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N-Heterocyclic Carbene-Mediated Enantioselective Addition of Phenols to Unsymmetrical Alkylarylketenes

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Abstract: Chiral N-heterocyclic carbenes (NHCs) mediate the enantioselective addition of 2-phenylphenol to unsymmetrical alkylarylketenes, delivering α-alkyl-α-arylacetic acid derivatives with good levels of enantiocontrol (up to 84% *ee*). Enantiodivergent stereochemical outcomes are observed using 2-phenylphenol and benzhydrol in the NHC-promoted esterification reaction using a triazolium precatalyst derived from pyroglutamic acid, consistent with distinct mechanistic pathways operating within these processes.

Keywords: asymmetric catalysis; enantioselectivity; esters; ketenes; N-heterocyclic carbenes; organocatalysis

Introduction

Enantiomerically pure α-alkyl-α-arylacetic acid derivatives possess a wide spectrum of biological activities.[1] A variety of methodologies have been developed for their preparation in enantiomerically enriched form,[2] although only relatively limited strategies for their catalytic asymmetric synthesis have been developed. One such approach to their preparation involves the asymmetric addition of alcohols to unsymmetrical disubstituted ketenes mediated by a chiral catalyst.[3,4] Historically, asymmetry in these reactions can be achieved through the use of a stoichiometric chiral alcohol,[5] with pantolactone typically giving excellent levels of diastereoselectivity.[6] Pracejus first showed that brucine and quinine derivatives promote the addition of methanol to methylphenylketene with good enantioselectivities (up to 76% *ee* at −110 °C),[7] while Simpkins has also shown that quinine derivatives generate good enantioselectivities (up to 94% *ee* at −78 °C) for thiophenol addition to alkyltrialkylsilylketenes.[8] Fu and co-workers have demonstrated that planar chiral heterocycles **2** and **3** catalyse the addition of methanol (up to 80% *ee* in the presence of di(*tert*-butyl)pyridinium triflate at −78 °C)[9a] and phenols (up to 94% *ee* at room temperature), respectively, to a range of alkylarylketenes (Figure 1).[9b]

A number of mechanistic proposals have been put forward to account for these types of transformations.[10] It is widely accepted that the catalytic effect of amines in ketene esterification reactions can be understood through two mechanistic extremes, with an initial reaction step involving either formation of an amine alcohol complex and subsequent base-catalysed addition of the alcohol to the ketene carbonyl to generate an ion pair (pathway 1, Figure 2), or nucleophilic attack of the amine to the ketene carbonyl to generate a zwitterionic enolate (pathway 2, Figure 2). Both reaction manifolds have attracted support, with Pracejus favouring the former for the brucine-catalysed esterification of methylphenylketene,[7] and Fu also favouring a similar pathway for asymmetric ketene esterifications with phenols promoted by **3**.[9b] Extensive calculations by Houk and co-workers also favour this mechanism for the stoichiometric asymmetric addition of chiral alcohols such as pantolactone to ketenes.[11] However, Fu preferred the Lewis base mechanism for ketene-catalysed esterification with methanol using catalyst **2** in the presence of presence of di(*tert*-butyl)pyridinium triflate.[9a]

In recent years N-heterocyclic carbenes (NHCs) have been identified as organocatalysts in a diverse series of reactions.[12] The majority of these processes use NHCs to promote umpolung,[13] conjugate umpolung or homoenolate reactivity,[14] enolate formation from α-functionalised aldehydes,[15] 1,2-additions,[16]

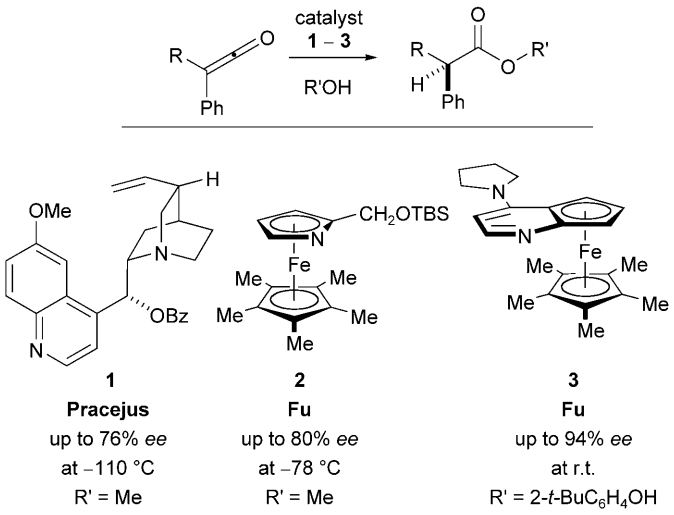


Figure 1. Catalytic asymmetric esterifications of alkylarylketenes with MeOH and 2-*t*-BuC_6H_4OH by Pracejus and Fu.

redox reactions,[17] oxidations,[18] ring expansions,[19] or acyl transfer reactions.[20] As part of a research programme aimed at developing catalytic Lewis base-mediated reaction processes,[21,22] we, simultaneously with Ye, have explored the ability of NHCs to promote the formal [2+2]cycloaddition of ketenes with *N*-tosyl- or *N*-Boc-imines respectively.[23] Further studies by the Ye group have extended NHC-mediated catalysis employing ketenes to ketene dimerisation,[24] formal [4+2]cycloadditions,[25] and β-lactone synthesis with α-oxoaldehydes.[26] A further recent publication from the Ye group concerning the ability of NHCs to promote the catalytic asymmetric addition of benzhydrol to a range of alkylarylketenes (34–95% *ee*) through a proposed Lewis-base mediated mechanism[27] prompts us to disclose our complimentary studies concerning the ability of chiral NHCs to promote the enantioselective addition of phenols to alkylarylketenes (Figure 3).

At the onset of our studies, we chose to focus upon the ability of phenols, rather than alcohols, to participate in the NHC-mediated esterification of ketenes. Given the established precedent for deprotonation of phenols with an imidazolinylidene NHC, consistent with their expected acid/base properties,[28,29] plus Fu's proposal of Brønsted acid-mediated catalysis for the esterification of ketenes with phenols using planar chiral **3**, it seemed feasible that a similar pathway may be followed using NHCs.[7] Interestingly, a number of NHC-mediated reaction processes have previously employed aliphatic alcohols and phenols as a reaction component, including the redox esterification of α,β-unsaturated aldehydes[17] and alkynyl aldehydes.[30] NHCs also promote transesterification reactions[20a–e] and kinetic resolution processes,[20f–h] in which a Lewis base-promoted mechanism has generally been assumed.[31] However, Movassaghi et al. have proposed that NHC-catalyzed amidation of esters with amino alcohols proceeds through the NHC acting as a carbon-centred Brønsted base, resulting in nucleophilic activation of the alcohol for an initial transesterification event, followed by a rapid *O*- to *N*-acyl transfer reaction.[32,33]

Despite these differing mechanistic proposals, Rovis et al. have elegantly demonstrated that phenols can perform the enantioselective protonation of NHC-generated azolium enolates and subsequent esterification, generating α-chloro esters in excellent *ee* (84–93% *ee*) from α,α-dichloro aldehydes (Figure 4).[17e] This transformation is thought to proceed *via* an azolium enolate **11** and subsequent protonation/phenoxide trapping, and as such is mechanistically similar to a possible Lewis-base promoted ketene

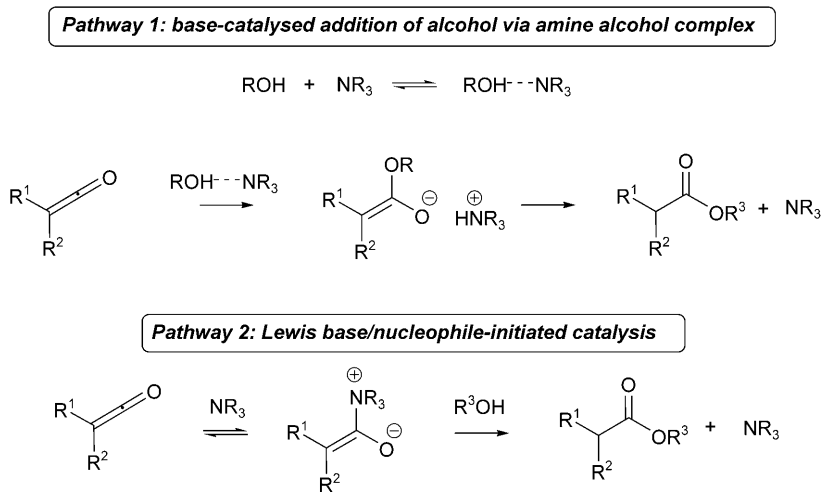


Figure 2. Accepted mechanisms for amine catalysed addition of alcohols to ketenes.

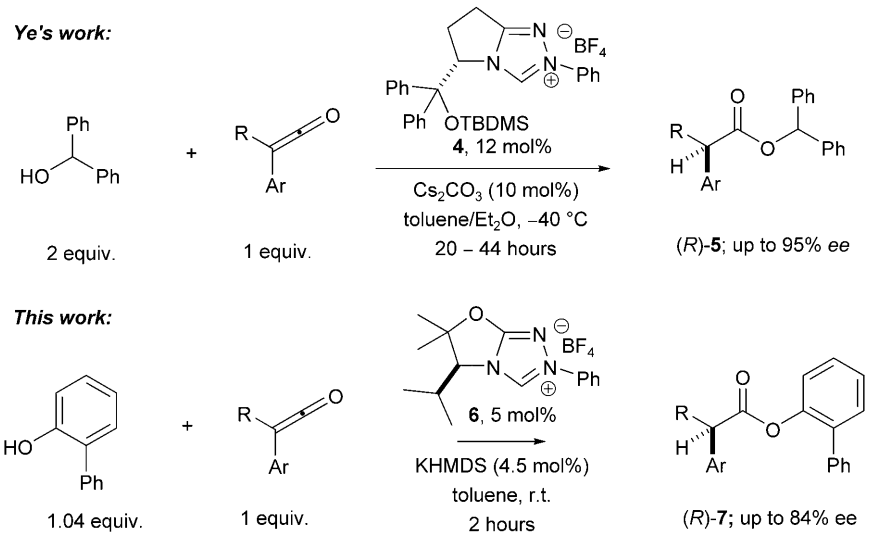


Figure 3. Comparison of Ye's NHC-catalysed asymmetric ketene esterification using benzyhdrol (Lewis base catalysis) and this work using phenols.

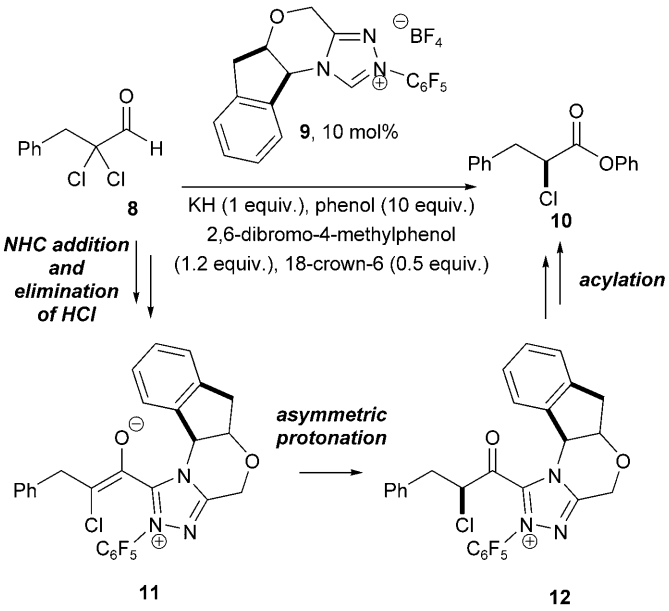


Figure 4. Rovis' NHC-mediated asymmetric synthesis of α-chloro esters using phenol.

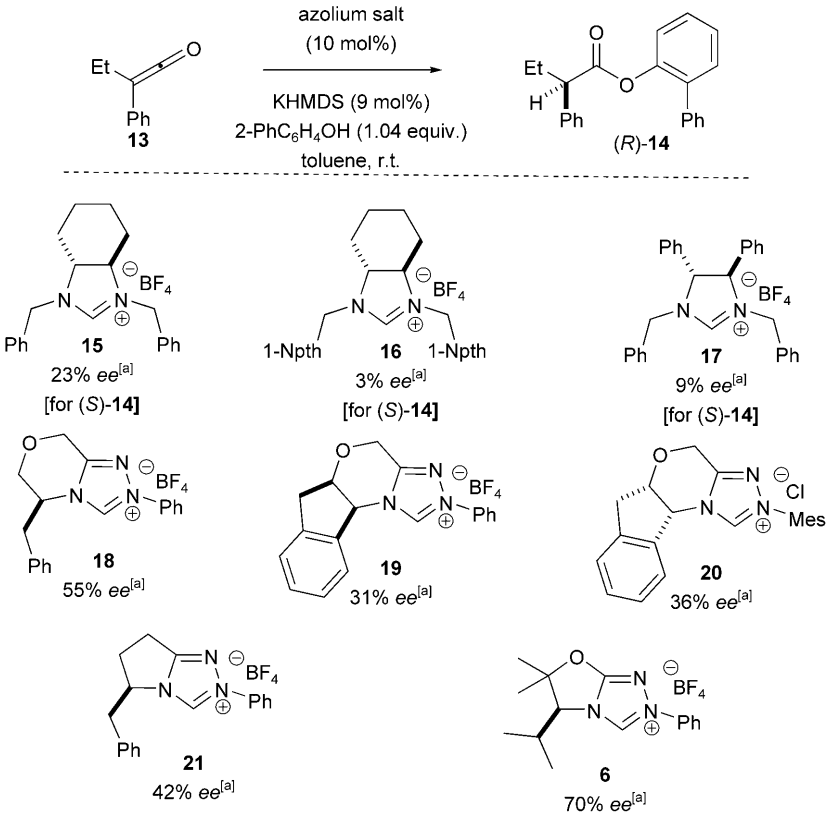
esterification using NHCs and a phenol, although the azolium enolate intermediate would be generated in an alternative manner.

Given these mechanistic questions and established literature precedents, we were intrigued to determine if NHCs could promote asymmetric catalysis of the reaction of alkylarylketenes with phenols, and to compare both the level and sense of enantioselectivity in these reactions with that established by Ye for the addition of benzhydrol to ketenes. We delineate herein our efforts within this area.

Results and Discussion

Preliminary Catalyst Screening

Initial studies sought to demonstrate the feasibility of inducing asymmetry in the NHC-mediated addition of phenols to ketenes, and screened the ability of a range of chiral NHCs to catalyse the asymmetric addition of 2-phenylphenol to ethylphenylketene **13** as a model system for reaction optimisation. Background experiments showed that 2-phenylphenol does not add to ethylphenylketene **13** to generate ester (±)-**14** at a synthetically viable rate, although ester formation is catalysed by base – addition of KHMDS (9 mol%) to 2-phenylphenol promoted full conversion of ethylphenylketene to ester (±)-**14**. Initial experiments used a series of C_2-symmetrical imidazolium salts **15**–**17** (10 mol%) as precatalysts, with deprotonation using KHMDS (9 mol%) used to prepare the corresponding NHC *in situ*. Subsequent addition of ethylphenylketene **13** and 2-phenylphenol at ambient temperature gave good conversion to the desired ester product, but only low enantioselectivity (up to 23% *ee*) was observed. Further catalyst evaluation screened a series of triazolium salt precatalysts using identical conditions. Only modest enantioselectivity (31–55% *ee*) was observed with triazolium precatalysts **18**–**21**, although it is noteworthy that precatalysts **19** and **20** of opposite absolute configuration but bearing N-phenyl and N-mesityl substituents both generate preferentially (*R*)-**14** in 31% and 36% *ee*, respectively.[34] In this initial screen, the most promising level of enantioselectivity was obtained using the oxazolidinone-derived triazolium salt **6**, giving (*R*)-**14** in 70% *ee* (Scheme 1). The absolute configuration of (*R*)-**14** was confirmed through reduction with $LiAlH_4$



Scheme 1. Screening of azolium salts for stereoselectivity in the formation of phenol esters from ketenes. [a] Determined by HPLC analysis

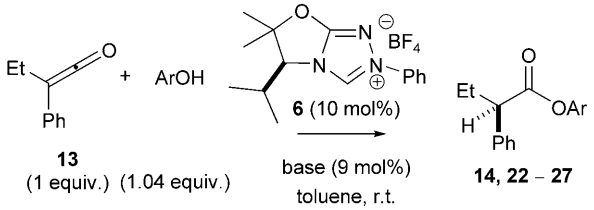
to afford (*R*)-2-phenylbutan-1-ol (70% *ee*) and comparison of its specific rotation with the literature.[35]

Reaction Optimisation

Having identified triazolium salt **6** as a promising pre-catalyst candidate, optimisation of the enantioselectivity of this process initially focused upon variation of the phenol component using either KHMDS or NaH in toluene. Under standardised conditions, phenol gave only modest enantioselectivity, while screening a range of 2-substituted phenols incorporating electron-donating, electron-withdrawing, alkyl or phenyl substituents showed that 2-phenylphenol was optimal, giving the corresponding ester (*R*)-**14** in up to 84% *ee* using NaH as base (Table 1).

Further optimisation focused upon modulation of the stereodirecting group within the triazolium skeleton as well as base and solvent variation (Table 2). Evaluation of triazolium salts **28** and **29** using KHMDS generated products with marginally improved *ee* to **6** (entries 2 and 3), while with NaH salt **6** proved optimal (entry 4), resulting in triazolium salt **6** being used for further reaction evaluation. Using **6** and KHMDS in toluene the *ee* of this process proved

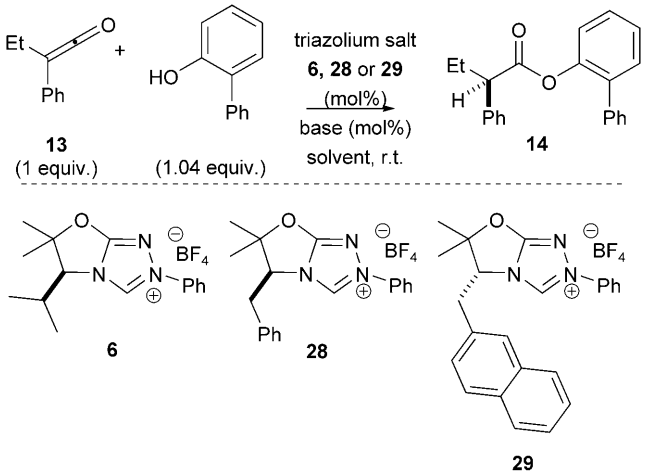
Table 1. Probing the effect of phenol and base upon stereoselectivity in the NHC mediated ketene esterification process.



Entry	ArOH	Base	Ester	*ee*
1	PhOH	KHMDS	**22**	39%[a]
2	PhOH	NaH	**22**	18%[a]
3	2-$MeOC_6H_4OH$	KHMDS	**23**	60%[a]
4	2-$MeOC_6H_4OH$	NaH	**23**	54%[a]
5	2-*i*-$PrOC_6H_4OH$	KHMDS	**24**	42%[a]
6	2-*i*-$PrOC_6H_4OH$	NaH	**24**	45%[a]
7	2-$CF_3C_6H_4OH$	KHMDS	**25**	20%[b]
8	2-*i*-PrC_6H_4OH	KHMDS	**26**	60%[b]
9	2-*t*-BuC_6H_4OH	KHMDS	**27**	42%[b]
10	2-*t*-BuC_6H_4OH	NaH	**27**	55%[b]
11	2-PhC_6H_4OH	KHMDS	**14**	70%[a]
12	2-PhC_6H_4OH	NaH	**14**	84%[a]

[a] Determined by HPLC analysis.
[b] Determined by reduction to the corresponding alcohol and subsequent Mosher's ester analysis and comparison with authentic racemic standards.

Table 2. Probing the effect of base, solvent, and catalyst upon stereoselectivity.



Entry	Catalyst (mol%)	Solvent	Base (mol%)	*ee*[a]
1	**6** (10)	toluene	KHMDS (9)	70%
2	**28** (10)	toluene	KHMDS (9)	77%
3	**29** (10)	toluene	KHMDS (9)	75%[b]
4	**6** (10)	toluene	NaH (9)	84%
5	**29** (10)	toluene	NaH (9)	78%[b]
6	**6** (10)	THF	KHMDS (9)	55%
7	**6** (10)	CH_2Cl_2	KHMDS (9)	14%
8	**6** (10)	toluene	NEt_3 (9)	6%
9	**6** (10)	toluene	Cs_2CO_3 (9)	66%
10	**6** (10)	toluene	NaHMDS (9)	74%
11	**6** (5)	toluene	KHMDS (4.5)	84%
12	**6** (2)	toluene	KHMDS (1.5)	82%
13	**6** (5)	toluene	KHMDS (4.5)	76%[c]

[a] Determined by HPLC analysis.
[b] (*S*)-**14** was preferentially formed.
[c] 5 equiv. of 2-PhC_6H_4OH was used.

independent of NHC concentration from 20 to 50 mM, although using THF or CH_2Cl_2 resulted in decreased product *ee* (entries 6 and 7). Further base variation showed that poor enantioselectivity was observed using NEt_3, presumably reflecting a dominant base-catalysed process. It proved practically easiest to use KHMDS as a base to evaluate the effect of reduced azolium salt loadings, with an optimal *ee* of 84% observed (entries 11 and 12). Slightly reduced *ee* was observed with an excess of 2-phenylphenol (entry 12) in contrast to the beneficial effect of excess phenol observed in the asymmetric synthesis of α-chloroesters from α,α-dichloroaldehydes employing chiral NHCs employed by Rovis.[17e]

Further mechanistic investigations showed that initial deprotonation of salt **6**, presumably generating the corresponding NHC quantitatively *in situ*, is necessary for optimal enantioselectivity in this process. After initial NHC generation, reversal of the order of addition of ketene **13** and 2-phenylphenol results in effectively equal enantioselectivity (72% and 70% *ee*, respectively). However, addition of KHMDS to a mixture of salt **6** and 2-phenylphenol, or initial deprotonation of 2-phenylphenol with KHMDS and addition of salt **6**, followed by ketene **13**, results in markedly reduced enantioselectivity (30% and 38% *ee*, respectively).[36] As deprotonation of 2-phenylphenol (1.1 equiv.) with KHMDS (9 mol%) and addition of ethylphenylketene **13** results in quantitative formation of ester (±)-**14**, the reduced stereoselectivity of these latter processes may reflect a competitive non-stereoselective reaction pathway involving catalysis promoted by 2-phenylphenolate.

Product stability experiments indicate that no transesterification products are observed upon retreatment of (*R*)-**14** with phenol and the NHC derived from **6**, although partial epimerisation was observed upon retreatment of (*R*)-**14** with the NHC derived from **6** (10 mol%) and KHMDS (9 mol%) for 2 h (70% *ee* to 64% *ee*). However, monitoring the reaction conversion and product enantiomeric excess upon generation of (*R*)-**14** from ethylphenylketene using **6** and KHMDS showed that, even at 5 mol% catalyst loading, the reaction is effectively complete (>95% conversion by ^{1}H NMR spectroscopic analysis) within 10 min, with the *ee* of the product essentially invariant of reaction time up to the standard reaction time of two hours.[36] It is notable that the reaction time in this ketene esterification reaction is markedly enhanced in comparison to that employing precatalyst **4** and benzhydrol (typically >20 h at −40 °C).

Further studies showed that asymmetric induction in this reaction shows an inverse correlation with temperature. Optimal enantioselectivity [giving (*R*)-**14**] was observed at room temperature employing **6**, with low but opposite stereoinduction [giving (*S*)-**14**] observed below −30 °C (Figure 5). A related phenomenon involving inversion of configuration of the product esters with reaction temperature has been noted by Pracejus in the alkaloid-catalysed addition of alcohols to ketenes, with these results postulated to result not from a change in mechanism, but from a mixture of entropic and enthalpic effects on the stability of diastereoisomeric transition states.[37,38] This temperature effect is opposite to that noted by Fu, who observed optimal *ee* at low temperature (~−70 °C) for the Lewis base-mediated asymmetric addition of methanol to alkylarylketenes,[9a] which presumably reflects a fast, uncatalysed background reaction at room temperature and an asymmetric Lewis base-promoted reaction at low temperature.

Reaction Generality

Having fully evaluated reaction conditions and reagents for the model reaction, the generality of this procedure was evaluated. For experimental simplicity

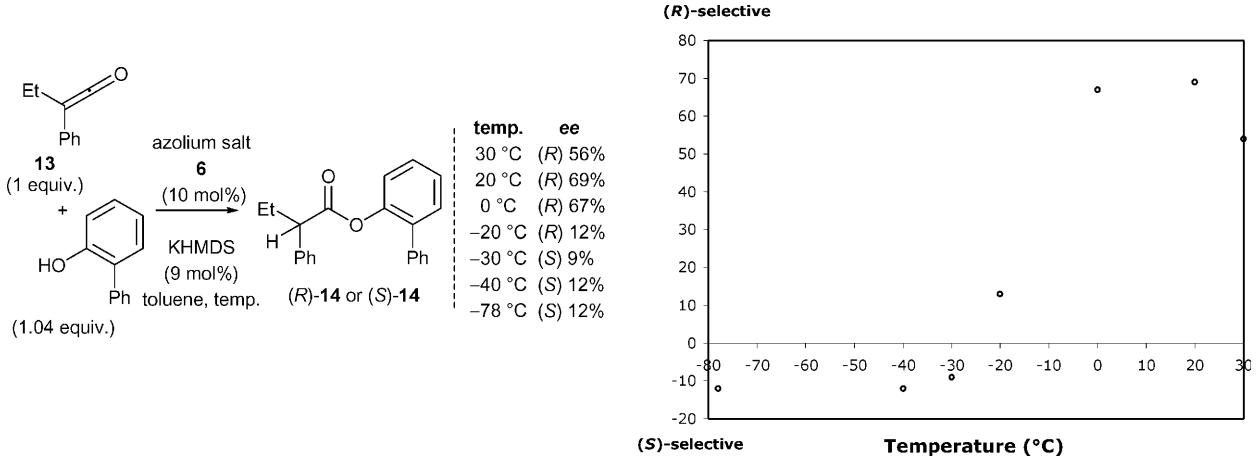


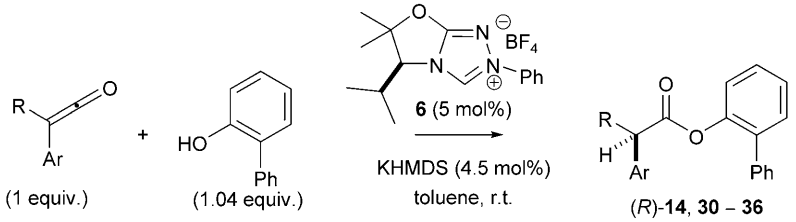
Figure 5. Variation of product *ee* with temperature for the NHC-promoted esterification of ethylphenylketene.

a standard reaction protocol using 5 mol% of azolium salt **6** and KHMDS (4.5 mol%) in toluene at room temperature was adopted (Table 3). These results demonstrate that structural variation of both the C(2)-alkyl and C(2)-aryl substituent of the ketene is readily tolerated, generating the corresponding ester products in good isolated yield (65–91%) and 58–84% *ee* (entries 1–7). However, 2-substitution within the aryl moiety of the ketene gave products with markedly reduced *ee*, an observation that parallels the results of Ye[27] (entry 8).

Enantiodivergent NHC-Mediated Esterification

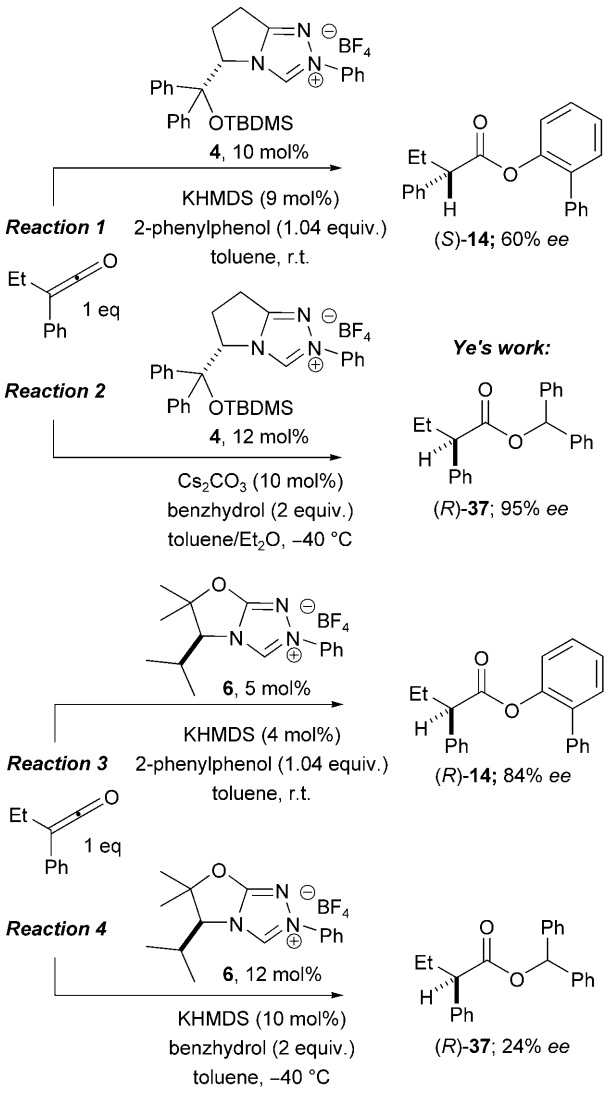
The stereochemical outcome of the NHC-mediated transformation detailed herein is intriguing. Esterification of ethylphenylketene using the NHC derived from **6** and 2-phenylphenol generates an (*R*)-configured ester product **14** in the same enantiomeric series to that observed by Ye et al. using the NHC derived from precatalyst **4** with benzhydrol, despite their respective stereodirecting groups having the opposite stereochemical sense (Scheme 2, reactions 2 and 3).[39] Fascinated by this stereochemical outcome, the ability of the NHC derived from precatalyst **4** to deliver asymmetry in the esterification of ethylphenylketene with 2-phenylphenol was evaluated, giving (*S*)-**14** in 60% *ee*.[40] This result indicates that enantiodivergent reaction pathways are observed with precatalyst **4** in the esterification of ethylphenylketene using benzhydrol and 2-phenylphenol (Scheme 2, reactions 1 and 2). Taking the recognised mechanistic pathways available for ketene derived esterification processes into

Table 3. Generality of the asymmetric addition of 2-phenylphenol to alkylarylketenes.



Entry	Ar	R	Product (yield [%])	*ee*[a,b]
1	Ph	Et	**14** (79%)	84%
2	Ph	*n*-Bu	**30** (79%)	58%
3	Ph	*i*-Bu	**31** (65%)	72%
4	4-$MeOC_6H_4$	Et	**32** (70%)	70%
5	4-FC_6H_4	Et	**33** (75%)	74%
6	4-MeC_6H_4	Et	**34** (91%)	76%
7	4-ClC_6H_4	Et	**35** (86%)	58%
8	2-ClC_6H_4	Et	**36** (76%)	33%

[a] Determined by HPLC analysis.
[b] The absolute configurations of **30**–**36** were assigned by analogy to that proven unambiguously for (*R*)-**14**.



Scheme 2. Comparison of ketene esterification reactions using precatalysts **4** and **6**.

consideration (Figure 2), the enantiodivergent outcome of this process mediated by precatalyst **4** may simplistically derive from a change from one mechanistic pathway to the other upon using benzhydrol or 2-phenylphenol. We subsequently evaluated precatalyst **6** in the asymmetric esterification reaction of ethylphenylketene with benzhydrol. In our hands, and in contrast to 2-phenylphenol, benzhydrol undergoes a significant uncatalysed background reaction with ethylphenylketene at room temperature, giving ~50% conversion to ester (±)-**37** at room temperature in toluene within 2 h. Attempted asymmetric esterification with benzhydrol using the NHC derived from precatalyst **6** under a range of conditions, including cooling of the reaction temperature and modulation of the base from KHMDS to Cs_2CO_3 led to essentially racemic product at temperatures from room temperature to −78°C. In our hands, the optimal *ee* using precatalyst **6** was observed employing an inverse addition protocol using KHMDS as the base, generating (*R*)-**37** in a modest 24% *ee* at −40°C (Scheme 2, reaction 4). These results are consistent with asymmetric induction in these NHC-promoted transformations operating according to different molecular recognition events that are catalyst and substrate dependent.

In conclusion, chiral NHCs can efficiently promote the asymmetric addition of 2-phenylphenol to a range of alkylarylketenes, generating α-alkyl-α-arylacetic acid derivatives with good levels of enantioselectivity (up to 84% *ee*) using precatalyst **6** and KHMDS. Enantiodivergent stereochemical outcomes are observed with the use of 2-phenylphenol and benzhydrol in the NHC-promoted esterification reaction using precatalyst **4**, consistent with distinct mechanistic pathways operating within these processes with this catalyst. A Brønsted acid/Lewis base-mediated mechanistic switch is tentatively proposed to account for the observed enantiodivergence in these pathways. Current studies are focused upon probing fully the mechanism of this transformation as well as developing alternative applications of enantiomerically pure NHCs in asymmetric catalysis.

Experimental Section

General Experimental Procedure for the Synthesis of 2-Phenylphenol Esters from Ketenes

A 0.5 M solution of KHMDS in toluene (0.045 mL, 0.0225 mmol, 4.5 mol%) was added to a suspension of triazolium salt **6** (8.6 mg, 0.025 mmol, 5 mol%) in toluene (2 mL) under an argon atmosphere and the mixture was stirred for 20 min at room temperature. A solution of the corresponding ketene (0.5 mmol, 1 equiv.) in toluene (8 mL) was added, followed by 2-phenylphenol (88 mg, 0.52 mmol, 1.04 equiv.), and then the reaction mixture was stirred for 2 h at room temperature before concentration. The residue was purified by column chromatography to give the corresponding ester.

Preparation of (*R*)-2-Phenylphenyl 2-Phenylbutanoate (14)

Following the general procedure, ester (*R*)-**14** was obtained as a colourless oil after chromatography (petrol-Et_2O 90:10); yield: 0.125 g (79%). ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.36–6.97 (14 H, m), 3.49 (1 H, t, J = 7.6 Hz), 2.06–1.94 (1 H, m), 1.77–1.66 (1 H, m), 0.75 (3 H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ = 172.7, 148.2, 138.7, 137.7, 135.5, 131.3, 129.3, 129.0, 128.8, 128.5, 128.4, 127.7, 126.6, 123.1, 53.8, 27.0, 12.4; IR (thin film): ν_{max} = 2968, 1753, 1478, 1265, 1137, 738, 699 cm^{-1}; MS: (Cl): m/z = 119.1 (100), 317.1 (50, M+H$^+$); HR-MS (Cl$^+$): m/z = 317.1546, $C_{22}H_{21}O_2$ requires: 317.1542 (1.4 ppm). The enantiomeric excess of **14** was determined by HPLC analysis using a Chiralpak AD-H column (10% *i*-PrOH in hexanes, flow rate = 1.0 mL min^{-1}):

$t_R(S)$ 5.17 min and $t_R(R)$ 8.43 min, 84% *ee*; $[\alpha]_D^{20}$: −33.2 (*c* 1, $CHCl_3$).

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References

[1] a) N. Bodor, R. Woods, C. Raper, P. Kearney, J. J. Kaminski, *J. Med. Chem.* **1980**, *23*, 474; b) M. F. Landoni, A. Soraci, *Curr. Drug Metab.* **2001**, *2*, 37.

[2] For a recent example, see: X. Dai, N. A. Strotman, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 3302.

[3] For a review, see: T. T. Tidwell, *Angew. Chem.* **2005**, *117*, 6973; *Angew. Chem. Int. Ed.* **2005**, *44*, 6812.

[4] For a review of asymmetric synthesis using ketenes, see: R. K. Orr, M. A. Calter, *Tetrahedron* **2003**, *59*, 3545.

[5] E. Anders, E. Ruch, A. Ugi, *Angew. Chem.* **1973**, *85*, 16; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 25.

[6] a) R. D. Larsen, E. G. Corley, P. Davis, P. J. Reider, E. J. Grabowski, *J. Am. Chem. Soc.* **1989**, *111*, 7650; b) C. E. Cannizzaro, K. N. Houk, *J. Am. Chem. Soc.* **2004**, *126*, 10992; c) R. Akkari, M. Calmes, N. Mai, M. Rolland, J. Martinez, *J. Org. Chem.* **2001**, *66*, 5859.

[7] a) H. Pracejus, *Justus. Liebigs. Ann. Chem.* **1960**, *634*, 9; b) H. Pracejus, H. Matje, *J. Prakt. Chem.* **1964**, *24*, 195; c) H. Pracejus, G. Kohl, *Justus. Liebigs. Ann. Chem.* **1969**, *722*, 1.

[8] A. J. Blake, C. L. Friend, R. J. Outram, N. S. Simpkins, A. J. Whitehead, *Tetrahedron Lett.* **2001**, *42*, 2877.

[9] a) B. L. Houdous, J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 2637; b) S. L. Wiskur, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 6176.

[10] W. T. Brady, W. L. Vaughn, E. F. Hoff, *J. Org. Chem.* **1969**, *34*, 843; A. Tille, H. Pracejus, *Chem. Ber.* **1967**, *100*, 196; P. J. Lillford, D. P. N. Satchell, *J. Chem. Soc. B* **1968**, 889; J. Jähme, C. Rüchardt, *Tetrahedron Lett.* **1982**, *23*, 4011.

[11] C. E. Cannizzaro, T. Strassner, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 2668; see also ref.[6b]

[12] For recent reviews of the ability of NHCs to catalyse organocatalytic processes, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988.

[13] For select examples see: a) J. H. Teles, J.-P. Melder, K. Ebel, R. Schneider, E. Gehrer, W. Harder, S. Brode, D. Enders, K. Breuer, G. Raabe, *Helv. Chim. Acta* **1996**, *79*, 61; b) M. S. Kerr, J. Read deAlaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298; c) D. Enders, U. Kallfass, *Angew. Chem.* **2002**, *114*, 1822; *Angew. Chem. Int. Ed.* **2002**, *41*, 1743; d) Y. Hachisu, J. W. Bode, K. Suzuki, *Adv. Synth. Catal.* **2004**, *346*, 1097; e) A. E. Mattson, A. R. Bharadwaj, A. M. Zuhl, K. A. Scheidt, *J. Org. Chem.* **2006**, *71*, 5715; f) M. C. Myers, A. R. Bharadwaj, B. C. Milgram, K. A. Scheidt, *J. Am. Chem. Soc.* **2005**, *127*, 14675; g) J. L. Moore, M. S. Kerr, T. Rovis, *Tetrahedron* **2006**, *62*, 11477; h) A. E. Mattson, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 4508, A. Orellana, T. Rovis, *Chem. Commun.* **2008**, 730; i) J. Read deAlaniz, M. S. Kerr, J. L. Moore, T. Rovis, *J. Org. Chem.* **2008**, *73*, 2033; j) F. T. Wong, P. K. Patra, J. Seayad, Y. Zhang, J. Y. Ying, *Org. Lett.* **2008**, *10*, 2333; k) S. C. Cullen, T. Rovis, *Org. Lett.* **2008**, *10*, 3141; l) Q. Liu, S. Perreault, T. Rovis, *J. Am. Chem. Soc.* **2008**, *130*, 14066.

[14] For examples, see: a) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370; c) A. Chan, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 905; d) M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131; e) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 5334; f) E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2416; g) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2740; h) M. Rommel, T. Fukuzumi, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 17266; i) Q. Liu, T. Rovis, *Org. Lett.* **2009**, *11*, 2856. For the use of α′-hydroxyenones as α,β-unsaturated aldehyde surrogates see: j) P.-C. Chiang, M. Rommel, J. W. Bode, *J. Am. Chem. Soc.* **2009**, *131*, 8714.

[15] a) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418; b) M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 15088; c) E. M. Phillips, M. Wadamoto, A. Chan, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 3167; *Angew. Chem. Int. Ed.* **2007**, *46*, 3107; d) M. He, B. J. Beahm, J. W. Bode, *Org. Lett.* **2008**, *10*, 3817.

[16] For select examples, see: a) J. J. Song, F. Gallou, J. T. Reeves, Z. Tan, N. K. Yee, C. H. Senanayake, *J. Org. Chem.* **2006**, *71*, 1273; b) Y. Suzuki, M. D. Abu Bakar, K. Muramatsu, M. Sato, *Tetrahedron* **2006**, *62*, 4227; c) T. Kano, K. Sasaki, T. Konishi, H. Mii, K. Maruoka, *Tetrahedron Lett.* **2006**, *47*, 4615.

[17] For select examples, see: a) K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126; b) N. T. Reynolds, J. Read deAlaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518; c) A. Chan, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 905; d) K. Zeitler, *Angew. Chem.* **2005**, *117*, 7674; *Angew. Chem. Int. Ed.* **2005**, *44*, 7506; e) N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406; f) S. S. Sohn, J. W. Bode. *Org. Lett.* **2005**, *7*, 3873; g) S. S. Sohn, J. W. Bode, *Angew. Chem.* **2006**, *118*, 6167; *Angew. Chem. Int. Ed.* **2006**, *45*, 6021; h) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796; i) J. W. Bode, S. S. Sohn, *J. Am. Chem. Soc.* **2007**, *129*, 13798; j) H. U. Vora, J. R. Moncecchi, O. Epstein, T. Rovis, *J. Org. Chem.* **2008**, *73*, 9727; k) C. Noonan, L. Baragwanath, S. J. Connon, *Tetrahedron Lett.* **2008**, *49*, 4003.

[18] a) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.* **2007**, *9*, 371; b) B. E. Maki, K. A. Scheidt, *Org. Lett.* **2008**, *10*, 4331; c) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Tetrahedron* **2009**, *65*, 3102.

[19] a) B. Alcaide, P. Almendros, G. Cabrero, M. P. Ruiz, *Chem. Commun.* **2007**, 4788; b) G.-Q. Li, Y. Li, L.-X. Dai, S.-L. You, *Org. Lett.* **2007**, *9*, 3519; c) G.-Q. Li, Y. Li, L.-X. Dai, S.-L. You, *Adv. Synth. Catal.*, **2008**, *350*, 1258; d) L. Wang, K. Thai, M. Gravel, *Org. Lett.* **2009**, *11*, 891; e) G.-Q. Li, L.-X. Dai, S.-L. You, *Org. Lett.* **2009**, *11*, 1623;.

[20] For transesterification, see: a) G. A. Grasa, R. M. Kissling, S. P. Nolan, *Org. Lett.* **2002**, *4*, 3583; b) G. A. Grasa, T. Güveli, R. Singh, S. P. Nolan, *J. Org. Chem.* **2003**, *68*, 2812; c) E. F. Connor, G. W. Nyce, M. Myers, A. Möck, J. L. Hedrick, *J. Am. Chem. Soc.* **2002**, *124*, 914; d) G. W. Nyce, J. A. Lamboy, E. F. Connor, R. M. Waymouth, J. L. Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587; e) G. W. Nyce, T. Glauser, E. F. Connor, A. Möck, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2003**, *125*, 3046; for kinetic resolution processes see: f) Y. Suzuki, K. Yamauchi, K. Muramatsu, M. Sato, *Chem. Commun.* **2004**, 2770; g) T. Kano, K. Sasaki, K. Maruoka, *Org. Lett.* **2005**, *7*, 1347; h) Y. Suzuki, K. Muramatsu, K. Yamauchi, Y. Morie, M. Sato, *Tetrahedron* **2006**, *62*, 302.

[21] For an excellent recent review of Lewis base-mediated reaction processes see S. E. Denmark, G. L. Beutner, *Angew. Chem.* **2008**, *120*, 1584; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.

[22] a) J. E. Thomson, K. Rix, A. D. Smith, *Org. Lett.* **2006**, *8*, 3785; b) J. E. Thomson, C. D. Campbell, C. Concellón, N. Duguet, K. Rix, A. M. Z. Slawin, A. D. Smith, *J. Org. Chem.* **2008**, *73*, 2784; c) C. D. Campbell, N. Duguet, K. A. Gallagher, J. E. Thomson, A. G. Lindsay, A. O'Donoghue, A. D. Smith, *Chem. Commun.* **2008**, 3528; d) C. Joannesse, C. Simal, C. Concellón, J. E. Thomson, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 2900; e) J. E. Thomson, A. F. Kyle, C. Concellón, K. A. Gallagher, P. Lenden, L. C. Morrill, A. J. Miller, C. Joannesse, A. M. Z. Slawin, A. D. Smith, *Synthesis* **2008**, *17*, 2805; f) C. Joannesse, C. P. Johnston, C. Concellón, C. Simal, D. Philp, A. D. Smith, *Angew. Chem.* **2009**, *121*, 9076–9080; *Angew. Chem. Int. Ed.* **2009**, *48*, 8914–8918.

[23] a) N. Duguet, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1108; b) Y. R. Zhang, L. He, X. Wu, P. L. Shao, S. Ye, *Org. Lett.* **2008**, *10*, 277.

[24] H. Lv, Y.-R. Zhang, X.-L. Huang, S. Ye, *Adv. Synth. Catal.* **2008**, *350*, 2715.

[25] a) Y.-R. Zhang, H. Lv, D. Zhou, S. Ye, *Chem. Eur. J.* **2008**, *14*, 8473; b) X.-L. Huang, L. He, L. P.-L. Shao, S. Ye, *Angew. Chem. Int. Ed.* **2009**, *48*, 192.

[26] L. He, H. Lv, Y.-R. Zhang, S. Ye, *J. Org. Chem.* **2008**, *73*, 8101.

[27] X.-N. Wang, H. Lv, X.-L. Huang, S. Ye, *Org. Biomol. Chem.* **2009**, *7*, 346.

[28] J. A. Cowan, J. A. C. Clyburne, M. G. Davidson, R. L. W. Harris, J. A. K. Howard, P. Küpper, M. A. Leech, S. P. Richards, *Angew. Chem.* **2002**, *114*, 1490; *Angew. Chem. Int. Ed.* **2002**, *41*, 1432.

[29] Nolan et al. have demonstrated that NHCs can interact with methyl acetate, generating an isolable Claisen condensation adduct that is presumably initiated by deprotonation using the NHC, see: G. A. Grasa, R. Singh, N. M. Scott, E. D. Stevens and S. P. Nolan, *Chem. Commun.* **2004**, 2890.

[30] K. Zeitler, *Org Lett.* **2006**, *8*, 637.

[31] For selected polymerisation protocols catalysed by NHCs that presumably proceed *via* a Lewis-base mechanism, see: G. W. Nyce, T. Glauser, E. F. Connor, A. Moeck, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2003**, *125*, 3046; A. P. Dove, R. C. Pratt, B. G. G. Lohmeijer, D. A. Culkin, E. C. Hagberg, G. W. Nyce, R. M. Waymouth, J. L. Hedrick, *Polymer* **2006**, *47*, 4018; A. P. Dove, H. Li, R. C. Pratt, B. G. G. Lohmeijer, D. A. Culkin, R. M. Waymouth, J. L. Hedrick, *Chem. Commun.* **2006**, 2881; D. A. Culkin, W. Jeong, S. Csihony, E. D. Gomez, N. P. Balsara, J. L. Hedrick, R. M. Waymouth, *Angew. Chem.* **2007**, *119*, 2681; *Angew. Chem. Int. Ed.* **2007**, *46*, 2627; N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. G. G. Lohmeijer, J. L. Hedrick, *Chem. Rev.* **2007**, *107*, 5813; W. Jeong, E. J. Shin, D. A. Culkin, J. L. Hedrick, R. M. Waymouth, *J. Am. Chem. Soc.* **2009**, *131*, 4884.

[32] M. Movassaghi, M. A. Schmidt, *Org. Lett.* **2005**, *7*, 2453.

[33] Further studies by Movassaghi have demonstrated that the acidity of the alcohol component is important in determining the extent of alcohol-NHC interactions, see: M. A. Schmidt, P. Müller, M. Movassaghi, *Tetrahedron Lett.* **2008**, *49*, 4316.

[34] A related phenomenon, involving inversion of product configuration through variation of the *N*-phenyl and *N*-mesityl substituents within a chiral NHC has been observed by Ye et al., see ref.[25b]

[35] $[\alpha]_D^{20}$: −15.4 (*c* 1.08, $CHCl_3$); ref.[35a] $[\alpha]_D^{23}$: −21.1 (*c* 1.00, $CHCl_3$), >99% *ee*; $[\alpha]_D^{20}$: −12.8 (*c* 1.00, MeOH); ref.[35b] $[\alpha]_D^{23}$: −12.6 (*c* 1.20, MeOH), 62% *ee*; see Supporting Information for full details; a) C. H. Senanayake, R. D. Larsen, T. J. Bill, J. Liu, E. G. Corley, P. J. Reider, *Synlett* **1994**, 199; b) K. Naemura, M. Murata, R. Tanaka. M. Yano, K. Horose, Y. Tobe, *Tetrahedron: Asymmetry* **1996**, *7*, 3285.

[36] See Supporting Information for full details.

[37] For the work of Pracejus see ref.[7]; for a review, see: H. Buschmann, H.-D. Scharf, N. Hoffmann, P. Esser, *Angew. Chem.* **1991**, *103*, 480; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477.

[38] For related work by Yamashita and co-workers concerning esterification of ketenes with polymer bound catalysts, see: T. Yamashita, H. Yasueda, Y. Miyauchi, N. Nakamura, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1532; T. Yamashita, H. Yasueda, N. Nakatani, N. Nakamura, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1183; T. Yamashita, H. Yasueda, N. Nakamura, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2165.

[39] One explanation for this stereochemical outcome may be that the conformation of the ring bearing the stereodirecting group in the NHCs derived from precatalyst **4** (prepared from a pyrrolidinone) or precatalyst **6** (prepared from an oxazolidinone) are different, with a resultant change in sense of stereoinduction. For a recent example that exemplifies the conformational flexibility of pyrrolidinone derived NHCs and its effect upon reaction asymmetry, see: D. A. DiRocco, K. M. Oberg, D. M. Dalton and T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 10872.

[40] Optimal levels of asymmetry (60% *ee*) were observed using employed an inverse addition protocol; under standard reaction conditions competitive ketene dimerisation, and a fluctuation in ester product *ee* from 2% *ee* to 30% *ee* was observed.

