Diiminium Nucleophile Adducts are Stable and Convenient Lewis Superacids

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Dedicated to the memory of Gerhard Maas.

Abstract:

Strong Lewis acids are essential tools for a manifold of chemical procedures that aim to react weakly basic centres but their scalable deployment is severely limited by their costs and safety concerns. We report that dicationic relatives of guanidinium can be conveniently synthesised in a two-step one-pot procedure from tetramethylurea. Triflic anhydride is used to generate an isouronium intermediate. Substitution of the bound triflate with pyridines yield the dicationic tetramethyldiiminium ditriflate nucleophile adducts (TMDINu). Their proposed diiminium character is demonstrated by substituting pyridine from the corresponding adduct with other nucleophiles. The observation of a chelation effect in the 2,2'-bipyridine adducts supports Lewis acidic character of the diiminium π-system and flexibility towards accepting another bond. High fluoride, hydride, and oxide affinities are demonstrated, leading to their classification as soft and hard Lewis superacids. An example reaction is reported which shows that the tetramethyldiiminium ditriflate pyridine complex (TMDIPy) is effective in the activation of electron-poor amines for amide couplings.

Main Text:

Lewis acidic reagents and catalysts are essential tools for the activation of basic functional groups, e.g., in esterification and amidation reactions, in the hydrogenation of carbonyls, and in the depolymerisation of polyesters (*1-4*). Trivalent boron and aluminium compounds are affordable and have a broad utility in this context (*5-8*). Divalent cationic nitrenium and tetravalent cationic phosphonium reagents are promising competitors (*9, 10*). Stronger reagents were generated based on structures isoelectronic to neutral trivalent boron centres such as silicon cations (*11-13*) and even phosphorous dications (*14, 15*). Efforts regarding carbon-based Lewis acids mostly focussed on trityl cations, wherein particularly the more acidic fluorinated examples are rarely isolable (*16-19*). The more reactive Lewis acids typically require inconvenient and costly procedures during their preparation and application. We envisioned generating Lewis superacids by utilising neutral leaving groups for interim stabilisation of one of the charges of carbodications. This enabled the synthesis of diiminium dications under mild conditions.

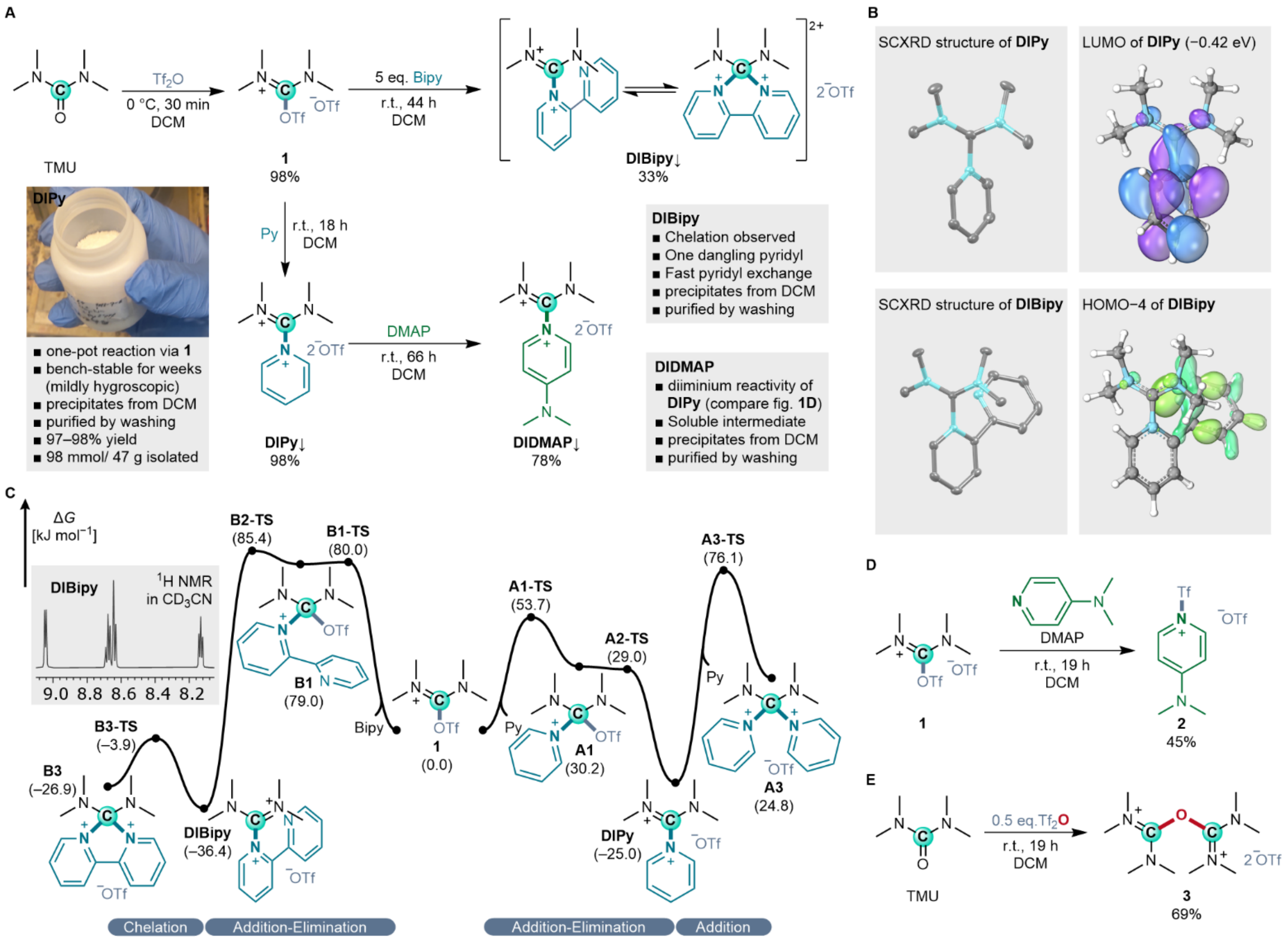
Even urea halides with their mediocre leaving groups can be used as synthetic equivalents for carbodications (*20, 21*). The π-stabilisation from the two nitrogen substituents leads to dissociation of one of the halides, even in the case of chlorides. This is also the case with isouronium salts such as **1**, which contain the same reactive formamidinium unit as their halide parents but bear better leaving groups. They can be generated with triflic anhydride directly from urea derivatives (Tf_2O, Figure 1A) (*22-24*). Seminal studies by Maas showed that isouronium anhydride **3** as access point to diiminium chemistry but they were not utilized as Lewis acidic reagents, which was discussed in more detail within this work (*25-27*). We report herein our findings on 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 were investigated computationally and in fluoride, hydride, and oxide abstraction reactions, the latter was applied in an amide coupling.

O-triflyl tetramethylisouronium triflate **1** was generated in a single step from commercially available tetramethylurea (TMU) with triflic anhydride in 98% yield (Figure 1A) (*22*). The salt **1** is a moisture-sensitive, viscous ionic liquid with a melting point of 19 °C. This salt appears to be mildly temperature-sensitive, showing “charring” at room temperature (r.t.) after a few days. Substitution of the bound triflate with pyridine (Py), which succeeds in a one-pot procedure directly from TMU, leads in an exergonic reaction to the precipitation of the salt **DIPy**. The suspension is filtered and washed with dichloromethane (DCM) to give the pure adduct **DIPy** in 98% yield which was upscaled to a 100 mmol scale (47 g). Maas synthesised **DIPy** by adding Py to Stang’s anhydride **3** (*22, 25, 26*). We were able to isolate **3** in an improved 69% yield with an increased reaction time (Stang reported 19%). The route to **DIPy** via **3** remains uncompetitive as it involves a sacrificial equivalent (eq.) of TMU, 2 eq. of Py, and the use of **3** enforced a more polar solvent choice (MeCN) which does not lead to the convenient precipitation of **DIPy** and a slightly lower yield (94%) (*25-27*). While mild hygroscopic behaviour was observed, **DIPy** did not show decomposition during benchtop storage and frequent use over one month. Hydrolysis restoring the TMU was observed in wet CD_3CN above 80 °C. Our computational model supported a simple addition-elimination mechanism (S_N2t) with a rate-determining initial association of Py with a free energy barrier of 54 kJ mol^{-1} (level of theory: DLPNO-CCSD(T)/aug-cc-pVTZ//PBEh-3c/def2-mSVP, solvation model: CPCM(DCM); a detailed description and references can be found in the supporting material). A barrierless dissociation of the triflate ion follows to give **DIPy** (overall −25 kJ mol^{-1}). Addition of a second Py molecule was strongly disfavoured (50 kJ mol^{-1}). Single crystal X-ray diffraction (SCXRD) shows C–NMe_2 bond lengths of 1.31 Å (1.307(2) Å and 1.312(3) Å) and a C–pyridinium-N bond length of 1.448(2) Å, which is shorter than average bond lengths in amines (1.47 Å) (*28*). Our model agreed within < 0.01 Å or 1° with all bond lengths and angles within the CN_3 unit and predicted no distortions > 0.01 Å or 1° when comparing the gas phase with solution models in DCM and MeCN.

It required 44 h and an excess of the donor 2,2′-bipyridine (Bipy) to form the adduct **DIBipy** in a poor yield (33%, Figure 1A). This can be expedited to only 1 h in a microwave (MW) at 100 °C (yield ~ 70%) but these more drastic conditions lead to the formation of minor impurities which we were not able to remove. The added driving force through precipitation of the product appears to be crucial, as this compound was inaccessible through the route via **3** in MeCN (*26*). A computed barrier of 40 kJ mol^{-1} separates the singly coordinated **DIBipy** from the doubly coordinated structure **B3**, which is just 10 kJ mol^{-1} less stable (Figure 1C). A few related carbodicationic Bipy adducts $[R_2C(Bipy)]^{2+}$ (R = H, Ph) are known (*29, 30*). No chelation effect was observed in these cases, which was supported by our model determining the chelated form of $[Ph_2C(Bipy)]^{2+}$ to be 147 kJ mol^{-1} more stable than the open form. 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 empty π–orbital at the diiminium carbon atom (Figure 1B). The structure of **DIBipy** was surprisingly rigid in the crystalline form with a distance from the diiminium C to the dangling pyridyl nitrogen atom of 261 pm being determined both at −153 °C (2.609(1) Å) and at 107 °C (2.612(3) Å). The orientation of the pendant pyridyl indicates the strong electrophilicity of the diiminium carbon atom, as steric considerations would suggest the opposite orientation. Only four resonances were observed in the ^{1}H nuclear magnetic resonance (NMR) spectrum (CD_3CN, 600 MHz, 26 °C) of **DIBipy**. Combined with the computational data, this supports fast exchange of the coordination sites via the doubly coordinated **B3**. The rotation barriers of the C–NMe_2 bonds were determined by variable temperature NMR in CD_3CN to be 54 kJ mol^{-1} which is significantly lower than in **DIPy** with 69 kJ mol^{-1} (modelled: 64 kJ mol^{-1}). Attempts to model the corresponding rotational transition state of **DIBipy** failed. But the determined barrier that is traversed during C–NMe_2 rotation from the chelate **B3** (55 kJ mol^{-1} from **DIBipy**) is in excellent agreement with the experiment which supports chelation as the main cause for the lowered rotational barrier. Aligning with the increasing weight of evidence that the concepts of coordination chemistry apply well to carbon better than previously assumed (*31-34*), we found here a classic chelation effect with one dangling pyridyl in fast exchange with the coordinated pyridyl.

Pyridine appeared to strike the ideal balance between a quick reaction with **1** and selectivity for the formation of the desired complex. This reaction appeared previously impossible as Maas described that **1** and similar compounds tend to triflylate nucleophiles rather than participating in substitution reactions (*23, 24*). Even 4-(dimethylamino)pyridine (DMAP), which is closely related to Py, attacked at the triflyl sulphur atom to give the *N*-triflyl DMAP triflate **2** (Figure 1D). A detour via **3** was also reported to enable the synthesis of **DIDMAP** but involves again a sacrificial eq. of the urea (*26*). Substitution of pyridine with DMAP succeeded smoothly in **DIPy** without triflylation and demonstrated enhanced diiminium reactivity over **1**. A soluble intermediate was formed almost instantaneously on addition of DMAP to a suspension of **DIPy** in DCM. The dicationic product **DIDMAP** precipitated and was isolated by filtration in good yield (78%).

Figure 1. Synthesis and structure of diiminium complexes **DINu**.

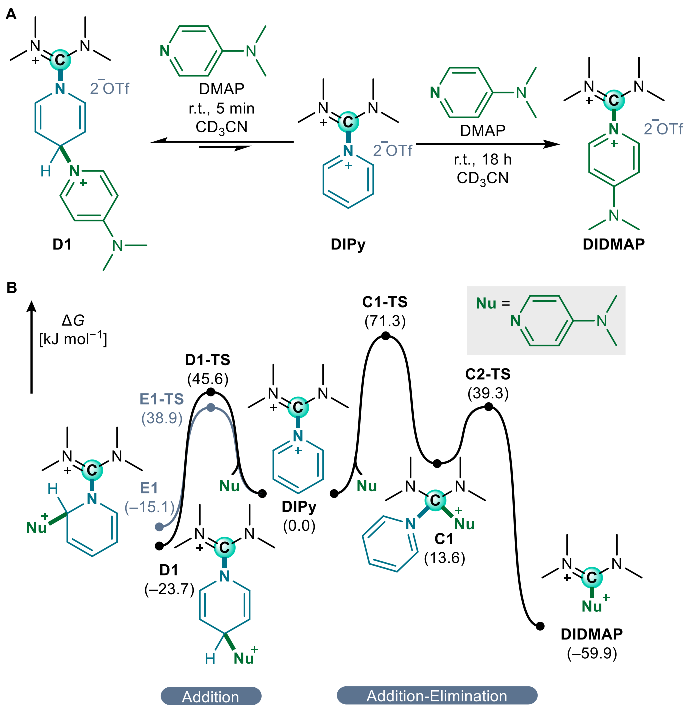


A, The synthesis of diiminium adducts **DIPy** and **DIBipy** succeeds from the isouronium salt **1**. **DIPy** can be used for coupling stronger nucleophiles than pyridine. Reactant additions were partially performed at decreased temperatures, see supporting information for details. **B**, Solid state structures of **DIPy** (and LUMO) and **DIBipy** (and HOMO) at 50% probability level. Hydrogen atoms are omitted in the SCXRD structures. **C**, Computed free energy profile of the reaction of **1** with Py (structures **A**) and Bipy (structures **B**). The inlay shows the aromatic region of the ^{1}H NMR spectrum (CD_3CN, 600 MHz) of **DIBipy**. **D**, As opposed to **DIPy**, **1** acts as triflylating agent when reacting with DMAP. **E**, Isouronium anhydrides **3** can be formed from **1** with remaining TMU.

Monitoring the reaction of **DIPy** with DMAP in CD_3CN by ^{1}H NMR showed the rapid formation of intermediate **D1** with broken pyridine-aromaticity (Figure 2A), an often favourable reaction in pyridinium salts (*35*). Minor amounts of the substitution product **DIDMAP** were already detected after 5 min; full conversion was seen 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 more stable *para*-adduct **D1** (Figure 2B). Equilibration by re-aromatisation under elimination of DMAP allows traversing of the rate-determining barrier of 71 kJ mol^{-1} (95 kJ mol^{-1} from **D1**) associated with the addition of DMAP to the diiminium carbon atom of **DIPy**. Elimination of pyridine gives the thermodynamic product **DIDMAP** (−60 kJ mol^{-1}). Maas reacted **DIPy** with the monoanions of several geminal CH-diacids which led to ring-opening of the pyridinium moiety under the formation of a double bond with the former Py-C2 (*26*, *36*, *37*). Only select methylene-active nucleophiles (e.g. the malonitrile anion $[HC(CN)_2]^-$) in combination with specific **DINus** lead to substitution at the diiminium carbon atom

(*26*). We could not detect any ring-opening reactivity with nucleophiles that do not allow the formation of a double bond. **DIPy** acted isoelectronic to trivalent boron compounds with their electron-deficient π-system but, after Lewis pair formation, was able to restore this isoelectronic relationship and a Lewis acidic character by elimination of the previously assumed base.

Figure 2. Mechanistic insights into substitution of pyridine with DMAP in **DIPy**.



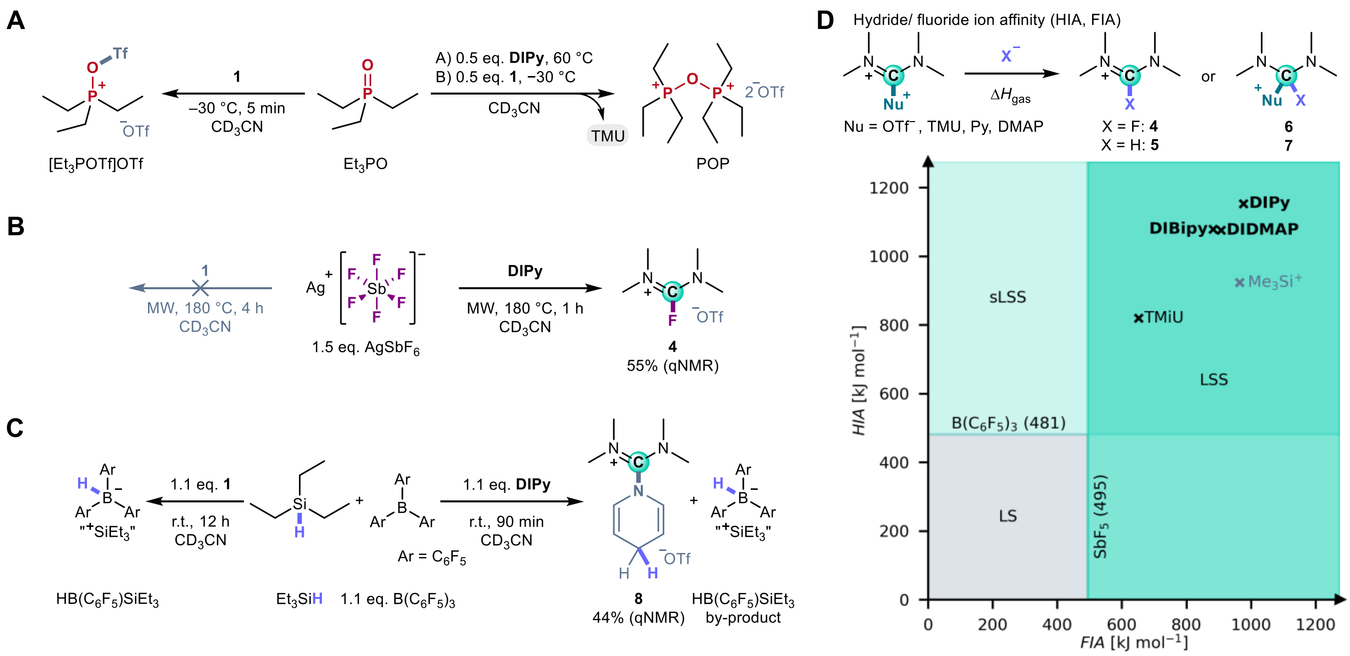
A, Monitoring the reaction of **DIPy** with DMAP by ^{1}H NMR monitoring allowed the observation of the *para*-addition intermediate **D1**, whereas the substitution product was found after 18 h. **B**, Computational reaction free energy profile of the three potential addition/ substitution reactions between DMAP and **DIPy** modelled in MeCN.

The ^{31}P NMR shift of Et_3PO shifts 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 (*38, 39*), we observed the formation of TMU from our reagents. **1** and **DIPy** both abstracted oxygen from Et_3PO leading to the formation of $[Et_3POPEt_3](OTf)_2$ (POP, Figure 3A). Some related reagents $[R_3POPR_3](OTf)_2$ were published in a work titled "Seeking the ideal dehydrating reagent" (known as Hendrickson reagents) (*40, 41*). Their dehydrating capability can be reasoned with the thermodynamically favourable formation of a P=O bond when they capture oxygen from a substrate. Triflic anhydride (experiments are described in the supporting material) or thionylium dications can promote the same transformation (*42*). **DIPy** reacted slower than **1** and needed a temperature of 60 °C rather than already reacting at −30 °C but **DIPy** led to a much more controllable process. **1** acted as triflylating agent and breaks down POP to form $[Et_3POTf]OTf$ when 1 eq. or more were present. Similar off-track reactivity was not observed with **DIPy**. Excess **1** also decomposed to a mixture of compounds when heated or reacted for prolonged periods, whereas no signs of decomposition of **DIPy** were visible after 18 h at 60 °C.

Lewis acids that can abstract fluoride ions from SbF_5 are considered Lewis superacids (LSA) (*5*). We were not able to observe fluoride abstraction from 1.5 eq. $AgSbF_6$ with **1** or **DIPy** at r.t. in CD_3CN. Heating the mixtures in CD_3CN in a microwave (180 °C, 1 h) showed that the pyridinium complex **DIPy** was a competent LSA. A yield of 55% of the tetramethylfluoroformamidinium triflate **4** (Figure 3B) was determined by quantitative NMR (qNMR). The thermal instability of **1** led to its decomposition without the production of significant amounts of the fluoroformamidinium **4**. Soft Lewis superacidity (sLSA) was probed by a competition experiment in which a minor excess of **DIPy** and $B(C_6F_5)_3$ (1.1 eq. each) were reacted with Et_3SiH at r.t. for 90 min in CD_3CN. 44% of the *para*-addition product **8** (determined by qNMR) were found with **DIPy** (Figure 3C). Increased reaction times or temperatures lead to a loss in yield. Substitution of Py with hydride at the diiminium unit to give the formamidinium **5** was computed to be exergonic but was not observed. This may be due a lack of a hydride shuttle mechanism after decomposition of the silyl cation. No formamidinium **5** was detected when using the isouronium salt **1**; it was outcompeted by the borane. The diiminium adduct **DIPy** was determined to be a competent soft and hard Lewis superacid whereas the isouronium salt **1** was ineffective in this regard.

To quantitatively determine the hard and soft Lewis acidities of the **DINu** salts, we computed gas phase fluoride and hydride ion affinities (*FIA*, *HIA*) according to Greb's and Krossing's scheme (*43-46*). The nucleophile-stabilised **DINu** were computed to show exceptionally high *FIA*s (907–982 kJ mol^{-1}) and *HIA*s (1079–1243 kJ mol^{-1}). All of them surpass the *HIA* of the trimethylsilyl cation, and **DIPy** surpassed even its *FIA* (Figure 3D) (*5, 45*). The isolable *meta*-hexafluoromethylated trityl cation as one of the strongest trityl-based Lewis acids, in comparison, has an *HIA* of 960 kJ mol^{-1} (*16*). Charge stabilisation both due to the +M effect in DMAP and donation of the dangling pyridyl nitrogen lead to similar slightly reduced *FIA* and *HIA* in **DIDMAP** and **DIBipy** compared to **DIPy**. The anhydride **3** was found to be very competitive with a placement on both scales between **DIPy** and **DIDMAP/DIBipy**. An associative mechanism (giving **6** and **7**) was favoured in gas phase enthalpies in almost all cases whereas free energies in solution predict dissociation of the donor to give tetramethylfluoroformamidinium **4** or the tetramethylformamidinium **5**, respectively.

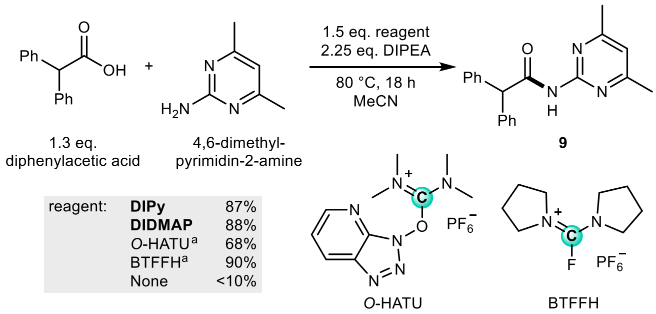
Figure 3. Gauges of the Lewis (super-)acidity of **1** and diiminium adducts **DINu**.



A, The attempted Gutmann-Beckett analysis showed that **1** and **DIPy** abstract oxygen from Et_3PO under formation of TMU. **1** acts again as triflylating reagent when used in stochiometric amounts or in excess. **B**, **DIPy** can abstract fluoride from $AgSbF_6$ while decomposition was observed with **1**. **C**, **DIPy** outcompetes $B(C_6F_5)_3$ in the hydride abstraction from Et_3SiH while no conversion of **1** was observed. **D**, Computational gas phase hydride and fluoride ion affinities (*HIA/XIA*) of the DINus **DINu** and the isouronium **1**. *XIA* [kJ mol⁻¹]: **DIPy**: 982, **DIBipy**: 883, **DIDMAP**: 907, **1**: 652, **3**: 919. *HIA* [kJ mol⁻¹]: **DIPy**: 1153, **DIBipy**: 1079, **DIDMAP**: 1243, **1**: 820, **3**: 1130 (dissociative to give **5**).

The DINus **DINu** are closely related to the successful guanidinium/isouronium-based peptide coupling reagents (including, e.g., the compounds dubbed as *O*-HATU, HAPyU, and COMU) (*47*). They typically feature anionic leaving groups. We expected the dicationic salts **DINu** with their neutral leaving groups to be more active reagents than these relatives for the activation of electron-deficient amines. The reaction of the bulky diphenylacetic acid with 4,6-dimethylpyrimidine in the presence of 1.5 eq. of coupling reagent and 2.25 eq. of diisopropylethylamine (DIPEA) after 18 h at 80 °C, indeed, gave isolated yields of the amide **9** of 87% with **DIPy** and 88% with **DIDMAP**. Only 68% were received with the commonly used *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium-hexafluorophosphate (*O*-HATU, Figure 4A). The use of *O*-HATU was also discouraged for its explosive properties (*48*). Bis(tetramethylene)fluoroformamidinium hexafluorophosphate (BTFFH) was previously introduced for tackling such problematic amide formations (*49-51*) We obtained 90% of the amide **9** with BTFFH under our modified conditions (88% were reported) (*49*). Both *O*-HATU and BTFFH, however, are relatively expensive. Both **DINu** performed comparably to BTFFH giving 87% (**DIPy**) and 88% (**DIDMAP**) of **9**.

Figure 4. Performance of **DIPy**, **DIDMAP**, *O*-HATU, and BTFFH in an amide formation with a bulky carboxylic acid and an electron-deficient amine. The amines were added, and heating was commenced, after stirring at r.t. for 30 min. [a] Reaction performed in DCM.



The presented diiminium nucleophile adducts are a group of conveniently available and handleable Lewis superacids with strong fluoride, hydride, and oxide abstraction properties. Our preliminary results combined with price and safety considerations suggest that they are competitive amide coupling reagents. We anticipate these reagents to find broad application through the development of derivatives and the investigation of their performance in the activation of further nucleophiles.

Data availability: The data that support the findings in this work are available within the paper and Supplementary Information. SCXRD structures are available at the Cambridge Crystallographic Data Centre under CCDC2203327–CCDC2203330.

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Additional information

Supplementary information: The online version contains supplementary material available at XXXXXXXXX.

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Figure Legends

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