

Catalytic Asymmetric Additions of Enol Silanes to In Situ Generated Cyclic, Aliphatic *N*-Acyliminium Ions

Oleg Grossmann, Rajat Maji, Miles H. Aukland, Sunggi Lee, and Benjamin List*

Abstract: Strong and confined imidodiphosphorimidate (IDPi) catalysts enable highly enantioselective substitutions of cyclic, aliphatic hemiaminal ethers with enol silanes. 2-Substituted pyrrolidines, piperidines, and azepanes are obtained with high enantioselectivities, and the method displays a broad tolerance of various enol silane nucleophiles. Several natural products can be accessed using this methodology. Mechanistic studies support the intermediacy of non-stabilized, cyclic *N*-(*exo*-acyl)iminium ions, paired with the confined chiral counteranion. Computational studies suggest transition states that explain the observed enantioselectivity.

Since early reports in the 1950s, *N*-acyliminium ions have been used as highly reactive intermediates in a plethora of carbon–carbon-bond-forming approaches to natural products, and other biologically active molecules.^[1–6] Despite significant advances in this field, however, stereocontrol of such reactions has remained challenging, and catalytic enantioselective approaches, with few notable exceptions, require arene stabilization.^[7–19] Intermolecular catalytic asymmetric reactions proceeding via cyclic, aliphatic *N*-alkoxycarbonyliminium ions are particularly difficult to control, arguably due to a lack of conjugated π -systems, which facilitate ionization and catalyst-substrate interactions. Remarkably, despite their great potential as intermediates toward a variety of pharmaceuticals and natural

products, *N*-(*exo*-acyl)iminium ions have proven to be a challenge for asymmetric catalysis. We hypothesized that the difficulty in taming these highly reactive iminium ions may originate from 1) their extreme electrophilicity and 2) the existence of two rapidly interconverting *s*-*cis*/*s*-*trans* conformers.^[20,21]

Given the ability of very strong and confined IDPi catalysts in controlling reactions of flexible, high energy cations, we reasoned that these organocatalysts could provide a solution to this long standing challenge. Herein, we report a highly enantioselective silylium-IDPi-catalyzed Mukaiyama–Mannich reaction, in which enol silanes react with in situ generated *N*-(*exo*-acyl)iminium ions to furnish various useful α -substituted nitrogen heterocycles, including intermediates toward several natural products (Figure 1).

Saturated nitrogen heterocycles constitute essential pharmacophores in drugs and natural products and general methods for their enantioselective synthesis are still highly sought after.^[22] Conceptually, the addition of nucleophiles to in situ generated cyclic *N*-acyliminium ions is a particularly attractive solution to this problem. Important examples of this type of reactivity include asymmetric Reissert-type reactions and other addition to *N*-acyl(iso)quinolinium ions.^[7–10] The concepts of asymmetric anion-binding catalysis and of asymmetric counteranion directed catalysis (ACDC) appear to be particularly promising in controlling *N*-acyliminium ion reactivity, and chiral thiourea derivatives and BINOL-derived phosphoric acids have indeed been used in this context.^[11–16,23,24] However, despite the versatility of cyclic, aliphatic *N*-(*exo*-acyl)iminium ions,^[25–31] controlling their reactivity via enantiopure counteranion remained elusive. Previous approaches invariably required in situ generated chiral nucleophiles, significantly limiting their scope.^[18,32]

Our group has challenged itself with the design of a general methodology to tackle this difficult reaction, in which various silylated nucleophiles react selectively with different iminium ion precursors. However, despite intense

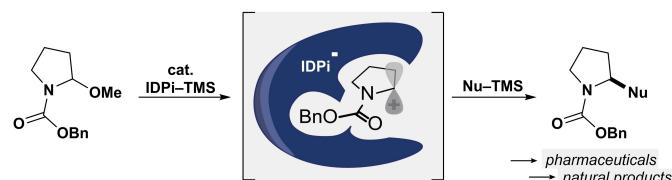


Figure 1. Controlling extremely electrophilic *N*-(*exo*-acyl)iminium ion via ACDC.

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Homogeneous Catalysis

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investigations during the last decade, none of our previously preferred acid catalysts led to promising results. Motivated by our studies on silylium-based asymmetric counteranion-directed catalysis (*Si*-ACDC) with strong and confined acids,^[33–55] we hypothesized that silylated IDPi catalysts should generate *N*-acyliminium ions from hemiaminal ethers and also enable efficient enantiofacial differentiation of these electronically and sterically unbiased cations.

Our studies began by investigating the reaction of racemic cyclic hemiaminal ether **1a** as *N*-(*exo*-acyl)iminium ion precursor with commercially available enol silane **2a** in the presence of different organocatalysts developed in our group (Table 1). Full conversion to the desired product **3a** was observed with chiral disulfonimide (DSI) catalyst **4a** within 16 h but without any enantioselectivity. This result illustrates the extreme difficulty associated with *N*-(*exo*-acyl)iminium ions because DSIs are excellent catalysts for reactions of other acyclic *N*-acyliminium ions.^[36,37] Contrarily, imidodiphosphate (IDP) **5a** and imino-imidodiphosphate (*i*IDP) **6a** gave no conversion, presumably due to the insufficient Lewis acidity of the corresponding silylated catalysts. Remarkably however, we found that the signifi-

cantly more acidic imidodiphosphorimidate (IDPi) catalyst **7a** provided both high activity and promising enantioselectivity (67:33 e.r.) at r.t. (Entry 4). The selectivity was further increased to 89:11 e.r. by lowering the temperature to -70°C . A stepwise increase in enantioselectivity was observed by extending the fluoroalkyl-substituents (see Supporting Information, Table S2) at the *meta*-positions of the 3,3'-substituents on the BINOL backbone, peaking with perfluoro-*n*-hexyl-substituents, which led to an e.r. of 96.5:3.5 (Entry 6). We also studied the effect of the leaving groups of the *N*-acyliminium ion precursors **1**. Switching from hemiaminal methyl ether **1a** to ethyl ether **1b** had little effect on the enantioselectivity, but the reactivity dropped significantly to only 15 % conversion (Entry 7). Interestingly, simple hydroxy hemiaminal **1c** provided a similar reactivity and selectivity profile as hemiaminal ether **1a**, although an additional equivalent of enol silane **2a** was required to reach full conversion (Entry 8). With the optimal *N*-acyliminium ion precursor **1a**, we isolated 90 % of the corresponding product on a 0.1 mmol scale without any deterioration of enantioselectivity. Under the developed conditions we also investigated various other functionalized reaction partners.

Acetophenone-derived enol silanes with electron-neutral, electron-withdrawing and electron-donating substituents gave typically $>80\%$ isolated yields and high enantioselectivities (Table 2, **3a–j**). Heterocyclic nucleophiles were also highly reactive (**3k**, **3l**), although with a noticeable decrease of enantioselectivity in the case of the enol silane **2k**, which delivered the product with an e.r. of 91.5:8.5.

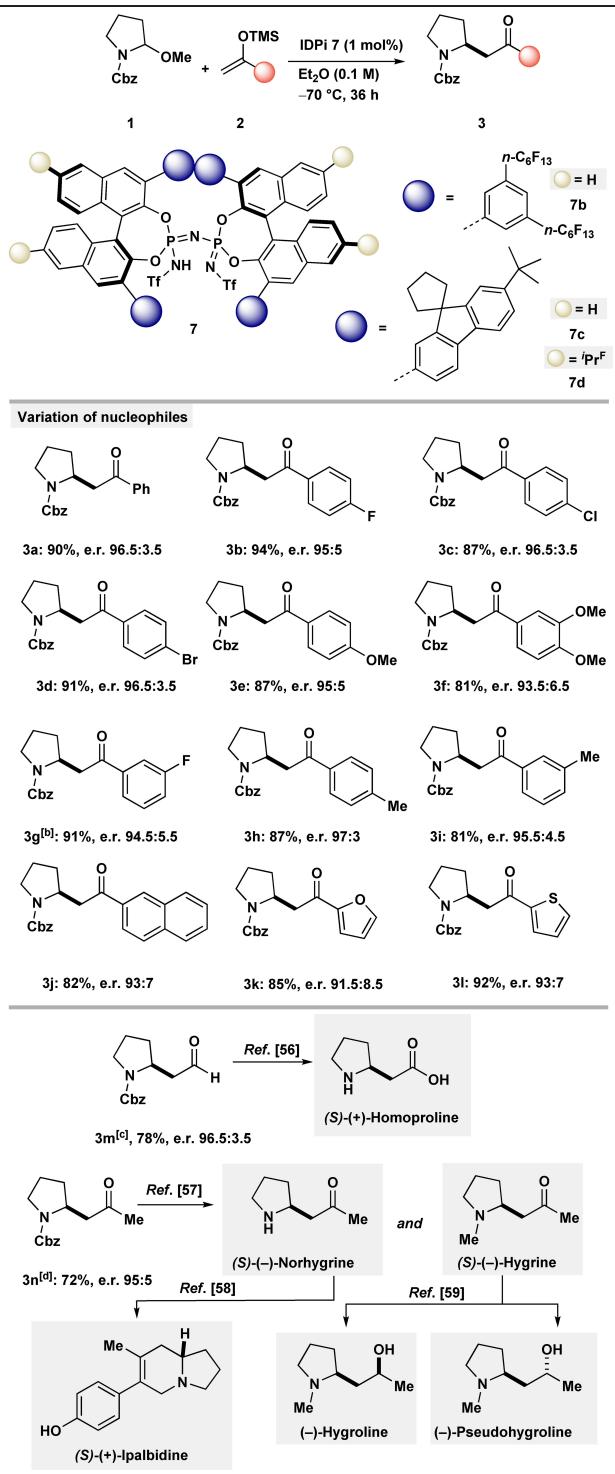
Next, we turned our attention to structurally distinct enol silanes and chose acetaldehyde-derived enol silane **2m** as potentially highly useful nucleophile. Remarkably, only the desired substitution product **3m** was observed without any subsequent aldol side reactions. Although the reactivity was satisfactory, the enantiocontrol with the previously best catalyst was poor (see Supporting Information, Table S4). We hypothesized that the weak enantiodiscrimination was mainly caused by reduced π - π interactions between catalyst **7b** and the small enol silane **2m** such that a different IDPi would be necessary toward enantiocontrolling this addition. Among our IDPi libraries, spirocyclopentyl-3-fluorenyl-substituted catalysts were identified as promising candidates (see Supporting Information, Table S4) and we found the *tert*-butyl-substituted variant **7c** to catalyze the reaction with good yield (78 %) and high enantioselectivity (96.5:3.5 e.r.). Aldehyde **3m** is a known precursor of (*S*)-homoproline.^[56] At this stage we were optimistic that our new catalyst would also be proficient in handling other small enol silanes and subjected acetone-derived enol silane **2n** to our reaction conditions. Indeed, we observed high enantioselectivity, but unfortunately with low reactivity. Ultimately, we decided to introduce electron-withdrawing groups at the 6,6'-positions of the BINOL backbone to further increase the acidity of the catalyst, whilst preserving the geometry of the active site. The newly developed catalyst **7d**, which is readily available (see Supporting Information), catalyzed the addition with **2n** successfully to the (nor)hygrine and (pseudo)hygrine precursor **3n** with 72 % yield and 95:5 e.r.

Table 1: Reaction development.^[a]

Entry	1	Catalyst	T [°C]	Conv. [%] ^[b]	e.r. ^[c]
1 ^[d,e]	1a	4a	r.t.	>95	50:50
2 ^[d,e]	1a	5a	r.t.	<5	ND
3 ^[d]	1a	6a	r.t.	<5	ND
4	1a	7a	r.t.	>95	67:33
5	1a	7a	-70	>95	89:11
6	1a	7b	-70	>95	96.5:3.5
7	1b	7b	-70	15	96:4
8 ^[f]	1c	7b	-70	>95	96:4
9 ^[g]	1a	7b	-70	>95 (90 ^[h])	96.5:3.5

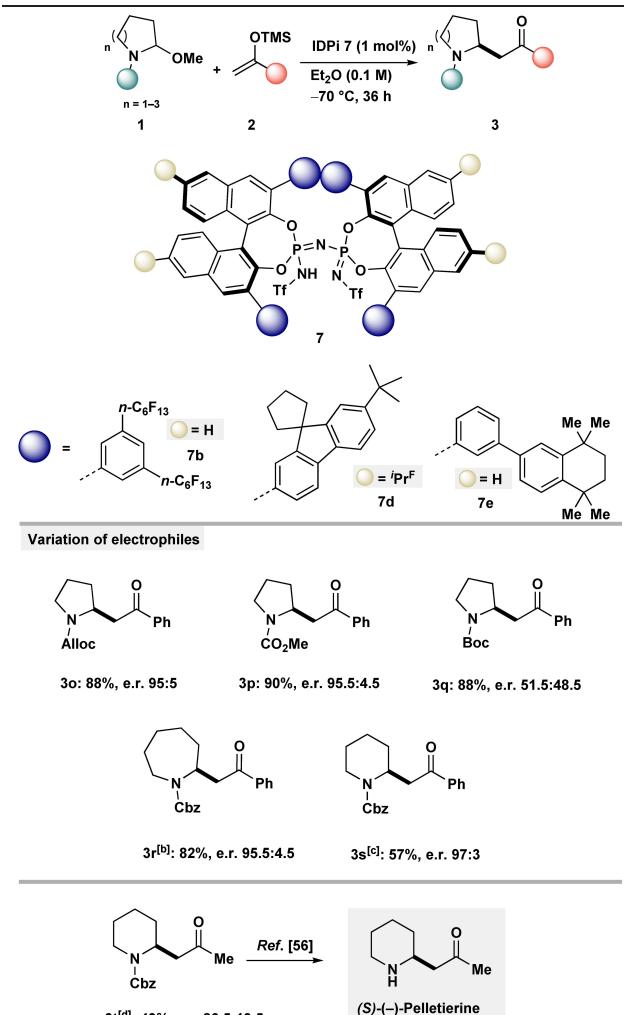
[a] Unless otherwise noted, reactions were performed on a 0.05 mmol scale with 2.0 equiv of **2a** and 1 mol% catalyst in Et_2O (0.1 M).

[b] Conversions were determined by NMR spectroscopy with an internal standard. [c] Enantiomeric ratios (e.r.) were determined by HPLC on a chiral stationary phase. [d] Reactions were carried out in CH_2Cl_2 . [e] 5 mol% catalyst. [f] 3.0 equiv. of **2a**. [g] 0.1 mmol scale. [h] Isolated yield; ND = not determined.

Table 2: Scope of the nucleophiles.^[a]

[a] Unless otherwise indicated, reactions were conducted with 0.1 mmol of substrate 1, 2.0 equiv of nucleophile 2 and 1 mol % of 7b. Yields are of the isolated compounds. Enantiomeric ratios were determined by HPLC on a chiral stationary phase. [b] -60°C . [c] 7.5 mol % of 7c was used. [d] -80°C , 1 mol % of 7d was used. Cbz = carbobenzyloxy, iPrF = perfluoroisopropyl.

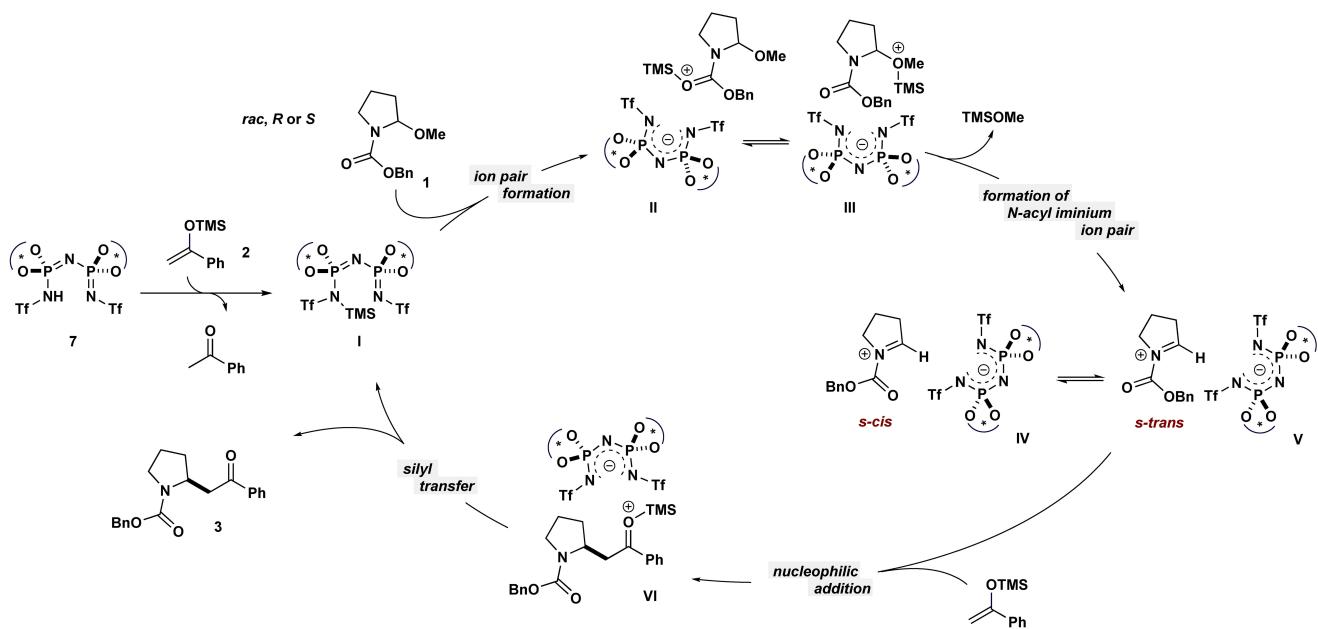
For the scope of the electrophiles (Table 3), we initially tested different carbamate protecting groups and noticed

Table 3: Scope of the electrophiles.^[a]

[a] Unless otherwise indicated, reactions were conducted with 0.1 mmol of substrate 1, 2.0 equiv of nucleophile 2 and 1 mol % of 7b. Yields are of the isolated compounds. Enantiomeric ratios were determined by HPLC on a chiral stationary phase. [b] -60°C , 5 mol % of 7c was used. [c] -45°C , 1 mol % of 7e was used. [d] -40°C , 1 mol % of 7d was used. Cbz = carbobenzyloxy, Alloc = allyloxycarbonyl, Boc = tert-butyloxycarbonyl, iPrF = perfluoroisopropyl.

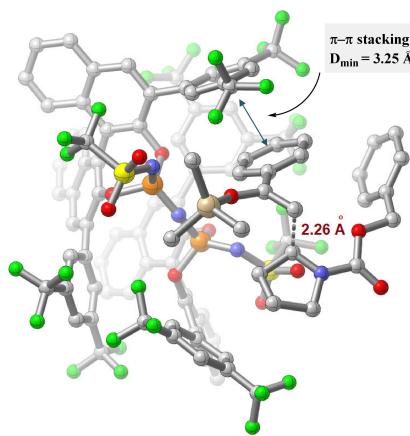
only marginal differences in reactivity and selectivity between carbobenzyloxy-(Cbz), allyloxycarbonyl-(Alloc) and methoxycarbonyl-protected hemiaminal ethers with 2a in the presence of catalyst 7b (3o/p). In contrast, the *tert*-butoxycarbonyl (Boc)-protected substrate furnished product 3q as a racemate, suggesting that increasing the steric bulk of the carbamate alkyl group diminishes the *N*-acyliminium ion interaction with the catalyst anion in the enantiodetermining step. Owing to the conformational differences between the pyrrolidinium, piperidinium and azepinium *N*-alkoxycarbonyliminium ions, we expected that different catalysts would be required to enantiodifferentiate these intermediates. Fortunately, using our previously best catalysts as a benchmark, we quickly identified IDPi 7c as an efficient catalyst for the enol silane addition to the *N*-(exo-

A. Proposed Catalytic Cycle



B. Computational Studies

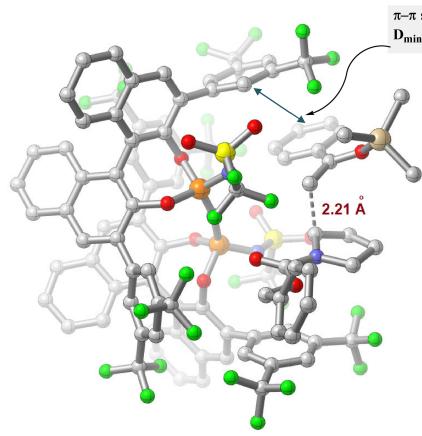
Major TS



0.0 (0.0)

experimental e.r. (at 203 K) = 89:11
predicted e.r. (at 203 K) = 87.5:12.5

Minor TS



0.75 (0.56)

Figure 2. Mechanistic rationale: A) Proposed catalytic cycle. B) Computational studies: DFT optimized stereodetermining TS structures of the enol silane **2a** addition to the *N*-acyliminium-IDPi **1a–7a** ion pair. Energy differences [ΔG^\ddagger (ΔE^\ddagger)] are computed at the M06-2X/def2-TZVP//PBE-D3/def2-SVP level of theory, and all energy values are in kcal mol^{-1} . Hydrogen atoms were omitted for clarity. Extent of stabilizing π – π interaction responsible for the stereoinduction.

acyl)azepinium intermediate furnishing product **3r** in high yield and high enantioselectivity. Accessing product **3s** on the other hand required yet another IDPi catalyst (see Supporting Information, Table S5). After a thorough investigation, catalyst **7e** enabled enantiocontrolling the reaction of *N*-(*exo*-acyl)piperidinium ion with enol silane **2a** as the nucleophile. Product **3r** was obtained in 57 % isolated yield with an e.r. of 97:3. Finally, we used our benchmark catalysts for the substitution on piperidine **1e** with isopropenoxy-trimethylsilane **2n** and obtained the corresponding

(*S*)-(*-*)-pelletierine precursor **3t** with IDPi **7d** in 46 % isolated yield with an enantiomeric ratio of 86.5:13.5. It is noteworthy that product **3a** and its derivatives access a palette of different pyrrolidine and *sedum alkaloids* in only a few literature known steps.^[56–59] In total we accessed the precursors for (*S*)-(*+*)-homoproline and six pyrrolidine and *sedum alkaloids* with high yields and enantioselectivities.

To further confirm that the reactions indeed proceed through *N*-(*exo*-acyl)iminium ions, we subjected enantio-merically-enriched hemiaminal methyl ether **1a** to the

reaction conditions (see Supporting Information). We found that each enantiomer leads to the same optically pure product (at full conversion, 96:4 e.r. in both cases), which in connection with the results of hemiaminal ethyl ether **1b** and hydroxy hemiaminal **1c** strongly supports that an S_N1 mechanism is in operation, involving a cyclic *N*-(*exo*-acyl)iminium intermediate paired with the chiral anion. In agreement with previous mechanistic studies, we propose a catalytic cycle as shown in Figure 2A. The reaction commences with the *in situ* silylation of the IDPi catalyst **7** by enol silane **2**, to furnish the *N*-silylated catalyst **I** and/or its diastereomeric *O*-Si-silatropomers. Hemiaminal methylether **1a** then reacts with silylated catalyst **I**, generating initially the silyl-oxocarbenium ion-IDPi anion pair **II**. Subsequently, the TMS group activates the leaving group **III** and releases TMSOMe, simultaneously forming the interconvertible *s-trans* or *s-cis* *N*-(*exo*-acyl)iminium ion-IDPi anion pairs **IV** and **V**. The enol silane **2** then reacts with either isomer **IV** or **V**, resulting in intermediate **VI**. Finally, silyl transfer from the newly formed silyl-oxocarbenium ion onto its counteranion releases product **3** and regenerates the silylated catalyst **I**.

A Density Functional Theory (DFT) study was undertaken to gain additional insight into the nature of stereoinduction (see Supporting Information). The computed lowest energy transition states (TSs) from **IV/V** to **VI** for the major and minor enantiomeric pathways were identified with good congruence between the calculated and experimental enantiomeric ratios (Figure 2B). The computational study suggests that the catalyst indeed differentiates between the *s-trans* (major TS) and *s-cis* (minor TS) conformers. In agreement with our empirical hypotheses, the calculations show that while the *N*-acyliminium ion lies in the anionic catalyst pocket, the carbamate protecting group points outside of the pocket consistent with the observation that the reaction tolerates different *N*-protecting groups (Cbz, Alloc and CO₂Me). In addition, the high *re-face* selectivity observed in the reaction can be rationalized due to the superior π - π interaction in the major TS ($D_{\min} = 3.25$ Å, compared to $D_{\min} = 3.45$ Å in minor TS) between the nucleophile and ion pair **V**.^[60] This is consistent with the fact that aliphatic nucleophiles, which lack the π -interaction with this catalyst, led to an erosion of selectivity (see Supporting Information). Indeed, this also emphasizes the requirement for a different catalyst system to handle aliphatic nucleophiles.

In conclusion, we have developed a direct enantioselective Mukaiyama–Mannich-type addition of enol silanes to *in situ* generated *N*-(*exo*-acyl)iminium ions from hemiaminals or hemiaminal methyl ethers. Control experiments and theoretical investigations are consistent with the reaction proceeding via a Si-ACDC-based S_N1 mechanism, involving a non-stabilized, aliphatic, cyclic *N*-(*exo*-acyl)iminium ion paired with a confined IDPi anion. High levels of enantioselectivity across a broad range of substrates have been achieved with four newly-developed IDPi catalysts, demonstrating the applicability of this method for the preparation of valuable 2-substituted pyrrolidines, piperidines and azepanes—highlighted by the synthesis of the precursors for

(*R*)-(+)-homoproline and formal synthesis of the six pyrrolidine and sedum alkaloids (*S*)-(-)-norhygrine, (*S*)-(-)-hygrine, (*S*)-(+)-ipalbidine, (–)-hygroleine, (–)-pseudohygrine and (*S*)-(-)-pelletierine. Furthermore, our catalytic system can control the addition of the enol silane derived from acetaldehyde with not just high enantioselectivity, but also high chemoselectivity towards the addition to the *N*-(*exo*-acyl)iminium species and without addition to the resulting aldehyde. Further investigations towards the synthesis of biologically active compounds, pharmaceuticals and additional natural products are currently ongoing in our group.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Lewis acids · *N*-acyliminium ions · Mukaiyama–Mannich reaction · imidodiphosphorimidates · organocatalysis

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