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N-silyl oxyketene imines are underused yet highly versatile reagents for catalytic asymmetric synthesis

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The reactions of acyl anion equivalents (d^1 synthons) with carbonyl electrophiles allow for the construction of a wide range of molecules useful for the synthesis of biologically active compounds, natural products and chiral ligands. Despite their utility, significant challenges still exist for developing catalytic, enantioselective variants of these reactions. For example, the asymmetric benzoin process, arguably the most characteristic reaction of d^1 synthetic equivalents, finds no general solution for reactions involving aliphatic acyl anions. In this Article, we introduce a new class of stable, isolable silyl ketene imines derived from protected cyanohydrins. These nucleophiles serve as acyl anion equivalents in Lewis base catalysed aldol addition reactions and allow for the preparation of cross-benzoin and glycolate-aldol products in high yield and with exceptional diastereo- and enantioselectivities.

The deprotonation of protected cyanohydrins and the subsequent reactions of the resulting metallo ketene imines with carbon-based electrophiles is a well-established method for constructing carbon − carbon bonds[1–5]. When applied to carbonyl additions, extremely versatile β-hydroxy cyanohydrins (**2**) are obtained (Fig. 1). The usefulness of these products arises from the ability of cyanide to act as either a leaving group through deprotection/retro-cyanation (path a, Fig. 1), or to be revealed as a carbonyl compound through hydrolysis, reduction or organometallic addition (path b, Fig. 1). Unfortunately, the generation of metalated ketene imines requires stoichiometric quantities of strong amide or alkyllithium bases, which severely limits the extension of this process to a catalytic, enantioselective variant. In this Article, a new class of stable, isolable *N*-silyl oxyketene imines (**1**) derived from protected cyanohydrins is introduced. These latent nucleophiles harness the reactivity of a metallo ketene imine and allow for the catalytic, enantioselective synthesis of β-hydroxy cyanohydrins and their subsequent application to cross-benzoin and glycolate aldol reactions.

The potential benefits that nucleophilic cyanohydrins offer in asymmetric addition reactions have been recognized in recent years. A chiral-auxiliary-based method has been developed in which benzaldehyde cyanohydrin, modified with an ephedrine-derived *O*-phosphate, undergoes highly diastereoselective alkylations and Michael reactions[6]. The obvious drawbacks to this process are the use of stoichiometric amounts of alkyllithium bases and the additional steps required for removal and recovery of the auxiliary. A novel strategy for accessing the anions of protected cyanohydrins that circumvents the need for strong bases is the cyanide-promoted 1,2-Brook rearrangement[7,8] of acyl silanes[9–13]. Others have successfully applied this process to catalytic, enantioselective acylations of cyanohydrins by using a chiral (salen)aluminium alkoxide catalyst and benzyl cyanoformate as both the source of cyanide and the acylating reagent[14,15]. Although this reaction represents a benchmark for asymmetric reactions of metallated cyanohydrins, the observed enantioselectivities are highly substrate-dependent and reach a maximum at 91:9 er.

A related study reported the catalytic, enantioselective cross-benzoin reaction of acyl silanes with aldehydes catalysed by TADDOL-derived metallophosphites[16]. These reactions also proceed through a nucleophile-promoted Brook rearrangement, but do not involve the intermediacy of a cyanohydrin anion. Cross-benzoin adducts comprising two different aromatic aldehydes are obtained in good yield and enantioselectivity (91:9 to 96.5:4.5 er), but the yields and selectivities are significantly reduced with aliphatic aldehydes or acyl silanes. Although limitations in substrate scope are observed, this method represents the current state of the art for achieving non-enzymatic, catalytic, enantioselective cross-benzoin products[17].

Among all the useful addition reactions of cyanohydrin-derived anions, curiously, the aldol process remains underdeveloped. The

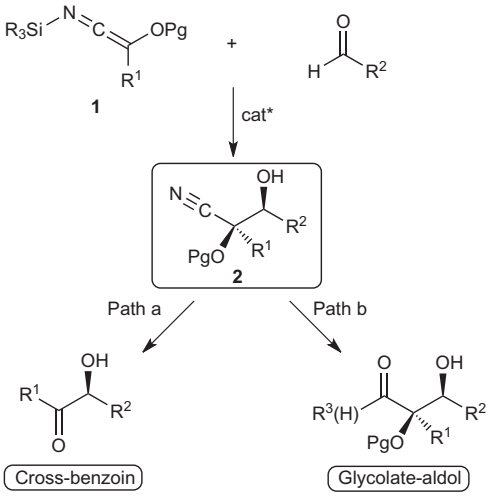

Figure 1 | Reaction pathways available to *N*-silyl oxyketene imines. Aldol reactions of *N*-silyl oxyketene imines (**1**) with aldehydes to afford β-hydroxy nitrile products (**2**) are presented. The ability of the *N*-silyl oxyketene imines to serve as acyl anion equivalents is realized by deprotection and retrocyanation of **2** (path a). Alternatively, glycolate-aldol products containing a protected stereogenic tertiary alcohol are revealed by reduction or organometallic addition to the nitrile (path b).

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products of these reactions are analogous to the aldol additions of α-substituted glycolate enolates and have a fully substituted α-stereogenic centre. Very few methods are capable of delivering this structure in a stereocontrolled fashion. A chiral auxiliary method has been reported in which a boron enolate is generated by the 1,2-Wittig rearrangement of an *O*-benzylglycolate derived from a chiral alcohol[18]. More recently, the catalytic, enantioselective additions of 5H-oxazole-4-ones with aldehydes catalyzed by chiral guanidines have been reported[19]. The oxazole-4-one products are obtained in good yield and enantioselectivity, but the diastereoselectivity is highly dependent on the substrates. Additionally, the reaction is limited to cyclic donors, which further emphasizes the challenges inherent in controlling enolate geometry for acyclic disubstituted substrates[20,21]. Although the preparation of secondary alcohols by catalytic, enantioselective glycolate aldol additions is known[22–24], this last method is the first in which tetrasubstituted stereogenic centres are obtained.

Previous studies from these laboratories[25] and others[26] have documented the advantages that silyl ketene imines offer in the catalytic, enantioselective synthesis of compounds containing quaternary stereogenic centres. These nucleophiles are readily prepared in high yield and purity by the deprotonation of disubstituted alkyl or aryl nitriles, followed by trapping of the resulting anion with an appropriate trialkylsilyl chloride. Surprisingly, the analogous reactions of protected cyanohydrins are practically unknown. A single account on the deprotonation of trimethylsilyl-protected cyanohydrins by lithium diisopropylamide, and subsequent trapping with trimethylsilyl chloride, appeared in 1992 (ref. 27). This study revealed that the site of silylation of the metallo ketene imine is highly responsive to the size of the alkyl substituent of the cyanohydrin. For example, the cyanohydrins derived from acetaldehyde gave, exclusively, the *C*-silylated nitrile, whereas the cyanohydrin derived from 2-methylpropanal gave primarily the *N*-silylated ketene imine (90:10 ratio, *N*- to *C*-silylation). Intermediate results are observed with the cyanohydrin prepared from 1-hexanal (60:40, *N*- to *C*-silylation), but interestingly the ratio changes in favour of *C*-silylation upon standing for 5 days at 25 °C (16:84, *N*- to *C*-silylation). These results suggest that the initial product distribution is, at least partially, under kinetic control and that the *C*-silylated isomer is the thermodynamically more stable product. Despite these promising findings, no subsequent reports on the preparation and/or use of silyl ketene imines derived from protected cyanohydrins are on record.

Results

Synthesis of *t*-butyl protected cyanohydrins. The work of Cunico and Kuan demonstrates the crucial role that steric effects play in obtaining *N*-silyl oxyketene imines versus the more thermodynamically favoured *C*-silylated isomers. Therefore, the first goal of the current study was to identify and synthesize a suitably protected cyanohydrin that would allow for the selective formation of the ketene imine. Specifically, an *O*-protecting group was sought that met the following criteria: (i) the protecting group must be sterically bulky so that silylation at the less encumbered *N*-terminus will be favoured; (ii) the protecting group must be able to be installed under acidic conditions because of the sensitivity of cyanohydrins to basic media; (iii) the protecting group must be stable to alkyl lithium and amide bases; and (iv) the introduction and removal of the protecting group must be high yielding and scalable.

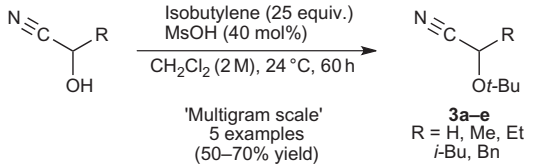
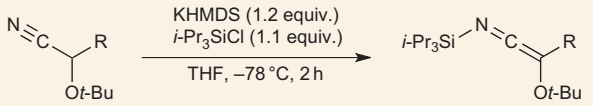


Figure 2 | Synthesis of tert-butyl protected cyanohydrins.

Table 1 | Preparation of *N*-silyl oxyketene imines from tert-butyl protected cyanohydrins.



3b–f 4b–f

Entry	R	Product	Yield (%)*	υ_{max} (cm^{-1})†
1	Me	**4b**	94	2,037
2	Et	**4c**	94	2,033
3	*i*-Bu	**4d**	93	2,036
4	Bn	**4e**	93	2,039
5	Allyl‡	**4f**	97	2,037

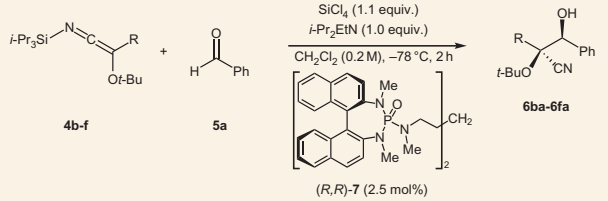
General reaction conditions: **3** (3.6–5.9 mmol), KHMDS (1.2 equiv.), *i*-Pr_3SiCl (1.1 equiv.), THF (1.0 M), −78 °C, 2 h. *Yield of crude ketene imine obtained after filtration and removal of volatiles by high vacuum. †FT-IR of neat liquids on NaCl plates. ‡Starting material prepared by alkylation of tert-butyl protected formaldehyde cyanohydrin.

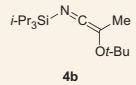
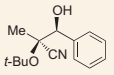
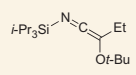
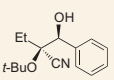
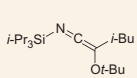
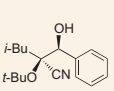
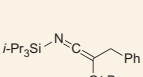
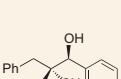
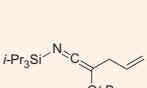
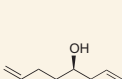
The tert-butyl group embodies all of these characteristics; however, methods for installing this moiety on a cyanohydrin are very rare. A single example by Watt and colleagues describes a scalable process for the protection of formaldehyde cyanohydrin using isobutylene and a catalytic amount of sulfuric acid[28]. Following this precedent, tert-butyl protected cyanohydrins derived from aliphatic aldehydes could be obtained reproducibly in 30−40% yields and on a multigram scale. Careful inspection of the ^{1}H nuclear magnetic resonance (NMR) spectra of the crude reaction mixtures revealed that the low yields were in part due to a competitive Ritter process[29], which consumed one equivalent of the cyanohydrin and yielded the corresponding tert-butyl amide. In the mechanism of the Ritter reaction, water is required to hydrolyse the tert-butyl nitrilium ion intermediate. Thus, rigorous exclusion of moisture from these reactions should prevent this side process from occurring. To this end, a new procedure was developed, in which the crude cyanohydrins were thoroughly dried with $MgSO_4$ and then distilled before use. Additionally, anhydrous methanesulfonic acid was used as the acid catalyst and the loading was raised to increase the reaction rate. Under these optimized reaction conditions, analytically pure tert-butyl protected cyanohydrins were obtained in moderate to good yield and on a multigram scale after distillation (Fig. 2). With a practical and scalable route for the preparation of various tert-butoxy nitriles, studies aimed at the synthesis of *N*-silyl oxyketene imines were undertaken.

Synthesis of *N*-silyl oxyketene imines from tert-butyl protected cyanohydrins. The capacity for metallated nitriles to undergo competitive *C*-silylation is well documented, and previous studies have shown that the size of the silylating agent influences the site of silylation[30–32]. In the case of protected cyanohydrins, the smaller size of the intervening oxygen atom could attenuate the influence of the protecting group and result in a higher degree of *C*-silylation relative to disubstituted alkyl or aryl nitriles. In this case, the steric bulk of the silyl group could play an important role in the selective synthesis of *N*-silyl oxyketene imines.

Accordingly, triisopropylsilyl chloride (TIPSCl) was selected as the silylating agent and the deprotonation/silylation of tert-butyl protected cyanohydrins was studied under various conditions. Gratifyingly, it was found that *N*-silyl oxyketene imines could be prepared in excellent yield and selectivity by the use of potassium *bis*(trimethylsilyl)amide (KHMDS) as the base at −78 °C in tetrahydrofuran (THF) (Table 1)[33]. The products were obtained as liquids in high purity by simple filtration through Celite and

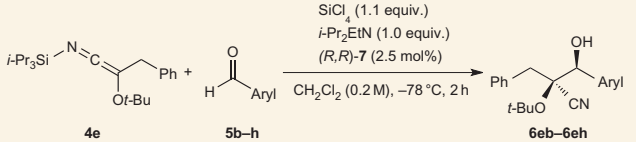
Table 2 | Survey of *N*-silyl oxyketene imines in the addition to benzaldehyde catalysed by (*R,R*)-7.

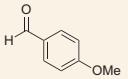
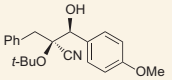
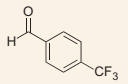
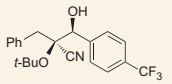
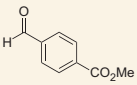
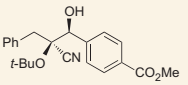
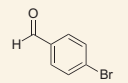
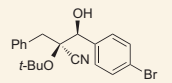
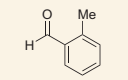
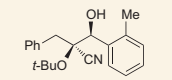
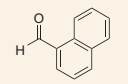
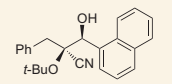
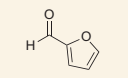
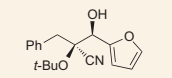


Entry	Nucleophile	Product	Yield (%)*	dr†	er‡
1	 4b	 6ba	84	96:4	>99:1[S]
2	 4c	 6ca	92	98:2	>99:1
3	 4d	 6da	92	98:2	>99:1
4	 4e	 6ea	93	99:1	>99:1
5	 4f	 6fa	90	99:1	>99:1

General reaction conditions: **5** (1.0 mmol), **4** (1.2 equiv.), (*R,R*)-**7** (2.5 mol%), $SiCl_4$ (1.1 equiv.), *i*-Pr_2EtN (1.0 equiv.), CH_2Cl_2 (0.2 M), −78 °C, 2 h. *Yield of analytically pure material. †Determined by ^1H NMR analysis of the crude reaction mixture. ‡Determined by chiral stationary phase supercritical fluid chromatography (CSP-SFC). [S]Determined by CSP-SFC analysis after conversion to the 3,5-dinitrobenzoyl ester.

Table 3 | Survey of aromatic aldehydes in the addition of phenylacetaldehyde-derived ketene imine 4e.



Entry	Aldehyde	Product	Yield (%)*	dr†	er‡
1	 5b	 6eb	93	98:2	>99:1
2	 5c	 6ec	93	99:1	>99:1
3	 5d	 6ed	91	98:2	98.6:1.4
4	 5e	 6ee	95	98:2	>99:1
5	 5f	 6ef	93	99:1	98.9:1.1
6	 5g	 6eg	89	99:1	93.5:6.5
7	 5h	 6eh	91	99:1	>99:1

General reaction conditions: **5** (1.0 mmol), **4** (1.2 equiv.), (*R,R*)-**7** (2.5 mol%), $SiCl_4$ (1.1 equiv.), *i*-Pr_2EtN (1.0 equiv.), CH_2Cl_2 (0.2 M), −78 °C, 2 h. *Yield of analytically pure material. †Determined by ^1H NMR analysis of the crude reaction mixture. ‡Determined by CSP-SFC analysis.

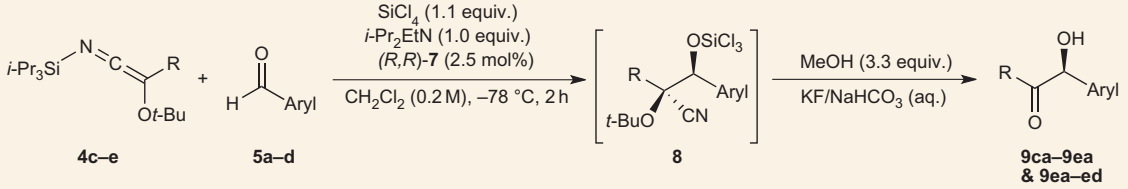
removal of volatile materials under vacuum. The *N*-silyl oxyketene imines were stable for months when stored at 4 °C, although partial isomerization to the *C*-silylated nitrile was observed upon distillation. Additionally, the compounds were surprisingly resistant to hydrolysis and could be filtered and handled in air without significant decomposition. Analysis of the liquids by infrared spectroscopy revealed an intense band at 2,030 cm^{-1}, which is a characteristic feature of the ketene imine functional group (Table 1). The exclusive formation of the *N*-silyl isomer highlights the importance of the *O*-tert-butyloxy and *N*-triisopropylsilyl groups. This feature is especially relevant in the context of preliminary studies performed with methyl, benzyl and trimethylsilyl protected cyanohydrins, all of which provided mixtures of *N*- and *C*-silylated products.

Aldol reactions of *N*-silyl oxyketene imines

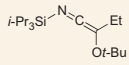
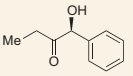
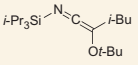
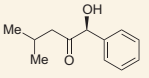
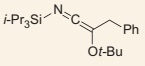
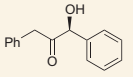
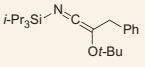
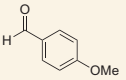
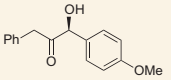
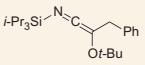
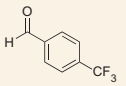
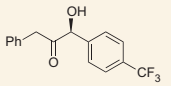
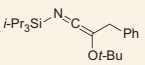
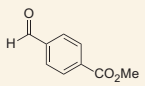
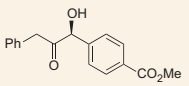
Although the selective synthesis of *N*-silyl oxyketene imines represents a significant advance in ketene imine chemistry, the ability of these compounds to participate in catalytic, enantioselective carbonyl addition reactions was unknown. Previous studies showed that a broad range of silylated nucleophiles[24,34–39], including silyl ketene imines[25], are susceptible to Lewis base catalysed[40], $SiCl_4$-mediated aldol additions. To determine if *N*-silyl oxyketene imines would be competent nucleophiles in this system, ketene imine **4b** was combined with benzaldehyde, 2.5 mol% of (*R,R*)-**7** and a stoichiometric quantity of $SiCl_4$. Under these reaction conditions the aldol product **6ba** was produced in good yield, high diastereoselectivity and excellent enantioselectivity (Table 2, entry 1). To establish the generality of this transformation, other *N*-silyl oxyketene imines were evaluated in the addition to benzaldehyde. In all cases, the resulting diol products were obtained in high yield and with exceptional diastereo- and enantioselectivities for a number of different *N*-silyl oxyketene imines (Table 2, entries 2–5). The diastereoselectivity for the addition was responsive to the size of the alkyl substituent of the ketene imine such that the dr increased with more sterically demanding groups. Importantly, a synthetically versatile allyl-substituted diol product **6fa** was produced in excellent yield and stereoselectivity (Table 2, entry 5).

To further explore the scope of this aldol process a number of different aromatic aldehydes were examined in the addition of

Table 4 | Lewis base catalysed cross-benzoin reactions of *N*-silyl oxyketene imines with aromatic aldehydes.



4c–e 5a–d 8 9ca–9ea & 9ea–ed

Entry	Nucleophile	Aldehyde	Product	Yield (%)	er
1	 4c	 5a	 9ca	79*	99.0:1.0‡
2	 4d	 5a	 9da	82*	98.9:1.1‡
3	 4e	 5a	 9ea	84†	>99/1§
4	 4e	 5b	 9eb	75†	>99/1§
5	 4e	 5c	 9ec	77†	>99/1§,‖
6	 4e	 5d	 9ed	78†	>99/1§,¶

General reaction conditions: **5** (1.0 mmol), **4** (1.4 equiv.), (*R*,*R*)-**7** (2.5 mol%), $SiCl_4$ (1.1 equiv.), *i*-Pr_2EtN (0.2 equiv.), MeOH (3.3 equiv.), CH_2Cl_2 (0.2 M), −78 °C, 2 h. *Yield of chromatographically homogeneous material. †Yield of analytically pure material after single recrystallization from toluene. ‡Determined by CSP-SFC analysis on chromatographically homogeneous material. §Determined by CSP-SFC analysis after single recrystallization from toluene. ‖96.1:3.9 er was obtained before recrystallization. ¶96.5:3.5 er was obtained before recrystallization.

phenylacetaldehyde-derived ketene imine **4e** (Table 3). Reactions with electron-rich-, electron-poor-, sterically hindered- and hetero-aromatic aldehydes all afforded diol products in high yield and excellent diastereo- and enantioselectivities. Only in the addition to 1-naphthaldehyde was a moderate reduction in the enantioselectivity observed (entry 6, 93.5:6.5 er); however, other hindered aromatic aldehydes such as 2-tolualdehyde participated with high enantioselectivity (entry 5, 98.9:1.1 er). The reaction rates for the addition of *N*-silyl oxyketene imines to aliphatic aldehydes were very slow, and studies aimed at increasing this rate are ongoing[37]. Interestingly, α,β-unsaturated aldehydes undergo highly site-selective 1,4-additions; however, the current catalyst structure is not suitable for achieving even modest stereoselectivities at this remote position[41].

Cross-benzoin reactions of *N*-silyl oxyketene imines. On the basis of the now classic studies by Stork[1], it was initially imagined that cross-benzoin products would be obtained by deprotection of the isolated aldol products (**6**) under acidic conditions, followed by basic work-up to trigger retrocyanation. Although this route should be viable, it was envisioned that cross-benzoin adducts could also be obtained more directly, by taking advantage of the immediate product of the reaction, trichlorosilyl ether **8** (Table 4). The hydrolytically labile trichlorosilyl ether could be used for *in situ* deprotection (through the release of HCl) and then the cross-benzoin products could be obtained following a basic work-up. To test this hypothesis, the aldol addition of propionaldehyde-derived *N*-silyl oxyketene imine **4c** with benzaldehyde was performed and the reaction was quenched with 3.3 equiv. of methanol. The corresponding cross-benzoin product **9ca** was obtained in good yield and excellent enantioselectivity after the standard basic work-up with aqueous $KF/NaHCO_3$ (Table 4, entry 1). Following this encouraging result, other combinations of *N*-silyl oxyketene imines and aromatic aldehydes were examined to test the generality of this novel process (Table 4, entries 2−6). The resulting α-hydroxy carbonyl compounds were isolated in good yield and excellent enantioselectivity. Importantly, good correlations were observed between the enantiomeric ratios of the aldol products and the corresponding cross-benzoin adducts (for example, entry 2, Table 2 versus entry 1, Table 4). This correlation demonstrates that the stereogenic centre in the cross-benzoin product does not undergo significant epimerization during the basic work-up. Only in the cases of strongly

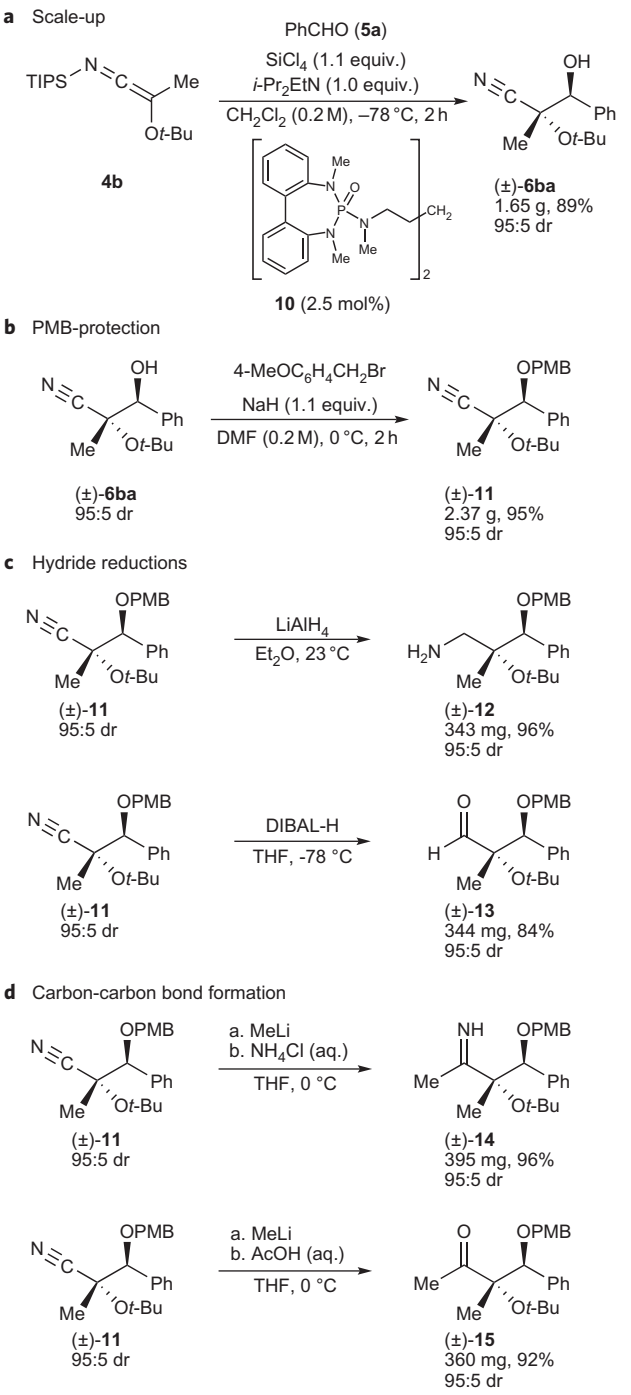


Figure 3 | Transformations of nitriles 6ba and 11. a, The scalability of the Lewis base catalysed aldol addition of *N*-silyl oxyketene imine **4b** with benzaldehyde is demonstrated by increasing the scale to 8 mmol in aldehyde. **b**, Complementary protection of the secondary alcohol of aldolate product **6ba** as a *p*-methoxybenzyl ether sets the stage for manipulation of the nitrile functionality. **c**, The transformations of product **11** by hydride reduction of the nitrile is illustrated. In these reactions, either amine **12** or aldehyde **13** could be obtained by judicious choice of the metal hydride reagent. **d**, The versatility of product **11** is further demonstrated by methyl lithium addition to the nitrile. In these reactions, both the direct product of addition (methyl imine **14**) or the product resulting from hydrolysis (methyl ketone **15**) could be obtained by simply varying the acidity of the reaction work-up.

electronegative aryl substituents (Table 4, entries 5,6) were minor losses in the enantioselectivity of the cross-benzoin products observed; nevertheless, enantiomerically pure compounds could easily be obtained by a single recrystallization from toluene. To our knowledge, these are the first examples of a catalytic, enantioselective cross-benzoin reaction that involve an aliphatic aldehyde as one of the coupling partners.

Transformations of the aldol products. The ability to access cross-benzoin products in high yield and enantioselectivity through deprotection and retrocyanation of the β-hydroxy cyanohydrins demonstrates the highly versatile nature of these products. Other useful pathways available to these compounds are transformations of the nitrile by reduction or organometallic addition. An important advantage of these manipulations is that the stereochemically defined tertiary alcohol, which was set in the aldol addition, is preserved. The products would allow access to stereochemically complex polyols and amino alcohols, which could be relevant synthetic intermediates en route to biologically active compounds. Although the functional group manipulations of nitriles are well described[42,43], the application to hindered nitriles is not trivial. For this reason, a thorough examination of these transformations was undertaken for the nitrile products relevant to this work (Fig. 3).

β-Hydroxy nitrile **6ba** was chosen for the current study, and was prepared with high diastereoselectivity and on a gram scale by the addition of *N*-silyl oxyketene imine **4b** to benzaldehyde catalysed by racemic biphenyl-derived bisphosphoramide **10** (Fig. 3a). Because **6ba** was obtained with high diastereoselectivity, any evidence for epimerization in the subsequent transformations could easily be secured by inspection of the ^{1}H NMR spectra of the crude reaction mixtures. To evaluate the nucleophilic transformations, it was deemed prudent to first protect the secondary alcohol of the aldol product as its 4-methoxybenzyl (PMB) ether. Treatment of the sodium salt of **6ba** with 4-methoxybenzyl bromide afforded **11** in high yield and with no change in the diastereomeric composition (Fig. 3b).

Next, the reduction of **11** with two different metal hydride agents was studied (Fig. 3c). Reduction of the nitrile to the corresponding protected amino alcohol **12** was accomplished with $LiAlH_4$. No epimerization was observed and analytically pure **12** was conveniently obtained in excellent yield after distillation. Partial reduction of **11** with diisobutylaluminum hydride (DIBAL-H) and hydrolysis of the resulting imine afforded aldehyde **13** in good yield and high diastereoselectivity.

Finally, the addition of organometallic reagents to **11** was studied. These reactions are highly valuable as they allow for the creation of new carbon − carbon bonds with a variety of nucleophilic species. Preliminary investigations with methylmagnesium bromide showed a slow rate of addition (>24 h); however, the analogous reaction with methyllithium showed complete consumption of **11** in less than 2 h. Interestingly, quenching the reaction with aqueous NH_4Cl solution resulted in the isolation of analytically pure imine **14** in high yield after distillation (Fig. 3d). Although the isolation of imines is uncommon for nitrile addition reactions, it is not unprecedented for cases where sterically hindered nitriles are used[44]. The methyl ketone product **15** could also be obtained in similar yield by simply changing the conditions of the hydrolysis to the use of concentrated aqueous acetic acid. Importantly, both imine **14** and ketone **15** were obtained without loss in diastereoselectivity.

Discussion

In situ kinetic analysis (infrared spectroscopy) for the addition of *N*-silyl oxyketene imines to benzaldehyde in the presence of stoichiometric quantities of $SiCl_4$ revealed that, in the absence of the Lewis base, no appreciable background reaction occurred ($t_{1/2} > 4$ h, see Supplementary Information). Alternatively, executing the reaction with 2.5 mol% of a chiral bisphosphoramide catalyst and

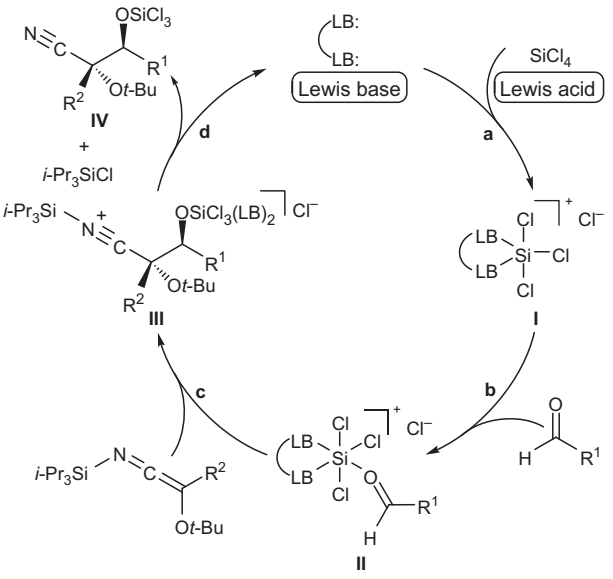


Figure 4 | Proposed catalytic cycle for *N*-silyl oxyketene imine additions to aromatic aldehydes via Lewis base activation of Lewis acids. The proposed catalytic cycle commences with the binding of the bisphosphoramide Lewis base to the weak Lewis acid silicon tetrachloride. This complexation of the Lewis base leads to polarization of the Lewis acid and eventually ionization of a chloride ion to generate a chiral trichlorosilyl cation (**I**). Coordination of the aldehyde to the activated Lewis acid and enantioselective addition of the *N*-silyl oxyketene imine leads to the nitrilium ion intermediate **III**. Desilylation of **III** by nucleophilic chloride and subsequent regeneration of the Lewis base catalyst delivers aldol product **IV** as the trichlorosilyl ether.

1.1 equiv. of $SiCl_4$, an extremely facile addition is observed as noted by loss of the aldehyde absorbance at 1,702 cm^{-1} ($t_{1/2} < 2$ min). The rate data are striking when compared to previous studies on Lewis base catalysed aldol additions of silyl ketene imines[25]. In such cases, a significant background reaction is observed in the addition to benzaldehyde, although the relative catalysed rates were still competitive enough to achieve high enantioselectivities. The extraordinary enantioselectivities observed in the current study might be ascribed to the absence of an achiral background reaction. This scenario is ideal for achieving high enantioselectivities, because reaction can only occur when the Lewis base is bound to the weakly Lewis acidic $SiCl_4$. This mode of catalysis ensures that the chiral Lewis base is present during the stereochemistry-determining step of the reaction, and showcases the power of Lewis base catalysis (Fig. 4)[45].

The absolute and relative configurations of the aldol products were unambiguously assigned by single-crystal X-ray diffraction analysis of **6da** obtained by addition of ketene imine **4d** to benzaldehyde. Independent assignment of the absolute configuration for the cross-benzoin products was achieved by comparison of the optical rotation of **9ca** to a known compound[46]. Both methods confirmed an *S*-absolute configuration at the secondary alcohol centre and verify that the aldehyde undergoes nucleophilic addition to the *Re* face. This sense of asymmetric addition is in agreement with all other addition reactions to aldehydes reported for this catalyst system[37].

In conclusion, a new class of silyl ketene imines derived from tert-butyl protected cyanohydrins has been described. Use of these nucleophiles in Lewis base catalysed aldol additions affords β-hydroxy cyanohydrins in good yields, high diastereoselectivities and exceptional enantioselectivities. The ability of *N*-silyl oxyketene imines to act as acyl anion equivalents was also demonstrated by merely altering the conditions of the reaction work-up. This modification allowed for the preparation of cross-benzoin products derived from aliphatic aldehydes in good yields and excellent enantioselectivities. The versatility of the β-hydroxy cyanohydrins was highlighted by three different transformations of the nitrile group. These functional group manipulations allowed access to amino alcohols and α-hydroxy aldehydes or ketones containing a stereogenic tertiary alcohol in good yields and high selectivities. Future work will focus on the application of this novel class of nucleophiles to other classes of umpolung reactions such as Stetter-type additions and homoenolate chemistry.

Methods

Full experimental details and characterization of compounds can be found in the Supplementary Information. The crystallographic coordinates of **6da** have been deposited with the Cambridge Crystallographic Data Centre (CCDC; deposition no. 761034). These data can be obtained free of charge from the CCDC at www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the preparation of *N*-silyl oxyketene imines. To a flame-dried, 50-ml Schlenk flask under an atmosphere of argon was added 0.96 g of KHMDS (4.8 mmol, 1.2 equiv.) and 4.8 ml of anhydrous THF (1.0 M in KHMDS). The solution was cooled to −78 °C (internal) and a mixture of 0.82 g tert-butoxy nitrile **3e** (4.0 mmol) and 0.95 ml (4.4 mmol, 1.1 equiv.) TIPSCl in 6.3 ml of anhydrous THF was added via cannula over 10 min while stirring. The resulting bright yellow reaction mixture was stirred for 2 h at −78 °C and then allowed to warm to 0 °C. The reaction mixture was concentrated under vacuum (1.0 mmHg) to give a thick, orange gel (~3 ml). Anhydrous hexanes was added (20 ml) and the mixture was stirred vigorously under argon. The heterogeneous solution was opened to air and filtered through a pad of Celite into a flame-dried, tared flask. The resulting, clear orange filtrate was concentrated under high vacuum (0.5 mmHg) to afford 1.33 g (93%) of **4e** as an orange liquid, which was used in subsequent reactions without further purification.

General procedure for aldol reaction of *N*-silyl oxyketene imines with aromatic aldehydes. To a flame-dried, 10-ml, Schlenk flask were added 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv.), 102 μl of benzaldehyde (1.00 mmol) and 5.0 ml of anhydrous CH_2Cl_2 (0.2 M) under an atmosphere of argon. The solution was stirred, cooled to −78 °C (internal) and 175 μl of *N,N*-diisopropylethylamine (1.00 mmol, 1.0 equiv.) and 130 μl of $SiCl_4$ (1.1 mmol, 1.1 equiv.) were added via syringe. The resulting yellow solution was stirred for 5 min at −78 °C, then 0.9 ml of a 1.33 M solution of silyl ketene imine **4e** (1.2 mmol, 1.2 equiv.) in anhydrous CH_2Cl_2 was added dropwise via syringe. The reaction was stirred for 2 h at −78 °C before 0.65 ml of a 2:1:1 mixture of $Et_3N/CH_2Cl_2/MeOH$ was added via syringe. The quenched reaction mixture was stirred for 5 min at −78 °C and then transferred to a stirred, sat. aq. solution of $NaHCO_3$ (10 ml) and KF (10 ml). The biphasic mixture was stirred vigorously for 1 h at room temperature and then filtered through a pad of Celite and transferred to a separatory funnel where the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml) and the organic extracts were combined, washed with brine (1 × 25 ml), and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* and the resulting crude material was purified by column chromatography (25 g silica gel, hexanes/EtOAc gradient; 9:1 to 8:1) to afford 286 mg of **6ea** (93%) as viscous yellow oil. The diastereomeric ratio was determined to be 99:1 by ^{1}H NMR (500 MHz) analysis of the crude product. The enantiomeric ratio was determined to be >99:1 by CSP-SFC analysis of the chromatographically homogeneous material.

General procedure for the cross-Benzoin reaction of *N*-silyl oxyketene imines with aromatic aldehydes. To a flame-dried, 10-ml, single-necked Schlenk flask were added 21 mg of (*R,R*)-**7** (0.025 mmol, 0.025 equiv.), 102 μl of benzaldehyde (1.00 mmol) and 5.0 ml of anhydrous CH_2Cl_2 (0.2 M in aldehyde) under an atmosphere of argon. The solution was cooled to −78 °C (internal) and then 35 μl of *N,N*-diisopropylethylamine (0.2 mmol, 0.2 equiv.) and 130 μl of $SiCl_4$ (1.1 mmol, 1.1 equiv.) were added via syringe. The solution was stirred for 5 min at −78 °C and then 0.84 ml of a 1.66 M solution of silyl ketene imine **4e** (1.4 mmol, 1.4 equiv.) in anhydrous CH_2Cl_2 was added dropwise via syringe. The reaction mixture was stirred for 2 h at −78 °C and then 135 μl of CH_3OH (3.3 mmol, 3.3 equiv.) was added. The quenched reaction mixture was stirred for 30 min at −78 °C and then warmed to 0 °C and stirred for 1.5 h before being transferred to a stirred, sat. aq. solution of $NaHCO_3$ (10 ml) and KF (10 ml). The biphasic mixture was stirred vigorously for 2 h at room temperature and then filtered through a pad of Celite and transferred to a separatory funnel where the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml) and the organic extracts were combined, washed with brine (1 × 25 ml), and dried over Na_2SO_4. The solution was filtered and concentrated *in vacuo* to produce a crude white solid that was purified by column chromatography (25 g silica gel, CH_2Cl_2/Et_2O, 40:1) to afford 200 mg of **9ea** (88%) as a white solid. The solid was further purified by recrystallization from hot toluene (~5 ml) to provide 190 mg (84%) of fine, white needles. The

enantiomeric ratio was determined to be 99.4:0.6 by CSP-SFC analysis of the chromatographically homogeneous material and >99:1 after recrystallization.

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T.W.W. planned and carried out the experimental work. S.E.D. initiated and directed the project. The manuscript was written jointly by the authors.

Additional information

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