fluoride **4a** and ylide precursor **3a**. *N*-Heterocyclic carbenes (NHCs) have been shown to activate acyl fluorides,[9] and provided a starting place for optimisation. Bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene, IMes (**A1**), generated from the imidazolium salt precursor, was able to catalyse the formation of pyrrolidine **2a**, which was isolated in 21% yield (Table 1, entry 1). Changing from toluene to THF increased the yield moderately (Table 1, entry 1 *cf.* 2), as did increasing the steric demand of the NHC through the use of 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene IPr (**A2**) (Table 1, entry 3). Finally generation of IPr (**A2**) by deprotonation of the imidazolium in toluene followed by filtration to remove salt byproducts increased the yield to 58% (Table 1, entry 4). The role of endogenous metal salts and Lewis acid additives is well documented.[11]

While this yield is serviceable, alternate nucleophilic catalysts were trialled to improve the reaction. Although catalytic DABCO (**B**)[12] and isothiourea (**C**)[13] provided 20 and 70% of the expected pyrrolidine **2a** (Table 1, entries 5 and 6), we were pleased to find that 10 mol% DMAP (**D**) gave pyrrolidine **2a** in 85% yield (Table 1, entry 7). Furthermore, the catalytic loading could be decreased to 1 mol% with no detrimental effect on the reaction (Table 1, entry 8). However, when performed with 0.1 mol% DMAP the reaction was very slow, and after 36 h had failed to reach completion (Table 1, entry 9).

With conditions that allowed nucleophilic catalysis of the 1,3-dipolar cycloaddition in hand, the generality of the

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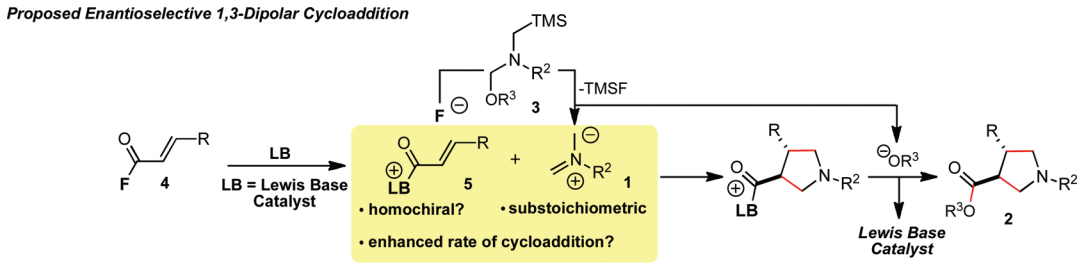
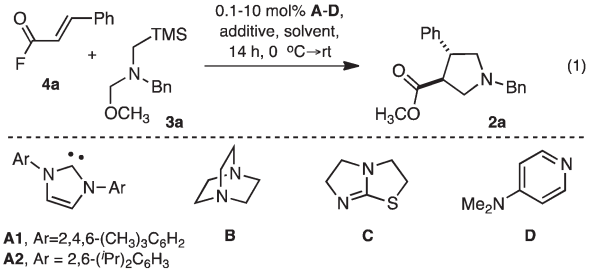
†Electronic supplementary information (ESI) available: ^{1}H- and ^{13}C-NMR spectra of all reported compounds as well as additional experimental procedures. See DOI: 10.1039/c2ob26047f



Scheme 1 Reaction design.

Table 1 Selected optimisation studies



Entry	[mol%] cat.	Additives	Solvent	Yield **3a**[a]
1	10% **A1**	10% KO^{t}Bu	Toluene	21
2	10% **A1**	10% KO^{t}Bu	THF	34
3	10% **A2**	10% KO^{t}Bu	THF	38
4	10% **A2**[b]	—	THF	58
5	10% **B**	—	THF	70
6	10% **C**	—	THF	20
7	10% **D**	—	THF	85
8	**1 mol% D**	—	**THF**	**81**
9	0.1 mol% **D**	—	THF	48[c]

[a] Isolated yield following flash column chromatography. [b] Generated from the imidazolium and isolated from KCl. [c] Isolated yield after 36 h.

transformation was examined (Table 2). In contrast to other cycloadditions exploiting unstabilised azomethine ylide **1**, the ether in precursor **3** is required for catalyst turnover, and is ultimately found in the ester functionality of the pyrrolidine product **2** (see Scheme 1). Thus, studies began by examining the chemistry of ylide precursors **3a–d** bearing methyl through to *t*-butyl ethers (Table 1, entry 1). In all cases these ylide precursors reacted smoothly with cinnamoyl fluoride **4a** to provide pyrrolidines **2a–d** in good yields. Even the hindered *t*-butyl ester containing pyrrolidine **2d** could be produced in 62% yield (Table 1, entry 1d).

Next the scope with respect to the dipolarophile was examined, initially using a range of cinnamoyl fluorides (**4e–i)** with differing electronic and steric demand. In all cases the pyrrolidines (**2e–i**) were formed in acceptable yields using the standard reaction conditions (Table 1, entry 2). Heteroaromatic groups, in the form of a 2-furyl, could be included at the β-position of the α,β-unsaturated acyl fluoride (*i.e.* **4j**) giving rise to pyrrolidine **2j** in 79% yield (Table 1, entry 3). α,β,γ,δ-Unsaturated acyl fluoride **4k** was also viable providing only pyrrolidine **2k** in 76% isolated yield (Table 1, entry 4), with none of the possible (4 + 3) product formed.[14] When the ylide precursor contained an *S*-methyl benzyl group (*i.e.* **3l**), pyrrolidine **2l** formed with no diastereoselectivity (Table 1, entry 5). This result is consistent with other studies exploiting this chiral auxiliary that proceed with modest diastereoselectivity.[15] Similarly, menthol derived ylide precursor **3m** provided pyrrolidine **2m** in good yield (Table 1, entry 6), but with no diastereoselectivity (*vide infra*).

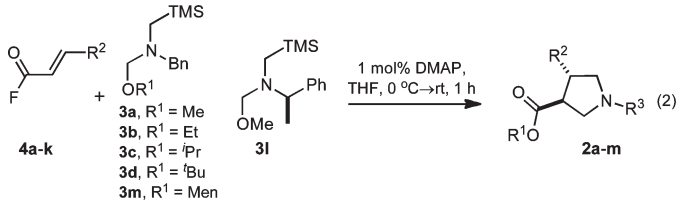
Lewis base catalysis without α,β-unsaturated acyl fluorides

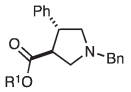
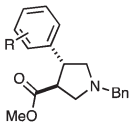
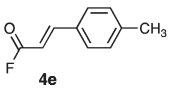
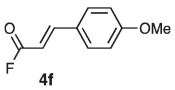
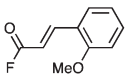
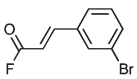
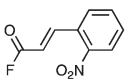
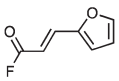
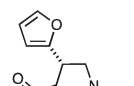
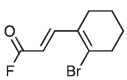
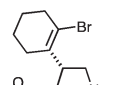
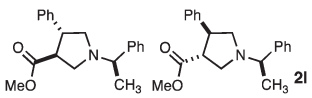
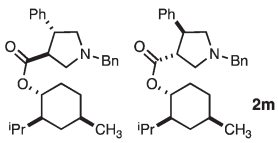
The low catalyst loading, mild conditions and short reaction times, allow favourable comparison to more established approaches. While the necessity of acyl fluorides **4** may be viewed as a limitation, we have found these materials to be easily prepared, and stable when stored appropriately. However, to address this potential limitation modified reaction conditions were developed exploiting commercially available benzoyl fluoride as a sacrificial fluoride source.[16] In this case Lewis base mediated defluoronation generates benzoyl pyridinium and fluoride, the later triggers the 1,3-dipolar cycloaddition with turnover achieved through conversion of the former to the benzoate ester. These reaction conditions were investigated using a range of α,β-unsaturated esters **6**. When methyl and ethyl cinnamates **6a–q** were examined their dipolar cycloaddition with ylide precursor **3a** was complete at room temperature after 6 h (Table 3, entry 1). In all cases yields were comparable to those obtained starting with the acyl fluoride (Table 2, entry 2 *cf.* Table 3, entry 1). In addition the reaction was compatible with esters bearing heteroaromatic motifs (Table 3, entry 2), while the reaction with ethyl propiolate **6s** could be achieved to yield the dihydropyrrole **2s** in good yield (Table 3, entry 3). This later transformation could not be achieved from the acid fluoride due to difficulties preparing the substrate. In all cases separation of the pyrrolidine from the methyl benzoate byproduct was easily achieved by flash column chromatography.

Mechanistic studies

Having demonstrated the generality of the reaction attention was directed towards an enantioselective variant. For this to be viable the cycloaddition between acyl pyridinium **5** and ylide **1** (Scheme 2, Path A) must be faster than esterification of **5** to provide **6t**, and also cycloaddition between the α,β-unsaturated acid fluoride **4e** and ylide **1** (Scheme 2, Path B). To investigate these questions a competition study between acyl fluoride **4e** and ester **6a** was undertaken. The major product of this reaction was

Table 2 Scope of the DMAP catalysed 1,3-dipolar cycloaddition



Entry	Acyl fluoride (**4**)	Ylide precursor **3**	Product **2**	Yield[a]
1	 **4a**			
a		**3a**	**2a**, R^1 = Me	81
b		**3b**	**2b**, R^1 = Et	81
c		**3c**	**2c**, R^1 = ^{i}Pr	68
d		**3d**	**2d**, R^1 = ^{t}Bu	62
2				
a	 **4e**	**3a**	**2e**, R = *p*Me	80
b	 **4f**	**3a**	**2f**, R = *p*OMe	73
c	 **4g**	**3a**	**2g**, R = *o*OMe	75
d	 **4h**	**3a**	**2h**, R = *m*Br	72
e	 **4i**	**3a**	**2i**, R = *o*NO_2	65
3	 **4j**	**3a**	 **2j**	79
4	 **4k**	**3a**	 **2k**	76
5	 **4a**	**3l**	 **2l**	80[b]
6		**3m**	 **2m**	80[b]

[a] Isolated yield following flash column chromatography. [b] Isolated in a 1 : 1 ratio as determined by ^{1}H-NMR analysis.

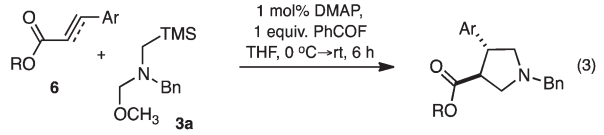
pyrrolidine **2e**. If this reaction proceeds *via* an ester intermediate (*i.e.* **6t**) then the major product would be pyrrolidine **2a**, since this can form directly from **6a** (Scheme 1, Path C). The formation of **2e** as the major product indicates that the dipolarophile in this reaction is either acyl pyridinium **5**, or acyl fluoride **4e** and the reaction occurs *via* Path A or B.

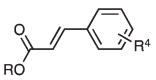
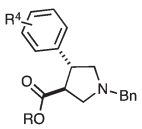
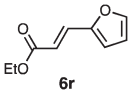
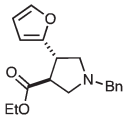
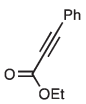
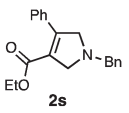
Further support for cycloaddition *via* either Path A or B can be gleaned from considering the reaction of homochiral menthol ester **6u** (Scheme 3). When reacted with ylide precursor **3a**, using conditions previously described in Table 3, pyrrolidine **2m** formed as a 2 : 1 mixture of diastereoisomers.[17] In contrast when pyrrolidine **2m** was prepared from the menthol containing ylide precursor **3m** and cinnamoyl fluoride **4a** a 1 : 1 mixture was obtained (Table 2, entry 6). If menthol ester **6u** was an intermediate in the later transformation, then it should form with the same diastereoselectivity in both cases.

To clarify whether the dipolarophile is acyl pyridinium **5** or acyl fluoride **4e** the competition described in Scheme 2 was repeated using TFA to generate the ylide, followed by a work-up to convert acyl fluoride pyrrolidine **7** to the ester. In this case the acyl pyridinium intermediate **5** cannot form. When conducted the same ratio of cycloadducts was obtained as in Scheme 2. Combined, these results indicate that the 1,3-cycloaddition between the acyl fluoride **4e** and ylide precedes with at least the same rate as the cycloaddition with the acyl pyridinium **5**.

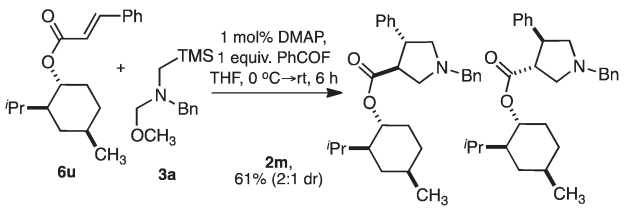
Further evidence for preferential cycloaddition between the α,β-unsaturated acyl fluoride and the unstabilised azomethine ylide was obtained by *in situ* ^{19}F-NMR analysis of the reaction mixture. If cycloaddition occurs solely *via* the pyridinium then two fluorine-containing materials should be observed, the α,β-unsaturated acyl fluoride and TMSF. In contrast, a third fluorine-containing compound, *i.e.* **7**, would be observable if the 1,3-dipolar cycloaddition occurs with the α,β-unsaturated acid fluoride. In the event, a new signal was observed at 40.09 ppm when the reaction was monitored by ^{19}F-NMR (Scheme 4). This signal is typical of an acyl fluoride, and was attributed to acyl pyrrolidine **7** (Scheme 4).[18]

Table 3 Scope of the DMAP catalyzed 1,3-dipolar cycloaddition of α,β-unsaturated esters

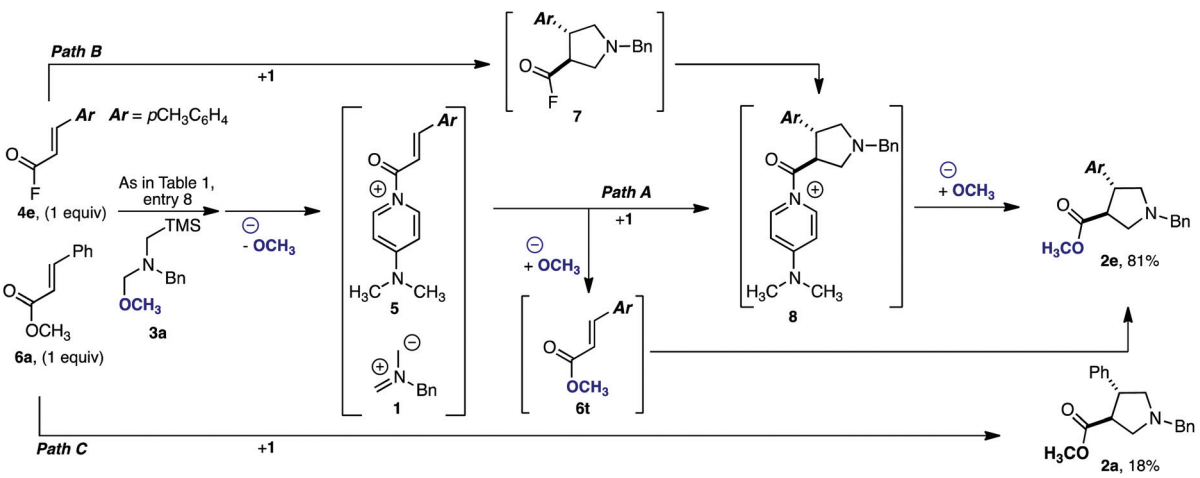


Entry	Ester **6**	Product **2**	Yield[a]
			
1a	**6a**, R = Me R^4 = H	**2a**	89
b	**6g**, R = Me, R^4 = *o*-Me	**2g**	93
c	**6i**, R = Et, R^4 = *o*-NO_2	**2i**	65
d	**6n**, R = Et, R^4 = *o*-CH_3	**2n**	91
e	**6o**, R = Et, R^4 = *p*-NO_2	**2o**	82
f	**6p**, R = Et, R^4 = *o*-MeO	**2p**	91
g	**6q**, R = Et, R^4 = *o*-Br	**2q**	72
2	 **6r**	 **2r**	67
3	 **6s**	 **2s**	90

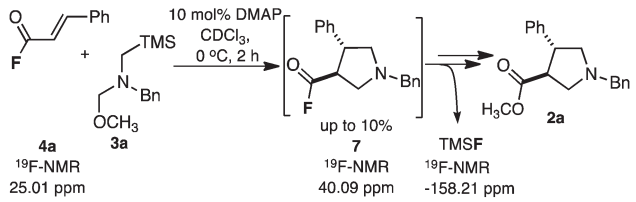
[a] Isolated yield following flash column chromatography.



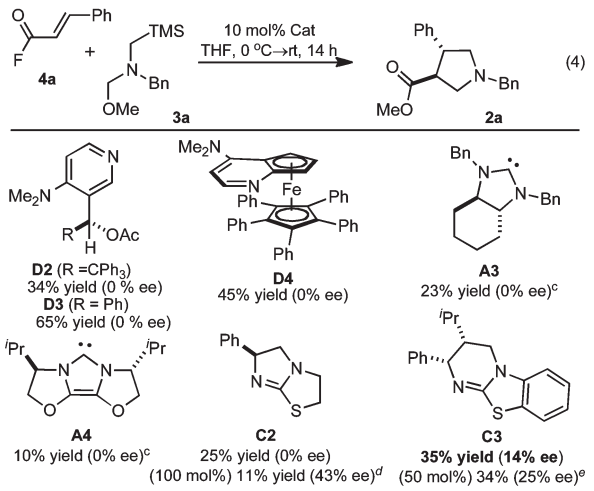
Scheme 3 Diastereoselective 1,3-dipolar cycloaddition with menthol **6v**.



Scheme 2 DMAP catalysed competition between α,β-unsaturated acyl fluoride **4e** and ester **6a**.



Scheme 4 Key signals from reactions monitored with ^{19}F-NMR.



[a]Isolated yield following flash column chromatography [b]Enantiomeric excess determined by HPLC analysis using chiral stationary phases. [c]Reaction performed from -20 °C to room temperature. [d]Reaction performed in dioxane. [e]Slow addition of acyl fluoride **4a** by syringe pump over 14 hours.

Chart 1 Studies into the enantioselective 1,3-dipolar cycloaddition[a,b].

Enantioselective 1,3-dipolar cycloaddition of unstabilised azomethine ylides

The facile cycloaddition between unstabilised azomethine ylide **1** and α,β-unsaturated acyl fluorides makes the development of an enantioselective variant of this reaction challenging. Of course the kinetics of the 1,3-dipolar cycloaddition will be controlled by the nature of the specific catalyst. Thus, we decided to screen a range of common chiral Lewis bases (Chart 1, eqn (4)). When homochiral DMAP derivatives[19] of Vedejs (**D2** and **D3**)[20] and Fu (**D4**)[21] were exposed to the reaction conditions they failed to induce any enantioselectivity. In addition known chiral NHCs (**A3** and **A4**)[22] failed to induce asymmetry. Finally, chiral isothioureas[23] were investigated. When 10 mol% tetramisole (**C2**) was trialled no enantioselectivity was observed. However, with 100 mol% **C2**, and sequential addition of reagents, pyrrolidine **2a** formed with 35% ee, although in moderate yield. The enantioselectivity could be increased to 43% ee by exploiting dioxane as the solvent. While an exhaustive study of isothioureas was not undertaken we found that 10 mol% **C3**[24] provided pyrrolidine **2a** in an improved 35% yield and 14% ee. By increasing the catalyst loading to 50 mol% and adding the acyl fluoride **4a** over 14 h the enantioselectivity could be improved to 25%. Although the selectivity and yield are clearly not optimal, results using **C3** suggest the possibility of an enantioselective Lewis-base catalysed 1,3-dipolar cycloaddition.

Conclusions

The 1,3-dipolar cycloaddition of unstabilised azomethine ylide **1** with electron poor olefins has been achieved using Lewis base catalysis. Optimal conditions exploit 1 mol% DMAP and allow a broad range of cycloadducts to be generated. In addition, use of benzoyl fluoride as a sacrificial fluoride source allows the cycloaddition to be achieved with readily accessible α,β-unsaturated esters. Together these procedures increase the flexibility with which 1,3-dipolar cycloadditions of unstabilised azomethine ylides can be achieved. Competition and ^{19}F-NMR studies indicate that, in the former reaction, the cycloaddition occurs preferentially between the α,β-unsaturated acyl fluoride and the azomethine ylide.

Studies with homochiral isothiourea catalyst **C3** demonstrate that low levels of enantioselectivity can be achieved. While these are modest, they provide proof of principle for such a strategy. Future studies are focused on the development of new chiral Lewis base catalysts capable of delivering α,β-unsaturated Lewis base adducts with greatly enhanced reactivity.

Experimental

General experimental

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 400 MHz for proton, 100 MHz for carbon nuclei and 282 MHz for fluorine. High resolution mass spectra (HRMS) (ESI) were recorded using NaI for accurate mass calibration. Flash column chromatography was performed on silica gel (LC60A, 40–63 μm silica media) using compressed nitrogen. Thin layer chromatography (TLC) was performed using aluminium-backed plates coated with 0.2 mm silica. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable stain followed by heating. Tetrahydrofuran and dioxane were distilled from sodium benzophenone ketyl, toluene from sodium metal, and dichloromethane from calcium hydride. Azomethine ylide precursors prepared using procedures communicated by Padwa[2] and others.[3] Starting acyl fluorides were prepared according to the procedure of Chen *et al.*[25] Starting esters **6** were prepared according to procedures of Chuzel and Piva[26] or Brooks and Chan.[27]

General procedure for the 1,3-cycloaddition using α,β-unsaturated acyl fluorides

A flame dried and N_2 purged round bottom flask was charged with a magnetic stirrer bar, acid fluoride **4a–k** (0.2 mmol), ylide precursor **3a–m** (0.22 mmol) and THF (3 mL). The resultant solution was magnetically stirred and cooled to 0 °C as a solution of DMAP (0.002 mmol, 0.24 mg) in THF (1 mL) was added. The reaction was stirred at 0 °C for 1 h, then warmed to room temperature over 10 min. Solvent was removed *in vacuo*, and the residue purified *via* flash column chromatography to provide the pyrrolidine **2a–m** (Table 2).

(3*S*,4*R*)-Methyl 1-benzyl-4-phenylpyrrolidine-3-carboxylate and (3*R*,4*S*)-methyl 1-benzyl-4-phenylpyrrolidine-3-carboxylate (2a).[28] Clear oil; R_f 0.39 (1 : 4 v/v ethyl acetate–hexanes); IR

ν_{max} 3080, 3030, 1745, 1676, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (m, 10H), 3.70 (d, J_{AB} = 13.0 Hz, 1H), 3.65 (d, J_{AB} = 13.0 Hz, 1H), 3.66 (s, 3H), 3.11–2.99 (m, 4H), 2.89–2.87 (m, 1H), 2.78–2.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 144.3, 138.9, 128.8, 128.7, 128.4, 127.6, 127.2, 126.7, 61.9, 60.1, 57.6, 52.1, 51.8, 47.1.

(3*S*,4*R*)-Ethyl 1-benzyl-4-phenylpyrrolidine-3-carboxylate and (3*R*,4*S*)-ethyl 1-benzyl-4-phenylpyrrolidine-3-carboxylate (2b).[29] Clear oil; R_f 0.46 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3061, 3028, 2792, 1731, 1630, 1451 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13–7.04 (m, 10H), 4.02–3.94 (m, 2H), 3.57 (d, J_{AB} = 13.0 Hz, 1H), 3.53–3.50 (m, 1H), 3.51 (d, J_{AB} = 13.0 Hz, 1H), 2.94–2.85 (m, 3H), 2.75–2.71 (m, 1H), 2.65–2.61 (m, 1H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 144.4, 139.0, 128.8, 128.6, 128.4, 127.6, 127.1, 126.6, 61.9, 60.8, 60.1, 57.6, 52.0, 47.1, 14.3.

(3*S*,4*R*)-isoPropyl 1-benzyl-4-phenylpyrrolidine-3-carboxylate and (3*R*,4*S*)-isopropyl 1-benzyl-4-phenylpyrrolidine-3-carboxylate (2c). Clear oil; R_f 0.37 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3061, 3028, 1731, 1676, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.18 (m, 10H), 3.79 (sep, J = 6.0 Hz, 1H), 3.74–3.64 (m, 3H), 3.15–2.97 (m, 3H), 2.94–2.90 (m, 1H), 2.78–2.74 (m, 1H), 1.14 (d, J = 6.0 Hz, 3H), 1.13 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 144.2, 139.0, 128.8, 128.7, 128.4, 127.6, 127.2, 126.7, 88.1, 72.4, 62.0, 60.1, 57.4, 52.0, 47.0, 22.6; HRMS (ESI) *m/z* found $(M + H)^+$ 324.1963, $C_{21}H_{25}NO_2$ requires $(M + H)^+$, 324.1958.

(3*S*,4*R*)-*tert*Butyl 1-benzyl-4-phenylpyrrolidine-3-carboxylate and (3*R*,4*S*)-*tert*butyl 1-benzyl-4-phenylpyrrolidine-3-carboxylate (2d).[30] Clear oil; R_f 0.47 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3061, 3027, 2792, 1734, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.18 (m, 10H), 3.71 (d, J_{AB} = 13.0 Hz, 1H), 3.64 (d, J_{AB} = 13.0 Hz, 1H), 3.61–3.56 (m, 1H), 3.05–2.96 (m, 3H), 2.86–2.82 (m, 1H), 2.78–2.74 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 144.3, 139.9, 128.8, 128.6, 128.4, 127.7, 127.1, 126.5, 80.7, 62.0, 60.1, 57.5, 52.9, 47.2, 28.2.

(3*S*,4*R*)-Methyl 1-benzyl-4-(*p*-tolyl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-methyl 1-benzyl-4-(*p*-tolyl)pyrrolidine-3-carboxylate (2e).[31] Clear oil; R_f 0.38 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3060, 3026, 2789, 1734, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.10 (m, 9H), 3.71 (d, J_{AB} = 13.0 Hz, 1H), 3.66 (s, 3H), 3.66 (d, J_{AB} = 13.0 Hz, 1H), 3.12–2.99 (m, 3H), 2.92–2.88 (m, 2H), 2.75–2.71 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 141.2, 139.0, 136.2, 129.4, 128.8, 128.4, 127.4, 127.1, 62.0, 60.1, 57.5, 52.1, 52.0, 46.9, 21.2.

(3*S*,4*R*)-Methyl 1-benzyl-4-(4′-methoxyphenyl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-methyl 1-benzyl-4-(4′-methoxyphenyl)-pyrrolidine-3-carboxylate (2f).[32] Clear oil; R_f 0.17 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3029, 2951, 2835, 2793, 1732, 1438, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 4H), 7.25–7.23 (m, 3H), 6.84–6.82 (m, 2H), 3.78 (s, 3H), 3.70 (d, J_{AB} = 13.2 Hz, 1H), 3.65 (s, 3H), 3.64 (d, J_{AB} = 13.2 Hz, 1H), 3.06–2.97 (m, 4H), 2.89–2.87 (m, 1H), 2.73–2.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 158.4, 138.9, 136.3, 128.5, 128.4(9), 128.4(2), 127.2, 114.1, 62.0, 60.1, 57.5, 55.4, 52.0, 51.9, 46.5; HRMS (ESI) *m/z* found $(M + H)^+$ 326.1753, $C_{20}H_{24}NO_3$ requires $(M + H)^+$ 326.1751.

(3*S*,4*R*)-Methyl 1-benzyl-4-(2′-methoxyphenyl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-methyl 1-benzyl-4-(2′-methoxyphenyl)-pyrrolidine-3-carboxylate (2g).[33] Clear oil; R_f 0.33 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3027, 2949, 2835, 2795, 1733, 1437, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.16 (m, 7H), 6.93–6.89 (m, 1H), 6.84–6.82 (m, 1H), 4.03–3.97 (m, 1H), 3.77 (s, 3H), 3.72 (d, J = 13.0 Hz, 1H), 3.65 (s, 3H), 3.64 (d, J = 13.0 Hz, 1H), 3.16–3.12 (m, 1H), 3.02–2.98 (m, 2H), 2.93–2.89 (m, 1H), 2.78–2.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 157.3, 139.0, 131.6, 128.9, 128.4, 127.7, 127.1, 126.3, 120.8, 110.7, 60.1, 60.0, 57.6, 55.4, 51.9, 49.7, 41.7; HRMS (ESI) *m/z* found $(M + H)^+$ 326.1757, $C_{20}H_{24}NO_3$ requires $(M + H)^+$ 326.1751.

(3*S*,4*R*)-Methyl 1-benzyl-4-(3′-bromophenyl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-methyl 1-benzyl-4-(3′-bromophenyl)-pyrrolidine-3-carboxylate (2h). Clear oil; R_f 0.43 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3061, 3027, 2793, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (m, 1H), 7.37–7.30 (m, 5H), 7.27–7.24 (m, 2H), 7.17–7.13 (m, 1H), 3.67 (s, 3H), 3.69–3.64 (m, 2H), 3.63–3.61 (m, 1H), 3.11–3.04 (m, 2H), 2.96–2.92 (m, 1H), 2.83–2.79 (m, 1H), 2.76–2.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 146.9, 138.8, 130.6, 130.2, 129.8, 128.8, 128.5, 127.2, 126.3, 122.7, 61.5, 59.9, 57.4, 52.2, 51.7, 46.6; HRMS (ESI) *m/z* found $(M + H)^+$ 374.0758, $C_{19}H_{20}{}^{79}BrNO_2$ requires $(M + H)^+$ 374.0750.

(3*S*,4*R*)-Methyl 1-benzyl-4-(2′-nitrophenyl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-methyl 1-benzyl-4-(2′-nitrophenyl)pyrrolidine-3-carboxylate (2i). Clear oil; R_f 0.2 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3028, 1734, 1608, 1578, 1525, 1354 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 6.7 Hz, 1.3 Hz, 1H), 7.70 (dd, J = 6.7 Hz, 1.3 Hz, 1H), 7.57 (td, J = 6.7 Hz, 1.3 Hz, 1H), 7.38–7.24 (m, 6H), 4.10–4.06 (m, 1H), 3.71 (d, J_{AB} = 12.9 Hz, 1H), 3.67 (d, J_{AB} = 12.9 Hz, 1H), 3.67 (s, 3H), 3.29–3.25 (m, 1H), 3.12–3.06 (m, 1H), 2.97–2.91 (m, 2H), 2.70–2.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 149.9, 139.7, 138.7, 133.2, 129.3, 128.8, 128.5, 127.4, 127.3, 123.8, 61.6, 59.9, 57.6, 52.4, 52.2, 41.4; HRMS (ESI) *m/z* found $(M + H)^+$ 341.1501, $C_{19}H_{20}N_2O_4$ requires $(M + H)^+$ 341.1496.

(3*S*,4*S*)-Methyl 1-benzyl-4-(furan-2′-yl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-methyl 1-benzyl-4-(furan-2′-yl)pyrrolidine-3-carboxylate (2j). Clear oil; R_f 0.37 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3027, 2951, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.14 (m, 6H), 6.19 (dd, J = 2.0 Hz, 1.2 Hz, 1H), 6.00 (m, 1H), 3.73 (apparent q, J = 7.2, 1H), 3.61 (d, J_{AB} = 13.2 Hz, 1H), 3.61 (s, 3H), 3.55 (d, J_{AB} = 13.2 Hz, 1H), 3.14–3.09 (m, 1H), 2.97–2.88 (m, 1H), 2.88–2.81 (m, 2H), 2.62 (dd, J = 7.2 Hz, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 157.1, 142.6, 139.7, 129.8, 129.4, 128.2, 111.3, 106.2, 60.8, 59.8, 57.9, 53.2, 49.3, 41.4; HRMS (ESI) *m/z* found $(M + H)^+$ 286.1444, $C_{17}H_{19}NO_3$ requires $(M + H)^+$ 286.1438.

(3*S*,4*R*)-Methyl 1-benzyl-4-(2′-bromocyclohex-1-en-1-yl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-methyl 1-benzyl-4-(2′-bromocyclohex-1-en-1-yl)pyrrolidine-3-carboxylate (2k). Clear oil; R_f

0.42 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3028, 2933, 2859, 2838, 1733, 1435 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.23 (m, 5H), 3.91–3.86 (m, 1H), 3.68 (s, 3H), 3.66 (d, J_{AB} = 12.8 Hz, 1H), 3.56 (d, J_{AB} = 12.8 Hz, 1H), 2.94–2.88 (m, 2H), 2.80–2.71 (m, 2H), 2.53–2.48 (m, 3H), 2.19–2.15 (m, 2H), 1.73–1.61 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 138.9, 135.3, 128.7, 128.4, 127.1, 121.2, 60.0, 57.3(2), 57.2(5), 52.1, 48.0, 46.4, 37.2, 26.9, 24.9, 22.8; HRMS (ESI) *m/z* found $(M + H)^+$ 378.1068, $C_{19}H_{24}{}^{79}BrNO_2$ requires $(M + H)^+$ 378.1063.

(3*S*,4*R*,1′*R*)-Methyl 4-phenyl-1-(1′-phenylethyl)pyrrolidine-3-carboxylate and (3*R*,4*S*,1′*R*)-methyl 4-phenyl-1-(1′-phenylethyl)-pyrrolidine-3-carboxylate (2l).[34] Clear oil; R_f 0.5 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3060, 3027, 2780, 1734, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.18 (m, 10H), 3.66 (s, 1.5H), 3.64 (s, 1.5H), 3.63–3.61 (m, 1H), 3.34–3.29 (m, 1H), 3.16–3.01 (m, 2H), 2.96–2.88 (m, 1H), 2.85–2.78 (m, 1.5H), 2.65–2.61 (m, 0.5H), 1.41 (d, J = 6.4 Hz, 1.5 H), 1.39 (d, J = 6.4 Hz, 1.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8(0), 174.7 (6), 145.5, 145.3, 144.5, 144.2, 128.7, 128.6, 128.5, 128.5, 127.5(8), 127.5(7), 127.5(4), 127.3, 127.1(8), 127.1(5), 127.1 (0), 126.7, 65.4, 65.3, 60.8, 60.6, 56.6, 56.3, 52.0(3), 52.0(2), 52.0(1), 51.6, 47.0, 46.9, 23.3, 23.2.

General procedure for the 1,3-cycloaddition with esters and unstabilised ylides

A flame dried and N_2 purged round bottom flask was charged with a magnetic stirrer bar, benzoyl fluoride (0.2 mmol), ester **6a–t** (0.2 mmol), ylide precursor **3a** (0.22 mmol) and THF (3 mL). The resultant solution was magnetically stirred and cooled to 0 °C as a solution of DMAP (0.002 mmol) in THF (1 mL) was added. The reaction was allowed to stir at 0 °C for 30 min, then warmed to room temperature over 6 h. Solvent was removed *in vacuo*, and the residue purified *via* flash column chromatography to yield desired pyrrolidines **2a–s** (Table 3).

(3*R*,4*S*,1′*R*,2′*S*,4′*R*)-2′-Isopropyl-4′-methylcyclohexyl 1-benzyl-4-phenylpyrrolidine-3-carboxylate and (3*S*,4*R*,1′*R*,2′*S*,4′*R*)-2′-isopropyl-4′-methylcyclohexyl 1-benzyl-4-phenylpyrrolidine-3-carboxylate (2m). Clear oil; R_f 0.51 (1 : 9 v/v ethyl acetate–hexanes); IR ν_{max} 3027, 2933, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.18 (m, 10H), δ 4.70–4.62 (m, 1H), 3.76–3.61 (m, 3H), 3.10–3.00 (m, 3H), 2.92–2.85 (m, 1H), 2.79–2.74 (m, 1H), 1.97–1.94 (m, 1H), 1.75–1.60 (m, 4H), 1.51–1.42 (m, 1H), 1.34–1.24 (m, 2H), 1.07–0.97 (m, 1H), 0.88 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 1H), 0.79 (d, J = 6.8 Hz, 2H), 0.70 (d, J = 7.2 Hz, 1H), 0.67 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9(9), 173.8, 144.4, 144.1, 139.1, 128.8, 128.7, 128.6, 128.4, 127.6(4), 127.6, 127.1, 126.6(2), 126.6, 74.7, 62.1, 60.1, 57.7, 52.3(2), 52.3, 47.6, 47.1(4), 47.1, 41.1, 41.0, 34.4, 31.5, 26.3, 26.1, 23.5, 23.4, 22.2, 20.9, 16.3 (14 signals overlapping); HRMS (ESI) *m/z* found $(M + H)^+$ 420.2897, $C_{28}H_{37}NO_2$ requires $(M + H)^+$ 420.2902.

(3*S*,4*R*)-Ethyl 1-benzyl-4-(*p*-tolyl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-ethyl 1-benzyl-4-(*p*-tolyl)pyrrolidine-3-carboxylate (2n).[35] Clear oil; R_f 0.42 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3060, 3027, 2789, 1730, 1451 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.10 (m, 9H), 4.15–4.08 (m, 2H), 3.70 (d, J_{AB} = 13.2 Hz, 1H), 3.65 (d, J_{AB} = 13.2 Hz, 1H), 3.65–3.61 (m, 1H), 3.06–2.99 (m, 3H), 2.91–2.87 (m, 1H), 2.76–2.72 (m, 1H), 2.32 (s, 3H), 1.21 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 141.4, 139.1, 136.2, 129.3, 128.8, 128.4, 127.5, 127.1, 62.0, 60.8, 60.1, 57.6, 52.0, 46.8, 21.1, 14.4.

(3*S*,4*R*)-Ethyl 1-benzyl-4-(4′-nitrophenyl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-ethyl 1-benzyl-4-(4′-nitrophenyl)pyrrolidine-3-carboxylate (2o).[36] Clear oil; R_f 0.42 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3028, 2980, 2793, 1729, 1600, 1517, 1492, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16–8.14 (m, 2H), 7.52–7.50 (m, 2H), 7.36–7.26 (m, 5H), 4.17–4.12 (m, 2H), 3.78–3.74 (m, 1H), 3.72 (d, J_{AB} = 10.0 Hz, 1H), 3.67 (d, J_{AB} = 10.0 Hz, 1H), 3.21–3.17 (m, 1H), 3.07–3.02 (m, 1H), 2.97–2.93 (m, 1H), 2.85–2.76 (m, 2H), 1.23 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 152.7, 146.9, 138.7, 128.7, 128.5 (1), 128.4(6), 127.4, 124.0, 61.2, 61.1, 59.8, 57.4, 52.1, 46.7, 14.3.

(3*S*,4*R*)-Ethyl 1-benzyl-4-(2′-methoxyphenyl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-ethyl 1-benzyl-4-(2′-methoxyphenyl)pyrrolidine-3-carboxylate (2p).[32] Clear oil; R_f 0.36 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3061, 3029, 2957, 2834, 2790, 1729, 1448, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.23 (m, 7H), 6.85–6.83 (m, 2H), 4.16–4.10 (m, 2H), 3.78 (s, 3H), 3.72–3.59 (m, 3H), 3.07–2.97 (m, 3H), 2.90–2.86 (m, 1H), 2.75–2.71 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 158.3, 139.0, 136.4, 128.8, 128.5, 128.4, 127.1, 114.0, 62.0, 60.8, 60.1, 57.5, 55.4, 52.1, 46.4, 14.4 (2 signals overlapping or missing).

(3*S*,4*R*)-Ethyl 1-benzyl-4-(2′-bromophenyl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-ethyl 1-benzyl-4-(2′-bromophenyl)-pyrrolidine-3-carboxylate (2q). Clear oil; R_f 0.44 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3063, 3027, 2838, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, J = 6.0 Hz, 1.6 Hz, 1H), 7.51 (dd, J = 6.8 Hz, 1.2 Hz, 1H), 7.38–7.23 (m, 6H), 7.07–7.03 (m, 1H), 4.19–4.11 (m, 3H), 3.72 (d, J_{AB} = 12.8 Hz, 1H), 3.67 (d, J_{AB} = 12.8 Hz, 1H), 3.21–3.17 (m, 1H), 3.09–3.04 (m, 1H), 3.01–2.97 (m, 1H), 2.81–2.77 (m, 2H), 1.23 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 144.1, 139.0, 132.8, 128.8, 128.6, 128.4, 128.0(3), 128.0(2), 127.2, 124.6, 61.4, 61.0, 60.0, 57.5, 51.5, 46.1, 14.3; HRMS (ESI) *m/z* found $(M + H)^+$ 388.0914, $C_{20}H_{22}{}^{79}BrNO_2$ requires 388.0907.

(3*S*,4*R*)-Ethyl 1-benzyl-4-(furan-2′-yl)pyrrolidine-3-carboxylate and (3*R*,4*S*)-ethyl 1-benzyl-4-(furan-2′-yl)pyrrolidine-3-carboxylate (2r). Clear oil; R_f 0.39 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3062, 3028, 2795, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.26–7.14 (m, 6H), 6.13 (dd, J = 2.8 Hz, 1.2 Hz, 1H), 5.93 (d, J = 2.8 Hz, 1H), 4.01 (q, J = 7.2 Hz, 2H), 3.67 (apparent q, J = 7.2 Hz, 1H), 3.52 (d, J_{AB} = 13.2 Hz, 1H), 3.49 (d, J_{AB} = 13.2 Hz, 1H), 3.05–2.99 (m, 1H), 2.92–2.88 (m, 1H), 2.84–2.76 (m, 2H), 2.58 (dd, J = 7.2 Hz, 2.0 Hz, 1H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 156.1, 141.5, 138.6, 128.8, 128.4, 127.2, 110.2, 105.2, 61.0, 59.8, 58.8, 56.8, 48.5, 40.4, 14.3; HRMS (ESI) *m/z* found $(M + H)^+$ 300.1598, $C_{18}H_{21}NO_3$ requires $(M + H)^+$ 300.1594.

Ethyl 1-benzyl-4-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (2s).[37] Clear oil; R_f 0.35 (1 : 4 v/v ethyl acetate–hexanes); IR ν_{max} 3059, 3027, 2978, 2789, 1715, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 10H), 4.10 (q, J = 7.2 Hz, 2H), 3.92 (br s, 4H), 3.85 (s, 2H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 156.6, 144.0, 138.8, 133.2, 133.1, 132.9, 132.5, 132.2, 131.6, 130.2, 64.4, 60.2, 58.9, 58.8, 8.9.

Procedure for competition studies

A flame dried and N_2 purged round bottom flask was charged with a magnetic stirrer bar, acid fluoride (0.2 mmol), ester (0.2 mmol), ylide precursor (0.22 mmol) and 5 ml of anhydrous THF. The resultant solution was magnetically stirred and cooled to 0 °C and a solution of DMAP (0.002 mmol) in THF was added. The reaction was allowed to stir at 0 °C for 1 h, before being warmed to room temperature and stirred for a further 1 h. Solvent was removed *in vacuo*, and the residue purified *via* flash column chromatography (1 : 4, v/v ethyl acetate–hexanes) with both pyrrolidine products collected without seperation. The ratio of products formed were determined by ^1H NMR analysis, with comparison to previously reported data.

General procedure for the 1,3-cycloaddition with esters and unstabilised ylides using chiral catalysts

A flame dried and N_2 purged round bottom flask was charged with a magnetic stirrer bar, acid fluoride **4a** (0.2 mmol), ylide precursor **3a** (0.22 mmol) and THF (3 mL). The resulting stirred solution was cooled to 0 °C in an ice bath and a solution of the chiral catalyst (0.02 mmol) in THF (1 mL) was added in one portion. The reaction was allowed to warm to room temperature over the course of 14 h. Solvent was removed *in vacuo*, and the residue was purified *via* flash column chromatography (1 : 4 v/v ethyl acetate–hexanes) to yield pyrrolidine **2a**.

When using NHC catalysts **A3** and **A4**: A flame dried and N_2 purged round bottom flask was charged with a magnetic stirrer bar, the NHC precursor (0.02 mmol) and THF (2 ml). The resulting stirred mixture was treated with KO^{t}Bu (0.02 mmol) and allowed to stir for 1 h. The reaction vessel was then cooled to −20 °C and a solution of acid fluoride (0.2 mmol) and ylide precursor (0.2 mmol) in THF (3 ml) added dropwise. The reaction was allowed to warm to room temperature and then stirred overnight. Solvent was removed *in vacuo*, and the residue purified *via* flash column chromatography (1 : 4 v/v ethyl acetate–hexanes) to yield pyrrolidine **2a**. Enantiomeric excess was determined by HPLC analysis, Daicel AD-H, λ = 238 nm, hexane–i-PrOH = 98 : 2; 0.5 ml min^{-1}, fraction t_r = 13.78 min (major enantiomer) and 15.18 (minor enantiomer) (see ESI†).

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