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Isothiourea-Catalysed Asymmetric *C*-Acylation of Silyl Ketene Acetals

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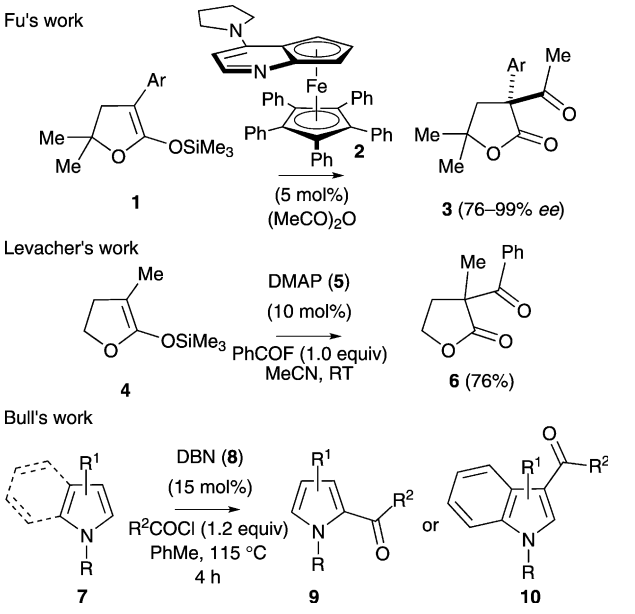
Abstract: Screening of a range of chiral isothioureas and acyl donors to promote the asymmetric *C*-acylation of silyl ketene acetals indicates that C(2)-aryl-dihydropyrimidobenzothiazole-derived isothioureas and propionic anhydride give optimal reactivity and enantioselectivity in this process. Under optimised conditions 3-acyl-3-aryl or 3-acyl-3-alkylfuranones are prepared in good yields and moderate to excellent enantioselectivities (up to 98% *ee*; *ee* = enantiomeric excess).

Keywords: acylation · asymmetric synthesis · isothioureas · organocatalysis · silyl ketene acetals

Introduction

The asymmetric alkylation or conjugate addition of 1,3-dicarbonyl species is a widely recognised and useful tool in synthesis, offering the preparation of functionalised building blocks with the potential for further synthetic manipulation.[1] Alternative strategies for the synthesis of these building blocks, such as the development of methods that allow the *C*-acylation or *C*-carboxylation of enolates, are much less developed. One of the most widely recognised problems associated with this latter process is competitive *O*- and *C*-acylation, leading to mixtures of *O*- and *C*-functionalised products.[2] A number of ingenious processes to solve these issues have been developed, including the tetrabutylammonium fluoride (TBAF) promoted *C*-acylation of silyl enol ethers[3] or Lewis acid promoted *C*-acylation of enolsilanes.[4] Alternative methodologies, such as Mander's seminal work utilising cyanoformates,[5] have been used to allow the *C*-carboxylation of ketone enolates to generate β-keto esters. Over the past decade a plethora of Lewis base[6] catalyst architectures capable of delivering *C*-carboxyl derivatives with high enantiomeric excess (*ee*) through the implementation of asymmetric Steglich[7] or Black rearrangements[8] have been developed. Gröger and Dietz have also shown that isothioureas promote the asymmetric *C*-acylation of oxazolyl acetates (*O*- to *C*-acyl transfer) with good *ee*.[9] Alternative Lewis base strategies that allow the *C*-acylation of enolates include the approach by Fu and Mermerian, utilising the planar, chiral 4-(pyrrolidino)pyridine (PPY) derivative **2** to promote the enantioselective *C*-acetylation of cyclic and acyclic silyl ketene acetals that bear an α-aryl or α-alkenyl substituent with acetic anhydride.[10] This elegant approach has been extended by Fu and Mermerian to allow the asymmetric *C*-acylation of silyl ketene imines, with application to the synthesis of Verapamil.[11] Levacher and co-workers subsequently showed that 4-dimethylaminopyridine (DMAP, **5**) could promote the efficient *O*-benzoylation of silyl enol ethers with benzoyl fluoride, and limited examples of the DMAP-mediated *C*-benzoylation of silyl ketene acetals, such as **4**, with benzoyl fluoride.[12] An interesting recent development in Lewis base catalysed *C*-acylations by Bull and co-workers has shown that 1,5-diazabicyclo(4.3.0)non-5-en (DBN, **8**) is an efficient catalyst for Friedel–Crafts acylations of pyrroles and indoles (Scheme 1).[13]



Scheme 1. Catalytic *C*-acylation/*C*-benzoylation strategies of silyl ketene acetals by Fu and Levacher, and the Friedel–Crafts acylation of pyrroles and indoles by Bull.

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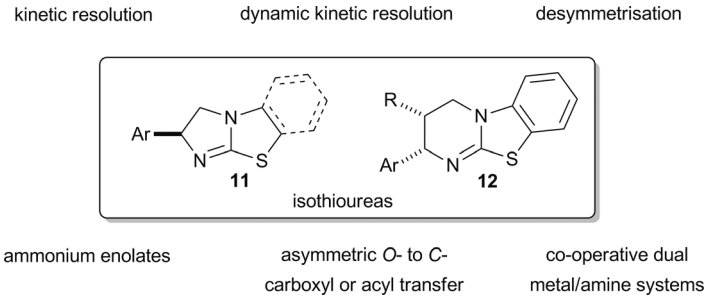
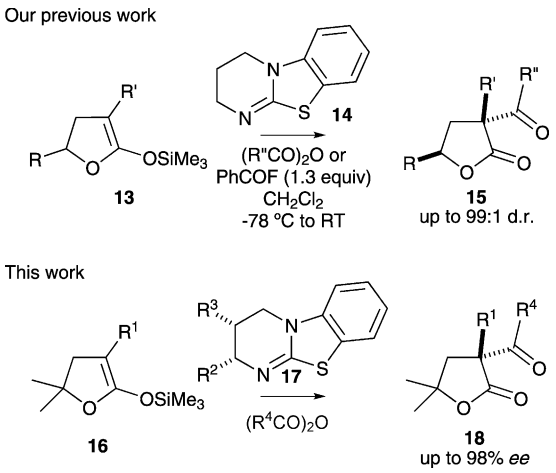
Among the recent developments in asymmetric acyl or carboxyl transfer processes with Lewis bases, the use of isothioureas of the generic structures **11** and **12** (Scheme 2), in-



Scheme 2. Applications of isothioureas in asymmetric catalysis.



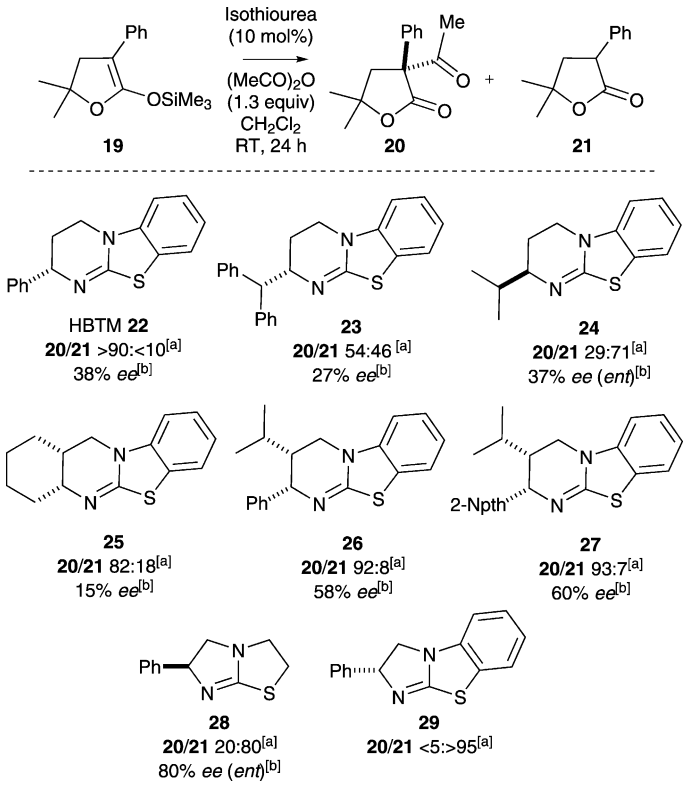
Scheme 3. Proposed isothiourea-promoted asymmetric *C*-acylation of silyl ketene acetals.

itially introduced by Birman and co-workers, is particularly notable.[14] These bench- and air-stable catalyst architectures are either commercially available or are prepared in a few simple steps from readily available materials and have been used in a range of asymmetric acylation protocols including kinetic resolutions,[15] dynamic kinetic resolutions[16] desymmetrisations[17] and *O*- to *C*-carboxyl[18] and acyl transfer processes.[9] Their recent incorporation into co-operative dual-catalytic systems with Co(salen) complexes,[19] as well as their use as catalysts for the generation of ammonium enolates from carboxylic acids[20] with applications to desymmetrising aldol cyclisations,[21] as well as intra- and intermolecular Michael addition reactions[22] has further expanded their synthetic utility, arguably allowing this structural motif to be recognised as a privileged catalyst architecture.

Building upon these precedents and on our interest in Lewis base mediated catalytic transformations involving N-heterocyclic carbenes (NHCs)[23] and isothioureas,[24] we have recently shown that the isothiourea DHPB (DHPB = 3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole) **14** promotes the highly diastereoselective *C*-acylation of silyl ketene acetals such as **13**.[25] We wished to extend this process to allow the asymmetric *C*-acylation of silyl ketene acetals **16** by using chiral isothioureas (Scheme 3). Herein, we demonstrate that C(2)-aryl-substituted dihydropyrimidobenzothiazole-derived isothioureas are efficient catalysts for this transformation and delineate the scope and limitations of this transformation.

Results and Discussion

Optimisation studies: Initial optimisation studies probed the effectiveness of a range of chiral 3,4-dihydropyrimido[2,1-*b*]benzothiazole-based isothioureas (**22**–**29**) as Lewis base promoters (10 mol%) for the *C*-acetylation of silyl ketene acetal **19** with acetic anhydride (1.3 equiv) at room temperature. As a benchmark standard, isothiourea (HBTM, homobenzotetramisole **22**) gave good levels of conversion to the desired *C*-acyl product **20**, generating <10% of the parent lactone **21** (Scheme 4, ratio **20**/**21** 93:7 determined by ^{1}H NMR spectroscopic analysis), although with only 38% *ee*. Alternative isothioureas **23** and **24** containing either C(2)-benzhydryl or C(2)-isopropyl substituents showed only modest product conversion and enantioselectivity under identical conditions, whereas good product con-



Scheme 4. Screening of the isothiourea reactivity and the enantioselectivity for the *C*-acylation of silyl ketene acetal **19** with acetic anhydride. [a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [b] Determined by HPLC analysis.

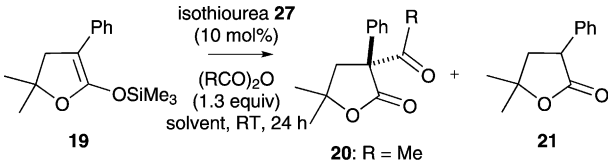
version but reduced enantioselectivity was observed by using the constrained tetracyclic isothiourea **25**. Improved enantioselectivity (up to 60% *ee*) and good levels of product conversion (>90%) was observed with the 2,3-disubstituted isothioureas **26** and **27** bearing a C(2)-aryl unit and a *cis*-C(3)-*i*Pr substituent. Evaluation of the alternative isothioureas tetramisole (**28**) and benzotetramisole (**29**) in this process gave poor conversion to the *C*-acetyl **20** (<20%), albeit with high enantioselectivity (80% *ee*) by using **28** (Scheme 4). The absolute configuration of **20** was assigned by comparison of its specific rotation [+138.0 ($c=0.5$ in CH_2Cl_2, 60% *ee*, prepared by using **27**)] to the literature [(*ent*) −213.0 ($c=0.9$ in CH_2Cl_2, 90% *ee*)].[10]

The large difference in catalytic activity observed by using isothioureas **22**–**29** in this model reaction is notable. The trends in reactivity (in terms of conversion to product **20**) observed in this system for the tetrahydropyrimidine-based catalysts **22**–**27** mirror their reactivity (in terms of rate and catalytic efficiency) in kinetic resolution processes.[15g] The beneficial effect upon enantioselectivity of the additional *cis*-C(3)-*i*Pr substituent in isothiourea **26** in comparison to HBTM (**22**) is also consistent with the work of Birman with HBTM-2,[15e] and our own studies that use **26**,[15g] in kinetic resolution processes. Qualitatively, the observed reactivity profiles for **22**–**27** also correspond to their relative nucleophilicities and Lewis basicities as measured photometrically through their reaction with benzhydrilium ions.[24b] Relating these properties of a given isothiourea directly to their organocatalytic activity in a specific reaction is difficult, however, as these are two important, but not the only properties that control catalyst reactivity in a given transformation.

Having identified isothioureas **26** and **27** as the most efficient *C*-acetylation catalysts with promising enantioselectivity, further optimisation focused upon the effect of the solvent and the acyl donor source with isothiourea **27**. For the acetylation of **19** with acetic anhydride at room temperature, optimal product enantioselectivities were observed in either CH_2Cl_2, *tert*-amyl alcohol or toluene, with reduced enantioselectivity in Et_2O or hexane, and optimal product conversion was observed by using CH_2Cl_2. Subsequent studies focused upon the effect of variation of the acyl donor. Benzoic anhydride or benzoyl fluoride led to the highest observed enantioselectivity at room temperature (76 and 69% *ee*, respectively) but only modest product conversion (<35%) in each case. The use of propionic anhydride gave good product conversion and increased enantioselectivity in comparison to acetic anhydride, whereas isobutyric anhydride gave only poor product conversion (<10%). Optimal enantioselectivity in this process was observed upon changing the reaction temperature (−78°C to RT), giving the *C*-propionyl **30** in 80% *ee* and 86% yield by using propionic anhydride (Table 1).

Reaction generality: With an optimised protocol in hand, the generality of this process was demonstrated through variation of the C(3)-substituent (aryl, heteroaryl and benzyl units) within a series of silyl ketene acetals by using propionic anhydride as the acyl source. Isothioureas **26** and **27** readily promote *C*-acylation of C(3)-aryl-substituted silyl ketene acetals, with substitution of the aryl unit readily tolerated. Optimal enantioselectivites (>90% *ee*) were observed with 3-(1-naphthyl) and 3-(2-methylphenyl) substituents, although the introduction of a 2-substituent upon a C(3)-aryl substituent does not generally lead to enhanced enantioselectivity. Furthermore, this asymmetric protocol gives markedly reduced enantioselectivity for 3-(2-thiophenyl) substitution (35% *ee*), yet tolerates C(3)-benzyl substitution with modest enantioselectivity (56% *ee*), indicating that asymmetric induction in this process is highly substrate dependent (Scheme 5).

Table 1. Isothiourea-promoted catalytic asymmetric *C*-acylation of silyl ketene acetal **19**.[a]



19

20: R = Me
30: R = Et
31: R = *i*Pr
32: R = Ph

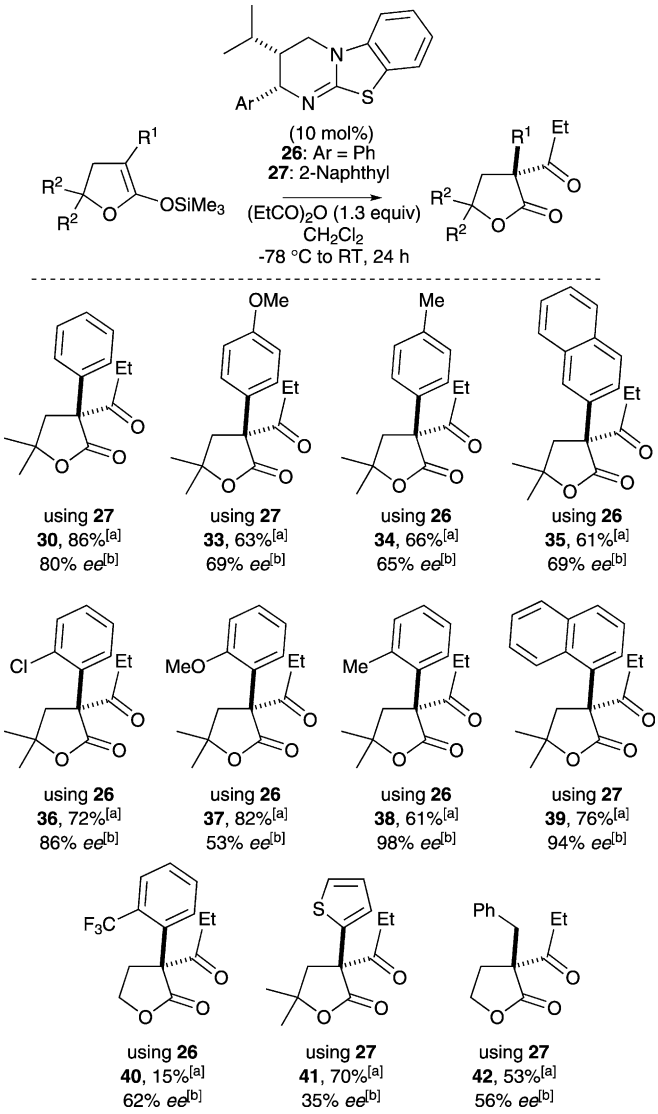
21

Entry	Solvent	Acyl source	R	Ratio *C*-acyl/**21**[b]	*ee* [%][c]
1	CH_2Cl_2	$(MeCO)_2O$	Me	93:7	60
2	toluene	$(MeCO)_2O$	Me	88:12	57
3	THF	$(MeCO)_2O$	Me	90:10	51
4	Et_2O	$(MeCO)_2O$	Me	80:20	40
5	hexane	$(MeCO)_2O$	Me	89:11	38
6	*tert*-amyl alcohol	$(MeCO)_2O$	Me	89:11	60
7	CH_2Cl_2	PhCOF	Ph	24:76	69
8	CH_2Cl_2	$(PhCO)_2O$	Ph	33:67	76
9	CH_2Cl_2	$(i\text{PrCO})_2O$	*i*Pr	9:91	–
10	CH_2Cl_2	$(EtCO)_2O$	Et	91:9	66
11[d]	CH_2Cl_2	$(EtCO)_2O$	Et	86:14	80

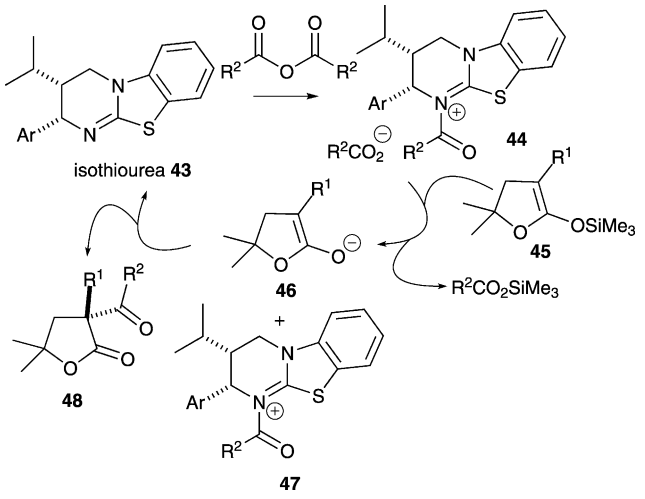
[a] All absolute configurations were assigned by analogy to that unambiguously determined for **20**. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [c] Determined by HPLC analysis with reference to racemic samples prepared by using DHPB (see the Supporting Information for full details). [d] Reaction temperature −78°C to RT.

Proposed mechanism and model for the asymmetric induction: Consistent with both the proposal by Fu,[10,11] and our previous work in this area,[25] we propose that the mechanistic course for this transformation requires initial formation of an activated acyl-isothiourionium ion such as **44** from the isothiourea and propionic anhydride, with desilyation of the silyl ketene acetal promoted by the carboxylate counterion generating enolate **24**. Subsequent asymmetric *C*-acylation of enolate **46** with **44** generates the *C*-acyl product **48** with good to high levels of enantioselectivity and regenerates the isothiourea (Scheme 6).

Consistent with this mechanistic model and with the previous work of Fu, the enantioselectivity of *C*-acylation in this process is independent of silyl substitution of the silyl ketene acetal, although the tri-*iso*-propylsilyl ketene acetal **49** proved much less reactive than the trimethylsilyl ketene

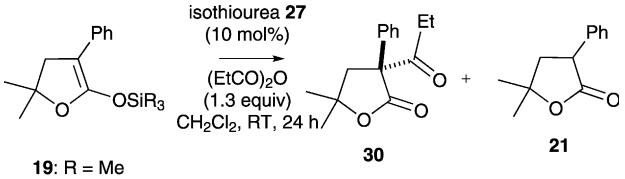


Scheme 5. Isothiourea-catalysed asymmetric *C*-acylation of silyl ketene acetals. All absolute configurations were assigned by analogy to that unambiguously determined for **20**. [a] Yield of isolated homogeneous product. [b] Determined by HPLC analysis with reference to a racemic samples prepared by using DHPB (see the Supporting Information for full details).



Scheme 6. Proposed mechanism for the isothiourea-promoted asymmetric *C*-acylation of silyl ketene acetals.

Table 2. Variation of the silyl unit in the asymmetric *C*-acylation of silyl ketene acetals.

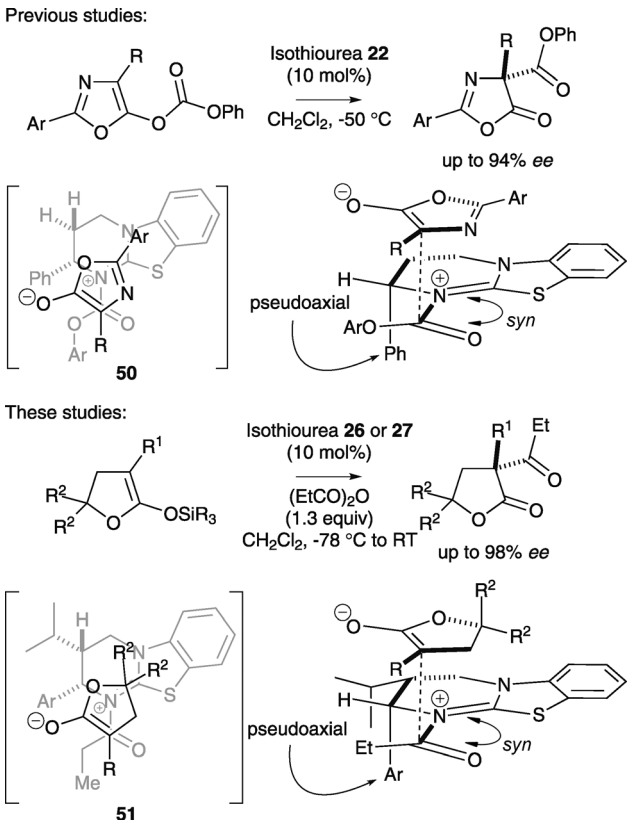


Entry	R	Ratio **30**/**21**[a]	*ee* [%][b]
1	Me	93:7	66
2	*i*Pr	26:74	64

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product; [b] Determined by HPLC analysis with reference to a racemic samples prepared by using DHPB (see the Supporting Information for full details).

acetal **19** under identical conditions (Table 2). Simplistically, this observation is consistent with the reaction proceeding preferentially through a free enolate rather than a hypervalent silicate species.

The chiral isothioureas **26** and **27** generate the same sense of asymmetric induction in this *C*-acylation protocol as observed previously in their highly enantioselective *C*-carboxylation reactions of oxazolyl carbonates.[18] By analogy to our previous transition state modelling for this *C*-carboxylation reaction (preferred transition state **50** shown schematically in Scheme 7), combined with the modelling studies from Birman and Houk on the origin of amidine (CF_3-PIP = 2-phenyl-6-trifluoromethyl-dihydroimidazo[1,2α]pyridine) catalysed kinetic resolutions,[26] a simplistic model to account for the enantioselectivity of the *C*-acylation of silyl ketene acetals is outlined below. We envisage that the *N*-propionyl group of the *N*-acylated isothiourea lies approximately coplanar with the tetrahydropyrimidine unit of the heterocycle, with the *syn* rotamer (C=O group *syn* to C=N) preferred. This forces the adjacent C(2)-aryl unit to adopt a pseudoaxial position, minimising 1,2-strain.[27] Preferential acylation of the enolate subsequently takes place *anti* to this stereodirecting axial unit, through a transition state such as **51**, in which the geminal dimethyl unit of the enolate is oriented toward the planar aromatic portion of the isothiourea, minimising interactions with the axial C(3)–H of the tetrahydropyrimidinium ion. Although this simple model accounts for the observed stereoselectivity in these transformations, this rationalisation does not account for the variation in the *ee* with C(3) substitution. Furthermore, the significant beneficial effect of the adjacent C(3)-*i*Pr substituent is also not immediately clear, although we postulate that this additional substituent may act to restrict the conformational



Scheme 7. Proposed simplistic model for the asymmetric *C*-acylation of silyl ketene acetals with isothioureas.

flexibility of the *N*-acyl intermediate, leading to higher stereocontrol.

Conclusion

In conclusion, chiral isothioureas promote the efficient asymmetric *C*-acylation of silyl ketene acetals with anhydrides with modest to high enantiocontrol (up to 98% *ee*). Ongoing studies within this laboratory are directed toward the demonstration of alternative reaction protocols that use isothioureas and other Lewis bases in asymmetric catalysis.

Experimental Section

For general experimental details see the Supporting Information. The Supporting Information also contains spectroscopic and HPLC data for all compounds.

General procedure for the isothiourea-catalysed asymmetric *C*-acylation of silyl ketene acetals: The requisite chiral isothiourea (10 mol%) was added to a solution of the required silyl ketene acetal (1.0 equiv) in the necessary anhydrous solvent under argon. The resulting mixture was stirred for five minutes at the requisite temperature, after which the required acyl species (1.3 equiv) was added. The reaction mixture was stirred overnight at the necessary temperature, exposed to air and concentrated in vacuo to yield a crude reaction product that was purified by chromatography.

Preparation of (*S*)-5,5-dimethyl-3-phenyl-3-propionyldihydrofuran-2-(3*H*)-one (30): Following the general procedure, compound **27** (18 mg, 0.0500 mmol, 10 mol%), compound **19** (131 mg, 0.500 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at −78 °C and $(EtCO)_2O$ (0.08 mL, 0.650 mmol, 1.3 equiv) at −78 °C to RT gave a product distribution containing **30**. Purification of the residue by flash column chromatography on silica gel (silica, Et_2O/40–60 petrol 5:95) gave **30** as a colourless oil (106 mg, 86%), which was shown by chiral HPLC [Daicel CHIRALCEL AS-H, 4.6×250 mm, 2-propanol/hexane 1:99, 0.5 mL min^{-1}, retention times of enantiomers: 16.00 (major), 18.50 min (minor)] to have 80% *ee*. $[\alpha]_D^{25} = +146.0$ ($c = 0.5$ in CH_2Cl_2, for product with 66% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.83 (t, $J = 7.2$ Hz, 3H), 1.16 (s, 3H), 1.31 (s, 3H), 2.15 (d, $J = 13.4$ Hz, 1H), 2.30 (dq, $J = 7.2$, 18.6 Hz, 1H), 2.71 (dq, $J = 7.2$, 18.6 Hz, 1H), 3.33 (d, $J = 13.4$ Hz, 1H), 7.16–7.30 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.5$, 28.8, 29.1, 32.0, 45.0, 68.1, 82.5, 126.7, 128.1, 129.5, 139.0, 172.9, 204.4 ppm; ν_{max} (film) = 2925, 2855, 1763, 1718 cm^{-1}; MS (NSI$^+$): *m/z* (%): 247 $[M+H]^+$ (100); HRMS (NSI$^+$): *m/z* calcd for $C_{15}H_{19}O_3^+$: 247.1329 $[M+H]^+$; found: 247.1331 (+0.9 ppm).

Preparation of (S)-3-(4-methoxyphenyl)-5,5-dimethyl-3-propionyldihydrofuran-2(3*H*)-one (33): Following the general procedure, compound **27** (18 mg, 0.0500 mmol, 10 mol%), compound **52** (146 mg, 0.500 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at −78 °C and $(EtCO)_2O$ (0.08 mL, 0.650 mmol, 1.3 equiv) at −78 °C to RT gave a product distribution containing **33**. Purification of the residue by flash column chromatography on silica gel (silica, Et_2O/40–60 petrol 10:90) gave **33** as a colourless oil (87 mg, 63%), which was shown by chiral HPLC [Daicel CHIRALCEL AS-H, 4.6×250 mm, 2-propanol/hexane 1:99, 0.5 mL min^{-1}, retention times of enantiomers: 29.05 (major), 35.77 min (minor)] to have 69% *ee*. $[\alpha]_D^{25} = +152.0$ ($c = 0.5$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (t, $J = 7.2$ Hz, 3H), 1.29 (s, 3H), 1.44 (s, 3H), 2.27 (d, $J = 13.4$ Hz, 1H), 2.45 (dq, $J = 7.2$, 18.5 Hz, 1H), 2.82 (dq, $J = 7.2$, 18.5 Hz, 1H), 3.42 (d, $J =$ 13.4 Hz, 1H), 3.84 (s, 3H), 6.89–6.95 (m, 2H), 7.29–7.34 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.5$, 28.8, 29.0, 31.8, 44.9, 55.4, 67.3, 82.5, 114.7, 127.9, 130.8, 159.3, 173.2, 204.7 ppm; ν_{max} (film) = 2979, 1755, 1716, 1610, 1513 cm^{-1}; MS (NSI$^+$): *m/z* (%): 294 $[M++NH_4]^+$ (100); HRMS (NSI$^+$): *m/z* calcd for $C_{16}H_{24}NO_4^+$: 294.1700 $[M+NH_4]^+$; found: 294.1701 (+0.4 ppm).

Preparation of (*S*)-5,5-dimethyl-3-propionyl-3-(*p*-tolyl)dihydrofuran-2-(3*H*)-one (34): Following the general procedure, compound **26** (15 mg, 0.0500 mmol, 10 mol%), compound **53** (138 mg, 0.500 mmol, 1.0 equiv), in CH_2Cl_2 (4 mL) at −78 °C and $(EtCO)_2O$ (0.08 mL, 0.650 mmol, 1.3 equiv) at −78 °C to RT gave a product distribution containing **34**. Purification of the residue by flash column chromatography on silica gel (silica, Et_2O/40–60 petrol 5:95) gave **34** as a colourless oil (86 mg, 66%), which was shown by chiral HPLC [Daicel CHIRALCEL AS-H, 4.6× 250 mm, 2-propanol/hexane 1:99, 0.5 mL min^{-1}, retention times of enantiomers: 14.90 (major), 16.98 min (minor)] to have 65% *ee*. $[\alpha]_D^{25} = +$ 150.0 ($c = 0.5$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J =$ 7.2 Hz, 3H), 1.23 (s, 3H), 1.39 (s, 3H), 2.23 (d, $J = 13.4$ Hz, 1H), 2.32 (s, 3H), 2.33–2.46 (m, 1H), 2.78 (dq, $J = 7.2$, 18.6, 1H), 3.38 (d, $J = 13.4$ Hz, 1H), 7.16 (d, $J = 8.2$ Hz, 2H), 7.19–7.24 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 8.4$, 21.1, 28.8, 29.0, 31.8, 44.9, 67.7, 82.4, 126.5, 130.1, 136.0, 137.9, 173.0, 204.5 ppm; ν_{max} (film) = 2979, 1756, 1716, 1514 cm^{-1}; MS (NSI$^+$): *m/z* (%): 261 $[M+H]^+$ (100); HRMS (NSI$^+$): *m/z* calcd for $C_{16}H_{21}O_3^+$: 261.1485 $[M+H]^+$; found: 261.1480 (−2.0 ppm).

Preparation of (S)-5,5-dimethyl-3-(naphthalen-2-yl)-3-propionyldihydrofuran-2(3H)-one (35): Following the general procedure, compound **26** (15 mg, 0.0500 mmol, 10 mol%), compound **54** (156 mg, 0.500 mmol, 1.0 equiv), in CH_2Cl_2 (4 mL) at −78 °C and $(EtCO)_2O$ (0.08 mL, 0.650 mmol, 1.3 equiv) at −78 °C to RT gave a product distribution containing **35**. Purification of the residue by flash column chromatography on silica gel (silica, Et_2O/40–60 petrol 5:95) gave **35** as a colourless oil (91 mg, 61%), which was shown by chiral HPLC [Daicel CHIRALCEL AS-H, 4.6×250 mm, 2-propanol/hexane 1:99, 0.5 mL min^{-1}, retention times of enantiomers: 21.97 (major), 25.84 min (minor)] to have 69% *ee*. $[\alpha]_D^{25} = +184.0$ ($c = 0.5$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.93$ (t, $J = 7.2$, 3H), 1.25 (s, 3H), 1.46 (s, 3H), 2.32–2.47 (m, 2H), 2.89 (dq, $J = 7.2$, 18.7 Hz, 1H), 3.52 (d, $J = 13.4$ Hz, 1H), 7.31 (dd, $J = 2.0$, 8.7 Hz,

1H), 7.49–7.54 (m, 2H), 7.81–7.89 (m, 3H), 7.99 ppm (d, $J=1.9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=8.4$, 28.9, 29.1, 32.1, 44.8, 68.3, 82.7, 124.1, 125.9, 126.9, 126.9, 127.7, 128.4, 129.5, 132.6, 133.4, 136.2, 172.9, 204.4 ppm; ν_{max} (film): 2979, 1754, 1716, 1598, 1507 cm^{-1}; MS (NSI$^+$) *m/z* (%): 297 $[M+H]^+$ (100); HRMS (NSI$^+$): *m/z* calcd for $C_{19}H_{21}O_3^+$: 297.1485 $[M+NH_4]^+$; found: 297.1480 (−1.8 ppm).

Preparation of (S)-3-(2-chlorophenyl)-5,5-dimethyl-3-propionyldihydrofuran-2(3*H*)-one (36): Following the general procedure, compound **26** (15 mg, 0.0500 mmol, 10 mol%), compound **55** (148 mg, 0.500 mmol, 1.0 equiv), in CH_2Cl_2 (4 mL) at −78 °C and $(EtCO)_2O$ (0.08 mL, 0.650 mmol, 1.3 equiv) at −78 °C to RT gave a product distribution containing **36**. Purification of the residue by flash column chromatography on silica gel (silica, Et_2O/40–60 petrol 5:95) gave **36** as a colourless oil (101 mg, 72%), which was shown by chiral HPLC [Daicel CHIRALPAK AD-H, 4.6×250 mm, 2-propanol/hexane 1:99, 0.5 mL min^{-1}, retention times of enantiomers: 15.30 (minor), 18.35 min (major)] to have 86% *ee*. $[\alpha]_D^{25}=+202.0$ ($c=0.5$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.94$ (t, $J=7.1$ Hz, 3H), 1.18 (s, 3H), 1.47 (s, 3H), 2.10–2.24 (m, 2H), 2.73 (dq, $J=7.1$, 19.0 Hz, 1H), 3.58 (d, $J=13.8$ Hz, 1H), 7.21–7.30 (m, 2H), 7.35–7.38 (m, 1H), 7.49–7.52 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 8.2, 29.0, 29.6, 32.7, 44.2, 68.8, 83.5, 127.6, 129.5, 129.6, 131.1, 133.0, 138.2, 172.4, 203.9 ppm; ν_{max} (film) = 3069, 2979, 2878, 1755, 1722, 1591, 1570 cm^{-1}; MS (NSI$^+$): *m/z* (%): 298 $[M+NH_4]^+$ (100); HRMS (NSI$^+$): *m/z* calcd for $C_{15}H_{21}ClNO_3^+$: 298.1204 $[M+NH_4]^+$; found: 298.1207 (+0.8 ppm).

Preparation of (*S*)-3-(2-methoxyphenyl)-5,5-dimethyl-3-propionyldihydrofuran-2(3*H*)-one (37): Following the general procedure, compound **26** (15 mg, 0.0500 mmol, 10 mol%), compound **56** (146 mg, 0.500 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at −78 °C and $(EtCO)_2O$ (0.08 mL, 0.650 mmol, 1.3 equiv) at −78 °C to RT gave a product distribution containing **37**. Purification of the residue by flash column chromatography on silica gel (silica, Et_2O/40–60 petrol 20:80) gave **37** as a colourless oil (113 mg, 82%), which was shown by chiral HPLC [Daicel CHIRALCEL AS-H, 4.6×250 mm, 2-propanol/hexane 1:99, 0.5 mL min^{-1}, retention times of enantiomers: 19.85 (minor), 25.00 min (major)] to have 53% *ee*. $[\alpha]_D^{25}=+84.0$ ($c=0.5$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.96$ (t, $J=7.2$ Hz, 3H), 1.26 (s, 3H), 1.46 (s, 3H), 2.02 (d, $J=13.6$ Hz, 1H), 2.23 (dq, $J=7.2$, 18.7 Hz, 1H), 2.71 (dq, $J=7.2$, 18.7 Hz, 1H), 3.50 (d, $J=$ 13.6 Hz, 1H), 3.74 (s, 3H), 6.89 (dd, $J=0.9$, 8.5 Hz, 1H), 6.97 (td, $J=1.1$, 7.6 Hz, 1H), 7.28–7.34 ppm (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta=$ 8.3, 29.1, 29.6, 31.8, 43.8, 55.2, 66.5, 83.3, 111.3, 121.1, 128.2, 129.3, 129.5, 156.1, 173.6, 205.0 ppm; ν_{max} (film) = 2978, 2939, 1754, 1721, 1599, 1586 cm^{-1}; MS (NSI$^+$): *m/z* (%): 294 $[M+NH_4]^+$ (100); HRMS (NSI$^+$): *m/z* calcd for $C_{16}H_{24}NO_4^+$: 294.1700 $[M+NH_4]^+$; found: 294.1693 (−2.3 ppm).

Preparation of (*S*)-5,5-dimethyl-3-propionyl-3-(*o*-tolyl)dihydrofuran-2-(3*H*)-one (38): Following the general procedure, compound **26** (15 mg, 0.0500 mmol, 10 mol%), compound **57** (138 mg, 0.500 mmol, 1.0 equiv), in CH_2Cl_2 (4 mL) at −78 °C and $(EtCO)_2O$ (0.08 mL, 0.650 mmol, 1.3 equiv) at −78 °C to RT gave a product distribution containing **38**. Purification of the residue by flash column chromatography on silica gel (silica, Et_2O/40–60 petrol 10:90) gave **38** as a colourless oil (79 mg, 61%), which was shown by chiral HPLC [Daicel CHIRALCEL OD-H, 4.6× 250 mm, 2-propanol/hexane 1:99, 0.5 mL min^{-1}, retention times of enantiomers: 12.34 (minor), 14.50 min (major)] to have 98% *ee*; $[\alpha]_D^{25}=+$ 210.0 ($c=0.5$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 0.99 (t, $J=7.2$ Hz, 3H), 1.25 (s, 3H), 1.51 (s, 3H), 2.05 (s, 3H), 2.08 (d, $J=13.2$ Hz, 1H), 2.16 (dq, $J=7.2$, 19.1 Hz, 1H), 2.93 (dq, $J=7.2$, 19.1 Hz, 1H) 3.60 (d, $J=$ 13.2 Hz, 1H), 7.18–7.23 (m, 1H), 7.24–7.28 (m, 2H), 7.46–7.50 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=8.3$, 20.2, 29.3, 29.5, 32.7, 43.9, 69.2, 82.9, 126.8, 127.9, 128.2, 132.5, 135.3, 138.7, 173.1, 206.1 ppm; ν_{max} (film) = 2979, 2938, 1754, 1717 cm^{-1}; MS (NSI$^+$): *m/z* (%): 261 ($[M+H]^+$, 41%); HRMS (NSI$^+$): *m/z* calcd for $C_{16}H_{21}O_3^+$ $[M+H]^+$: 261.1485; found: 261.1481 (−1.6 ppm).

Preparation of (*S*)-5,5-dimethyl-3-(naphthalen-1-yl)-3-propionyldihydrofuran-2(3*H*)-one (39): Following the general procedure, compound **27** (18 mg, 0.0500 mmol, 10 mol%), compound **58** (156 mg, 0.500 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at −78 °C and $(EtCO)_2O$ (0.08 mL, 0.650 mmol, 1.3 equiv) at −78 °C to RT gave a product distribution containing **39**. Purification of the residue by flash column chromatography on silica gel (silica, Et_2O/40–60 petrol 5:95) gave **39** as a white solid (113 mg, 76%), which was shown by chiral HPLC [Daicel CHIRALCEL OD-H, 4.6×250 mm, 2-propanol/hexane 1:99, 0.5 mL min^{-1}, retention times of enantiomers: 14.47 (minor), 17.01 min (major)] to have 94% *ee*; $[\alpha]_D^{25}=+268.0$ ($c=0.5$ in CH_2Cl_2); m.p. 70–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.85$ (t, $J=7.2$ Hz, 3H), 1.17 (s, 3H), 1.54 (s, 3H), 1.90 (dq, $J=7.2$, 19.0 Hz, 1H), 2.33 (d, $J=13.3$ Hz, 1H), 2.95 (dq, $J=7.2$, 19.0 Hz, 1H), 3.83 (d, $J=13.3$ Hz, 1H), 7.36 (dd, $J=1.0$, 8.2 Hz, 1H), 7.43–7.52 (m, 3H), 7.75 (dd, $J=1.1$, 7.3 Hz, 1H), 7.85 (d, $J=8.3$ Hz, 1H), 7.88–7.92 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=8.2$, 29.4, 29.4, 32.7, 44.5, 69.0, 83.2, 123.4, 125.5, 126.1, 126.3, 127.2, 129.3, 129.7, 130.2, 134.8, 135.9, 173.1, 207.1 ppm; ν_{max} (KBr) = 3055, 2980, 1717, 1598, 1509 cm^{-1}; MS (NSI$^+$): *m/z* (%): 314 $[M+NH_4]^+$ (100); HRMS (NSI$^+$): *m/z* calcd for $C_{19}H_{24}NO_3^+$: 314.1751 $[M+NH_4]^+$; found: 314.753 (+0.7 ppm).

Preparation of (*S*)-3-propionyl-3-(2-(trifluoromethyl)phenyl)dihydrofuran-2(3*H*)-one (40): Following the general procedure, compound **26** (15 mg, 0.0500 mmol, 10 mol%), compound **59** (151 mg, 0.500 mmol, 1.0 equiv), in CH_2Cl_2 (4 mL) at −78 °C and $(EtCO)_2O$ (0.08 mL, 0.650 mmol, 1.3 equiv) at −78 °C to RT gave a product distribution containing **40**. Purification of the residue by flash column chromatography on silica gel (silica, Et_2O/40–60 petrol 30:70) gave **40** as a colourless oil (22 mg, 15%), which was shown by chiral HPLC [Daicel CHIRALPAK AD-H, 4.6×250 mm, 2-propanol/hexane 1:99, 0.5 mL min^{-1}, retention times of enantiomers: 18.92 (minor), 21.48 min (major)] to have 62% *ee*; $[\alpha]_D^{25}=+186.0$ ($c=0.05$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.89$ (t, $J=7.1$ Hz, 3H), 2.11 (dq, $J=6.8$, 19.3 Hz, 1H), 2.21–2.26 (m, 1H), 2.58 (dq, $J=7.0$, 19.2 Hz, 1H), 3.50 (dt, $J=8.3$, 13.5 Hz, 1H), 4.02 (q, $J=$ 8.1 Hz, 1H), 4.34 (dt, $J=4.4$, 8.5 Hz, 1H), 7.43 (t, $J=7.5$ Hz, 1H), 7.51 (t, $J=7.6$ Hz, 1H), 7.60 (d, $J=8.0$ Hz, 1H), 7.68 ppm (d, $J=7.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=7.7$, 33.3, 33.6, 66.1, 66.2, 124.3, 127.9, 128.9, 129.5, 130.1, 132.8, 135.1, 173.9, 203.8 ppm; ν_{max} (film) = 2983, 2942, 1763, 1724, 1605, 1581 cm^{-1}; MS (ES$^+$): *m/z* (%): 309 $[M+Na]^+$ (100); HRMS (ES$^+$): *m/z* calcd for $C_{14}H_{13}F_3NaO_3^+$: 309.0714 $[M+Na]^+$; found: 309.0710 (−1.6 ppm).

Preparation of (*S*)-5,5-dimethyl-3-propionyl-3-(thiophen-2-yl)dihydrofuran-2(3*H*)-one (41): Following the general procedure, compound **27** (18 mg, 0.0500 mmol, 10 mol%), compound **60** (134 mg, 0.500 mmol, 1.0 equiv), in CH_2Cl_2 (4 mL) at −78 °C and $(EtCO)_2O$ (0.08 mL, 0.650 mmol, 1.3 equiv) at −78 °C to RT gave a product distribution containing **41**. Purification of the residue by flash column chromatography on silica gel (silica, Et_2O/40–60 petrol 5:95) gave **41** as a colourless oil (88 mg, 70%), which was shown by chiral HPLC [Daicel CHIRALCEL AS-H, 4.6×250 mm, 2-propanol/hexane 1:99, 0.5 mL min^{-1}, retention times of enantiomers: 19.25 (major), 21.92 min (minor)] to have 35% *ee*; $[\alpha]_D^{25}=+70.0$ ($c=0.5$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.95$ (t, $J=7.2$ Hz, 3H), 1.33 (s, 3H), 1.40 (s, 3H), 2.38 (d, $J=13.4$ Hz, 1H), 2.58 (dq, $J=7.2$, 18.7 Hz, 1H), 2.78 (dq, $J=7.2$, 18.7 Hz, 1H), 3.39 (d, $J=$ 13.4 Hz, 1H), 6.98 (dd, $J=3.6$, 5.2 Hz, 1H), 7.12 (dd, $J=1.2$, 3.6 Hz, 1H), 7.28 ppm (dd, $J=1.2$, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=8.4$, 28.5, 29.1, 31.3, 45.5, 64.6, 83.1, 126.2, 126.6, 127.4, 140.8, 172.6, 203.2 ppm; ν_{max} (film) = 3109, 2980, 1760, 1716 cm^{-1}; MS (NSI$^+$): *m/z* (%): 270 $[M+NH_4]^+$ (100); HRMS (NSI$^+$): *m/z* calcd for $C_{13}H_{20}NO_3S^+$: 270.1158 $[M+NH_4]^+$; found: 270.1162 (+1.3 ppm).

Preparation of (R)-3-benzyl-3-propionyldihydrofuran-2(3*H*)-one (42): Following the general procedure, compound **27** (18 mg, 0.0500 mmol, 10 mol%), compound **61** (124 mg, 0.500 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at −78 °C and $(EtCO)_2O$ (0.08 mL, 0.650 mmol, 1.3 equiv) at −78 °C to RT gave a product distribution containing **42**. Purification of the residue by flash column chromatography on silica gel (silica, Et_2O/ 40–60 petrol 10:90) gave **42** as a colourless oil (61 mg, 53%), which was shown by chiral HPLC [Daicel CHIRALCEL OD-H, 4.6×250 mm, 2-propanol/hexane 10:90, 1.0 mL min^{-1}, retention times of enantiomers: 11.19 (major), 12.63 min (minor)] to have 56% *ee*; $[\alpha]_D^{25}$=-4.0 (*c* 0.5 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.01$ (t, $J=7.2$ Hz, 3H), 2.05 (dt, $J=8.4$, 13.1 Hz, 1H), 2.64–2.83 (m, 3H), 3.05 (d, $J=14.0$ Hz, 1H), 3.36 (d, $J=14.0$ Hz, 1H), 3.72 (td, $J=4.2$, 8.8 Hz, 1H), 3.96–4.03 (m,

1H), 7.08 (dt, $J=2.1$, 7.8 Hz, 1H), 7.16–7.27 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=8.0$, 28.9, 31.7, 40.1, 62.1, 66.4, 127.6, 128.9, 129.8, 135.4, 176.0, 205.3 ppm; ν_{max} (film) = 2981, 2921, 1765, 1713 cm^{-1}; MS (NSI$^+$): *m/z* (%): 233 $[M+H]^+$ (40); ; HRMS (NSI$^+$): *m/z* calcd for $C_{14}H_{17}O_3^+$: 233.1172 $[M+H]^+$; found: 233.1172 (−0.1 ppm).

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