Probing the Impact of Solvent on Lewis Acid Catalysis via Fluorescent Lewis Adducts

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ABSTRACT

Over the years, various multiparameter methods have been developed to measure the strength of a Lewis acid. However, a major challenge for these measurements lies in the complexity that arises from variables such as solvent and other fundamental interactions, as well as perturbations of Lewis acids as their reaction environment changes. Herein, we evaluate the impact of solvent effects on the Fluorescent Lewis Adduct (FLA) method using a series of representative Lewis acids. The solution-state nature of the FLA method in particular, offers the ability to correlate Lewis Acid Units (LAUs) obtained from the FLA measurement with chemical reactivity. The binding of a Lewis acid in various solvents reveals a measurable dichotomy between both polarity and donor ability of the solvent. While not strictly separable, we observe that, as solvent polarity increases observed LAUs increase; however, as solvent donor ability increases, the observed LAUs decrease. This dichotomy was confirmed by titration data and catalytic Diels-Alder
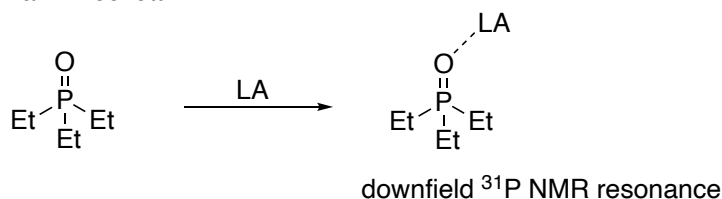
cycloaddition and hydrosilylation reactions, illustrating that solvation effects can be appropriately gauged by LAU values determined from the FLA method.
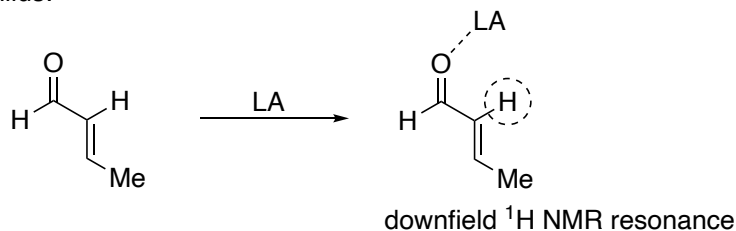
INTRODUCTION

Lewis acids have become essential throughout the chemical sciences, particularly in the field of catalysis[1-3] and organoelectronics.[4-6] The field of catalysis in particular, has seen great benefit from the emergence of frustrated Lewis pairs (FLP) and metal-free catalysis.[2,7-9] As Lewis acid chemistry begins to permeate other disciplines, the need for correlating the acceptor strength of a Lewis acid with their efficacies in their proposed application becomes vital. However, determining the specific reactivity of Lewis acids remains ambiguous, creating challenges in selecting an appropriate Lewis acid to achieve a desired reaction.[1] Currently, Lewis acidity cannot be described by a single measured property, and several parameters must be considered jointly in order to select a potent Lewis acid catalyst.[10-12] As such, multiparameter models based on spectroscopic and computational methods have been developed to quantitatively distinguish Lewis acidity, such as the Gutmann-Beckett method, the Childs method, ion affinity, and the global electrophilicity index (**Scheme 1**). However, these approaches may sometimes lead to inconclusive results depending on the applied method.[13-18]

Thus, we recently established a new methodology based on fluorescence spectroscopy to enumerate Lewis acidity, termed Fluorescent Lewis Adducts (FLA).[19,20] This method derives a basis for Lewis acidity by utilizing a series of fluorescent dithieno[3,2-*b*:2',3'-*d*]phosphole oxide Lewis base probes[21-23] that, when bound to a Lewis acid in solution, experience a bathochromic shift of their optical properties (**Scheme 1**).[19]
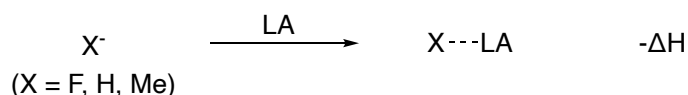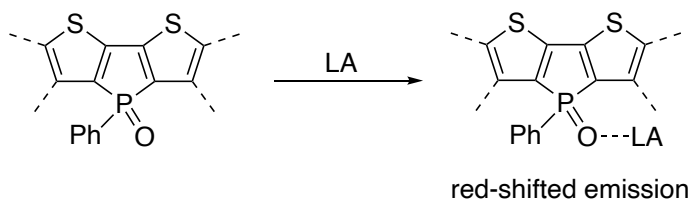
Gutmann-Beckett:

downfield ^{31}P NMR resonance

Childs:

downfield ^{1}H NMR resonance

Ion Affinity:

$$X^- \xrightarrow{\text{LA}} X\text{---}LA \qquad -\Delta H$$

(X = F, H, Me)

Global Electrophilicity Index (GEI):

$$\omega = \frac{\chi^2}{2\eta}$$

χ : Mulliken Electronegativity $\quad \eta$: Chemical Hardness

$\chi = -1/2(E_{HOMO} + E_{LUMO})$ $\quad \eta = E_{LUMO} - E_{HOMO}$

Fluorescent Lewis Adduct (FLA):

red-shifted emission

Scheme 1. Multiparameter models for measuring Lewis acidity (LA = Lewis acid).

The degree of the bathochromic shift is generally proportional to the Lewis-acid strength, as our method is based on the fact that Lewis-acid coordination alters the polarity of the exocyclic P=O bond with direct implications toward a lowered LUMO energy level, i.e., the π^*-system of the probe.[19,24] Similarly, by utilizing chromaticity, we incorporate a broad range of outer-sphere electronic permutations, allowing for a true "solution-state" measure, i.e., one that is more

consistent with the nature of the Lewis acid in solution than simply the measure of the impact to an isolated, 'naked' Lewis base itself.

The FLA method differs from typical Lewis-acid measurements in that it leverages the impact of the Lewis acid on several Lewis bases to determine the binding with an "ideal" Lewis base.[19,20] This affords the system high versatility, while the use of fluorescence and chromaticity specifically, affords a high sensitivity. Similarly, as this method can theoretically be performed in any solution, we refer to it as a "solution-state measurement". As long as the Lewis acid is not independently fluorescent, the FLA method provides the opportunity to gain important insight into the characteristics and reactivity of Lewis acids. Our initial proof-of-concept for the FLA method demonstrated its simplicity and sensitivity,[19] whereas in our subsequent paper, the robustness and broad scope was highlighted by expanding the library of measured Lewis acids to over 50 species, including both common and unique compounds that could not be measured by pre-existing methods.[20] These foundational contributions have provided a considerable step forward in developing the FLA method, allowing us to explore a variety of inherently dissimilar Lewis acids in an otherwise identical chemical environment. This approach provides a means for determining the *effective* Lewis acidity of a species in the given environment. Previously, the FLA method had been solely performed in toluene for its benign reactivity and the sufficient solvation of our probes and the many measured substrates. However, to provide true utility, we surmised that our method must also show robustness across varied chemical environments.

The solution-state measurements of the FLA method afford us the potential to measure how Lewis acids may differ under environmental changes, such as in the presence of additional donor species (including solvents) or varied polarity. We envisioned this to provide insight into the effectiveness of these Lewis acids in specific reaction environments and to allow us to correlate

the FLA measurement directly to catalytic efficacy in chemical reactions.[25,26] We now report the impact of solvent effects in the FLA method, showcasing the variability of Lewis acidity of a series of species due to different solvent environments. Furthermore, our methodology provides insight into additional aspects of Lewis-acid-catalyzed reactions and highlights some of the fundamental interactions and perturbations of Lewis acids as their reaction environment changes.

RESULTS AND DISCUSSION

Establishing the Impact of Solvent on the FLA Method

The FLA method utilizes multiple probes whose emission chromaticities span the commission international de l'éclairage (CIE) diagram (**Figure 1**).[20] In the context of this study, four probes (**1**, **2**, **7**, and **8**) were used to measure their respective emission profiles in varying polar solvents.[21-23] The selected solvents ranged in polarity from non-polar to polar based on the Dimroth-Reichardt $E_T(30)$ parameter; toluene (Tol, 33.9 kcal/mol), diethyl ether (Et$_2$O, 34.6 kcal/mol), chlorobenzene (PhCl, 37.5 kcal/mol), dichloromethane (DCM, 41.1 kcal/mol), and acetonitrile (MeCN, 46.0 kcal/mol).[27] Notably, the polarity of the respective solvents was found to by and large not affect the emissions of the probes (**Figure S1**). The lack of any notable solvatochromism with the Lewis base probes in the varying polar solvents enabled us to infer that any observed solvatochromism within the FLA method would be owed to the Lewis-adduct formation.
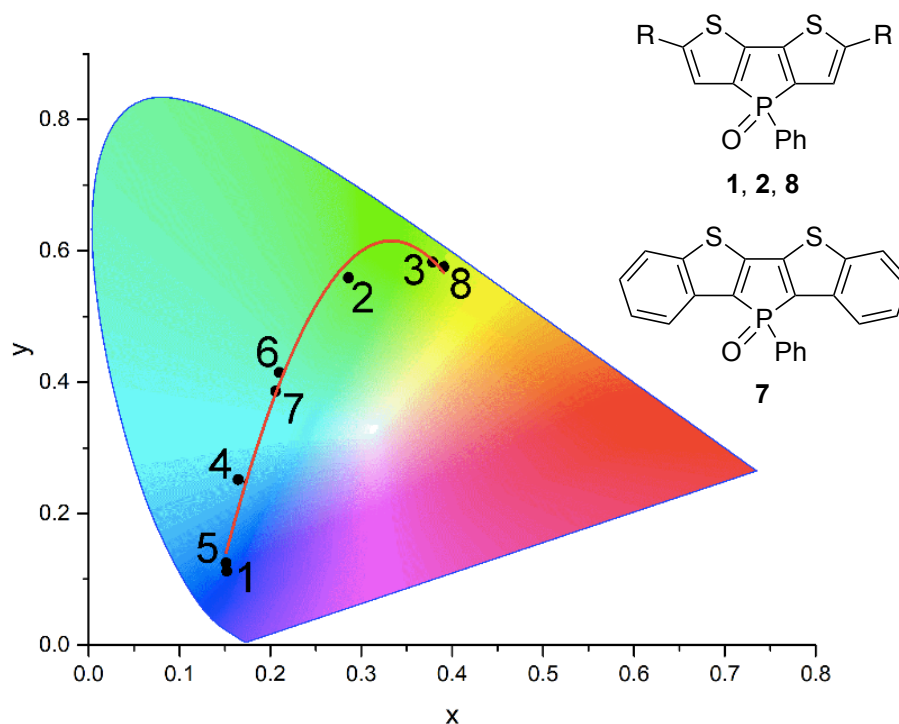
Figure 1. CIE diagram overlaid with the parabolic fit in toluene for eight dithienophosphole probes.[20] Probes **1**, **2**, **7**, and **8** were utilized in this study (**1**: R = H; **2**: R = Ph, **8**: R = 2-thienyl).

To explore the impact of solvent effects in the FLA method, we first selected $B(C_6F_5)_3$ as a representative Lewis acid due to its notoriety, as well as having generally served as a reference throughout our studies. Using our previously reported procedure,[20] the Lewis acid unit (LAU) values for $B(C_6F_5)_3$ in the various solvents were determined. In general, we observe increasing LAU values relative to the solvent polarity, as shown in **Figure 2** and **Table S3**. However, we also observe that the donor potential of the solvent can lower the LAU value as seen with Et_2O; utilizing a stronger donating solvent can allow for a more rapid generation of solvates, which limits the formation of the fluorescent Lewis adduct. For example, MeCN precluded formation of the FLA adduct with $B(C_6F_5)_3$ entirely, even with a large excess of Lewis acid, due to the strong Lewis acid-base adduct formed between the solvent and $B(C_6F_5)_3$.[28] To compare the donor potential of

the solvents chosen, we refer to the donor number introduced by Gutmann *et al.*, defined as the negative reaction enthalpy for the 1:1 adduct formation between the Lewis acid standard, SbCl$_5$, and the electron pair donor (EPD) solvents in 1,2-dichloroethane (0 kcal/mol).[29] The donor number measures the ability of a solvent to solvate the Lewis acid standard. The selected solvents used in this report ranged in donor ability from non-coordinating to coordinating; toluene (Tol, 0.1 kcal/mol), dichloromethane (DCM, 1.0 kcal/mol), chlorobenzene (PhCl, 3.0 kcal/mol), acetonitrile (MeCN, 14.1 kcal/mol), and diethyl ether (Et$_2$O, 19.2 kcal/mol).[29]
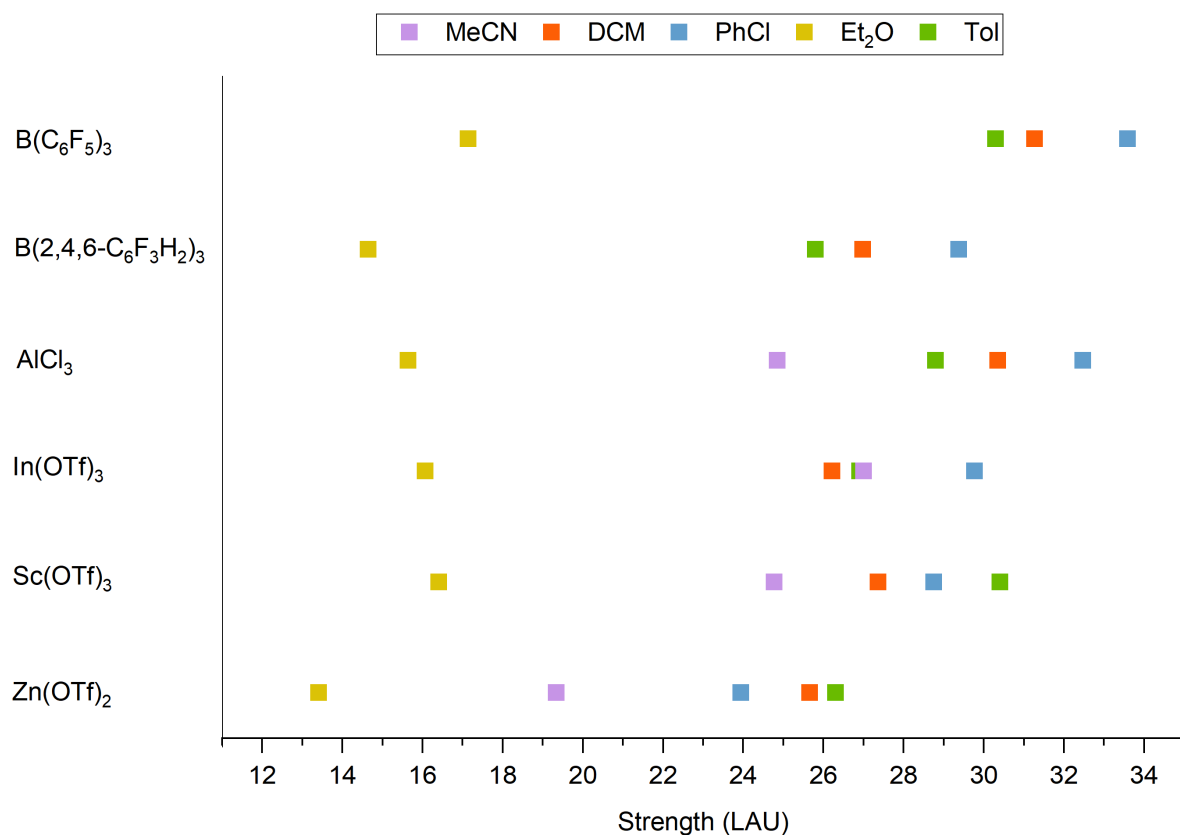

Figure 2. Lewis-acidity scale (in Lewis acid units, LAU) for: B(C$_6$F$_5$)$_3$, B(2,4,6-C$_6$F$_3$H$_2$)$_3$, AlCl$_3$, In(OTf)$_3$, Sc(OTf)$_3$, and, Zn(OTf)$_2$ in varying polar solvents.

To further elaborate the observed relationship between the FLA adduct and solvent in terms of polarity and donor potential, titration studies of $B(C_6F_5)_3$ against the probes **1**, **2**, **7**, and **8** were conducted in the various solvents.[30] The binding constants were determined from the concentration and the ratio of emission intensities of the adduct and the dithienophosphole oxide at equilibrium on the basis of **Equation S1**, and are presented in **Table S8**.[30] In toluene, the binding constant of probe **1** with $B(C_6F_5)_3$ was relatively large, $1x10^5$ M^{-1}, suggesting a strong interaction between the phosphoryl oxygen atom and the boron center. Upon introducing weakly coordinating solvents, such as DCM and PhCl, the binding constant lowered by nearly an order of magnitude to $\sim3x10^4$ M^{-1}. By employing an even stronger donating solvent, such as Et_2O, the binding constant lowered by another order of magnitude, $\sim3x10^3$ M^{-1}. In MeCN, however, no fluorescent Lewis adduct was formed and a binding constant could thus not be measured. As anticipated, the stronger the coordinating solvent, the weaker the binding constant and LAU value. For example, $B(C_6F_5)_3$ presented an LAU of 31.27 in DCM, 17.14 in Et_2O and was unmeasurable in MeCN. These results imply that the interaction between the Lewis-acid and Lewis-base probe becomes less prevalent in polar coordinating solvents. Polar solvents increase the *effective Lewis-acid strength* in solution, while strong donor solvents reduce or even quench the *effective Lewis-acid strength* by competing with binding to the Lewis acid. This dichotomy displays the complexity of Lewis acids, and the choice of solvent, an intuitive statement that our method now appropriately demonstrates in measurable terms for the first time.

In addition, the titration experiments conducted in diethyl ether specifically, afforded an intriguing perspective that arises from this dichotomy. Originally appearing anomalous, in the moderately coordinating solvent, a clear two-step equilibrium process was observed (**Figure S131**). Since, our FLA method consists of three components: a Lewis acid, a Lewis base, and the

solvent,[19] it is reasonable to propose that the interactions we observe are the difference in the binding of a free Lewis acid, and a solvated Lewis acid with the Lewis basic probe (**Scheme 2**).[31] The two-step equilibrium process was easily observed in the titration curves as two distinctly separate equilibria, specifically when utilizing the relatively weaker Lewis base **8**.[19,20] Upon increasing the relative donor strength of the dithienophosphole probe (via modification of the conjugated backbone), the rate of (a) increases (**Scheme 2**), resulting in an overlap in the measure of the two competing equilibria. Thus, utilizing the relatively strongest Lewis base probe **1**,[19,20] the two equilibria cannot be distinguished by the titration data. Although the competing reaction is occurring in solution, the rates have become so similar that they are nearly impossible to separate experimentally (**Figure S131**). These competing equilibria likely occur with other Lewis acids and solvent combinations; however, it may not be feasible to separate them.
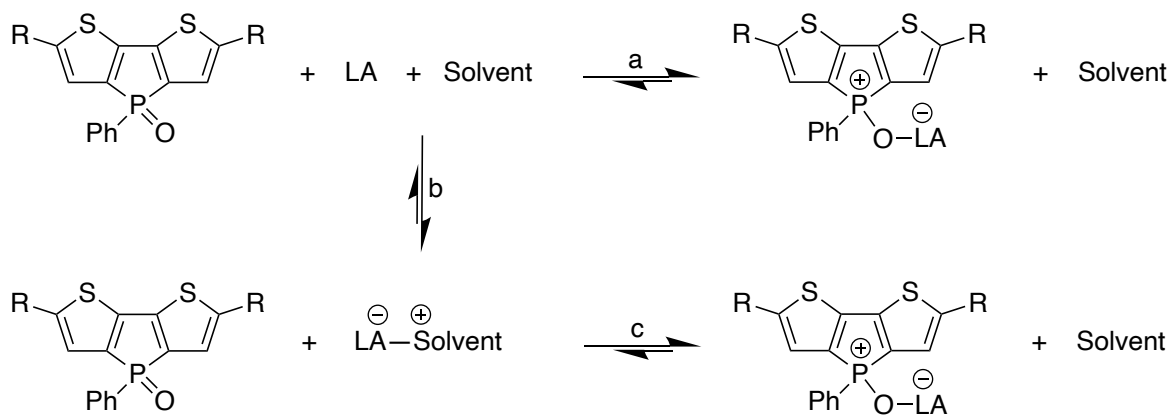
Scheme 2. Proposed competing equilibria during the formation of the fluorescent Lewis adduct (FLA). A stronger Lewis base (i.e., P=O) increases the forward rate of (a), while a stronger donor solvent (acetonitrile) increases the forward rate of (b). With a mild Lewis base and a mildly coordinating solvent such as Et$_2$O, (a) and (c) can both be seen and measured independently in part due to the slow rate of (b).

The initial focus conducted with $B(C_6F_5)_3$ in the varying polar solvents shed light on the dichotomy seen in the solvent properties of the FLA method. To further expand the scope on the variation of our methodology with respect to solvent effects, the following five representative Lewis acids were chosen based on their utility in catalysis: $AlCl_3$, $B(2,4,6-C_6F_3H_2)_3$, $In(OTf)_3$, $Sc(OTf)_3$ and $Zn(OTf)_2$.[19,32-37] The LAU values of these five Lewis acids were again determined using our previously reported procedure [20] and we observed the same trends as seen with $B(C_6F_5)_3$ in the different solvents. LAU values were generally found to proportionally increase relative to the polarity of the respective solvent, as shown in **Figure 2** and **Table S3**, whereas lower LAU values were observed with stronger donating solvents. As previously stated, these donating solvents allow for a more rapid generation of solvates, which limits the formation of the fluorescent Lewis adduct. The trends seen in the LAU values for these five different Lewis acids are consistent with the observed dichotomy seen in the titration studies with $B(C_6F_5)_3$.

In addition to the general trend presented above, we also observed that the magnitude of *polarity vs donicity* is strongly dependant on the Lewis acid strength. In the presence of a stronger Lewis acid, the LAU values tend to be more effected by the polarity of the solvent, whereas in the presence of a weaker Lewis acid, the LAU values tend to be more impacted by the donicity of the solvent. For instance, looking at $B(C_6F_5)_3$ and $AlCl_3$, which are considered strong Lewis acids in both the FLA method,[19,20] as well as other available current methods,[38,39] we observe higher LAU values in PhCl ($B(C_6F_5)_3$: 33.59 LAU and $AlCl_3$: 32.47 LAU) and in DCM ($B(C_6F_5)_3$: 31.27 LAU and $AlCl_3$: 30.35 LAU) compared to Tol ($B(C_6F_5)_3$: 30.25 LAU and $AlCl_3$: 28.89 LAU). However, when comparing the LAU values of a weaker Lewis acid, such as $Zn(OTf)_2$ we observed lower LAU values in PhCl (23.94 LAU) and in DCM (25.66 LAU) compared to Tol (26.48 LAU). After

analyzing the LAU scale with these six Lewis acids, we were able to clearly see that the strength of the Lewis acid can affect the magnitude of the solvent effect.

Thus, summarizing the impact of solvent on the LAU scale, we observe two key, yet not mutually exclusive, factors that influence measured Lewis acidity, the *polarity* and *donating potential* of the solvent.[27] However, due to the solution-state nature of our methodology, we propose that this distinction allows for an improved ability to determine the activity of a Lewis acid in a reaction based on solvent, potentially correlating the FLA measurements directly with catalytic reactions.

Validating the LAU Scale through Chemical Reactivity

The solvent study confirmed that the FLA method can measure the variance of a Lewis acid's acceptor ability in different environments, even those in which a competing equilibrium is occurring. To determine the value of this observation and the predictive potential of an LAU value with regard to chemical reactivity, we performed two Lewis-acid-catalyzed reactions to interpolate any correlation between catalytic activity and the FLA scale: Diels-Alder cycloaddition of 2,3-dimethyl-1,3-butadiene with methyl acrylate,[40] and hydrosilylation of benzophenone (**Scheme 3**).[41] These two reaction types are well established in the literature and are commonly used as representative examples in exploring Lewis acid catalysis. The progression of these reactions catalyzed by the same Lewis acids were monitored by ^{1}H NMR spectroscopy in the respective solvents.

Diels-Alder Cycloaddition

Hydrosilylation
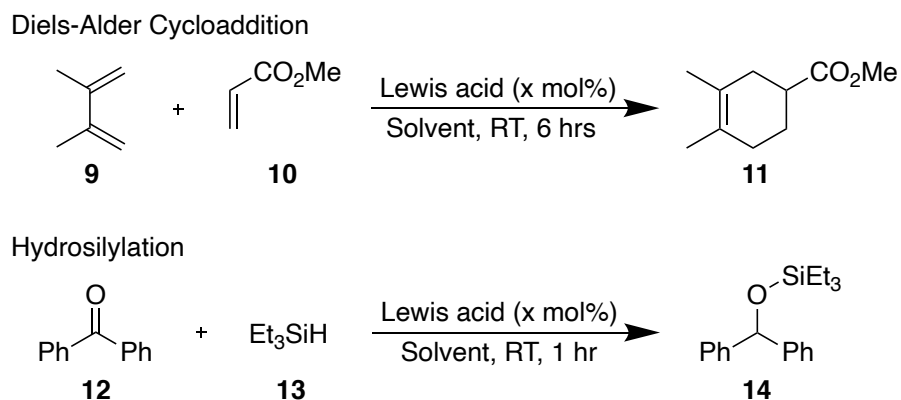
Scheme 3. The two representative Lewis-acid-catalyzed reactions used to interpolate any correlation between catalytic activity and the FLA method.

For the set of Diels-Alder cycloadditions, 2,3-dimethyl-1,3-butadiene (**9**) and methyl acrylate (**10**) were the chosen substrate combination to form the resultant methyl-3,4-dimethyl-3-cyclohexenecarboxylate (**11**). In the presence of 5 mol% AlCl$_3$, (**Table S9**), the progress of the reaction was significantly impacted by the polarity and donicity of the varying solvents, exemplified in **Figure 3**. The reaction in a more polar solvent progressed at a faster rate with a higher product conversion over 4 hours, while the coordinating ability of the solvent negatively influenced the progress of the reaction, demonstrated by a slower and lower product conversion over the same time frame. The results obtained from the Diels-Alder cycloaddition with AlCl$_3$ are as follows: DCM (87%, 30.35 LAU), PhCl (85%, 32.47 LAU), Tol (84%, 28.89 LAU), Et$_2$O (75%, 15.64 LAU), and MeCN (48%, 24.85 LAU).
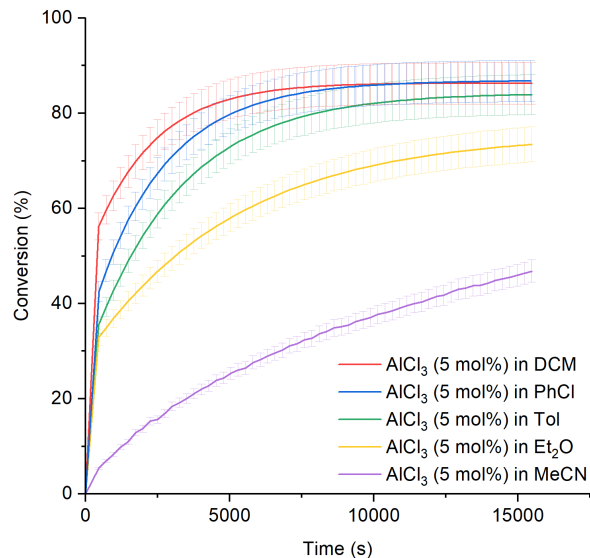
Figure 3. Product conversion in percent yield for the Diels-Alder cycloaddition over 4 hours with AlCl$_3$ as the Lewis acid catalyst in varying polar solvents.

Interestingly, the expected trend did not quite match for AlCl$_3$ in acetonitrile. When comparing the product conversion in the catalytic reaction to the LAU values in the FLA method, AlCl$_3$ in acetonitrile demonstrated a moderate LAU value (24.85), while in the Diels-Alder cycloaddition AlCl$_3$ in acetonitrile yielded a slower and lower product conversion (48% after 4 hours). The rate of the Diels-Alder cycloaddition can be greatly enhanced by polar organic solvents due to the stabilization of the transition state, however, if the donor ability of the solvent is stronger and has a greater potential to coordinate with the Lewis acid, the rate can be significantly lowered. The slight difference seen in the rate of the chemical reaction and the LAU value for AlCl$_3$ in acetonitrile may be the result of the predominant formation of solvated, monomeric AlCl$_3$, and the absence of other reactive species such as aggregates and mixed salt species.[20]

The FLA method affords a measure of the linear combination of all possible states of Lewis acid in solution, and therefore incorporates the potential mixture of solvents into the LAU value, to

represent the *effective* strength of the Lewis acid solution in the given application. While the FLA method can measure the averaged LAU value of all active Lewis acid species in solution, the catalytic reaction only accounts for the product conversion utilizing the free Lewis acid over a certain period. By employing a stronger donating solvent, such as acetonitrile, the Lewis-acid catalyst may be more prone to generate solvates, resulting in a lower amount of free Lewis acid being used to catalysis the reaction, thus leading to a slower reaction rate demonstrated by a lower product conversion.

To ensure the observed trends in $AlCl_3$ were not simply the result of the Lewis acid chosen, but instead a direct correlation to the FLA method, we explored the five other Lewis acids, $B(C_6F_5)_3$, $B(2,4,6-C_6F_3H_2)_3$, $In(OTf)_3$, $Sc(OTf)_3$, and $Zn(OTf)_2$ as catalysts under the same conditions. For $B(C_6F_5)_3$ and $B(2,4,6-C_6F_3H_2)_3$ (**Figure S134**) the same trends as for $AlCl_3$ were observed. Both the LAU values and the percent yield of product conversion in the Diels-Alder cycloaddition increased by solvent polarity and were lowered by donor ability; $B(C_6F_5)_3$: DCM (87%, 31.27 LAU), PhCl (83%, 33.59 LAU), Tol (80%, 30.25 LAU), Et_2O (72%, 17.14 LAU) and $B(2,4,6-C_6F_3H_2)_3$: DCM (20%, 26.98 LAU), PhCl (11%, 29.38 LAU), Tol (9%, 25.84 LAU), Et_2O (6%, 14.65 LAU).

To our surprise, the trend also holds for $In(OTf)_3$, despite evidently undergoing a retro Diels-Alder cycloaddition (rDA) (**Figure S133**); $In(OTf)_3$ is known to be a chemical activator for rDA reactions with certain dienes and dienophiles.[42] However, for $Sc(OTf)_3$, the reverse general trend was observed (**Figure S133**); *higher product conversion* was seen in *stronger coordinating solvents*; however, the LAU values did not correlate to product conversion. The results for $Sc(OTf)_3$ are as follows: MeCN (41%, 24.77 LAU), Et_2O (25%, 16.41 LAU), PhCl (21%, 28.75 LAU), Tol (16%, 30.37 LAU), and DCM (10%, 27.36 LAU). This deviation is likely due to

Sc(OTf)$_3$ losing a triflate moiety in coordinating solvents, en route to a stronger, cationic species that possibly remains coordinated to the product, de facto poisoning the catalyst.[35] Unfortunately, we were unable to make any comparisons with Zn(OTf)$_2$, as no product formation was observed in any of the solvents, likely due to both the insolubility and weak Lewis-acid strength of the zinc species.[19]

Nevertheless, a clear correlation between the LAU values and the product yield for the Diels-Alder cycloaddition was observed with the neutral boranes, AlCl$_3$, and In(OTf)$_3$. By increasing the polarity of the solvent, both the LAU value and percent yield increased, whereas in the presence of a stronger donating solvent, a decrease in LAU value and percent yield was seen. In general, the results obtained from the Diels-Alder reactions support our initial solvation studies, suggesting that the FLA method can accurately correlate LAU values to the solvent impact on catalytic activity.

We then investigated the hydrosilylation (**Table S10**) of benzophenone (**12**) with triethylsilane (**13**) as the chosen substrate combination toward triethyl(1,1-diphenylmethoxy)silane (**14**). For B(C$_6$F$_5$)$_3$ and B(2,4,6-C$_6$F$_3$H$_2$)$_3$, we observed similar results as seen in the Diels-Alder cycloaddition. The reaction progression varied significantly as a function of polarity and coordinating ability of the solvent (see **Figure S136**). On the other hand, we were unable to correlate our FLA method to "solution-state" measurements with the other four Lewis acids (AlCl$_3$, In(OTf)$_3$, Sc(OTf)$_3$, and Zn(OTf)$_2$). The latter is not surprising, given the well-established mechanism of borane-catalyzed hydrosilylation involving the coordination of the silane-H to the boron center as initial step, and the fact that these Lewis acids are generally not known to catalyze this reaction otherwise.[41,43]

The results obtained with the neutral boranes support our initial solvation studies and demonstrate that the solvent effect generally follows the impact measured by the FLA method (i.e., the LAU value). Thus, for a better, more solid comparison of Lewis acids, the following neutral boranes were applied in the reaction monitoring (**Figure 5** and **Table S3**): $B(C_6F_5)_3$, $B(p\text{-}C_6F_4H)_3$, $B(2,4,6\text{-}C_6F_3H_2)_3$, $B(3,4\text{-}C_6F_2H_3)_3$, and $B(4\text{-}C_6FH_4)_3$. As reported in the literature, the number and positioning of the fluorine substituents on the arylboranes have shown noticeable effects on Lewis acidity. Illustrated in our most recent paper,[20] the LAU values measured in toluene correlate well with the reported literature trends for Lewis acidity: $B(C_6F_5)_3$ (30.25 LAU) > $B(p\text{-}C_6F_4H)_3$ (29.23 LAU) > $B(3,4\text{-}C_6F_2H_3)_3$ (26.41 LAU) > $B(2,4,6\text{-}C_6F_3H_2)_3$ (25.84 LAU) > $B(4\text{-}C_6FH_4)_3$ (25.32 LAU). When applied in a specific solvent, such as dichloromethane, chlorobenzene, or diethyl ether, the trend was relatively the same as in toluene; the Lewis acid strength decreased in the following order: $B(C_6F_5)_3 \approx B(p\text{-}C_6F_4H)_3 > B(2,4,6\text{-}C_6F_3H_2)_3 > B(3,4\text{-}C_6F_2H_3)_3 > B(4\text{-}C_6FH_4)_3$ regardless of the solvent utilized.
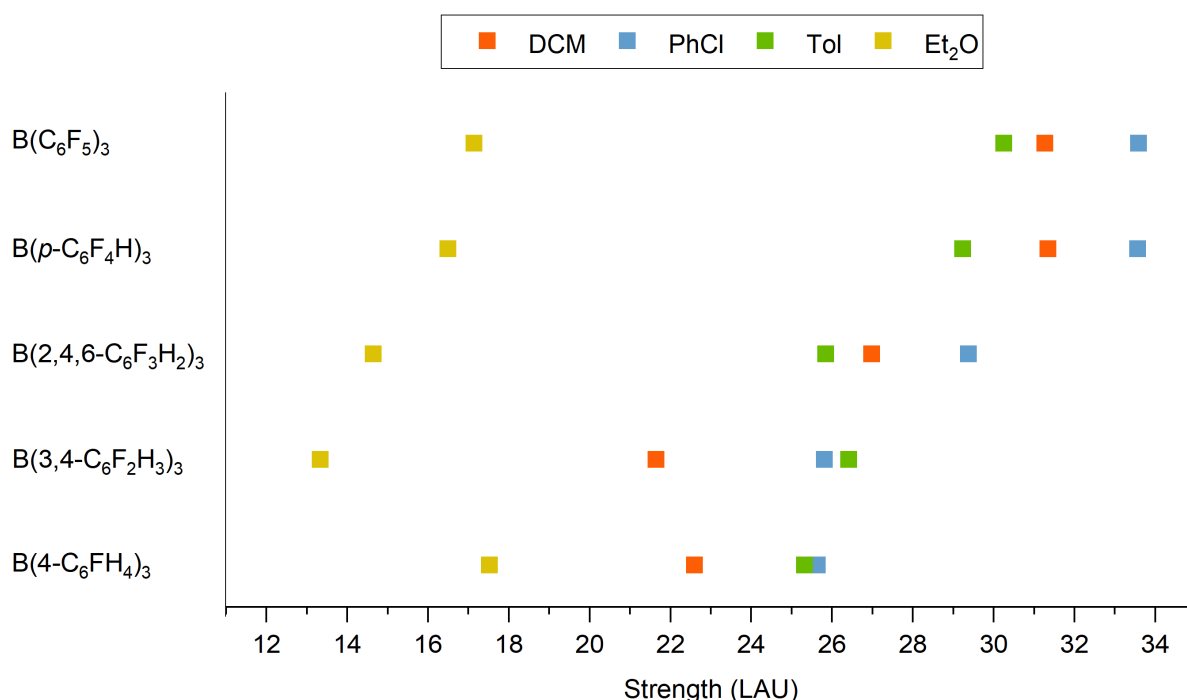
Figure 5. Lewis acidity scale measured in LAUs for following six Lewis acids: $B(C_6F_5)_3$, $B(p\text{-}C_6F_4H)_3$, $B(2,4,6\text{-}C_6F_3H_2)_3$, $B(3,4\text{-}C_6F_2H_3)_3$ and $B(4\text{-}C_6FH_4)_3$, in varying polar solvents.

Even with the decrease in the overall Lewis acid strength of the various arylboranes, the trend seen previously with $B(C_6F_5)_3$ showcasing the dichotomy of polarity and donor ability of the solvent was observed in the various neutral boranes with the exception of $B(4\text{-}C_6FH_4)_3$, due the formation of additional emissive species present in solution.[20] For instance, $B(C_6F_5)_3$ had an LAU of 33.59 in PhCl, 31.27 in DCM, 30.25 in Tol and 17.14 in Et_2O. The neutral boranes demonstrated higher LAU values in a more polar solvent, such as chlorobenzene, compared to a less polar solvent, like toluene, whereas the LAU values decreased in the presence of a more coordinating solvent, like diethyl ether, compared to a non-coordinating solvent, such as toluene. A clear correlation in LAU strength and solvent was seen with the neutral boranes, following in a decreasing order of $PhCl > DCM > Tol > Et_2O$.

Taken altogether, when applied to the Diels-Alder cycloaddition and hydrosilylation reactions, the LAU values proved to be consistent with the catalytic application of the Lewis acids in the respective solvent environments. For example, when monitoring the reaction progress of $B(p\text{-}C_6F_4H)_3$ in the Diels-Alder cycloaddition and hydrosilylation reactions in the various solvents, we observed higher product conversion in solvents with increased polarity, due to the increase in stabilization of the transition state in both reactions, whereas stronger donating solvents resulted in a slower product formation, shown in **Figure 6**. This trend holds consistently across the borane series while in the same solvent (**Figure S135** and **S137**): Slower reactions where a lower LAU value was measured, typically in stronger donating solvents, and faster reactions where higher LAU values were measured, with a weaker donating, but more polar solvent (see **Figures S134** and **Figures S136**). The results obtained from the Diels-Alder cycloaddition and hydrosilylation

reactions with the neutral boranes, reinforces our initial solvation studies and demonstrate that the solvent effect on Lewis acidity generally follows the impact measured by the FLA method.

A Diels-Alder Cycloaddition
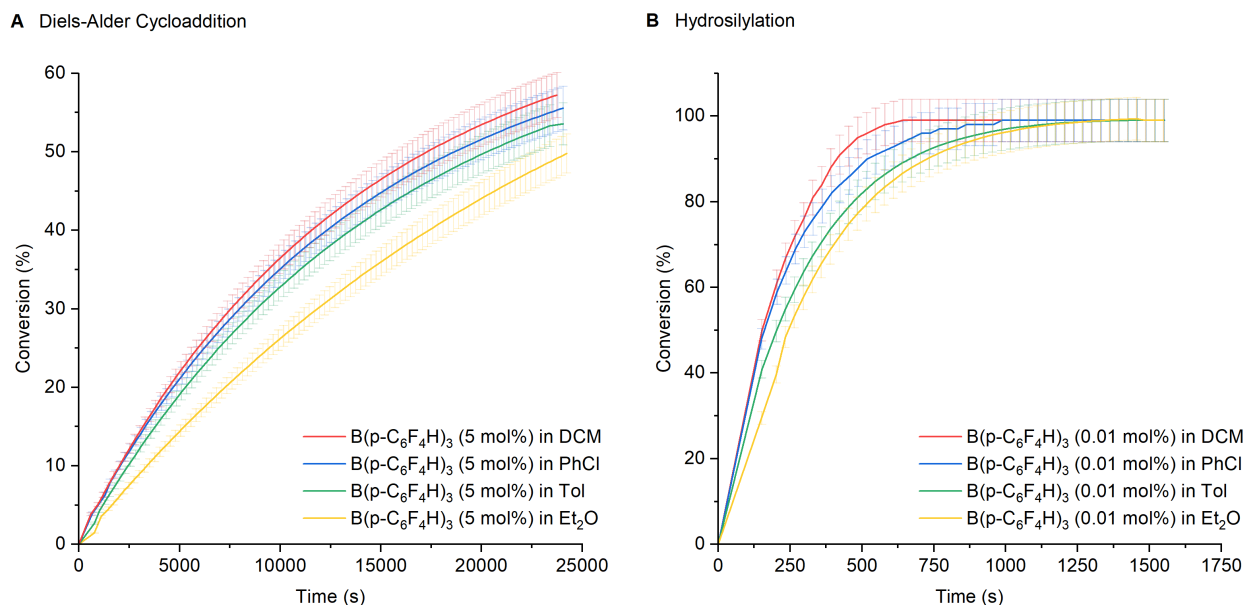
B Hydrosilylation

Figure 6. Product conversion in percent yield over time for the Diels-Alder cycloaddition (A) and hydrosilylation (B) of B(p-C$_6$F$_4$H)$_3$ in varying polar solvents.

Taking this into consideration, we finally sought to determine if an LAU value was universal, or in other words, does an LAU value for one Lewis acid in one solvent result in the same catalytic response as a different Lewis acid in a different solvent with the same LAU value? To probe this correlation, Lewis acids with similar LAU values were analyzed. We selected AlCl$_3$ in DCM (30.35 LAU) and B(C$_6$F$_5$)$_3$ in Tol (30.25 LAU). Both Lewis acids are considered relatively strong, based on other methodologies [38,39] and the FLA scale.[19,20] For our initial efforts, we focused on the Diels-Alder cycloaddition and observed after 3 hours an 86% yield for AlCl$_3$ in DCM and a 68% yield for B(C$_6$F$_5$)$_3$ in Tol, (see **Figure 7A**).

Despite nearly identical LAU measurements, we noticed that the rate of the reaction with $B(C_6F_5)_3$ in toluene did not proceed as quickly as $AlCl_3$ in dichloromethane, resulting in a 18% difference in product yield after 3 hours. As previously stated, polar solvents can help stabilize the transition state in the Diels-Alder cycloaddition, allowing the reaction to proceed at a faster rate. Since, dichloromethane is a more polar solvent compared to toluene, potentially the difference in solvent polarity is affecting the rate of the reaction. To elaborate on this concept, we then compared $AlCl_3$ in DCM (30.35 LAU) to $B(C_6F_5)_3$ in DCM (31.27 LAU) (**Figure 7B**). Although $B(C_6F_5)_3$ has a slightly higher LAU value, we were still able to see that in the presence of a more polar solvent like dichloromethane, the $B(C_6F_5)_3$-catalyzed reaction can proceed at a faster rate and yield a higher product conversion that is almost identical to using $AlCl_3$ in DCM ($B(C_6F_5)_3$ 85% and $AlCl_3$ 86% after 3 hours). We observed that the rate of the reaction was enhanced when carried out in a more polar organic solvent due to the stabilization of the transition state. This comparison suggests that the LAU values may be readable across the periodic table, and that catalytic ability of Lewis acids is not strictly due to strength alone, but other parameters such as solvent polarity and donicity need to be considered as well. The significant studies required to elucidate this are on-going and we hope to report these results in due course.
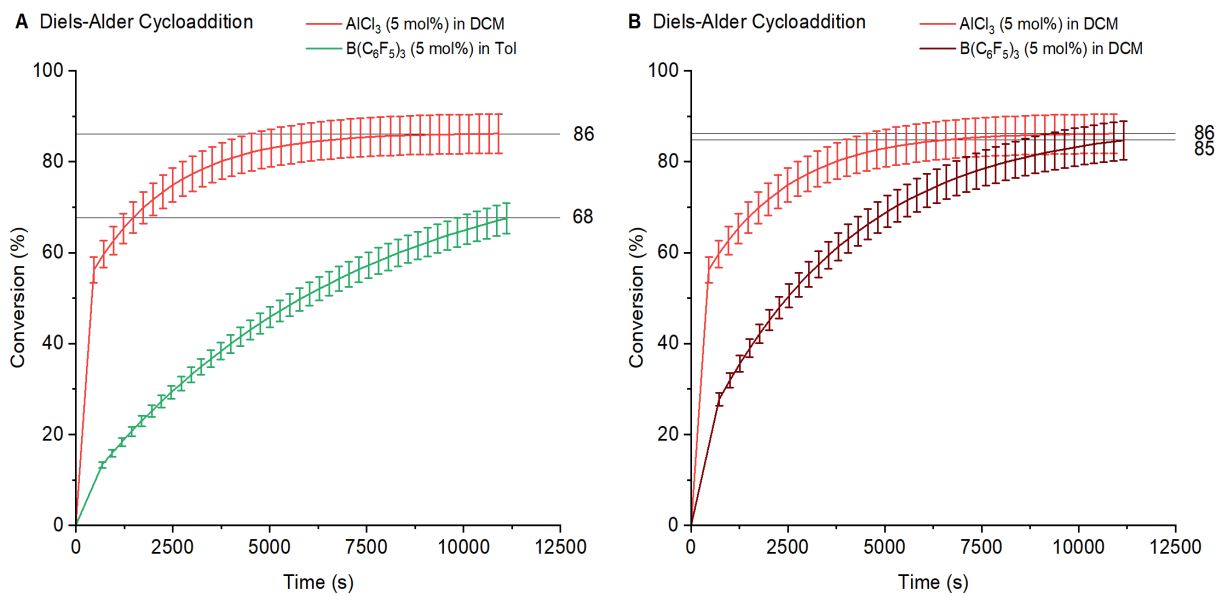
Figure 7. Comparable study of Lewis acids activity in the Diels-Alder cycloaddition with reported catalytic loadings and solvents utilized, monitored by product conversion rate in percent yield over time (3 hours).

CONCLUSION

In conclusion, we have demonstrated the impact of solvent on the FLA method and provided insights into predicting chemical reactivity. Two significant factors influencing the measured Lewis acidity in the FLA method are the polarity and donating potential of the solvent. In the presence of a more polar non-coordinating solvent, we observe higher LAU values compared to a less polar coordinating solvent. This trend generally holds true across varied Lewis acids and proves to be the case when measuring the catalytic ability of these species in varying solvents. Since, the FLA method is based on the binding affinity of a Lewis acid to a specific theoretical Lewis base in a particular solvent, we observed the binding of the free Lewis acid to the Lewis base probe. However, depending on the coordinating ability of the solvent, a complex equilibrium may be observed. This was specifically seen in the titration data with diethyl ether and a strong

Lewis acid. Two equilibria are present, and we hypothesize that the first equilibrium involves the free-Lewis acid, and the second equilibrium the solvated Lewis acid. This likely occurs in any donating solvent but was not always strictly separable in our measurements. In addition, the dichotomy seen in the FLA method can be observed in the chemical reactions conducted. As a result of the solution-state nature of the FLA methodology, we were able to provide insight into the effectiveness of these Lewis acids in specific reaction environments and demonstrate through reaction monitoring a correlation that links the FLA measurement directly to catalytic activity with very good accuracy.

Although the LAU scale in the FLA method correlated quite well when discussing catalytic efficiency of Lewis acids, there currently remain limitations to the method for it to be able to be truly predictive. While our method can be used to observe competing equilibria caused by solvation of a Lewis acid, and be used to discuss that effect on catalysts activity, it is limited strictly to binding of the Lewis acid, and not unbinding, which is vital in understanding how different Lewis acids behave differently in a catalytic environment, such as that using $Sc(OTf)_3$. Additionally, the method cannot account for deviating reaction mechanisms; for example the hydrosilylation of benzophenone is known to proceed using boranes, however, it is ineffective with other Lewis acids such as $AlCl_3$, $In(OTf)_3$, $Sc(OTf)_3$ or $Zn(OTf)_2$. This could only be predicted from prerequisite knowledge of the limitations of the reaction being performed and cannot be predicted by Lewis-acid strength alone. Nonetheless, the results of the binding of a Lewis acid, even as impacted by solvent, via both polarity and donor potential, and solvation can be appropriately gauged by the LAU value determined from the FLA method. To continue advancing the FLA approach into a more robust and practical method that can be used to predict chemical reactivity, we are further investigating approaches to measuring such discrepancies. We

are confident that the insights obtained in our study so far will further the understanding in predicting Lewis-acid reactivity and advancing the design and development of selective transformations relying on readily available Lewis-acid catalysts.

ASSOCIATED CONTENT

Supporting Information.

Experimental details, chromaticity data of all FLAs, emission and excitation data of all FLAs, catalytic reaction details and rate constants can be found in the Supporting Information online at

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ABBREVIATIONS

FLP, frustrated Lewis pair; FLA, fluorescent Lewis adduct; CIE, commission international de l'éclairage; LAU, Lewis acid unit; rDA, retro Diels-Alder cycloaddition.

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