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NHC-Mediated Chlorination of Unsymmetrical Ketenes: Catalysis and Asymmetry

James Douglas,[a] Kenneth B. Ling,[a] Carmen Concellón,[a] Gwydion Churchill,[b] Alexandra M. Z. Slawin,[a] and Andrew D. Smith*[a]

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NHCs promote the efficient chlorination of unsymmetrical disubstituted ketenes with a range of chlorinating agents; chiral NHCs display promising levels of asymmetric induction in the chlorination process with up to 61 % *ee* observed using 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone.

Introduction

A range of methods has been developed in recent years that allow the catalytic asymmetric α-chlorination of carbonyl compounds.[1] Notable protocols within this area include the organocatalytic enamine strategies of MacMillan[2] and Jørgenson,[3] as well as SOMO catalysis by MacMillan,[4] which all deliver α-chloro aldehydes with high *ee* values. Lectka has developed a series of elegant halogenation strategies using cinchona alkaloid derivatives with in situ generated ketenes that deliver α-halogenated esters in excellent *ee*,[5] while Rovis and co-workers have shown that chiral N-heterocyclic carbenes (NHCs) deliver α-chloro esters in high *ee* from α,α-dichloroaldehydes and phenols.[6] These tactics all give secondary alkyl halides with excellent levels of enantiocontrol,[7] with strategies for the generation of tertiary alkyl halides relatively less investigated.[8] Stoichiometric practices toward this goal have employed silyl enol ethers,[9] while the catalytic asymmetric halogenation of 1,3-dicarbonyls and related compounds have also been reported.[10] Notably, Fu has recently utilised planar chiral PPY derivative **10** to generate tertiary α-chloro esters with excellent enantiocontrol (up to 95% *ee*) from unsymmetrical disubstituted ketenes and 2,2,6,6-tetrachlorocyclohexanone **9** (Figure 1).[11,12]

As part of a research programme focused upon the development of applications of Lewis base catalysis[13] in synthesis,[14] we, together with extensive work from Ye, have probed the ability of NHCs[15] to promote the reaction of disubstituted ketenes and a range of electrophiles. This methodology has proven suitable for a number of formal [2+2][16] and [4+2][17] cycloaddition reactions, as well as asymmetric esterification reactions with benzhydrol[18] or 2-phenylphenol.[19] As an extension of this research, and building upon the literature precedents for catalytic α-halo-

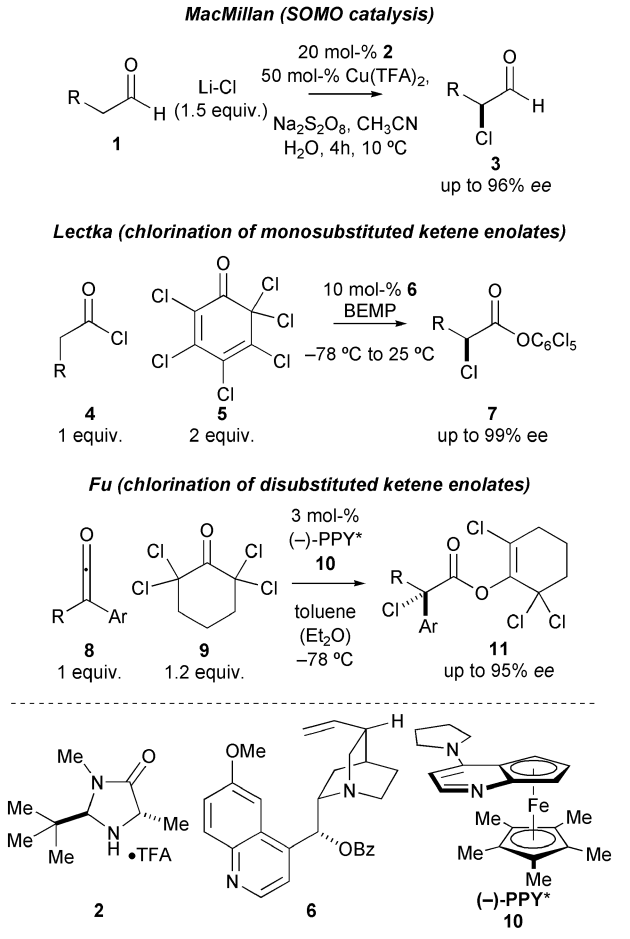

Figure 1. Selected strategies for the catalytic asymmetric α-halogenation of carbonyls.

[a] EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, KY16 9ST, UK
Fax: +44-1334-463808
E-mail: ads10@st-andrews.ac.uk
[b] AstraZeneca, Process Research and Development, Macclesfield, Cheshire, SK10 2NA, UK

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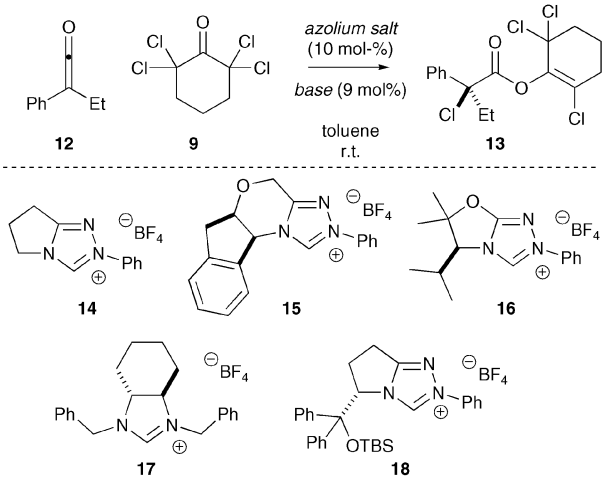
genation, we reasoned that NHCs may be able to promote the halogenation of unsymmetrical, disubstituted ketenes, giving access to a range of tertiary α-halo esters. We describe herein our results within this area.

Results and Discussion

Evaluating Chlorinating Agents with NHC-Mediated Catalysis

Preliminary studies began with evaluating the reactivity of 2,2,6,6-tetrachlorocyclohexanone **9** with NHCs as this reagent had given the highest enantioselectivities in the chlorination of ketenes by Fu et al.[11] In the presence of a range of azolium salt precatalysts **14**–**17** and using KHMDS as the base to generate the corresponding NHC in situ, no chlorination of ethyl phenyl ketene **12** was observed. However, in the presence of L-pyroglutamic-acid-derived precatalyst **18** and Cs_2CO_3 as the base, moderate conversion to the α-chloro ester in essentially racemic form was observed. Lowering the reaction temperature to –40 °C had no discernible effect on the enantioselectivity of this process, again returning **13** (<5% *ee*) in modest yield (Table 1).

Table 1. NHC-promoted chlorination of ethyl phenyl ketene using 2,2,6,6-tetrachlorocyclohexanone.

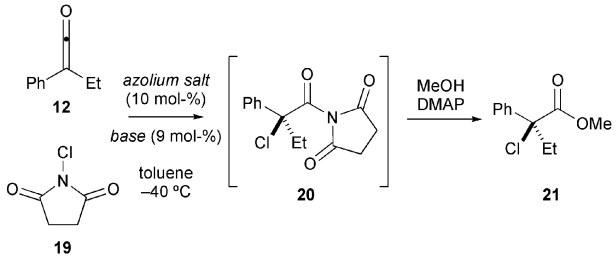


Entry	Azolium salt	Base	Yield (%)[a]	*ee* (%)[b]
1	**14**	KHMDS	–	–
2	**15**	KHMDS	–	–
3	**16**	KHMDS	–	–
4	**17**	KHMDS	–	–
5	**18**	Cs_2CO_3	47	<5
6[c]	**18**	Cs_2CO_3	35	<5

[a] Isolated yield. [b] Determined by chiral GC analysis of the corresponding methyl ester, see Supporting Information for details. [c] Reaction performed at –40 °C.

Due to the low reactivity of 2,2,6,6-tetrachlorocyclohexanone **9** in this protocol, our attention next turned to the more reactive chlorinating reagent *N*-chlorosuccinimide (NCS). Good conversion of ketene **12** was observed at –40 °C using NHCs generated from azolium salt precatalysts **14**–**18**, however the intermediate succinimide adduct **20** proved to be extremely unstable to any attempts at purification. To circumvent this issue, the crude reaction products were directly subjected to methanolysis, affording the corresponding α-chloro methyl esters in acceptable yields over the 2 steps. Again, only low levels of enantioselectivity were observed with all of the precatalysts screened, with L-valine-derived precatalyst **16** proving optimal in this case, giving **21** in 39% yield and 11% *ee* (Table 2).[20,21]

Table 2. NHC-promoted chlorination of ethyl phenyl ketene using NCS.

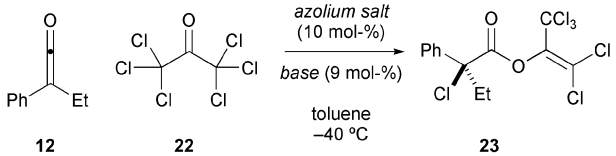


Entry	Azolium salt	Base	Yield of **21** (%)[a]	*ee* (%)[b]
1	**14**	KHMDS	0	–
2	**15**	KHMDS	39	<5
3	**16**	KHMDS	39	11
4	**17**	KHMDS	15	<5
5	**18**	Cs_2CO_3	28	<5

[a] Isolated yield. [b] Determined by chiral GC analysis, see Supporting Information for details.

The chlorinating reagent was next changed to hexachloroacetone **22**, and again good conversion of ketene **12** to the corresponding α-chloro ester **23** was observed in the presence of NHCs prepared from a range of azolium salt precatalysts. In this series, up to 29% *ee* was observed by employing the aminoindanol-derived precatalyst **15** (Table 3).[20,21]

Table 3. NHC-promoted chlorination of ethyl phenyl ketene using hexachloroacetone.



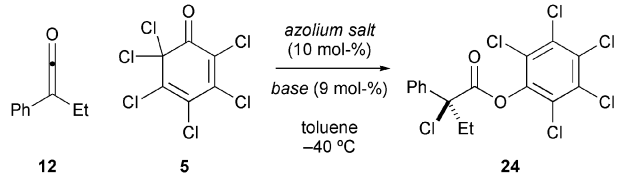
Entry	Azolium salt	Base	Yield (%)[a]	*ee* (%)[b]
1	**14**	KHMDS	44	–
2	**15**	KHMDS	47	29 (*ent*)
3	**16**	KHMDS	67	<5
4	**17**	KHMDS	72	8
5	**18**	Cs_2CO_3	37	<5

[a] Isolated yield. [b] Determined by chiral GC analysis of the corresponding methyl ester, see Supporting Information for details.

Finally, we changed the chlorinating reagent to 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone **5**. Good-to-excellent reactivity was observed using all precatalysts **14**–**18**, with L-pyroglutamic-acid-derived precatalyst **18** opti-

mal, giving the corresponding α-chloro pentachlorophenyl esters in excellent yields and up to 54% *ee*. Attempts to increase the enantioselectivity of the reaction by lowering the reaction temperature were unsuccessful. No reaction was observed when the reaction was maintained at –60 °C, whilst allowing the reaction to warm gradually from –60 °C to room temperature gave **24** in slightly reduced enantioselectivity. It was additionally found that employing a slight excess (1.1 equiv.) of ketene was optimal both in terms of enantioselectivity (up to 61% *ee*) and ease of purification, since it was often difficult to separate any remaining dienone **5** from the pentachlorophenyl ester **24** (Table 4).[20,21] In the racemic series the structure of α-chloro ester product **24** was unambiguously confirmed by X-ray crystallographic analysis (Figure 2).[22]

Table 4. NHC-promoted chlorination of ethyl phenyl ketene using 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone.



12 **5** **24**

Entry	Azolium salt	Base	Yield (%)[a]	*ee* (%)[b]
1	**14**	KHMDS	65	–
2	**15**	KHMDS	89	6
3	**16**	KHMDS	43	22
4	**17**	KHMDS	77	<5
5	**18**	Cs_2CO_3	92	57
6[c]	**18**	Cs_2CO_3	90	61
7[d]	**18**	Cs_2CO_3	86	53

[a] Isolated yield. [b] Determined by chiral GC analysis of the corresponding methyl ester, see Supporting Information for details. [c] 1.1 equiv. of ketene were used. [d] The reaction was warmed gradually from –60 °C to room temp.

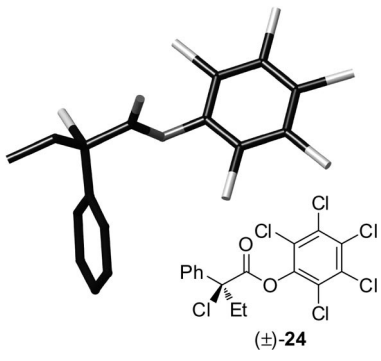
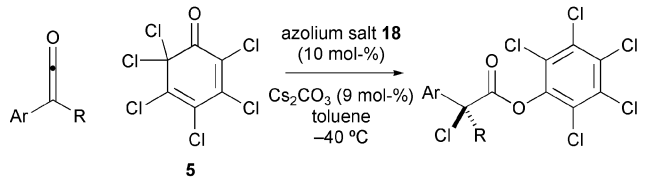


Figure 2. Molecular representation of the X-ray crystal structure of (±)-**24** (H atoms removed for clarity).

Further attempts to increase the enantioselectivity of the reaction by tuning the reactivity of the chlorinating reagent, in line with previous studies by Bartoli et al.[10d] and Mayr and Duan,[23] were unsuccessful[24] and so the optimised conditions were applied to a range of aryl-alkyl ketene substrates in order to probe the scope of the chlorinating reaction. 2- and 4-substitution of the aryl unit of the ketene is readily tolerated, as is variation of the alkyl chain from methyl to *n*-butyl, all giving excellent isolated yields (up to 97% yield) of the corresponding α-chloro ester with modest levels of enantioselectivity (26–61% *ee*) (Table 5).[25]

Table 5. Generality of the NHC-promoted chlorination of alkyl aryl ketenes using 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone.



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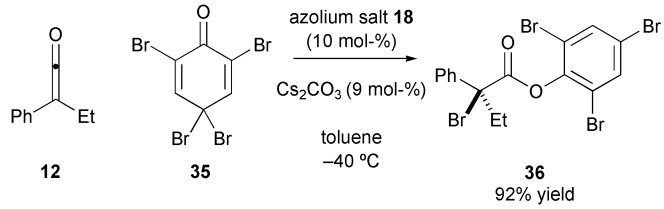
Entry	Ketene	Ar	R	Product	Yield (%)[a]	*ee* (%)
1	**12**	Ph	Et	**24**	90	61[b]
2	**25**	Ph	*n*Bu	**30**	67	34[c]
3[d]	**26**	4-MeC_6H_4	Et	**31**	88	48[c]
4	**27**	4-MeC_6H_4	Me	**32**	76	44[c]
5	**28**	2-ClC_6H_4	Et	**33**	97	26[c]
6	**29**	4-ClC_6H_4	Et	**34**	91	44[c]

[a] Isolated yield. [b] Determined by chiral GC analysis of the corresponding methyl ester, see Supporting Information for details. [c] Determined by ^1H NMR analysis of the corresponding (*S*)-α-methylbenzylamide, see Supporting Information for details. [d] 1.5 equiv. of ketene **26** and 25 mol-% of **18** were used.

Further investigations attempted to extend this methodology to the use of alternative halogenating reagents. Although no fluorination was observed under a range of conditions when using *N*-fluorobenzenesulfonimide (NFSI), excellent reactivity was observed with 2,4,4,6-tetrabromocyclohexa-2,5-dienone **35** as the halogenating reagent, giving α-bromo ester **36** in 92% isolated yield and 45% *ee* (Scheme 1). Unfortunately, exhaustive attempts to derivatise α-bromo ester **36** in order to exemplify its synthetic utility proved unsuccessful, with the forcing conditions required for transesterification or amidation resulting in elimination of HBr.

A variety of mechanistic possibilities exist in this reaction manifold, with one plausible mechanism for the chlorination reaction outlined below (Figure 3). Initial attack of in situ generated NHC **38** to ketene **12**, preferentially *anti*- to the aryl unit of the ketene,[26] generates azolium enolate intermediate **39**, with subsequent stereoselective chlorination affording enantiomerically enriched α-chloro acylazolium species **41**. Nucleophilic attack of the pentachlorophenolate anion **40** (which is generated as a by-product from the chlorination step) onto the acylazolium species **41** produces α-chloro ester **24** and liberates NHC **38** to re-enter the catalytic cycle. At this stage, it has not proven possible to delineate conclusively this mechanistic Scheme or to discount alternative reaction pathways.[27]



Scheme 1. NHC-promoted bromination of ethyl phenyl ketene using 2,4,4,6-tetrabromocyclohexa-2,5-dienone.

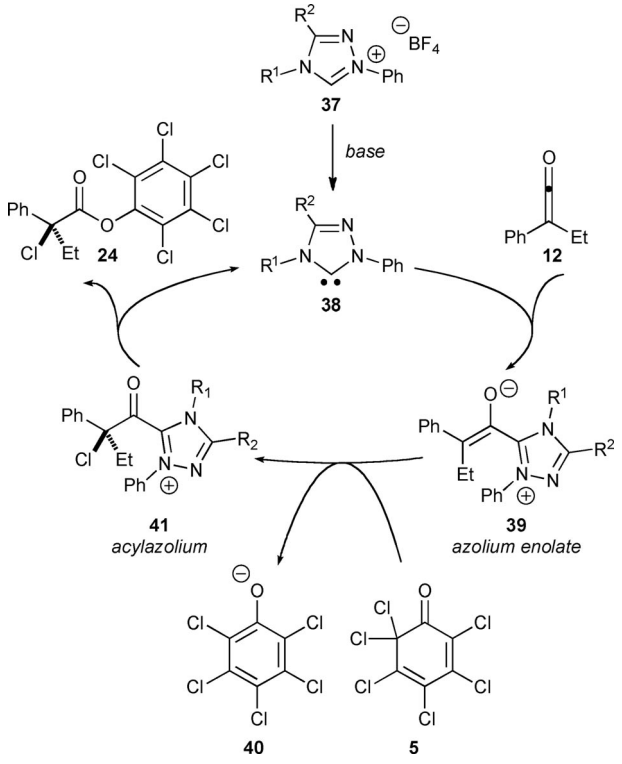


Figure 3. Proposed mechanism and catalytic cycle for the NHC-mediated chlorination of ketene **12** using 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone.

Conclusions

In conclusion, we have demonstrated that NHCs promote the efficient chlorination of disubstituted ketenes with a range of chlorinating agents, generating the corresponding tertiary α-halo esters in good yield. Chiral NHCs promote catalytic asymmetric halogenation using polyhalogenated quinones, with modest, although promising levels of asymmetric induction (up to 61% *ee*). Current studies are aimed at the further optimisation of the asymmetry in this reaction manifold and developing novel modes of asymmetric catalysis using enantiomerically pure NHCs.

Experimental Section

General: All reactions involving moisture-sensitive reagents were performed under an atmosphere of argon or nitrogen using standard vacuum line techniques and with dry solvents. All glassware was flame dried and allowed to cool under vacuum. "Room temperature" (room temp.) refers to 20–25 °C. Temperatures of –40 and –60 °C were obtained using an immersion cooler (HAAKE EK 90). "In vacuo" refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC_2 vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller. Dry solvents were obtained from a solvent purification system (MBraun, SPS-800). PE refers to the fraction of petroleum ether boiling between 40 and 60 °C. Triethylamine was distilled from CaH_2. Ketenes were prepared as previously reported[19] from the corresponding acid chloride. 2,2,6,6-Tetrachlorocyclohexanone **9** (Aldrich) was recrystallised from pentane/CH_2Cl_2. *N*-Chlorosuccinimide was recrystallised from distilled water and dried in vacuo for 48 h. 4,4,6-Tetrabromocyclohexa-2,5-dienone **35** was prepared according to the literature[28] with additional freeze drying and trituration with dry Et_2O. 5,7,7-Trichloroquinolin-8(7*H*)-one was prepared according to the literature.[10d] All other reagents were used directly as supplied without further purification. Flash column chromatography was carried out with silica gel 60 (0.043–0.060 mm) (Merck) or on aluminium oxide (activated, basic, Brockmann I, ca. 150 mesh) (Aldrich) in the solvent system stated. Analytical thin-layer chromatography was performed on commercially available pre-coated aluminium-backed plates (Merck silica Kieselgel 60 F_{254}). TLCs were visualised either by UV fluorescence (254 nm), or by staining with basic $KMnO_4$ solution. Melting points were recorded on an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Spectrum GX FT-IR Spectrometer and analysed either as thin films between NaCl plates (thin film) or via solid KBr disk (KBr) as stated. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and only structurally significant peaks are analysed. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz ^1H, 75.4 MHz ^{13}C) or a Bruker Avance 400 (400 MHz ^1H, 100 MHz ^{13}C) spectrometer in the deuterated solvent stated. ^{13}C NMR spectra were recorded with proton decoupling. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to residual solvent peaks or to $SiMe_4$ as an internal standard (δ = 0.00 ppm). Coupling constants, *J*, are quoted in Hz. The abbreviations s, d, t, dd, q and m denote singlet, doublet, triplet, doublet of doublets, quartet, and multiplet, respectively. The abbreviation Ar is used to denote aromatic. GC analysis was performed on a Fison 800 gas chromatograph using a CP-Chirasil-Dex CB column. Mass spectrometric (*m*/*z*) data were acquired by electrospray ionisation (ESI) or chemical ionisation (CI), at the EPSRC National Mass Spectrometry Service Centre, Swansea ($[M]^+$, $[M + H]^+$, $[M + NH_4]^+$ quoted). CI MS was carried out on a Micromass Quattro II spectrometer. High resolution ESI was carried out on a Finnigan MAT 900 XLT; a Thermofisher LTQ Orbitrap XL spectrometer was used to obtain high resolution ESI MS for accurate mass determination but also provided fragmentation data for the characterisation of samples. Values are quoted as a ratio of mass to charge in Daltons.

General Procedure A: To a flame dried Schlenk flask under an argon atmosphere was added azolium salt (0.050 mmol), base (0.045 mmol) and toluene (3 mL) and the mixture stirred for

20 min. A solution of the requisite ketene (0.50 mmol) in toluene (6 mL) was added, immediately followed by the requisite chlorinating reagent (0.50 mmol). Toluene (1 mL) was added to wash residual solid into solution and the reaction was stirred for 3 h at room temperature before concentration in vacuo. The resulting crude residue was purified by flash column chromatography (silica, PE) to provide the title compound.

General Procedure B: To a flame dried Schlenk flask under an argon atmosphere was added azolium salt (0.050 mmol), base (0.045 mmol) and toluene (3 mL) and the mixture stirred for 20 min. The mixture was then cooled to –40 °C in a cryostatic bath before addition of a –40 °C solution of the requsite ketene (0.50 mmol) in toluene (6 mL), immediately followed by the requisite chlorinating agent (0.50 mmol). Toluene (1 mL) was added to wash residual solid into solution and the reaction was stirred for 3 h at –40 °C before opening the flask to the air for 30 min and concentration in vacuo. The resulting crude residue was purified by flash column chromatography (silica, PE) to provide the title compound.

Representative experimental procedures for the synthesis of each compound are detailed below; full experimental details for all reactions performed are included in the Supporting Information.

2,6,6-Trichlorocyclohex-1-en-1-yl 2-Chloro-2-phenylbutanoate (13): General procedure A. Azolium salt **18** (28.5 mg, 0.05 mmol, 0.1 equiv.), Cs_2CO_3 (14.7 mg, 0.045 mmol, 0.09 equiv.), ketene **12** (73.1 mg, 0.5 mmol, 1.0 equiv.) in (6 mL) and **9** (118 mg, 0.05 mmol, 1.0 equiv.) in toluene (10 mL) for 16 h gave a crude product which purified by flash column chromatography (alumina, 25% EtOAc/PE) to give **13** as a colourless oil (90 mg, 47%) with spectroscopic data in accordance with the literature.[11] $[a]_D^{20}$ = 0.0 (c = 0.4, CH_2Cl_2). NMR: δ_H (400 MHz, $CDCl_3$) = 7.69–7.64 (m, 2 H, Ar*H*), 7.41–7.32 (m, 3 H, Ar*H*), 2.75–2.63 (m, 3× CH_2), 2.59–2.47 (m, 1 H, CH_2) overlapping 2.57 (t, J = 6.2 Hz, 2 H, CH_2), 2.01–1.94 (m, 2 H, CH_2) and 1.10 (t, J =7.2 Hz, 3 H, CH_2CH_3) ppm.

Methyl 2-Chloro-2-phenylbutanoate (16): General procedure B. Azolium salt **16** (17.4 mg, 0.050 mmol, 0.1 equiv.), KHMDS (0.5 M in toluene, 0.09 mL, 0.045 mmol, 0.09 equiv.), ketene **12** (73.1 mg, 0.5 mmol, 1.0 equiv.) and **19** (66.8 mg, 0.050 mmol, 1.0 equiv.) in toluene (10 mL) for 3 h at –40 °C before warming to room temp. gave a crude product. Treatment of the crude mixture with DMAP (183 mg, 1.50 mmol, 3.0 equiv.) in MeOH (5 mL) at room temp. for 16 h gave a crude product which was purified by flash column chromatography (silica, 5% EtOAc/PE) to give **21** as a colourless oil (47 mg, 39% yield, *with respect to ketene*) with spectroscopic data in accordance with the literature.[11] $[a]_D^{20}$ = –2.6 (c = 0.2, CH_2Cl_2). GC Analysis 11% *ee* [CP-Chirasil-Dex CB column; 100 °C (60 min) 1.0 °C/min to 120 °C; 11.6 psi H_2; retention times; 41.3 (minor), 43.7 (major)]. NMR: δ_H (300 MHz, $CDCl_3$) = 7.50–7.47 (m, 2 H, Ar*H*), 7.39–7.30 (m, 3 H, Ar*H*), 3.76 (s, 3 H, OCH_3), 2.51 (dq, J = 14.4 7.2 Hz, 1 H, CH_AH$_B$CH$_3$), 2.36 (dq, J = 14.4 7.2 Hz, 1 H, CH$_A$$H_BCH_3$) and 0.98 (t, J = 7.2 Hz, 3 H, CH_2CH_3) ppm.

Perchloroprop-1-en-2-yl 2-Chloro-2-phenylbutanoate (23): General procedure B. Azolium salt **17** (19.7 mg, 0.050 mmol, 0.1 equiv.), KHMDS (0.5 M in toluene, 0.090 mL, 0.045 mmol, 0.09 equiv.), ketene **12** (73.1 mg, 0.500 mmol, 1.0 equiv.) and **22** (0.050 mL, 0.050 mmol, 1.0 equiv.) in toluene (10 mL) for 3 h at –40 °C gave a crude product which was purified by flash column chromatography (silica, 2.5% EtOAc/PE) to give **23** as a colourless oil (148 mg, 72% yield). $[a]_D^{20}$ = +2.1 (c = 0.49, CH_3Cl). IR (thin film): ν_{max} = 2940, 1773 (C=O), 1600 (C=C), 1447, 1162, 1064, 997 and 762 cm^{-1}. NMR: δ_H (400 MHz, $CDCl_3$) = 7.65–7.60 (m, 2 H, Ar*H*), 7.42–7.32 (m, 3 H, Ar*H*), 2.66–2.51 (m, 2 H, CH_2CH$_3$) and 1.03 (t, J = 7.2 Hz, 3 H, CH_2CH_3) ppm. δ_C (75 MHz, $CDCl_3$) = 166.2, 142.4, 136.3, 128.7, 128.3, 127.0, 124.6, 90.4, 74.4, 34.0 and 8.7 ppm. *m/z* HRMS (CI$^+$), [M + NH$_4$]$^+$, $C_{13}H_{10}O_2{}^{35}Cl_6NH_4^+$ requires 425.9155, found 425.9150 (+1.1 ppm).

Perchlorophenyl 2-Chloro-2-phenylbutanoate (24): General procedure B. Azolium salt **18** (28.5 mg, 0.050 mmol, 0.1 equiv.), Cs_2CO_3 (14.6 mg, 0.045 mmol, 0.09 equiv.), ketene **12** (80 mg, 0.55 mmol, 1.1 equiv.) and **5** (150 mg, 0.50 mmol, 1.0 equiv.) in toluene (10 mL) for 3 h at –40 °C gave a crude product which was purified by flash column chromatography (silica, PE) to give **24** as a white solid (201 mg, 90% yield); m.p. 83–84 °C. $[a]_D^{20}$ = +14.8 (c = 0.50, $CHCl_3$). IR (KBr disk): ν_{max} = 2976, 1773 (C=O), 1386, 1362, 1190, 1183, 1082, 990, 912, 863, 827, 767, 745, 722 and 698. NMR: δ_H (400 MHz, $CDCl_3$) = 7.70–7.67 (m, 2 H, Ar*H*), 7.46–7.35 (m, 3 H, Ar*H*), 2.69 (dq, J = 14.5 7.2 Hz, 1 H, CH_AH$_B$CH$_3$), 2.56 (dq, J = 14.5 7.3 Hz, 1 H, CH$_A$$H_BCH_3$) and 1.09 (t, J = 7.2 Hz, 3 H, CH_2CH_3) ppm. δ_C (75 MHz, $CDCl_3$) = 166.7, 143.9, 137.3, 132.2, 132.0, 128.9, 128.6, 127.7, 127.1, 74.9, 34.3 and 9.1 ppm. *m/z* HRMS (CI$^+$), [M + NH$_4$]$^+$, $C_{16}H_{10}O_2{}^{35}Cl_6NH_4^+$ requires 461.9154, found 461.9150 (+0.8 ppm). GC Analysis (*of the corresponding methyl ester* **16**): 61% *ee* [CP-Chirasil-Dex CB column; 100 °C (60 min) 1.0 °C/min to 120 °C; 11.6 psi H_2; retention times; 46.7 (minor), 47.8 (major)].

Perchlorophenyl 2-Chloro-2-phenylhexanoate (30): General procedure B. Azolium salt **18** (28.5 mg, 0.05 mmol, 0.1 equiv.), Cs_2CO_3 (14.6 mg, 0.045 mmol, 0.09 equiv.), ketene **25** (95.8 mg, 0.55 mmol, 1.1 equiv.) and **5** (150 mg, 0.50 mmol, 1.0 equiv.) in toluene (10 mL) for 3 h at –40 °C gave a crude product which was purified by flash column chromatography (silica, PE) to give **30** as a white solid (158, 67% yield); m.p. 66–72 °C. $[a]_D^{20}$ = +5.9; 34% *ee*;[29] ν_{max} (KBr disk): 2959, 2933, 1773 (C=O) 1494, 1445, 1385, 1360, 1178, 1133, 1052, 981, 914, 825, 769, 721 and 702. NMR: δ_H (400 MHz, $CDCl_3$) = 7.69–7.66 (m, 2 H, Ar*H*), 7.44–7.34 (m, 3 H, Ar*H*), 2.61 (ddd, J = 14.6 10.9 4.1 Hz, 1× CH_2), 2.50 (ddd, J = 14.6 11.7 4.1 Hz, 1× CH_2) and 1.62–1.52 (m, 1× CH_2), 1.46–1.34 (m, 3× CH_2) and 0.93 (t, J 7.2, 3 H, CH_3) ppm. δ_C (75 MHz, $CDCl_3$) = 166.7, 143.9, 137.6, 132.2, 132.0, 129.0, 128.6, 127.8, 127.0, 74.3, 40.8, 26.7, 22.7 and 14.0 ppm. *m/z* HRMS (ES$^+$) [M + NH$_4$]$^+$, $C_{18}H_{14}O_2{}^{35}Cl_6NH_4^+$ requires 489.9459, found 489.9463 (–0.9 ppm).

Perchlorophenyl 2-Chloro-2-(*p*-tolyl)butanoate (31): General procedure B. Azolium salt **18** (71.3 mg, 0.125 mmol, 0.25 equiv.), Cs_2CO_3 (39.1 mg, 0.120 mmol, 0.24 equiv.), **26** (160.2 mg, 0.75 mmol, 1.5 equiv.) and **5** (150 mg, 0.05 mmol, 1.0 equiv.) in toluene (10 mL) for 3 h at –40 °C before warming to room temp. gave a crude product which was purified by flash column chromatography (silica, PE) to give **31** as a white solid (202 mg, 88% yield); m.p. 66–72 °C. $[a]_D^{20}$ = +7.4 (c = 0.50, $CHCl_3$); 48% *ee*. IR (KBr disk): ν_{max} = 2921, 1784 (C=O), 1511, 1452, 1386, 1362, 1205, 1130, 1067, 1020, 886, 791, 715 and 519. NMR: δ_H (400 MHz, $CDCl_3$) = 7.57–7.53 (m, 2 H, Ar*H*), 7.22 (d, J = 8.0 Hz, 2 H, Ar*H*), 2.67 (dq, J = 14.5 7.3 Hz, 1 H, CH_AH$_B$CH$_3$), 2.53 (dq, J = 14.5 7.3 Hz, 1 H, CH$_A$$H_BCH_3$) 2.38 (s, 2 H, ArC$H_3$) and 1.09 (t, J = 7.3 Hz, 3 H, CH_2CH_3) ppm. δ_C (75 MHz, $CDCl_3$) = 166.8, 144.0, 138.2, 134.4, 132.2, 132.0, 129.3, 127.8, 127.0, 74.9, 34.3, 21.2 and 9.1 ppm. *m/z* HRMS (ES$^+$) [M + NH$_4$]$^+$, $C_{17}H_{12}O_2{}^{35}Cl_6NH_4^+$ requires 475.9302, found 476.9307 (–1.0 ppm).

Perchlorophenyl 2-Chloro-2-(*p*-tolyl)propanoate (32): General procedure B. Azolium salt **18** (28.5 mg, 0.05 mmol, 0.1 equiv.), Cs_2CO_3 (14.6 mg, 0.045 mmol, 0.09 equiv.), ketene **27** (80.4 mg, 0.55 mmol, 1.1 equiv.) and **5** (150 mg, 0.50 mmol, 1.0 equiv.) in toluene (10 mL)

for 3 h at –40 °C gave a crude product which was purified by flash column chromatography (silica, PE) to give **32** as a white solid (169 mg, 76% yield); m.p. 66–68 °C. $[\alpha]_D^{20}$ = +12.8 (*c* = 0.53, $CHCl_3$); 44% *ee*. IR (KBr disk): ν_{max} = 2922, 1762 (C=O), 1512, 1444, 1382, 1360, 1202, 1185, 1084, 1053, 887, 815, 794, 721 and 518. NMR: δ_H (400 MHz, $CDCl_3$) = 7.65–7.57 (m, 2 H, Ar*H*), 7.25–7.22 (m, 2 H, Ar*H*), 2.39 (s, 3 H, ArCH_3) and 2.34 [s, 3 H, C(2)CH_3]; δ_C (100 MHz, $CDCl_3$) = 167.1, 144.0, 139.2, 136.0, 132.3, 132.1, 129.4, 127.8, 126.7, 69.2, 29.6 and 21.3 ppm. *m*/*z* HRMS (ES^+), $[M + NH_4]^+$, $C_{16}H_{14}O_2{}^{35}Cl_6NH_4^+$ requires 461.9148, found 461.9150 (–0.5 ppm).

Perchlorophenyl 2-Chloro-2-(2-chlorophenyl)butanoate (33): General procedure B. Azolium salt **18** (28.5 mg, 0.05 mmol, 0.1 equiv.), Cs_2CO_3 (14.6 mg, 0.045 mmol, 0.09 equiv.), ketene **28** (99.3 mg, 0.55 mmol, 1.1 equiv.) and **5** (150 mg, 0.50 mmol, 1.0 equiv.) in toluene (10 mL) for 3 h at –40 °C gave a crude product which was purified by flash column chromatography (silica, PE) to give **33** as a white solid (233 mg, 97% yield); m.p. 83–85 °C. $[\alpha]_D^{20}$ = +3.6 (*c* = 0.44, $CHCl_3$); 26% *ee*. IR (KBr disk): ν_{max} = 2982, 2940, 1781 (C=O), 1465, 1431, 1382, 1359, 1166, 1130, 1066, 988, 910, 822, 764, 754, 718, 726 and 674. δ_H (400 MHz, $CDCl_3$) = 8.01–7.98 (m, 1 H, Ar*H*), 7.45–7.32 (m, 3 H, Ar*H*), 3.11 (dq, *J* 14.8 7.4, 1 H, $CH_AH_BCH_3$), 2.65 (dq, *J* 14.8 7.4, 1 H, $CH_AH_BCH_3$) and 0.89 (t, *J* 7.4, 3 H, CH_2CH_3). δ_C (75 MHz, $CDCl_3$) = 164.9, 143.7, 134.1, 132.3, 132.0, 132.0, 131.0, 130.8, 130.3, 128.0, 127.1, 75.1, 31.4 and 8.6 ppm. *m*/*z* HRMS (ES^+), $[M + NH_4]^+$, $C_{16}H_9O_2{}^{35}Cl_7NH_4^+$ requires 495.8755, found 495.8760 (–1.1 ppm).

Perchlorophenyl 2-Chloro-2-(4-chlorophenyl)butanoate (34): General procedure B. Azolium salt **18** (28.5 mg, 0.05 mmol, 0.1 equiv.), Cs_2CO_3 (14.6 mg, 0.045 mmol, 0.09 equiv.), ketene **29** (99.3 mg, 0.55 mmol, 1.1 equiv.) and **5** (150 mg, 0.50 mmol, 1.0 equiv.) in toluene (10 mL) for 3 h at –40 °C gave a crude product which was purified by flash column chromatography (silica, PE) to give **34** as a white solid (218 mg, 91% yield); m.p. 88–92 °C. $[\alpha]_D^{20}$ = +6.2 (*c* = 0.53, $CHCl_3$); 44% *ee*. IR (KBr disk): ν_{max} = 2983, 2942, 1791 (C=O), 1595, 1491, 1390, 1362, 1172, 1099, 1081, 1018, 874, 820, 728, 717 and 517. NMR: δ_H (400 MHz, $CDCl_3$) = 7.65–7.60 (m, 2 H, Ar*H*), 7.43–7.38 (m, 2 H, Ar*H*), 2.68 (dq, *J* = 14.5 7.2 Hz, 1 H, $CH_AH_BCH_3$), 2.55 (dq, *J* = 14.5 7.2 Hz, 1 H, $CH_AH_BCH_3$) and 1.08 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3) ppm. δ_C (75 MHz, $CDCl_3$) = 166.2, 143.8, 136.0, 135.1, 132.3, 132.1, 128.7, 128.6, 127.6, 74.3, 34.4 and 8.9 ppm. *m*/*z* HRMS (ES^+) $[M]^+$, $C_{16}H_9O_2{}^{35}Cl_7^+$ requires 477.8417, found 477.8417 (+0.1 ppm).

2,4,6-Tribromophenyl 2-Bromo-2-phenylbutanoate (36): To a flame dried Schlenk flask under an argon atmosphere was added azolium salt **18** (28.5 mg, 0.05 mmol, 0.1 equiv.), Cs_2CO_3 (14.6 mg, 0.045 mmol, 0.09 equiv.) and toluene (3 mL) and the mixture stirred for 20 min. The mixture was then cooled to –40 °C in a cryostatic bath before addition of a solution of **12** at –40 °C (73.1 mg, 0.55 mmol, 1.1 equiv.) in toluene (6 mL), immediately followed by 2,4,4,6-tetrabromocyclohexa-2,5-dienone **35** (205 mg, 0.50 mmol, 1.0 equiv.). Toluene (1 mL) was added to wash residual solid into solution and the solution stirred for 3 h at –40 °C. The solution was warmeded to room temperature over 16 h then concentrated in vacuo to give a crude product which was purified by flash column chromatography (silica, 2% EtOAc/PE) to give **36** as a colourless oil (257 mg, 92% yield). $[\alpha]_D^{20}$ = +11.0 (*c* = 0.7, $CHCl_3$). IR (KBr disk): ν_{max} = 3071, 2976, 1762 (C=O), 1560, 1494, 1437, 1373, 1178, 1066, 953, 910, 857, 806, 743 and 694. NMR: δ_H (300 MHz, $CDCl_3$) = 7.74–7.71 (m, 2 H, Ar*H*), 7.66 (br. s, 2 H, $C_6H_2Br_3$), 7.41–7.31 (m, 3 H, Ar*H*), 2.78–2.61 (m, 2 H, CH_2CH_3) and 1.07 (t, *J* = 7.2 Hz, CH_2CH_3) ppm. δ_C (75 MHz, $CDCl_3$) = 167.1, 145.8, 137.6, 135.4, 129.0, 128.7, 128.6, 120.5, 118.6, 69.3, 35.3 and 10.7 ppm. *m*/*z* HRMS (ES^+) $[M + NH_4]^+$, $C_{16}H_{16}O_2N_1{}^{79}Br_4NH_4^+$ requires 569.7906, found 569.7909 (–0.5 ppm). HPLC (Chiralpak OJ-H, flow rate = 1.0 mL/min, isohexane/ethanol = 70:30): t_R = 2.5, 6.5 min. The absolute configuration of **36** could not be determined absolutely and was assigned by analogy to that of **24**.

Supporting Information (see also the footnote on the first page of this article): Full experimental details and spectroscopic data for all products are available.

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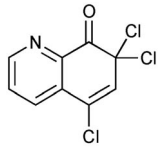

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