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Special Collection

Diiminium Nucleophile Adducts Are Stable and Convenient Strong Lewis Acids**

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This work is dedicated to the late Gerhard Maas.

Strong Lewis acids are essential tools for manifold chemical procedures, but their scalable deployment is limited by their costs and safety concerns. We report a scalable, convenient, and inexpensive synthesis of stable diiminium-based reagents with a Lewis acidic carbon centre. Coordination with pyridine donors stabilises these centres; the 2,2′-bipyridine adduct shows a chelation effect at carbon. Due to high fluoride, hydride, and oxide affinities, the diiminium pyridine adducts are promising soft and hard Lewis acids. They effectively produce acylpyridinium salts from carboxylates that can acylate amines to give amides and imides even from electronically intractable coupling partners.

Introduction

Lewis acidic reagents and catalysts are essential tools for the activation of basic functional groups, for example, in condensation reactions, the hydrogenation of carbonyls, cyclisation reactions, and the depolymerisation of polyesters.[1] Trivalent boron and aluminium compounds are affordable and have a broad utility in this context.[2] Divalent cationic nitrenium and tetravalent cationic phosphonium reagents are promising competitors.[3] Stronger reagents were generated based on structures isoelectronic to neutral trivalent boron centres such as silicon cations[4] and even phosphorous dications.[5] Efforts regarding carbon-based Lewis acids mostly focussed on trityl cations, wherein particularly the more acidic fluorinated examples are barely isolable.[6] Some further electron-deficient π-systems such as allenes, arenes, and iminium/pyridinium ions were used to create carbon Lewis acids,[6d,7] among which particularly iminium ions have a long history in organocatalysis.[8] This prompted the use of the iminium motif in the development of a series of Lewis acids.[9]

Anion, for example hydride, abstractions for synthetic purposes can be challenging and are oftentimes done with strong oxidants which limits the application scope.[10] "Frustrated" Lewis pairs (FLPs) are Lewis pairs that are frustrated from bonding due to steric congestion. They can circumvent some of these issues by directly capturing both the Lewis basic and acidic fragments generated by such abstraction reactions.[11] The preparation and application of reactive Lewis acids typically require inconvenient and costly procedures, which makes the development of selective strong Lewis acids important. We envisioned generating carbon-based Lewis acids by utilising neutral leaving groups for the interim stabilisation of one of the charges on formal diiminium dications.

Urea halides with their mediocre leaving groups can be used as synthetic equivalents for carbodications.[12] The π-stabilisation from the two nitrogen substituents leads to dissociation of one of the halides, even in the case of chlorides. This is also the case with isouronium salts such as **1**, which contain the same reactive formamidinium unit as their halide parents but bear a better leaving group (Figure 1A). They can be generated with triflic anhydride (Tf_2O) directly from urea derivatives like tetramethylurea (TMU).[13] Seminal studies by Maas showed that some diiminium pyridine adducts can be synthesised from the related isouronium anhydride **3**.[14] Owing in part to their difficult synthesis and the observation of pyridine decomposition pathways, these compounds did not find utilisation as Lewis acidic reagents even though their dicationic nature is promising. We report herein our findings on such dicationic salts that can be regarded as tetramethyldiiminium (TMDI, further abbreviated as DI) nucleophile adducts (DINu). A convenient, inexpensive, and scalable one-pot synthesis was designed, and their Lewis acidic properties

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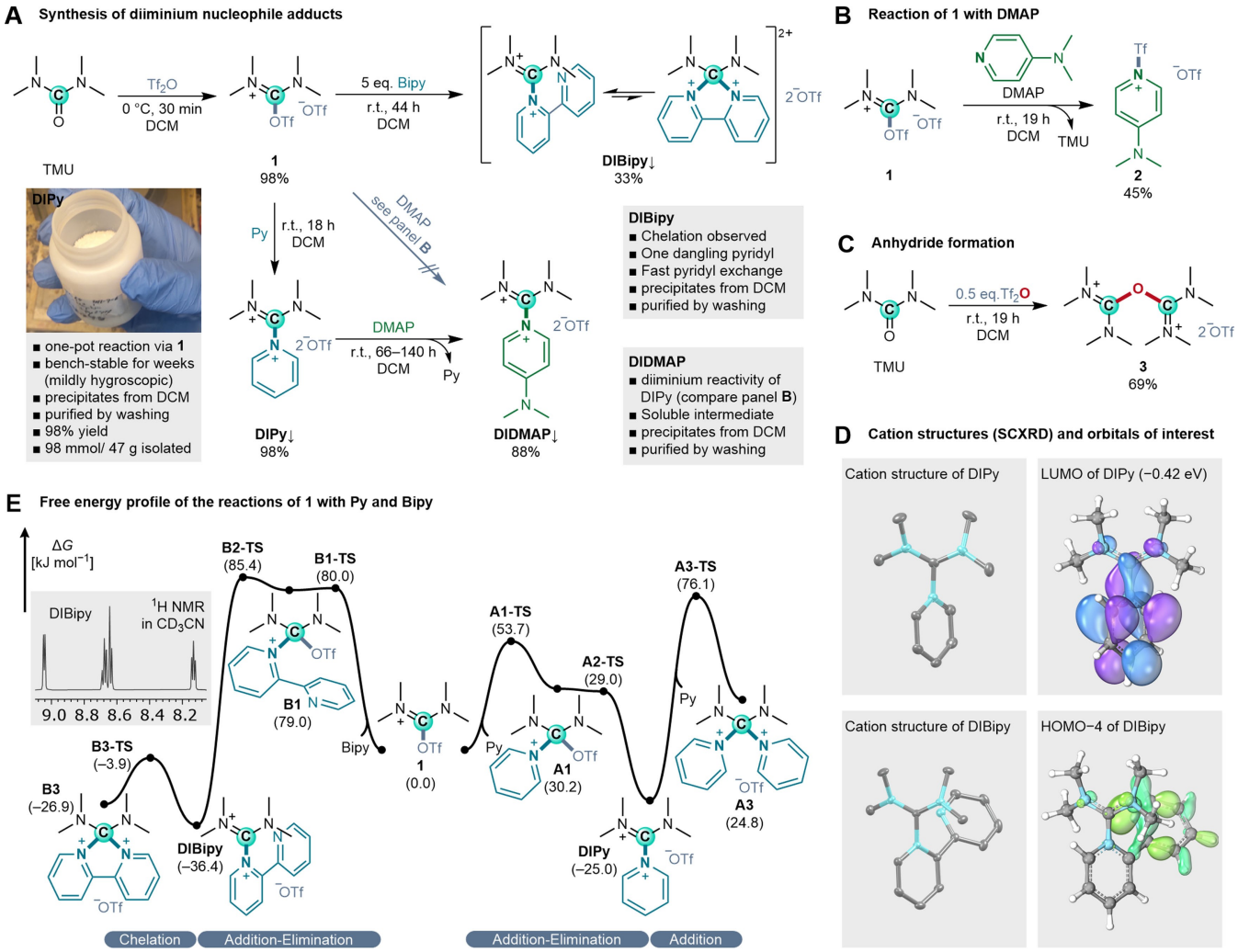

Figure 1. Synthesis and structure of diiminium complexes DINu. A) The synthesis of diiminium adducts DIPy and DIBipy succeeds from the isouronium salt **1**. DIPy can be used for coupling stronger nucleophiles than pyridine. Reactant additions were partially performed at decreased temperatures, see the Supporting Information for details. B) Unlike DIPy, **1** acts as a triflylating agent when reacting with DMAP. C) Isouronium anhydride **3** can be formed from **1** with remaining TMU. D) SCXRD structures in the solid state of DIPy (and LUMO) and DIBipy (and HOMO − 4) with thermal ellipsoids at 50% probability. Hydrogen atoms and triflate counterions are omitted in the SCXRD structures. Molecular orbital isosurfaces are displayed at a threshold enclosing 70% of the total electron density. E) Computed free-energy profile of the reaction of **1** with Py and Bipy (model: see refs. [15] and [16]). The inlay shows the aromatic region of the ^{1}H NMR spectrum (CD_3CN, 600 MHz) of DIBipy.

were investigated in fluoride, hydride, and oxide abstraction reactions. The latter was applied in the synthesis of amides and imides.

Results and Discussion

The salt **1** is a moisture-sensitive, viscous ionic liquid that decomposes at room temperature (r.t.). **1** and similar compounds tend to triflylate nucleophiles rather than participating in substitution reactions.[13b,c] **1** reacted with 4-(dimethylamino)pyridine (DMAP) as expected to give the *N*-triflyl-DMAP triflate **2** (Figure 1B). The less nucleophilic pyridine (Py) diverted from this behaviour and reacted smoothly through substitution at the carbon centre. This afforded DIPy which conveniently precipitated from dichloromethane (DCM, Figure 1A). The synthesis succeeded in one-pot procedure at a 100 mmol scale (47 g) starting from tetramethylurea in 98% yield. DIPy is mildly hygroscopic but air-stable over several weeks. Hydrolysis of DIPy only occurs in wet CD_3CN above 80 °C or after months of storage open to ambient air. We observed hydrolysis to selectively give to Py·HOTf and TMU·HOTf. Our computational model (Figure 1E) supported a simple addition-elimination mechanism for the formation of DIPy with a rate-determining initial addition of Py to **1** with a barrier of 54 kJ mol^{-1} (DLPNO-CCSD(T)/aug-cc-pVTZ/CPCM(DCM)//PBEh-3c/def2-mSVP/CPCM(DCM), see ref. [15]).[16]

Substitution of pyridine with the stronger donor DMAP succeeded smoothly in DIPy without triflylation and demonstrated enhanced diiminium reactivity over **1**. A soluble intermediate formed on addition of DMAP to a suspension of DIPy in DCM. The dicationic product DIDMAP precipitated and

was isolated by filtration in very good yield (88%) at a 10 mmol scale while a good yield (78%) was obtained at a 2.5 mmol scale. DIPy and DIDMAP could also be synthesised via **3**.[14b] An excess of the donor 2,2′-bipyridine (Bipy) was required to form the adduct DIBipy in 33% yield (Figure 1A). This compound was reportedly inaccessible via **3** in MeCN even at reflux.[14b]

Single crystal X-ray diffraction (SCXRD) analysis of DIPy (Figure 1D) showed C–NMe_2 bond lengths of 131 pm and a C–pyridinium–N bond length of 145 pm, which is even shorter than average bond lengths in alkylamines (147 pm).[17] and the Me–N bond in methylpyridinium iodide.[18] This suggests a cationic nature of the pyridyl which is underlined by a Löwdin atomic charge analysis of the electronic structure. The pyridine carries a total charge of 1.06 e, the diiminium unit carries 0.94 e. With DMAP being a stronger donor than Py, an increased Löwdin atomic charge was localised on the donor in DIDMAP (diiminium: 0.87 e, DMAP: 1.13 e).

The solid-state structure of DIBipy was rigid with a distance from the diiminium C to the dangling pyridyl nitrogen atom of 261 pm determined by SCXRD at −153 °C and at 107 °C. The orientation of the pendant pyridyl indicates the strong electrophilicity of the diiminium carbon atom leading to its coordination, while steric considerations would suggest the opposite orientation. A computed barrier of only 40 kJ mol^{-1} separates the singly coordinated DIBipy from its doubly coordinated isomer **B3**, which is just 10 kJ mol^{-1} less stable (Figure 1E). A few related carbodicationic Bipy adducts $[R_2C(Bipy)]^{2+}$ (R=H, Ph) are known which showed no active chelation due to a strongly favoured cyclised form.[19] The diiminium carbon atom in DIBipy assumes a trigonal pyramidal structure in the solid state with the lone pair of the non-covalently bound pyridyl nitrogen atom donating to the unoccupied π-system at the diiminium carbon atom (Figure 1D). Löwdin atomic charge analysis shows that Bipy acts as stronger donor than DMAP which can be reasoned by this dative interaction (diiminium: 0.83 e, Bipy: 1.17 e). The occurrence of only one set of pyridyl resonances in the ^{1}H nuclear magnetic resonance (NMR) spectrum of DIBipy at r.t. suggests fast exchange of the coordination sites (Figure S20 in the Supporting Information). Furthermore, free rotation of the C–NMe_2 units was observed at r.t., which was not the case for DIPy. The rotation barrier was determined by variable-temperature NMR to be 54 kJ mol^{-1} in DIBipy (Figure S56) which is significantly lower than in DIPy with 69 kJ mol^{-1} (Figure S57). The computed rotational barrier via **B3** (55 kJ mol^{-1}) is in excellent agreement with the experiments which indicates chelation as main cause for the decreased barrier. Aligning with the increasing weight of evidence that the concepts of coordination chemistry apply well to carbon,[7f,20] we found here a chelation effect on carbon with a dangling pyridyl in fast exchange with a coordinated pyridyl.

Both the structures in the solid state and Löwdin atomic charge analyses support an approximately even charge distribution between the diiminium and the pyridine units. The LUMO of DIPy shows large coefficients across the pyridine extending to the diiminium-carbon (Figure 1D). Fukui functions f^+(r) were computed at the DSD-BLYP–D3BJ/def2-QZVPP/CPCM(DCM) level to identify the most electrophilic sites (Figure 2A).[16o,u,21] The

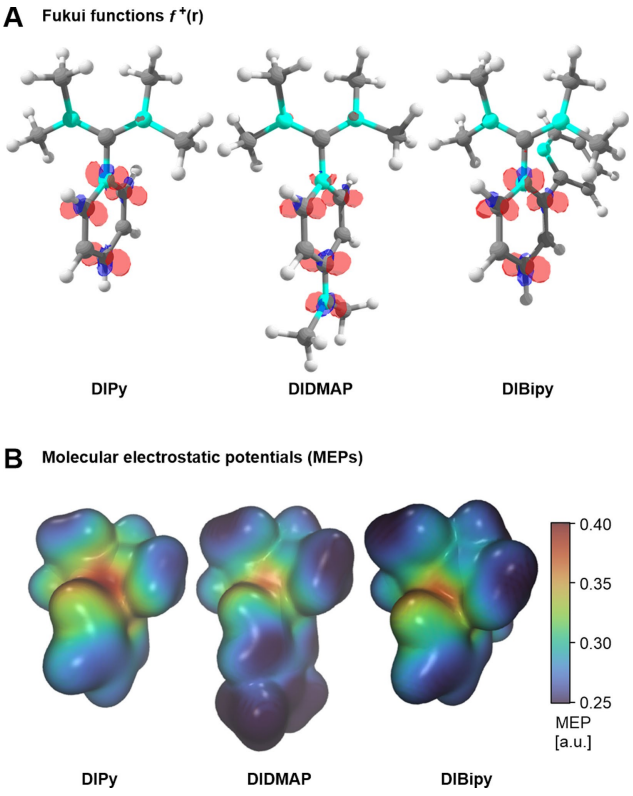

Figure 2. Computational electrophilicity indicators. A) Fukui functions f^+(r) of the DINu (ρ = 0.01, single points at DSD-BLYP–D3BJ/def2-QZVPP/CPCM(DCM) level).[16o,u,21] B) MEPs of the DINus projected onto their electron density isosurfaces (ρ = 0.003, model: see refs. [15] and [16]).

fukui functions suggest preference for attacks in *para*- and *ortho*-positions of the pyridines. DIPy and DIBipy also show large coefficients at the pyridine nitrogens. The observation of an exchange of Py with DMAP suggests a thermodynamic preference for attack at the diiminium carbon. Computed molecular electrostatic potentials (MEPs, with our general model, see refs. [15] and [16]) show high positive potentials at the diiminium carbon (Figure 2B). This can be reasoned with the three bound nitrogen atoms with their large electronegativity withdrawing electron density through the σ-bonds and leading to the electrons of the π-bonds in the diiminium unit being largely localised at the nitrogen atoms. DMAP and Bipy donate stronger but cannot negate the strongly positive potential at the diiminium carbon.

As the rather mild nucleophilicity difference between DMAP and Py led to a slow exchange between the donors, this reaction was ideal for probing details of the exchange mechanism that serves as foundation for the application of DINu as Lewis acids. Monitoring the reaction of DIPy with DMAP by ^{1}H NMR (Figures S62–S66) showed the rapid formation of intermediate **D1** with dearomatized Py (Figure 3A), a favourable reaction in such pyridinium salts which can lead to ring-opening.[14a,22] Full conversion to DIDMAP was reached after 18 h. Our computational model predicted very low barriers for both *ortho* and *para* addition (39 and 46 kJ mol^{-1}) which suggests rapid equilibration between these species to give the

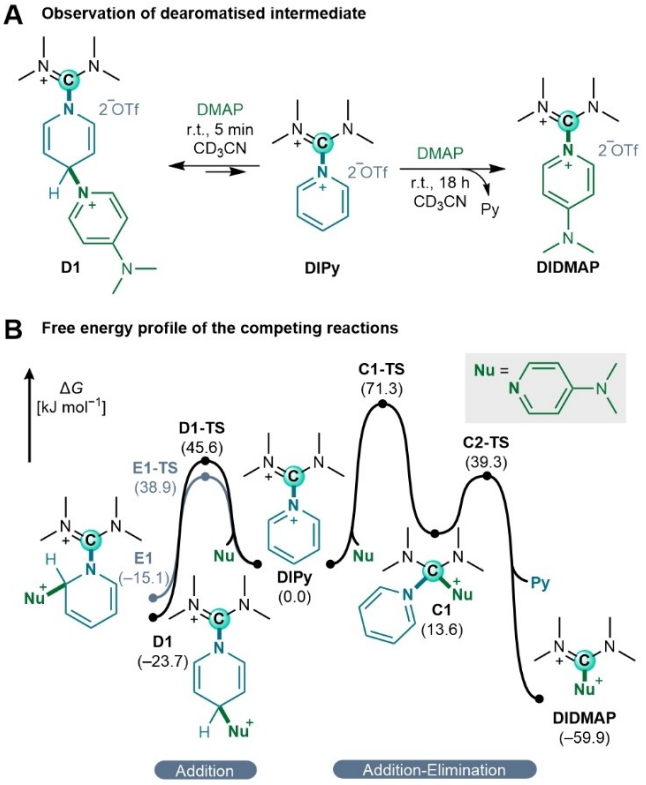

Figure 3. Mechanistic insights into the substitution of pyridine with DMAP in DIPy. A) Monitoring the reaction of DIPy with DMAP by ^{1}H NMR allowed observation of the *para*-addition intermediate **D1**, whereas the substitution product was found after 18 h. **B**) Reaction free-energy profile of the three potential addition/substitution reactions between DMAP and DIPy modelled in MeCN (model: see refs. [15] and [16]).

more stable *para* adduct **D1** (Figure 3B). The reactions observed under kinetic control agree with the electrophilic sites identified by the fukui functions (Figure 2A). Re-aromatisation under elimination of DMAP slowly allows the addition of DMAP to the diiminium carbon atom (barrier from **D1**: 95 kJ mol^{-1}). Elimination of pyridine gives the thermodynamic product DIDMAP (−60 kJ mol^{-1}). We could not detect any ring-opening reactivity. After the initial Lewis pair formation, a Lewis acidic character was restored by elimination of the previously bound Py.

We were then interested in gauging the Lewis acidity of the DINus. The ^{31}P chemical shift of Et_3PO varies strongly upon coordination of the oxygen atom to Lewis acids which is commonly used to gauge their strength. When we attempted to employ this Gutmann–Beckett method,[23] we observed the formation of TMU from our reagents, thus, no Gutmann–Becket acceptor number can be determined. DIPy and **1** both abstracted oxygen from Et_3PO leading to the formation of $[Et_3POPEt_3](OTf)_2$ (Figure 4A). Triflic anhydride (experiments are described in the Supporting Information) or thionylium dications can promote the same transformation.[24] The abstraction of oxygen from notoriously stable P=O bonds makes the discussed Lewis acids promising oxide abstractors/dehydrating reagents.[25] DIPy reacted slower than **1** but gave a much better behaved process without forming triflylated by-products.

Experimental and computational comparisons with established Lewis acids were then undertaken to support classification of the Lewis acidity of DINus. Lewis acidity is multidimensional and strongly depends on the used reference system. Among other classification thresholds, Lewis acids with higher fluoride ion affinity (*FIA*) than SbF_5 may be considered (hard) Lewis superacids (LSA) whereas acids with higher hydride ion affinity (*HIA*) than $B(C_6F_5)_3$ may be considered soft Lewis superacids (sLSA).[2a]

Fluoride abstraction from SbF_6^- was employed to determine hard Lewis superacidity (Figure 4B). While abstraction at r.t. failed, harshly heating solutions of DIPy and $MSbF_6$ in a microwave (180 °C, 4 h) promoted fluoride abstractions across different $MSbF_6$ (M=Ag, K, Ag/K, NBu_4) in yields of 53–68% determined by quantitative ^{1}H NMR (qNMR). The fluoroformamidinium **4** was generated under liberation of pyridine. Py-SbF_5 coordination would be expected but neither SbF_5 nor pyridine adducts were observed. Minor additional signals were detected in the aromatic and vinylic region of the ^{1}H NMR spectra, which suggests partial decomposition of the pyridine. The thermal instability of **1** led to its decomposition without the production of significant amounts of **4** (M=K, Ag). Soft Lewis superacidity (sLSA) was probed by a competition experiment in which DIPy and $B(C_6F_5)_3$ were simultaneously reacted with Et_3SiH at r.t. for 90 min (Figure 4C). 44% of the *para*-hydride-addition product **8** were found with DIPy by qNMR, while we only detected minor amounts of the Et_3SiH adduct with the borane.[1f,26] Triflate coordinated the silyl cation to give Et_3SiOTf alongside Et_3SiOH that was likely formed by a follow-up reaction with residual moisture. Increased reaction times or temperatures lead to a loss in yield. **8** was also produced in the absence of $B(C_6F_5)_3$, but the reaction was significantly slower. Full conversion was found after 3 d at 60 °C in a separate experiment for the reaction of DIPy with 4 equiv. Et_3SiH. The borane presumably catalyses this hydride abstraction.[1f] Our model suggests that **8** is metastable as substitution of Py with hydride to give the formamidinium **5** was computed to be thermodynamically favoured. The isouronium **1** did not produce **5**; it was outcompeted by the borane.

Several of the reactions discussed here can successfully be performed in DCM but no quantitative measurements can be undertaken therein due to the low solubility of the DINus which dictated the use of MeCN as solvent. Both, MeCN and liberated Py, can coordinate the products of anion abstraction reactions. A pure Lewis acidity can, thus, not be determined in the condensed phase but we can deduce the effective acidity in the specific reference reactions that were undertaken. While the isouronium salt **1** was ineffective, the pyridinium of DIPy acted as expected from a soft Lewis superacid and, under harsh conditions, the diiminium carbon acted as expected from a hard Lewis superacid.

To quantitatively determine the hard and soft Lewis acidities of the DINu salts, we computed *FIA*s and *HIA*s according to Krossing's and Greb's scheme, that is, negative gas phase enthalpies of addition reactions of fluoride and hydride ions.[27] As the DINus can react under elimination of the assumed nucleophile, we also computed the negative gas phase enthalpies for the substitution reactions with fluoride and

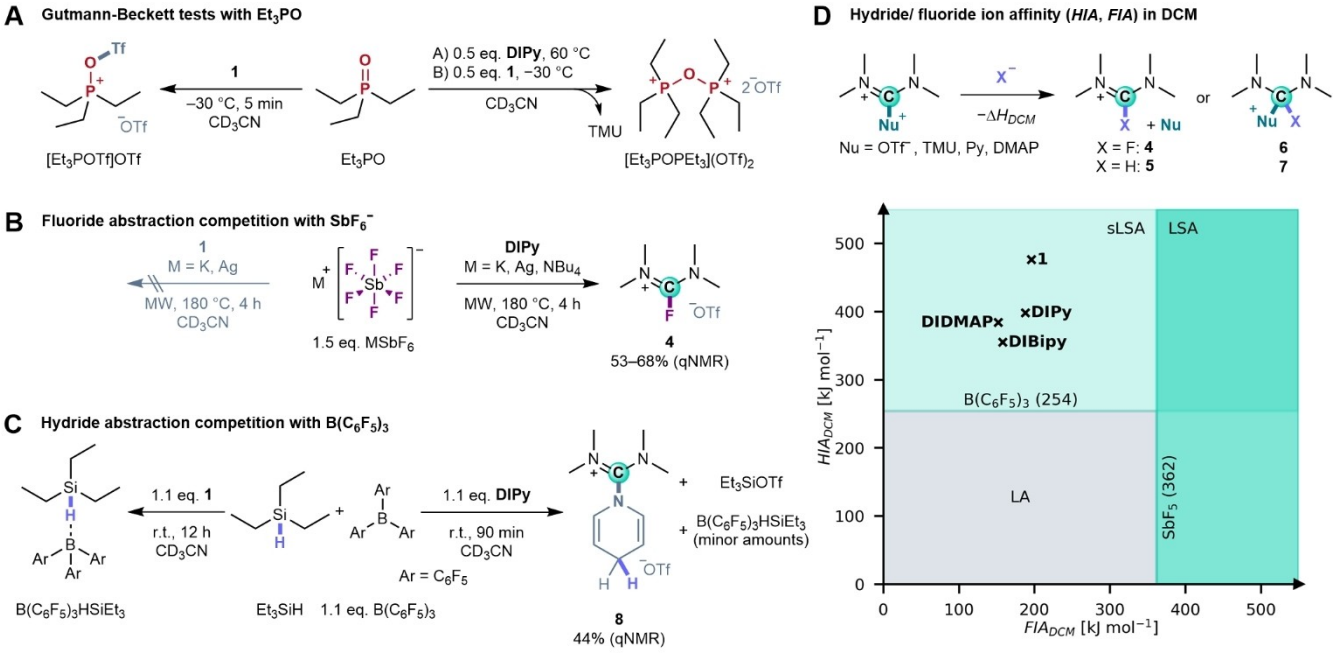

Figure 4. Gauges of the Lewis acidity of **1** and the DINus. A) The attempted Gutmann–Beckett analysis showed that **1** and DIPy abstract oxygen from Et_3PO under formation of TMU. Salt **1** acts again as triflylating reagent when used in stochiometric amounts or in excess. B) DIPy can abstract fluoride from $AgSbF_6$, whereas decomposition was observed with **1**. C) DIPy outcompetes $B(C_6F_5)_3$ in the hydride abstraction from Et_3SiH, whereas no conversion of **1** was observed. D) Negative computational hydride and fluoride substitution or addition enthalpies in DCM.[15] *FIA* [kJ mol^{-1}]: DIPy: 188, DIDMAP: 158, DIBipy: 152, **1**: 196, **3**: 183. *HIA* [kJ mol^{-1}]: DIPy: 398, DIDMAP: 355, DIBipy: 384, **1**: 476, **3**: 415.

hydride ions. (Figure 4D). Substitution (giving **4** or **5**) was preferred in some cases in DCM. An addition (giving **6** or **7**) was favoured in gas phase enthalpies. The more favourable of the two possible reactions is given herein and its negative enthalpy is loosely termed *FIA*/*HIA*. The individual data is given in the Supporting Information. The nucleophile-stabilised DINus show exceptionally high gas-phase *FIA*s (~950 kJ mol^{-1}, SbF_5: 495 kJ mol^{-1}) and *HIA*s (~1.1 MJ mol^{-1}, $B(C_6F_5)_3$: 481 kJ mol^{-1}). It must be noted, however, that solvation induces significant acidity dampening in ionic Lewis acids. DCM was chosen for the solvation model due to the large availability of comparable data. In solution, *FIA*s were ~160 kJ mol^{-1} (SbF_5: 362 kJ mol^{-1}) and *HIA*s were ~380 kJ mol^{-1} ($B(C_6F_5)_3$: 254 kJ mol^{-1}). Fluorinated trityl cations have considerably lower gas phase ion affinities but comparable values were modelled in DCM solution.[6e,28] The computational ion affinities support the classification of DINus as hard and soft Lewis superacids in the gas phase but only as soft Lewis superacids in solution.

It is not trivial to compare DINu with simple Lewis acids, as they do not strictly follow a "single action" acid-base pair formation mechanism. Their observed "double action" addition-elimination mechanism implies: i) determined acidities are associated with the acidity of the (currently) non-isolable parent diiminium dication; ii) in analogy to "frustrated" Lewis pairs, the liberated nucleophile can substitute abstracted fragments which leads to a net nucleophile metathesis and a more exergonic reaction than represented by pure ion affinities; iii) two bases or double bases such as oxides may be activated by a single electronic acid.

Amide formations were chosen for a first application survey. The observed high oxide affinity made DINus promising for this type of reaction, which is the most frequently employed one in drug discovery.[29] DINus carry the same formamidinium-head as successful guanidinium/isouronium-based amide/peptide coupling reagents, but these feature anionic leaving groups.[30] The dicationic DINus with neutral leaving groups should be more reactive, and thus, particularly useful for challenging amide formations. The reaction of the bulky diphenylacetic acid **9a** with 4,6-dimethylpyrimidine **10a** gave isolated yields of the amide **11a** of 87% with DIPy and 88% with DIDMAP (Figure 5, see the Supporting Information). Only 68% were received with the commonly used *O*-HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium-hexafluorophosphate). The DINus performed comparably to BTFFH (bis (tetramethylene)fluoroformamidinium hexafluorophosphate) which was introduced for tackling problematic amide formations via acyl fluoride intermediates (our conditions: 90%, reported: 88%).[31]

Amide formations mediated by DIDMAP were robust throughout a survey of different amines and carboxylic acids. Only a few of the targeted electron-poor amides were isolated previously, but they have been identified as broadly applicable pharmaceuticals (details listed in the Supporting Information). The carboxylic acid and the amine in **11a** were replaced with aliphatic and aromatic derivatives which induced only minor yield variations even when the aromatic units were substituted with an electron-donating methoxy or an electron-withdrawing nitro substituent in *para*-position. Good to very good yields were obtained (68–88%). Only the attempt to couple two

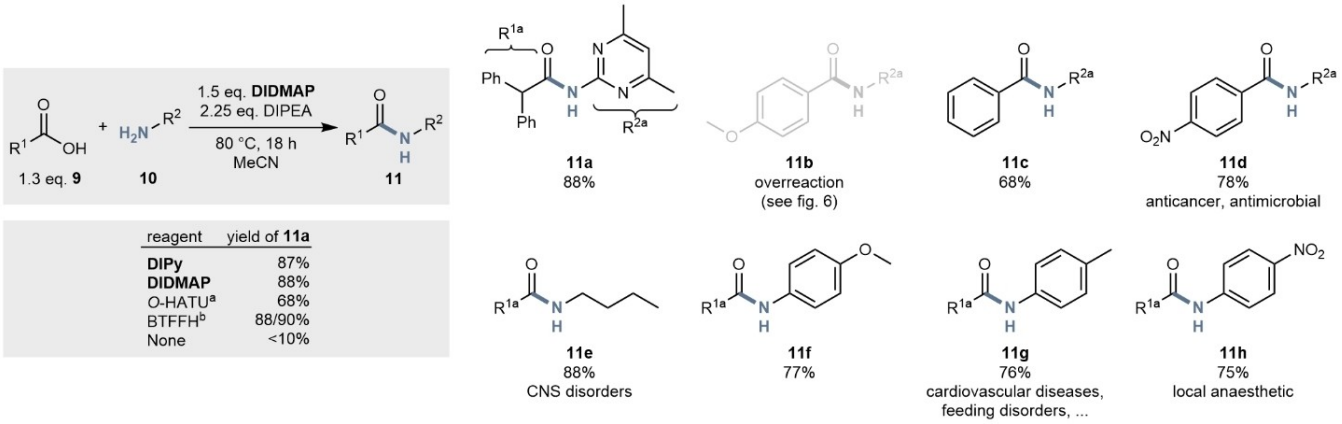

Figure 5. Performance of DIPy, DIDMAP, *O*-HATU, and BTFFH in amide formation and scope of amide formations with DIDMAP with potential or established applications of the products (see the Supporting Information for details). The amines were added, and heating was commenced, after stirring at r.t. for 30 min. *O*-HATU: *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium-hexafluorophosphate; BTFFH: bis(tetramethylene)fluoroformamidinium hexafluorophosphate. [a] Reaction performed in DCM. [b] Ulven's conditions with 4.5 equiv. of DIPEA[31a] and our conditions in DCM.

aliphatic bulky components, **9a** and *t*BuNH$_2$, led to no avail, and the more fragile coupling of a dipeptide showed epimerisation.

Anisic acid **9b** and pyrimidine **10a**, both possessing unfavourable electronic structures, overreacted and the further deactivated amide nitrogen was acylated again to give the imide **12** in 40% yield (Figure 6A). 63% were received after adapting the stoichiometry. BTFFH failed to even produce the amide, and 89% of the starting material were recovered in the form of the corresponding acyl fluoride **13a** (58%) and anhydride (31%). The formation of the acylpyridinium salt **13b** from **9a** and DIDMAP succeeded within 15 min at r.t. (Figures 6B and S196–S200). The electron-poor nature and excellent leaving group of acylpyridinium salts have been appraised and leveraged for more than a century.[32] The amide and imide formation with these challenging reactants were both modelled to be almost energy-neutral with **13a**, while they were strongly exergonic with **13b** (Figure 6C). DIDMAP conveniently generates these powerful acylation agents which enabled imide syntheses void the usually necessary pre-activation of the carboxylic acid or even transition-metal catalysis.[33] Imides are ubiquitous in nature and find application as cancer therapeutics, sedatives, and anticonvulsants, and are employed in agrochemistry.[33c]

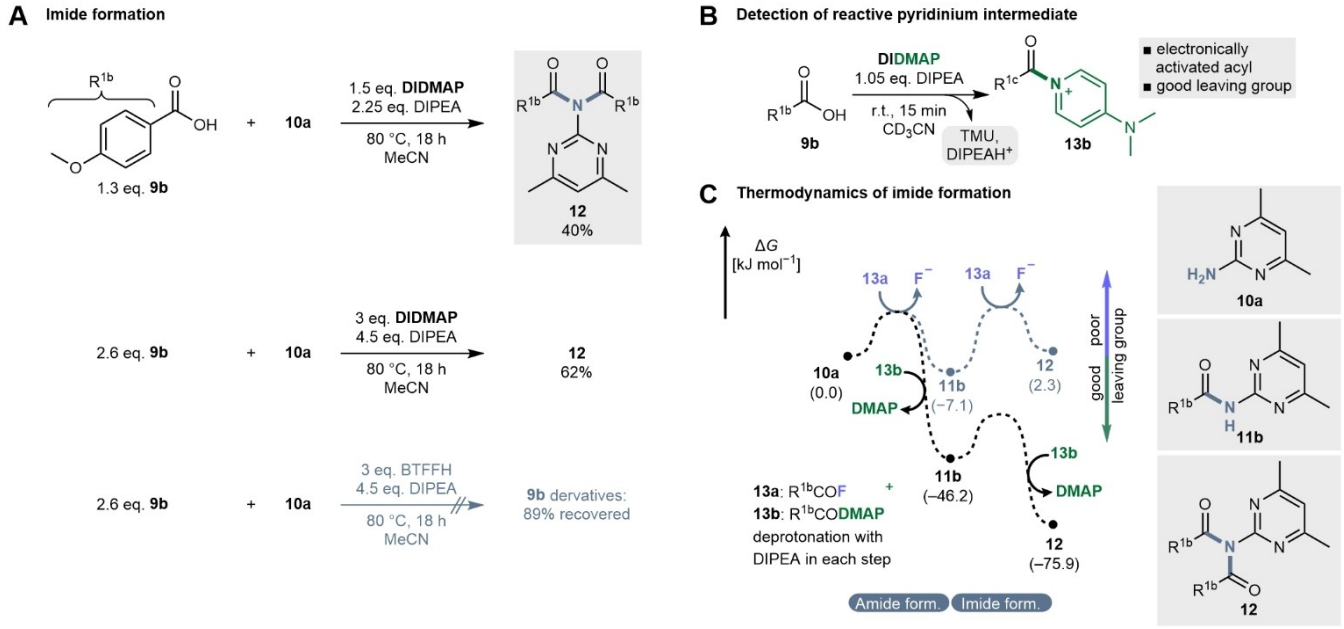

Figure 6. First insight into the application of DINu in imide formations. A) Imide formation succeeded with DIDMAP but not with BTFFH. B) Efficient acylpyridinium formation was detected by ^{1}H NMR (Figures S196–S200). C) Reaction free energies of amide and imide formation with fluoride or DMAP as leaving group modelled in MeCN.

Conclusions

The presented diiminium nucleophile adducts are a group of conveniently available and handleable Lewis acids with strong fluoride-, hydride-, and oxide-abstraction reactivity. They satisfy some measures for Lewis superacidity, particularly soft superacidity. Favourable reaction kinetics were observed, especially with oxygen nucleophiles, even in the abstraction of half an equivalent of oxide from a P=O bond. Our preliminary results combined with price and safety considerations suggest that they are excellent acylation reagents, for example, for amide and even imide coupling. These reagents could find broad application through the development of derivatives and the investigation of their performance in the activation of further nucleophiles.

Experimental Section

Experimental methods: All synthetic procedures were carried out in an argon-filled glovebox (O_2 and H_2O <3 ppm) or in Schlenk-type glassware in a dry argon atmosphere unless stated otherwise. Glassware used in these procedures was pre-heated in an oven at 120 °C for at least 2 h and flame-dried with a heat gun and flushed with dry argon thrice.

All chemicals were obtained from commercial suppliers and used without further purification unless stated otherwise. Tetramethylurea was distilled over CaH_2 and stored over 4 Å molecular sieves. Dichloromethane (DCM) and acetonitrile (MeCN) were dried with an MBRAUN solvent purification system (SPS-5) and stored over 4 Å molecular sieves. Deuterated solvents for anhydrous measurements were introduced to a glovebox as obtained from Eurisotop and stored over 4 Å molecular sieves. Cannula filtrations were performed with polytetrafluoroethylene (PTFE) cannulas capped with MN615 filter paper from Macherey–Nagel (retention capacity 4–12 μm) attached with PTFE tape. Column chromatography was performed with silica gel 60 M (40–60 μm) obtained from Macherey–Nagel. Thin-layer chromatography was performed with aluminium plates coated with a 0.2 mm layer of silica gel 60 M (40–60 μm) and a 254 nm UV fluorescent indicator obtained from Macherey–Nagel.

Nuclear magnetic resonance spectra were recorded either on a Varian V NMRS 400, Varian V NMRS 600, Bruker Avance Neo 400 or Bruker Avance Neo 600 spectrometer at 26 °C and were analysed with the software Mnova 14.2.3.[34] Chemical shifts δ were reported in parts per million (ppm). The residual solvent signals were used for referencing the chemical shifts δ in ^{1}H NMR spectra (1.94 ppm for CD_3CN, 5.32 ppm for CD_2Cl_2, 7.26 ppm for $CDCl_3$).[35] This shift was used for absolute referencing of all other spectra with the unified chemical shifts scale as recommended by IUPAC in its implementation in Mnova 14.2.3 (^{13}C: Me_4Si $\varphi=1$ %, $\Xi=25.145020$; ^{19}F: CCl_3F $\Xi=94.094011$; ^{31}P: H_3PO_4 external, $\Xi=40.480742$).[34,36] Multiplicities of the signals were given as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qui), septet (sept), multiplet (m), or broad signal (bs). Elemental analyses (CHN) were carried out in air with an Elementar VarioEL or a Bruker maXis II. High-resolution mass spectrometry (HRMS, further abbreviated as MS) was performed using a Thermo Scientific LTQ Orbitrap XL. Attenuated total reflection infrared spectra (ATR-IR) were measured on a PerkinElmer Spectrum 100 FTIR using the universal ATR (UATR) accessory and the signals were reported in cm^{-1}. Single-crystal X-ray data was measured using a Rigaku SuperNova dual-source Oxford diffractometer equipped with an Atlas detector using mirror-monochromated $Cu_{K\alpha}$ ($\lambda=1.54184$ Å) radiation. The data collection and reduction were performed using the program *CrysAlisPro*.[37] The structures were solved with intrinsic phasing (*SHELXT*)[38] and refined by full-matrix least squares on F^2 using the *Olex2* software,[39] which utilizes the *SHELXL* module.[40] Anisotropic displacement parameters were assigned to non-H atoms. All hydrogen atoms were refined using riding models with U_{eq}(H) of 1.5U_{eq}(C) for alkyl groups and U_{eq}(H) of 1.2U_{eq}(C) for all other C–H groups.

Computational methods: Calculations were performed in autodE 1.3.0.[16a] Low energy conformers were generated from simplified molecular-input line-entry system (SMILES) tags with the ETKDGv3 algorithm implemented in RDKit v. 2022.03.4.[16b] Conformer optimisations were performed using xTB 6.4.0[16c] at the GFN2-xTB level.[16d] Solution phase calculations used the generalized Born solvation model with hydrophobic solvent accessible surface area (GBSA) with parameters appropriate for dichloromethane.[16e,f] Feasibly low energy conformers as selected with autodE default settings were then optimised with ORCA 5.0.3[16g–i] with the triple-corrected composite method PBEh-3c/def2-mSVP[16j–m] utilising the RIJCOSX[16n] approximation for Coulomb and Hartree Fock exchange with the def2/J auxiliary basis.[16o] autodE's template-based algorithm including conformer screening was used for the localisation of most transition states. Relaxed potential energy scans as implemented in ORCA were used for localising rotational transition states, which were then optimised and further treated within autodE. Hessians were then computed in ORCA at the same level of theory for confirming the nature of the optimised structures as local minimum or maximum, respectively. autodE was used to compute the zero-point energy and free energy corrections based on the generated Hessian. The frequencies were scaled by 0.95 as advised for this functional and basis set combination.[16j] Low frequency vibration modes were treated with the quasi-rigid-rotor-harmonic-oscillator approximation (qRRHO, with $w_0=100$ cm^{-1}).[16p] Potential imaginary frequencies smaller than 40 cm^{-1} were not considered transition states and were treated as real frequencies within thermochemistry calculations (multiplication by $-i$). Electronic energies were obtained from single point calculations at the DLPNO-CCSD(T)[16q,r] level with the basis set aug-cc-pVTZ[41] and the auxiliary basis aug-cc-pVTZ/C[16s] for Coulomb-fitting. A T1 diagnostic of <0.02 was found in all cases which supports suitable quality of the Hartree Fock reference.[16t] The single point basis set choice was based on a benchmark described later herein. Optimisation, Hessian, and single point calculations in solution utilised the conductor-like polarisable continuum model (C-PCM) with parameters appropriate for DCM unless stated otherwise.[16u] Energies were calculated at a 1 M concentration and a temperature of 25 °C unless stated otherwise.

Compound energies are listed as E^{opt}, G^{cont}, H^{cont}, and E^{sp}. E^{opt} is the energy of the final structure at our level of theory used for geometry optimisation. E^{sp} is the energy of the compound at our single point calculation level. H^{cont} is the enthalpy contribution, i.e., zero-point energy ($H=E^{sp}+H^{cont}$). G^{cont} is the total free energy contribution, that is, the sum of the zero-point energy and entropy contributions ($G=E^{sp}+G^{cont}$).

Densities and molecular electrostatic potentials were computed with 80 grid intervals and displayed at $\rho=0.003$, utilising ORCA and a Python script available at https://gist.github.com/mretegan/5501553. Orbital representations were generated with IboView v20211019-RevA.[42] Density isosurfaces with a 70% threshold were shown. Fukui functions $f^+(r)$ were computed from single point calculations of the dications and the respective monocationic radicals at the DSD-BLYP[21a] level with D3BJ[21b,c] dispersion correction with the basis set def2-QZVPP[21d] and the auxiliary basis sets def2/J[16o] and def2-QZVPP/C.[21e] auxiliary basis sets and displayed at $\rho=0.01$.

Synthesis of the *N,N,N′,N′*-tetramethyldiiminium ditriflate pyridine complex (DIPy): The employed glassware was dried in an oven at

120 °C for at least 2 h before mounting the apparatus. A 250 mL three-necked round-bottomed flask is fitted with an adapter to the positive argon pressure from a Schlenk manifold, a scaled 50 mL dripping funnel, and a stopper. The apparatus is flushed with argon for 15 min before charging the flask with 100 mmol (12.0 mL, 1.00 equiv.) tetramethylurea. Anhydrous DCM is transferred via cannula to the dripping funnel to measure 50 mL which were then passed to the flask. The dripping funnel was then charged with 105 mmol (29.9 g, 1.05 equiv.) Tf_2O and anhydrous DCM was added to dilute the anhydride to a total of 50 mL. An ice/water bath was used to cool the reaction flask to 0 °C. The solution of Tf_2O was added dropwise to the reaction flask over 15 min. The reaction was stirred for 40 min at 0 °C (the reaction solution turned pale yellow during this period). The dripping funnel was then rinsed with 10 mL anhydrous DCM into the reaction flask and charged again with 100 mmol (8.1 mL, 1.00 equiv.) pyridine (which may cause mild fuming) and diluted to a total of 40 mL with anhydrous DCM. The solution of pyridine was added dropwise to the reaction flask over 15 min while vigorously stirring (a biphasic system can be observed when stirring slowly/not stirring). The cooling bath was removed, and the reaction was stirred vigorously overnight. Rapid crystallization was observed after circa 1 h. The reaction was stirred for a total of 18 h. Scratching with a glass rod can be used to induce crystallisation if it did not occur at this stage. The dripping funnel and stopper were unmounted to replace them with a septum and a triple flame-dried glass filter tube (pore size 10–20 μm) with a 500 mL Schlenk flask attached. The reaction solution was filtered and washed with 50 mL of anhydrous DCM (injected through the septum) three times. The remaining crystalline material in the reaction flask was broken down with a metal spatula where needed to allow transfer to the filter. The filtrate was removed, and the product was dried in vacuum. 97.8 mmol (46.7 g, 98%) of the colourless crystalline product were collected from the filter tube in the glovebox to avoid contamination with water. Photographic documentation is available in Table S1. Spectroscopic data agreed with data available from Maas' synthesis.[14b] ^{1}H NMR (CD_3CN, 599.86 MHz): $\delta = 9.15$ (dddd, $J = 6.5$, 1.4, 1.4, 1.4 Hz, 2H, py-C2*H*), 9.06 (tt, $J = 8.0$, 1.4 Hz, 1H, py-C4*H*), 8.46 (dddd, $J = 8.00$, 6.5, 1.4, 1.4 Hz, 2H, py-C3*H*), 3.54 (s, 6H, CH_3), 2.94 (s, 6H, CH_3). ^{19}F NMR (564.38 MHz, CD_3CN): $\delta = -80.1$ (6F, $^-$OTf). ^{13}C NMR (CD_3CN, 150.85 MHz): $\delta = 155.1$ (1 C, NCN), 153.8 (1 C, py-*C*4), 144.3 (2 C, py-*C*2), 129.7 (2 C, py-*C*3), 120.2 (q, $J = 320.5$ Hz, 2 C, OTf-*C*), 43.0 (2 C, $2CH_3$), 41.8 (2 C, $2CH_3$). MS (ESI(+), MeOH) *m/z* 805.13856 (805.14002 calcd. for [2 $(Me_2N)_2CPy^{2+} + 3$ $OTf^-]^+$), 249.05080 (249.05098 calcd. for $[(Me_2N)_2COTf]^+$). MS (ESI(−), MeOH) *m/z* 148.95299 (148.95257 calcd. for $[OTf]^-$). ATR-IR (neat) 3126, 3067, 2293, 2109, 1706, 1628, 1522, 1477, 1411, 1256, 1148, 1057, 1025, 918, 878, 795, 755, 719, 681. EA C 30.16, H 3.76, N 8.77 (calcd. C 30.19, H 3.59, N 8.80).

Synthesis of the *N,N,N′,N′*-tetramethyldiiminium ditriflate 4-(dimethylamino)pyridine complex (DIDMAP): A 100 mL Schlenk tube was charged with 10 mL anhydrous DCM and 10.0 mmol (4.77 g, 1.00 equiv.) of the *N,N,N,N*-tetramethyldiiminium ditriflate pyridine adduct DIPy. 10.5 mmol (1.28 g, 1.05 equiv.) of 4-(dimethylamino)pyridine were added, forming a clear yellow solution. The formed colourless precipitate was collected after 140 h of stirring at r.t. via filter cannula and the crude product was washed thrice with 25 mL DCM each. 8.75 mmol (4.55 g, 88%) of the colourless solid DIDMAP were collected. Spectroscopic data agreed with data available from Maas' synthesis.[14b] ^{1}H NMR (CD_3CN, 399.97 MHz): $\delta = 7.99$ (d, $J = 8.3$ Hz, 2H, ArC*H*), 7.07 (d, $J = 8.3$ Hz, 2H, ArC*H*), 3.36 (s, 6H, $ArN(CH_3)_2$), 3.35 (s, 6H, diiminium CH_3), 2.98 (s, 6H, diiminium CH_3). ^{19}F NMR (376.33 MHz, CD_3CN): $\delta = -80.1$ (6F, $^-$OTf). ^{13}C NMR (CD_3CN, 150.85 MHz): $\delta = 157.4$ (1 C, Ar-*C*NMe_2), 156.2 (1 C, NCN), 138.6 (2 C, ArCH), 120.2 (q, $J = 320.5$ Hz, 2 *C*, OTf-*C*), 108.2 (2 C, ArCH), 41.8 (2 C, diiminium-$N(CH_3)_2$), 40.8 (2 C, $ArN(CH_3)_2$), 40.3 (2 C, diiminium $N(CH_3)_2$). MS (ESI(+), MeOH) *m/z* 131.11753 (131.11789 calcd. for $[(Me_2N)_2COMe]^+$), 371.13501 (371.13592 calcd. for $[[(Me_2N)_2C(DMAP) + OTf]^+$), 371.13601 (371.13601 calcd. for $[[(Me_2N)_2C(DMAP) + OTf^-]^+$). ATR-IR (neat) 3078, 2952, 2294, 2055, 1895, 1679, 1654, 1595, 1525, 1465, 1406, 1355, 1263, 1197, 1143, 1060, 1027, 941, 917, 885, 833, 802, 754. EA C 32.26, H 4.21, N 10.72 (calcd. C 32.31, H 4.26, N 10.77).

Synthesis of the *N,N,N′,N′*-tetramethyldiiminium ditriflate 2,2′-bipyridine complex (DIBipy): A 100 mL Schlenk tube was charged with 10 mL anhydrous DCM and 2.50 mmol (300 μL, 1.00 equiv.) of tetramethylurea. The reaction mixture was cooled to 0 °C with an ice-water bath and 2.63 mmol (440 μL, 1.05 equiv.) Tf_2O were added dropwise over 3 min. After 30 min, 12.5 mmol (1.95 g, 5.00 equiv.) 2,2′-bipyridyl were added. The reaction was stirred for 44 h. A colourless precipitation was observed. The solvent was removed via filter canulla, and the crude product was washed thrice with 5 mL DCM each. 819 μmol (454 mg, 33%) of the off-white solid DIBipy were collected. ^{1}H NMR (CD_3CN, 600.44 MHz): $\delta = 9.04$ (ddd, $J = 5.5$, 1.6, 0.8 Hz, 2H, Bipy-C3/C6*H*), 8.68 (ddd, $J = 8.1$, 7.6, 1.6 Hz, 2H, Bipy-C4/C5*H*), 8.64 (ddd, $J = 8.1$, 1.4, 0.8 Hz, 2H, Bipy-C4/C5*H*), 8.13 (ddd, $J = 7.6$, 5.5, 1.4 Hz, 2H, Bipy-C3/C6*H*), 3.06 (s, 12H, CH_3). ^{19}F NMR (564.92 MHz, CD_3CN): $\delta = -80.1$ (6F, $^-$OTf). ^{13}C NMR (CD_3CN, 151.00 MHz): $\delta = 156.6$ (NCN), 147.7 (2 C), 147.4 (2 C), 146.0 (2 C, Bipy-*C*1, Bipy-*C*1′), 128.2 (2 C), 127.7 (2 C), 120.3 (q, $J = 320.5$ Hz, 2 C, OTf-*C*), 41.67 (4 C, CH_3). MS (ESI(+), MeOH) *m/z* 405.11821 (405.12027 calcd. for $[(Me_2N)_2CBipy^{2+} + OTf^-]^+$), 249.05016 (249.05098 calcd. for $[(Me_2N)_2COTf]^+$). ATR-IR (neat) 3064, 2301, 2154, 1919, 1698, 1618, 1560, 1509, 1470, 1444, 1413, 1260, 1151, 1063, 1026, 995, 919, 884, 788, 753, 705. EA C 36.72, H 3.62, N 10.04 (calcd. C 36.82, H 3.64, N 10.10).

General procedure for amide coupling reactions. 450 μmol (1.50 equiv.) of DIDMAP and 390 μmol (1.30 equiv.) of the carboxylic acid were dissolved in 1.5 mL anhydrous solvent in a 10 mL screw-capped vial equipped with a magnetic stirring bar in a glovebox. 675 μmmol (117 μL, 2.25 equiv.) of DIPEA were added while stirring. The reaction was left to stir for 30 min, after which 300 μmol (1.00 equiv.) of the amine were added. The reaction was then taken out of the glovebox and heated to 80 °C for 18 h in an oil bath. The reaction was quenched at r.t. with 2 mL of distilled water and the solution was transferred to a separation funnel. The aqueous phase was diluted with 8 mL of distilled water. The phases were separated, and the aqueous phase was extracted thrice with 20 mL of EtOAc. The combined organic phases were washed with 20 mL of brine and dried over anhydrous $MgSO_4$. The crude mixture was purified via column chromatography with silica gel and EtOAc/pentane. Evaporation of the solvents under vacuum afforded the product amide. The yield was determined by weight and a ^{1}H NMR spectrum was taken to confirm the identity and purity of the product. Compounds that were not previously reported were afterwards recrystallised from toluene layered with pentane to give colourless crystals used for characterisation.

Supporting Information

Single point and vibrational calculation data are deposited at ioChem-BD under DOI: 10.19061/iochem-bd-6-233.[43]

Deposition Numbers 2203327 (for **1**), 2203328 (for DIPy), 2203329 (for DIBipy at 120 K) and 2203330 (for DIBipy at 380 K) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Author Contributions

F.F.M. conceived and designed the study. J.W. and K.R. designed and conducted crystallographic experiments and analysed structural features. F.F.M., W.-B.H., and P.W. performed the pyridine substitution reactions. A.K.B. computed the substitution reaction free energy profile. Y.G. and F.F.M. performed fluoride abstraction reactions. A.B. explored potential applications. F.F.M., N.B., A.K.B., and P.W. performed acylation reactions. F.F.M. conducted all remaining parts. F.F.M. directed the research and wrote the draft. All authors agreed on the manuscript.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in ioChem-BD at https://doi.org/10.19061/iochem-bd-6-233, reference number 292021.

Keywords: amides · carbodications · carbocations · cations · Lewis acids

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[15] The employed pipeline for conformer sampling and transition state searches is described and referenced in detail in the Supporting Information. Final energies are (unless stated otherwise) free energies in solution at the DLPNO-CCSD(T)/aug-cc-pVTZ/CPCM(DCM)//PBEh-3c/def2-mSVP/CPCM(DCM) level of theory.

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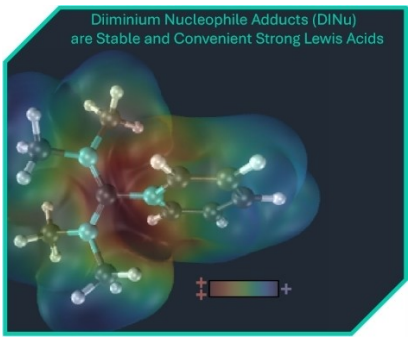
RESEARCH ARTICLE

Diiminium nucleophile adducts, convenient Lewis acids that satisfy some measures for superacidity, have been synthesised by coordination with stabilising pyridine donors. Even in their abstraction of half an equivalent of oxide from a P=O bond, favourable abstraction kinetics were observed. Our preliminary results combined with price and safety considerations suggest that the adducts are excellent acylation reagents.



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