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Harnessing the ambiphilicity of silyl nitronates in a catalytic asymmetric approach to aliphatic β^3-amino acids

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Nitronate anions, formally generated by α-deprotonating the corresponding nitroalkanes, are highly nucleophilic and versatile intermediates in many carbon-carbon bond forming reactions. In contrast, the corresponding silyl nitronates are ambiphilic and react, at the same carbon atom, with both, electrophiles and nucleophiles. However, while their nucleophilicity has been well exploited in catalytic enantioselective reactions with imines and aldehydes, utilizing the electrophilicity of silyl nitronates in asymmetric synthesis has remained elusive. We now report the facile, efficient, and general reactivity of readily available silyl nitronates with silyl ketene acetals, catalysed by highly Lewis-acidic and confined silylium imidodiphosphorimidate (IDPi) catalysts. The products of this reaction, so called nitroso acetals, are obtained in excellent enantioselectivity and can be easily converted into *N*-Boc-β^3-amino acid esters in a single step.

Introduction

Nitroalkanes, like carbonyl compounds, upon deprotonation, engage in useful (catalytic) transformations with electrophiles, including Henry and Michael-type reactions. A remarkable reactivity difference though arises upon silylation of these anions: while a silylated enolate pertains a high nucleophilicity and reacts with various classes of electrophiles in Lewis acid-mediated Mukaiyama-type reactions, the silylation of a nitronate anion creates a bi-reactive species, a so-called ambiphile, which can react with both, electrophiles and nucleophiles.[1] Silyl nitronates were first described by Ioffe *et al.* in 1974[2] and thoroughly investigated by Seebach and Torssell *et al.*[3–6] Although their distinct properties offer a new reactivity paradigm for nitro compounds, there are only limited examples on their application in chemical synthesis. Silyl nitronates as nucleophiles (Fig. 1a) were used by Jørgensen and co-workers in enantioselective bis(oxazoline) copper complex-catalysed Mukaiyama-Henry reactions with α-imino esters[7] and aldehydes[8], and by Maruoka *et al.* in ammonium bifluoride phase-transfer catalysed stereoselective Mukaiyama-Michael and Mukaiyama-Henry reactions.[9,10] An amine-catalysed single electron transfer-based strategy has also been employed for the α-nitroalkylation of aldehydes by MacMillan *et al.*[11] A key structural feature of silyl nitronates is the formally negatively charged and highly Lewis-basic oxygen atom. This property makes silyl nitronates susceptible toward activation by Lewis acids, in turn converting them into highly reactive electrophiles.[12,13] The phenomenon has been described by Ioffe and co-workers in silicon Lewis acid-catalysed reactions of mostly cyclic silyl nitronates with

silylated and stannylated nucleophiles.[14–20] However, to the best of our knowledge, catalytic asymmetric additions of nucleophiles to silyl nitronates have been entirely unknown, even though the nitroso acetal products of such processes should be direct precursors for highly valuable products such as β[3]-amino acids (Fig. 1b).[21]

In recent years, progress has been made in the field of asymmetric counteranion-directed silylium Lewis acid catalysis (silylium ACDC), using carbonyls, imines, or Michael acceptors as electrophiles in nucleophilic additions and cycloadditions.[22–29] Given the extraordinary activity of our chiral and confined imidodiphosphorimidate (IDPi) framework and the high oxophilicity of silicon, we envisioned using these catalysts in the asymmetric addition of silyl ketene acetals to silyl nitronates. We were particularly intrigued by this transformation since previously used and privileged acid catalysis motifs such as phosphoric acids, disulfonimides (DSI), and imidodiphosphates (IDP) failed to give the desired product (See Supplementary Table 1).

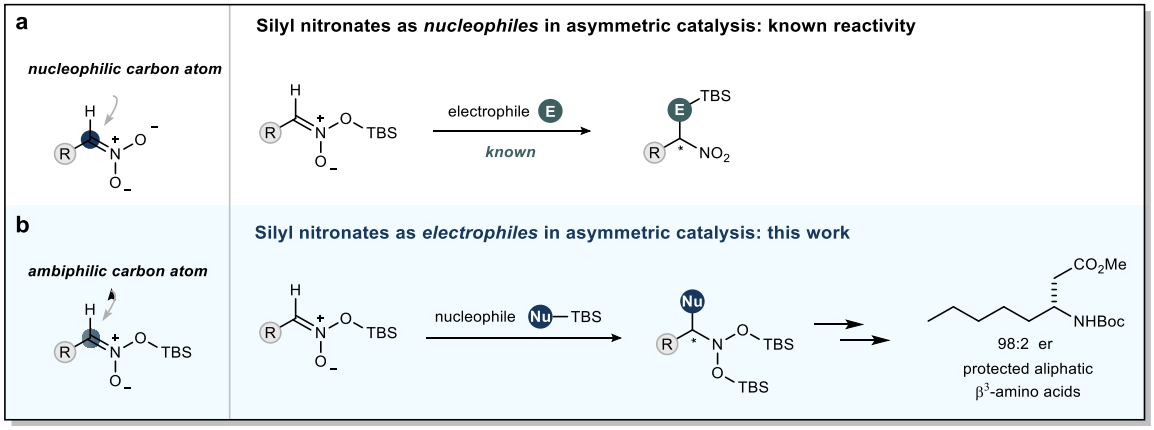

Fig. 1 | Outline of this study. a, well-established nucleophilic reactivity of silyl nitronates. **b,** this work: electrophilic activation of silyl nitronates in asymmetric synthesis as an entry point to aliphatic β[3]-amino acid esters.

Here we describe the IDPi-catalysed addition of silyl ketene acetals to silyl nitronates. The discovery was facilitated by implementation of a multi-substrate screening approach, enabling rapid and highly stereoselective evaluation of a broad class of substrates as potential precursors to valuable β[3]-amino acids. Additionally, we provide a range of multi-gram scale reactions under practical reaction conditions with catalyst loadings as low as 0.1 mol% as well as demonstrate complete catalyst-control in diastereoselective addition reactions when using substituted silyl ketene acetals. Finally, we observed and characterised the key intermediate ion pair consisting of the activated bis(siloxy)iminium cation and the catalyst anion by 2D NMR spectroscopy.

Results

Reaction optimization and multi-substrate screening. At the onset of this study, we explored the reaction of benzyl-substituted silyl nitronate **1b** with TBS ketene acetal **2a** mediated by a range of different IDPi catalysts **3**. While we could quickly identify IDPi **3e** as a suitable catalyst for this reaction furnishing the desired product with an excellent er of 93:7, unfortunately, a significant decrease in enantioselectivity was observed for several other silyl nitronate substrates. Realizing this rather common problem of single substrate optimisations, we set out to use a multi-substrate screening approach to quickly obtain information about the specific catalyst structure required for each class of substrates.[30,31] First, we established a chromatographic product assay toward screening several structurally distinct nitronates. The four representative substrates **1a–d** were selected according to the nature and size of the substituents (benzylic, substituted benzylic, heteroaromatic benzylic, aliphatic), and to enable product separation on a single chiral stationary high-performance liquid chromatography (HPLC) phase. After establishing a reliable HPLC assay, we subjected our substrate pool to silyl ketene acetal **2a** in single reaction vessels with each of the organocatalysts **3a–f** (Fig. 2). Simple phenyl-substituted IDPi **3a** gave only low to moderate enantioselectivity with all substrates. Notably, while introducing phenyl-substitution in the 3-position (**3b**) showed only small changes

in the observed enantioselectivity (with an enantiomeric ratio switch of product **4c**), a change in the sulfonamide core of the catalyst from triflyl to pentafluorophenylsulfonyl (**3c**) delivered a drastic increase in enantioselectivity for all substrates. Especially the 2-methyl-substituted phenyl- and furanyl-based systems **4a** (92:8 er) and **4c** (99.5:0.5 er) gave very high enantioselectivity. Even though catalyst **3e** had already been identified as best candidate for the enantioselective conversion of silyl nitronate **1b**, no clear trend was observed for the reaction of aliphatic chain-substrate **1d**. Remarkably, spiro-fluorenyl catalyst **3f**, previously introduced by our group[25], could deliver product **4d** with almost complete enantiocontrol (99.3:0.7 er).

Substrate Scope. As a result, catalysts **3c**, **3e**, and **3f** were selected for a broader substrate scope study. Using a wide range of nitronates (**1a–1x**) separately gave results that corresponded well to those obtained in the multi-substrate experiments, consistently providing high yields and enantioselectivities except for nitronate **1l**.

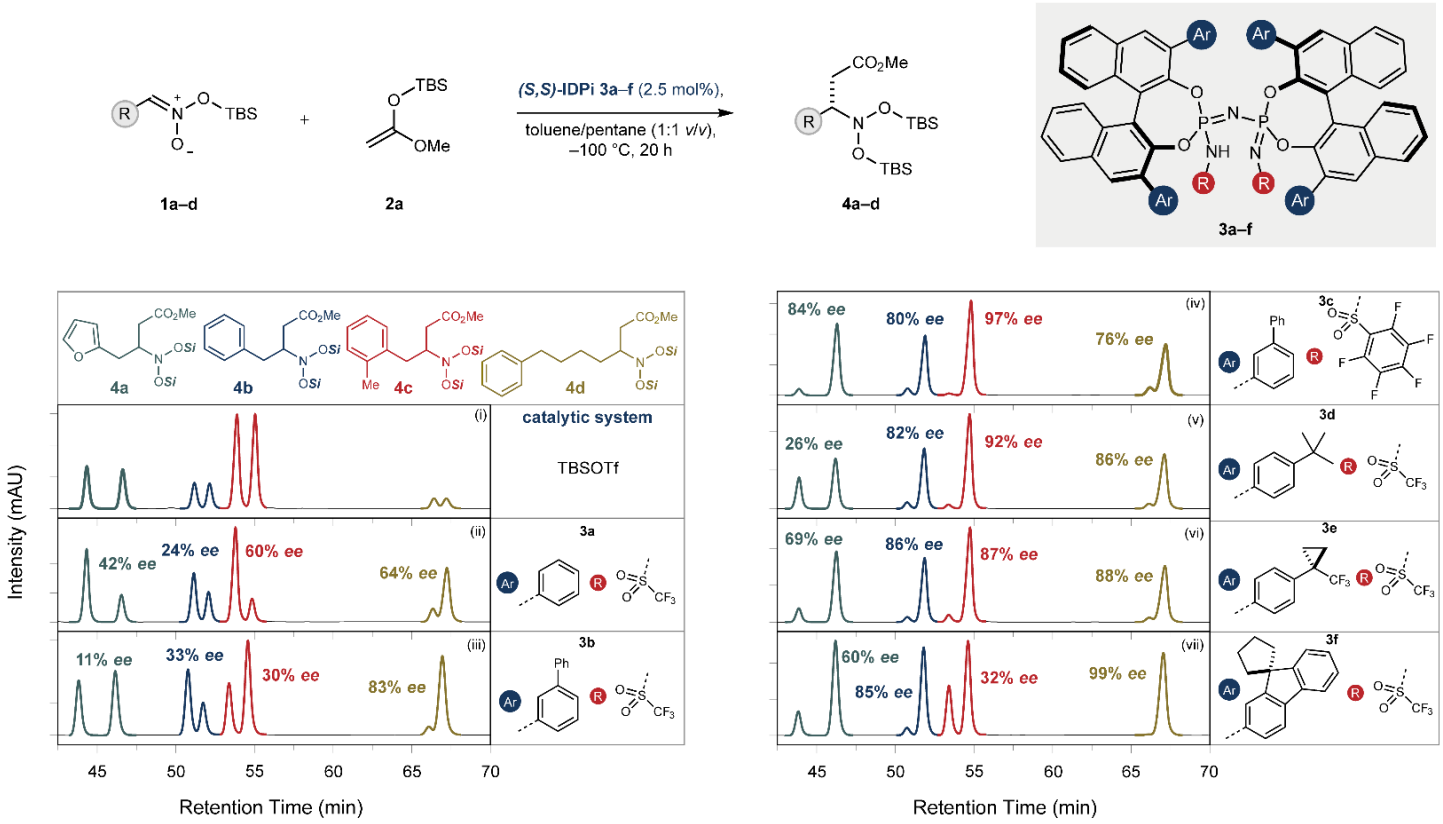

Fig. 2 | Multisubstrate screening approach. HPLC chromatogram of the stereoisomeric product mixture (reactions conducted on 0.025 mmol scale at –100 °C for 20 h; full conversion for all silyl nitronates determined by ^{1}H NMR spectroscopy; HPLC method: OJ-3R, 60:40 ACN/H_2O, 1 mL/min).

Irrespective of sterics, chain length, electronics, or substitution patterns, nitroso acetals **4b–4j** were formed in very good yields and with excellent enantioselectivities. Fortunately, heteroaromatic substituents that could potentially also coordinate to the Lewis acid also cleanly formed the desired products **4a**, **4k** and **4l** with excellent enantioselectivity.

Catalyst **3f** turned out to be broadly applicable for a wide range of functionalized aliphatic nitronates and delivered products with excellent yields and enantioselectivities (**4m–4x**). This reaction is well-suited for substrates containing additional Lewis-basic functional groups such as a nitrile, a silyl ether, a methyl ether, methyl ester and an amide, forming the corresponding products in moderate to good yields and with extremely high enantioselectivities (**4m–4q**). Ester-functionalised silyl nitronate **1p** gave product **4p** exclusively and, as in case of nitrile **1m**, with no evidence for any Mukaiyama–Claisen-type reactivity. Substrates with aliphatic halide (**1r** and **1s**), aliphatic unbranched and branched alkane (**1t** and **1u**), terminal olefin (**1v**) and terminal alkyne (**1w**) functionalities all furnish the corresponding nitroso acetals in good yields and with excellent levels of enantioselectivity (**4r–4w**). Remarkably, even a substrate possessing a ketone

functional group known to readily undergo Mukaiyama-aldol reactions under similar conditions[24] gave exclusively the desired nitroso acetal product **4x** in good yield and with excellent enantioselectivity. Moreover, we could expand the nucleophile scope of our reaction. When nitronates **1b** and **1k** were reacted with vinylogous silyl ketene acetal **2b**, the corresponding nitroso acetal products (**4y** and **4z**) were obtained in good yield and with excellent enantio- and γ-regioselectivity.

Practicability and diastereoselective variant. To demonstrate the robustness and scalability of this method, nitroso acetals **4c**, **4d**, **4h**, **4p** and **4t** were synthesised on a multi-gram scale starting from unpurified silyl nitronates in the presence of catalyst loadings as low as 0.1 mol% at –40 °C (–70 °C for **4c**). The reactions were completed within 6–24 h and the products were obtained with excellent yield and enantioselectivities (Fig. 4).

To investigate diastereoselective variants of our reaction, we reacted nitronate **1b** with ketene acetal *(Z)*-**2c** (7:93 *E*/*Z*) in the presence of catalyst **3f**. The corresponding *anti*-nitroso acetal **4A** was obtained with a 9:1 dr and excellent enantioselectivity of >99:1 er (Fig. 5a).

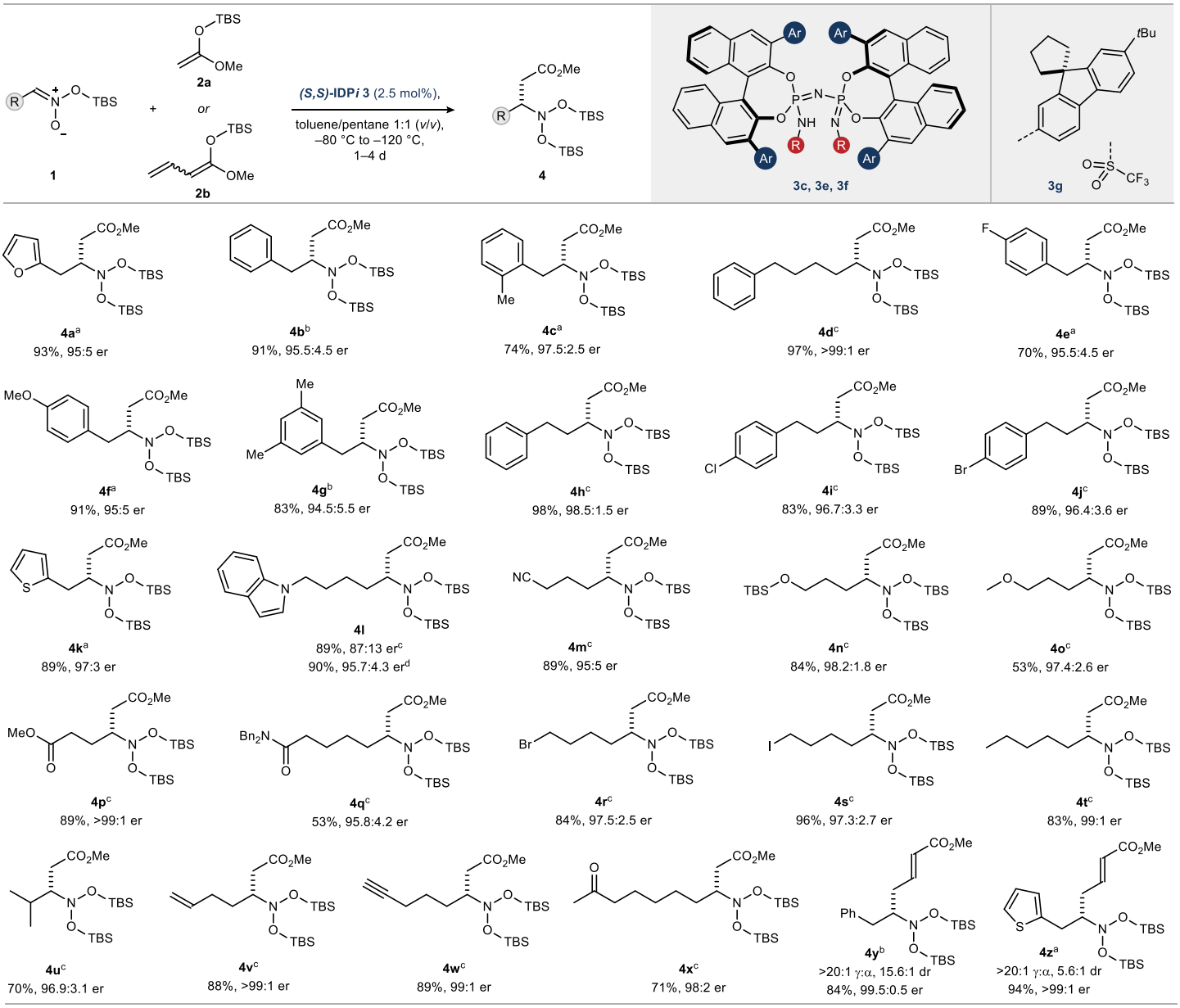

Fig. 3 | Substrate scope. Reaction of silyl nitronates 1 with silyl ketene acetal **2a** or **2b** using IDPi catalysts **3** (reactions conducted at 0.1 mmol scale; isolated yields; *a* = catalyst **3c**, *b* = catalyst **3e**, *c* = catalyst **3f**, *d* = catalyst **3g**).

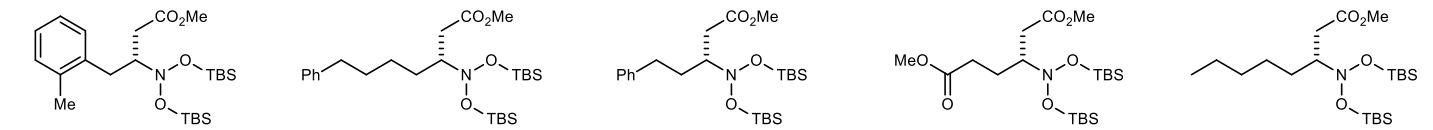

Fig. 4 | Upscaling. Demonstration of practical reaction conditions for the synthesis of several nitroso acetals on a multi-gram scale.

Using the isomeric silyl ketene acetal *(E)*-**2c** (92:8 *E*/*Z*) preferentially led to the corresponding *syn*-nitroso acetal **4B** with 3:1 dr and 98:2 er (Fig. 5b). Notably, when nitronate **1b** was reacted with silyl ketene acetal *(Z)*-**2c** (providing the *anti*-product with IDPi **3f**) in the presence of a different catalyst **3c**, *syn*-diastereoisomer **4B** was obtained exclusively (>20:1 dr) and with high enantioselectivity (Fig. 5c). The relative configuration of *syn*-**4B** was assigned from the x-ray crystal structure of derivative **5B** (Fig. 5d). A possible interconversion of (*Z*)-**2c** and (*E*)-**2c** has been excluded in several control experiments. Accordingly, we have developed a diastereoconservative variant in which the diastereoselectivity of the product directly correlates with the structure of the silyl ketene acetal and, more interestingly, a completely catalyst-controlled reaction enabling access to either the *syn*- or the *anti*-product with excellent stereoselectivity solely by choice of the respective IDPi. While we currently have no explanation for this remarkable phenomenon, further mechanistic investigations are ongoing and will be reported in due course.

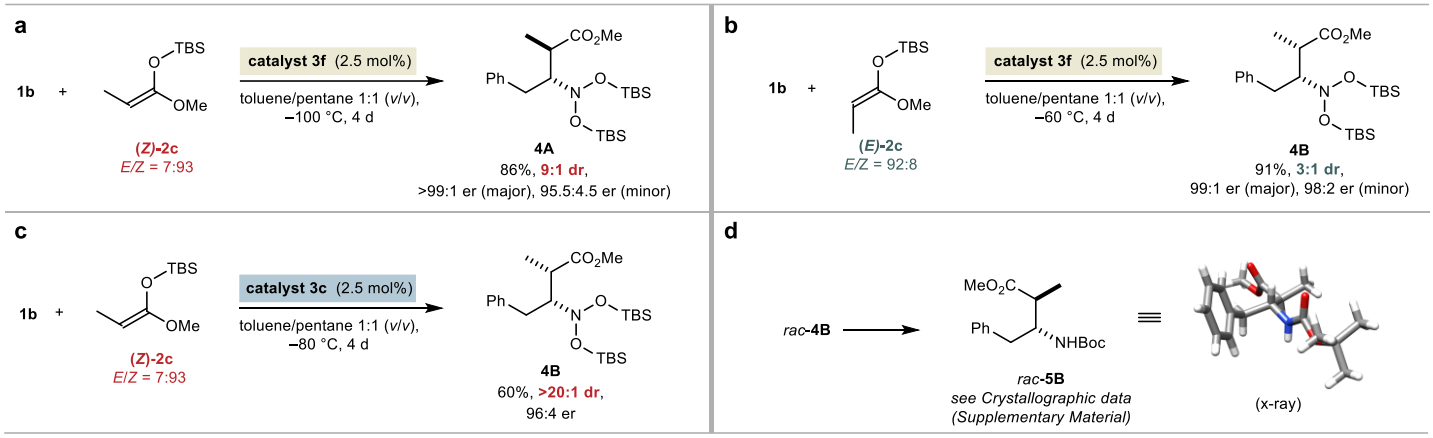

Fig. 5 | Diastereoconservation and diastereodivergence. Reactions of silyl ketene acetal **2c** with nitronate **1b** using IDPi catalysts **3** (reactions conducted at 0.1 mmol scale; isolated yields).

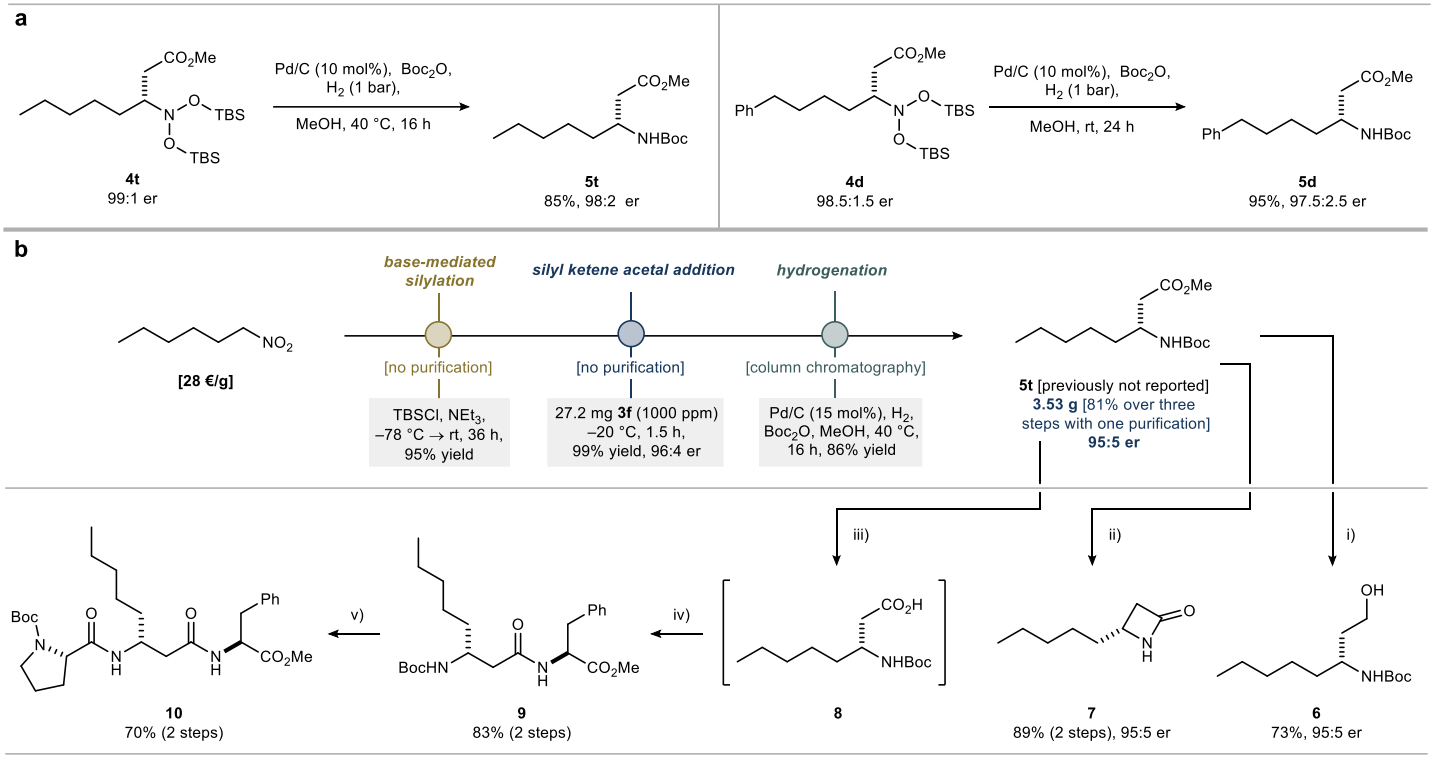

Fig. 6 | Further functionalizations of nitroso acetal products 4d and 4t. **a,** Reduction of compounds **4d** and **4t** to the corresponding *N*-Boc β-amino acid esters **5d** and **5t**. **b,** Practical multi-gram three-step sequence from 1-nitrohexane to β-amino acid ester **5t** followed by downstream modifications; i) $NaBH_4$, MeOH, THF, 65 °C, 20 h, ii) a) TFA, CH_2Cl_2, 25 °C, 20 min, b) LDA, THF, –78 °C, 3 h, iii) NaOH, MeOH, 0 → 25 °C, 2 h, iv) Phe-OMe·HCl, HATU, $(i\text{-Pr})_2NEt$, CH_2Cl_2, 25 °C, 16 h, v) a) TFA, CH_2Cl_2, 25 °C, 20 min, b) Boc-Pro-OH, HATU, NEt_3, CH_2Cl_2, 25 °C, 16 h.

With a simple and general methodology at hand, we aimed at exploring the utility of our nitroso acetal products. As a result of the observed high substrate tolerance, a broad range of both, novel and known β^3- and $\beta^{2,3}$-amino acids, which are of high interest for medicinal chemistry and pharmaceutical applications, should become available with excellent levels of enantiomeric excess *via* reduction.[32–35] Interestingly, previous reports on the reduction of nitroso acetals required Raney nickel as catalyst in combination with a fluoride source.[17,36] Fortunately, after investigating several reaction conditions, we found that simply subjecting our reaction products to catalytic amounts of Pd on activated carbon to an atmosphere of hydrogen gas in the presence of Boc_2O at room temperature or 40 °C exclusively delivered the desired *N*-Boc-protected β-amino acid methyl esters without significant erosion of enantiopurity. Following this protocol, nitroso acetals **4d** and **4t** were directly transformed into the corresponding *N*-Boc-protected β-amino acid methyl esters **5d** and **5t**. Out methodology is also well-suited to the gram-scale synthesis of such compounds, giving rapid access to large amounts of product **5t** from commercially available 1-nitrohexane in three steps with just one purification. This β-amino acid methyl ester **5t** was used as the starting point for further applications towards potentially bioactive compounds. Exhaustive reduction of the ester moiety provided primary alcohol **6**, and Boc-deprotection followed by cyclization in the presence of LDA gave access to β-lactam **7** in 89% over two steps with 95:5 er. Hydrolysis of the methyl ester to the free carboxylic acid **8** set the stage for a peptide synthesis that eventually resulted in tripeptide **10** bearing our newly synthesis D-β-amino acid residue.

Mechanistic studies. Inspired by previous mechanistic studies conducted by Mayr and Ioffe[37], we were keen on following the interaction of our activated silylium IDPi catalyst **3e** with silyl nitronate **1b** *via* NMR spectroscopy, with the hope to possibly characterise the critical ion pair intermediate (Fig. 7). First, acid catalyst **3e** was activated with an excess of *tert*-butyldimethyl(2-methylallyl)silane to afford silylium species **3e-TBS** (Fig. 7, IDPi **3e** vs. IDPi **3e-TBS**). Notably, four sets of doublet can be observed, most likely caused by C_2 symmetry-breaking coordination of the silylium ion to both of the diastereotopic oxygen atoms of the sulfonamide portion. After adding 0.5 equiv. of silyl nitronate **1b** to silylated IDPi **3e-TBS** (Fig. 7, step ii), a singlet at –10.1 ppm in the ^{31}P NMR with a 1:1 ratio

relative to the remaining doublet appears. Comparison of the ^{1}H NMR spectrum of the reaction mixture with isolated silyl nitronate **1b** shows a significant downfield shift of the nitronate α-proton (6.31 ppm to 7.59 ppm) and could be confirmed by 2D NMR spectroscopy (see Supplementary Figure 5). Interestingly, splitting of the doublet of the benzylic protons in free **1b** to one pair of diastereotopic protons in the reaction mixture makes interaction with the chiral catalyst become evident.

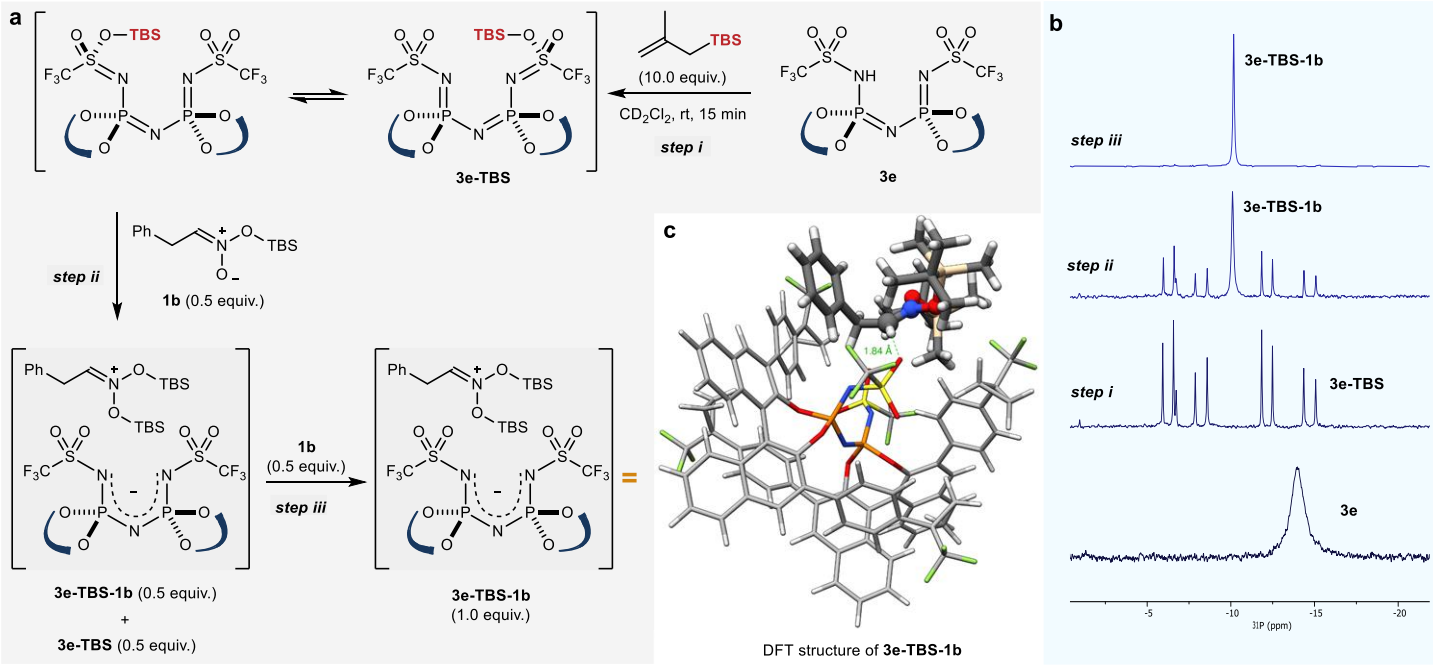

Fig. 7 | NMR characterisation of the ion pair between catalyst 3e and nitronate 1b. a, Sequence of catalyst silylation and nitronate addition leading to ion pair **3e-TBS-1b**. **b,** ^{31}P NMR traces corresponding to the respective steps in panel **a** (all measurements conducted at 193 K, see Supplementary Fig. 4 and 5 for further details). **c**, DFT structure of ion pair **3e-TBS-1b**.

Based on the spectroscopic evidence, it is reasonable to assume that the newly formed species can be characterised as the ion pair resulting from silyl transfer of the catalyst to the silyl nitronate, giving the IDPi anion complex of the highly activated bis(siloxy)iminium ion (**3e-TBS-1b**). Upon addition of 0.5 equiv. of **1b**, the remaining signals of the silylated IDPi **3e-TBS** cleanly converged to the singlet of the ion pair (Fig. 7, step iii). Even in the presence of an excess of silyl nitronate **1b**, no shift of the ion pair signal was observed. Additionally, the ^{1}H NMR spectrum of this reaction mixture clearly indicated the presence of two distinct species without significant exchange between the ion pair **3e-TBS-1b** and the silyl nitronate **1b**. This points towards the crucial influence of the IDPi anion in the stabilization of the activated bis(siloxy)iminium ion as a prerequisite for both high reactivity and enantioselectivity in the subsequent nucleophilic addition of the silyl ketene acetal. Additionally, to the best of our knowledge this is the first spectroscopic characterisation in silylium ACDC of an ion pair consisting of a silylated, cationic substrate and the chiral catalyst counteranion.

The ion-pair structure **3e-TBS-1b** was optimized using density functional theory (DFT). A large number of conformers was initially generated using a semiempirical method, and the low energy structures were refined at the PBE-D3/def2-svp level of theory. The most stable ion-pair conformer (Figure 7c) features a hydrogen bond between the C–H group of the nitronate **1b** and an oxygen atom of a sulfonyl group of the catalyst anion. A detailed description of the computational protocol can be found in the Supporting Information (see Supplementary Figure 5).

Conclusion

In conclusion, we present the facile and general catalytic asymmetric addition of silyl ketene acetals to silyl nitronates. These reactions are catalysed by strong and confined silylium-based Lewis acids that activate the ambiphilic substrate. This, in turn, generates a highly

electrophilic bis(siloxy)iminium ion, which could be characterised spectroscopically. We could rapidly identify a collection of suitable catalysts for this transformation using a multi-substrate screening approach, which enabled a broad range of silyl nitronates to readily engage in this reaction, furnishing the nitroso acetal products in almost quantitative yields and with excellent enantioselectivity. We showed the vital influence of our acids in controlling the diastereomeric outcome of the reaction simply by using a different catalyst substitution pattern. Moreover, this approach could be advanced to a practical and useful method to synthesise previously unknown *N*-Boc b^3-amino acid methyl esters on a multi-gram scale with high yields and excellent enantioselectivities, starting from simple commercially available nitroalkanes. These findings implicate the high synthetic potential of silyl nitronates as overlooked electrophilic substrates for asymmetric catalysis.

Methods

General procedure for the catalytic asymmetric addition of silyl ketene acetals to silyl nitronates. In an oven-dried GC vial with septum, the respective catalyst (4.0–4.5 mg, 2.5 mol%) was dissolved in toluene (200 µL, 0.50 M with respect to the nitronate) and reacted with the silyl ketene acetal (2.0 equiv., 0.20 mmol, 44 µL) for 10 min at room temperature to give the active silylium IDPi species. After transfer to a cryostat with the indicated temperature and stirring for 10 min, a stock solution of the silyl nitronate (1.0 equiv., 0.50 M in *n*-pentane, 200 µL) was added dropwise and the resulting reaction mixture was stirred for the indicated time period. Subsequently, the reaction was quenched by the addition of NEt_3 and MeOH (200 µL/mmol of silyl nitronate), stirred for 10 min at the indicated temperature and was then allowed to warm up to room temperature. The crude reaction mixture were directly purified *via* flash column chromatography using silica gel (4% MTBE in hexanes, solid phase previously flushed with hexanes/EtOAc/NEt_3 18:1:1 *v*/*v*) to give the nitroso acetal products as colourless oils.

Data availability

Experimental procedures as well as characterisation data are given in the Supplementary Information. Crystallographic data of *rac*-**5p** can be accessed *via* the Cambridge Crystallographic Data Centre (CCDC 2041572). Further data can be obtained from the corresponding author upon request.

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Author contributions

C.K.D. and B.L. designed this study. S.D., B.M. and C.K.D. conducted the experiments. B.L. oversaw the project S.D., B.M., C.K.D. and B.L. wrote the manuscript. S.D., B.M and C.K.D. wrote the supporting information. I.H. and G.B. carried out the electronic structure calculations.

Additional information

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[#] S.D., B.M. and C.K.D. contributed equally to this work.

Competing interests

A patent WO2017037141 (A1) filed by the Max-Planck-Institut für Kohlenforschung covers the IDPi catalyst class and its applications in asymmetric synthesis.

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