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Brønsted Acid Catalysis

To Protonate or Alkylate? Stereoselective Brønsted Acid Catalysis of C–C Bond Formation Using Diazoalkanes

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aziridines · Brønsted acids · diazo compounds ·
homogeneous catalysis · stereoselective reactions

A new means to activate diazoalkanes has been discovered and applied broadly over the past few years. Brønsted acids, both achiral and chiral, have been used to promote the formation of carbon–carbon and carbon–heteroatom bonds with a growing number of diazoalkane derivatives. Aside from their straightforward ability to build structural and stereochemical complexity in innovative new ways, these transformations are remarkable owing to their ability to skirt competitive diazo protonation—a reaction that has long been used to prepare esters efficiently and cleanly from carboxylic acids. In cases where achiral Brønsted acids are used, high diastereoselection can be achieved. Meanwhile, chiral Brønsted acids can deliver products with both high diastereo- and enantioselectivity. More recently, systems have emerged that combine Brønsted acids and either Lewis acids or transition metals to promote carbon–carbon bond formation from diazoalkanes.

1. Introduction

Transformations of the diazo group have been developed steadily from the very beginning of organic chemistry over a century ago.[1] One of the earliest applications of the diazoalkane reagent (e.g. diazomethane) was its use as an alkylating agent for the carboxylic acid functional group [Scheme 1, Eq. (1)]. The simplicity of the reaction protocol, combined with the ease of removal of only dinitrogen as a coproduct, made for a transformation that was often reliable, chemoselective, and high yielding.[2] As a result, complex mixtures of natural product extracts were routinely treated with diazomethane to convert carboxylic acid components into their more lipophilic ester derivatives. Moreover, the simplicity of the reaction mechanism lent itself to adaptation by students of organic chemistry for many years: for example, proton transfer to the diazomethane carbon,[3] followed by collapse of the ion pair to form the ester and dinitrogen.[4] In addition to esterification, reactions of the diazonium ion formed by protonation of a diazoalkane have also been used productively in rearrangement reactions.[5,6]

Diazoalkanes have become key components of a powerful collection of methylene transfer and C–H insertion reactions.[7,8] Scheme 1 depicts an example of the latter: the intermolecular, enantioselective functionalization of *N*-Boc-protected piperidine [Scheme 1, Eq. (2)].[9] In the category of methylene transfer, enantioselective variants of olefin cyclopropanation reactions using diazo precursors can also be highly efficient [Scheme 1, Eq. (3)].[10] The intermediate metallocarbene species can also be guided to insert into X–H bonds (X = heteroatom), including that of an alcohol, thiol, or amine group.[11]

Complementary to these transformations—based on an initial direct reaction between the diazoalkane and metal—is non-redox activation of diazoalkanes using Lewis acids.[12] This strategy has certainly been exploited, but has matured more slowly as a field within organic synthesis.[13] The power of this strategy is fully present in the enantioselective synthesis of *cis*-aziridines by Wulff and co-workers [Scheme 1, Eq. (4)].[14,15]

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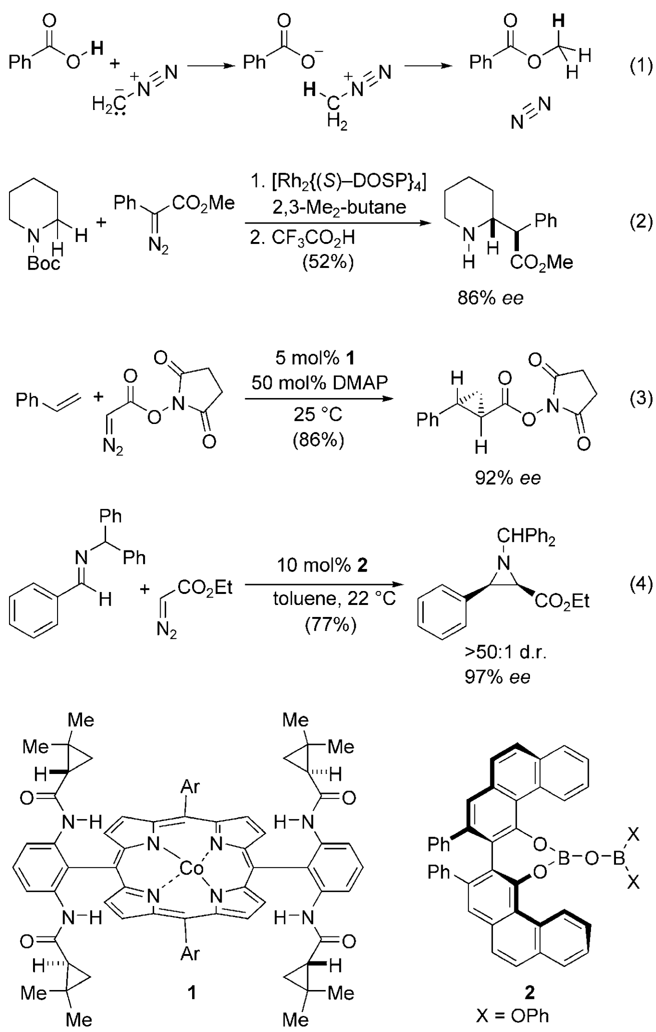

Scheme 1. Useful reactions of diazoalkanes. Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, *S*-DOSP = *S*-*N*-(*p*-dodecylphenylsulfonyl)prolinate.

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Hubert Muchalski, a native of Poland, received his BS/MS in chemistry from Wrocław University of Technology in 2006. He is currently a graduate student with Prof. Jeffrey N. Johnston at Vanderbilt University, where he has broadened the scope of the Brønsted acid catalyzed aza-Darzens and syn-glycolate Mannich reactions while exploring new reactions based on diazoimides.

Timothy L. Troyer received his BS in chemistry from Goshen College in 1996. Following a stint at Bristol Myers Squibb (CT), he began graduate studies with Prof. Jeffrey N. Johnston where he investigated the mechanism of the aza-Darzens reaction and developed a new Brønsted acid catalyzed syn-glycolate Mannich reaction. He received his PhD in 2008 from Vanderbilt University. He is currently an Assistant Professor of Chemistry at West Virginia Wesleyan College with interests in new organocarbenes and the isolation of bioactive natural products.

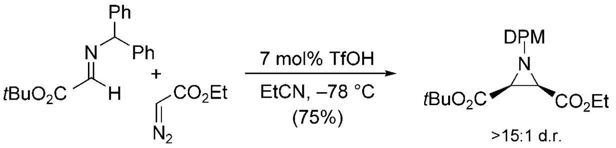
2. Brønsted Acid "Compatibility" with Diazo Compounds

With this historical backdrop, a diazoalkane was considered to be an unlikely candidate for development as a donor in transformations promoted or catalyzed by a Brønsted acid. Since 2004,[16] this perception has transformed both steadily and dramatically. This Minireview focuses on the range of advances made in recent years using Brønsted acids to activate electrophiles[17] toward carbon–carbon bond formation with diazoalkanes. Although the focus here is the diazoalkane, the rather surprising compatibility of strong Brønsted acids with other nucleophiles has also been discovered.[18,19] Even though the merits of organocatalysts that function solely by hydrogen bonding are readily accepted,[20] an understanding of the factors that affect the rate of proton transfer to the diazoalkane to form a C–H bond will be directly related to the pace at which new Brønsted acid promoted reactions will be developed. A diverse group of investigators have collectively identified a range of useful carbon–carbon bond-forming reactions amenable to Brønsted acid catalysis in this first five year period (2005–2009). In all of these cases, the activation mode can be viewed under the umbrella of Lewis acid catalysis, with the added challenge of avoiding competitive protonative decomposition of the diazoalkane that leads to alkylation [Scheme 1, Eq. (1)] or diazo coupling (e.g. ethyl diazoacetate→diethyl fumarate).

2.1. Brønsted Acid Catalyzed Additions to Azomethine

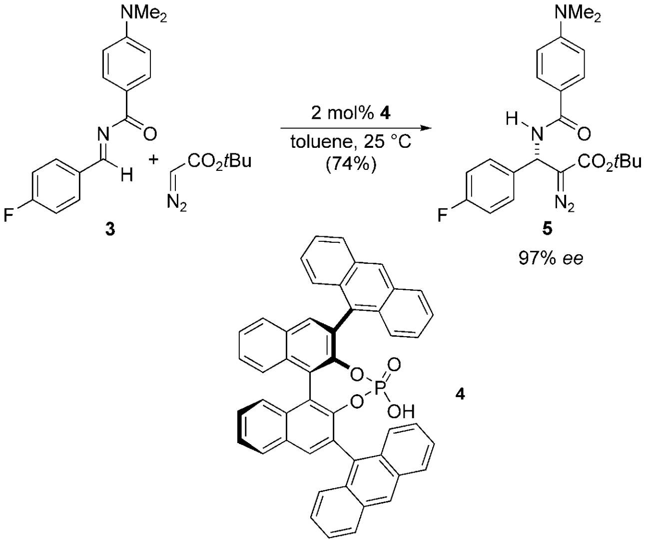
Our research group became interested in the development of Brønsted acid catalyzed carbon–carbon and carbon–nitrogen bond-forming reactions in parallel with the success of enantioselective catalysis by Brønsted acids. Although our motivation was the successful development of a chiral proton catalyst that functions through a polar ionic hydrogen bond,[21] we expected that considerable overlap would exist with catalysts functioning through polar, covalent hydrogen bond catalysis.[22,23] Furthermore, we sought transformations that build both structural and stereochemical complexity, and with the potential to underpin short, convergent syntheses of complex natural products.[24] Despite this motivation, it was immediately apparent that some strategic techniques germane to Lewis acid catalysis, such as the use of enolsilane nucleophiles, might not be compatible with a Brønsted acid catalyst.[25] As a result, we began our search for reagents that function as a latent nucleophilic carbon source in the presence of a Brønsted acid.

The work of Wulff and co-workers [Scheme 1, Eq. (4)] led us to the aza-Darzens reaction of ethyl diazoacetate with Schiff bases, as we perceived the boronate catalysts to be weakly Lewis acidic.[14a,b] Based on this assessment, we expected the activation barrier to the azomethine/diazoalkane reaction to be relatively low. Ethyl diazoacetate, in the absence of other reagents, dimerizes to diethyl malonate upon exposure to triflic acid. We soon found, however, that an imine can be activated toward reaction with ethyl diazoacetate using a rather strong Brønsted acid, namely triflic acid (Scheme 2).[16] *N*-Diphenylmethyl (DPM) imines derived from electron-deficient aldehydes provided short reaction times, high *cis*-diastereoselection, and good turnover in the production of aziridine,[26] which is the product of a formal [2+1] cycloaddition reaction. Despite the use of a strong Brønsted acid (TfOH) in these reactions, the iminium triflate is presumably the strongest acid at the reaction's earliest stage, and eventually becomes the aziridinium triflate as the catalyst begins to turn over. Meyer and co-workers have found this behavior to be more general by using substoichiometric amounts of *N*-alkyl pyridinium and viologen (*N*-alkyl or *N*-aryl) salts.[27] Although other Brønsted acids can effectively promote the reaction, triflic acid combines a high degree of Lewis acid strength with the practical conveniences associated with a liquid.



Scheme 2. Diastereoselective Brønsted acid catalyzed aza-Darzens reaction. Tf = trifluoromethanesulfonyl.

Not long after the discovery that even strong Brønsted acids could competitively activate imines relative to diazoalkane protonative decomposition, the Terada research group developed the first enantioselective carbon–carbon bond-forming reaction using *N*-acyl imines (Scheme 3).[28,29] Use of axially chiral phosphoric acid **4** in combination with benzoylated aryl aldimines, such as **3**, furnished the α-diazo ester **5** resulting from an addition/proton loss pathway. As the overall reaction is a net insertion reaction (of azomethine into the diazoester C_{α}–H bond), the chiral Brønsted acid can turn over in a catalytic cycle. Although the best enantioselection with chiral acid **4** was achieved with an imine bearing the electron-rich benzoyl group (as in **3**), there does not appear to be an electronic restriction within the aromatic aldimine substrate. Acylation of the imine nitrogen atom presumably serves two purposes. First, imine electrophilicity is inherently increased to assist activation by the chiral phosphoric acid, which is a much weaker Brønsted acid than triflic acid. Second, unlike the addition of ethyl diazoacetate to *N*-alkyl imines, the nitrogen atom of *N*-acyl imines does not evolve into a Brønsted base, thereby preserving the effective Lewis acidity of the system. Attenuation of the Brønsted basicity of the nitrogen atom further promotes turnover by the Brønsted acid catalyst. The proposed mechanism for this reaction involves the addition of the diazo "ylide" to the catalyst bound imine, thus leading to a discrete diazonium intermediate (**6**; Figure 1). Use of catalyst **4**, for reasons that are unclear, led to proton loss to reform the diazo functionality (**5**/**8**). This feature is both important, and perhaps underappreciated by the more casual observer, as the formation of products—believed to result from a 1,2-shift of an alkyl group (**9**) or a hydride (**10**)—are believed to be responsible for the formation of (achiral) dehydro β-amino acid coproducts (Figure 1).



Scheme 3. Phosphoric acid catalyzed enantioselective Mannich addition of α-diazo acetates to *N*-acyl imines.

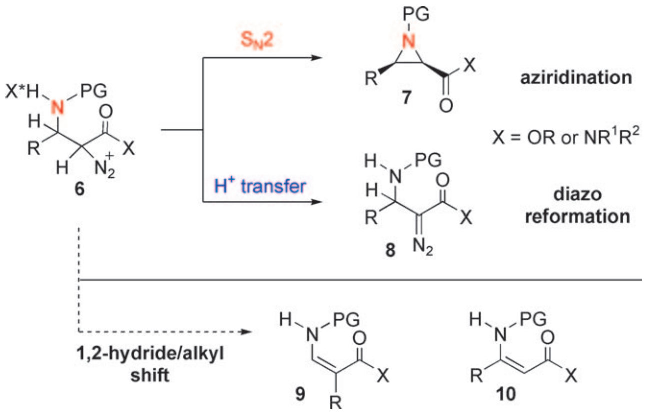
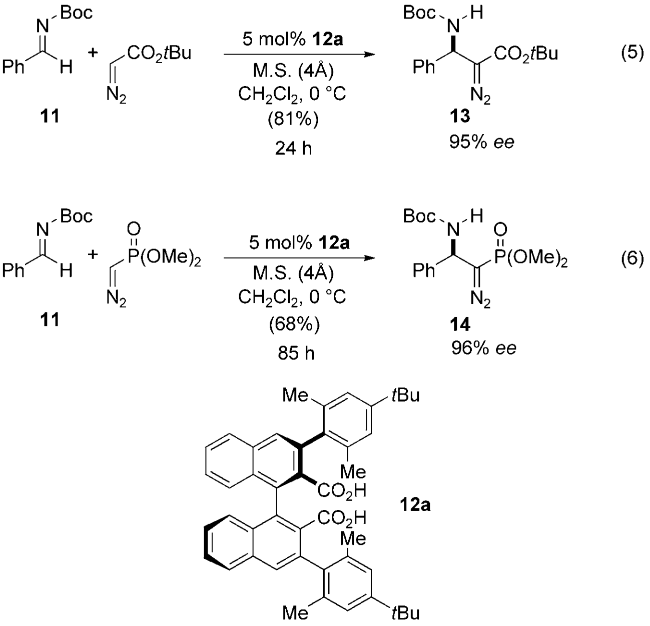


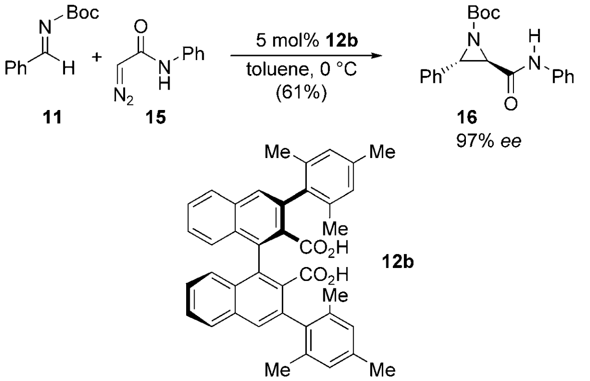
Figure 1. Divergent evolution of the putative diazonium intermediate to aziridine and α-diazo ester in additions of diazoalkanes to aldimines. PG = protecting group.

Hashimoto and Maruoka have identified similar behavior with axially chiral bis(carboxylic acid) **12a**, which is an effective promoter of Mannich additions of diazoalkanes to *N*-Boc-protected imines (Scheme 4). Like the system developed by Terada and co-workers, the catalyst is postulated to form a Lewis acid–imine complex that is more reactive as an electrophile than it is as a Brønsted acid toward the diazoalkane. Good enantioselection is observed within a range of electronically varied aryl aldimines.[30] Although a direct comparison to a chiral phosphoric acid was not provided, insight into reactivity could be gleaned by comparison of two diazoalkane donors. Addition of *tert*-butyl diazoacetate to *N*-Boc-protected benzaldimine **11** catalyzed by **12a** was complete within 24 hours [Scheme 4, Eq. (5)], meanwhile dimethyl (diazomethyl)phosphonate required a reaction time nearly four times longer to form adduct **14** [Scheme 4, Eq. (6)].[31] Nothing is yet known concerning the mechanism through which bis(carboxylic acid) **12a** activates the imine, particularly whether the carboxylic acid groups might work in concert to achieve maximum activation.[32] The efficacy of the carboxylic acid catalyst is interesting from a design standpoint, as it is likely to be similar to a phosphoric acid by measures of Brønsted acidity, but lacks the 'basic oxygen atom' often invoked by the research groups of Akiyama and Terada.[29] Furthermore, this Brønsted basicity of the phosphoric acid oxygen atom led Terada and co-workers to propose catalyst-mediated deprotonation of the putative diazonium ion intermediate **6**.[28] Also noteworthy is the observation that phosphoric acid **4** and bis(carboxylic acid) **12a** are axially homochiral but provide opposite enantiomers **5** and **13** with high selectivity. Again, a direct comparison is not available, but one would reasonably hypothesize that the azomethine substituent at the nitrogen center in **3** and **11** would not be solely responsible for the change in facial selectivity.



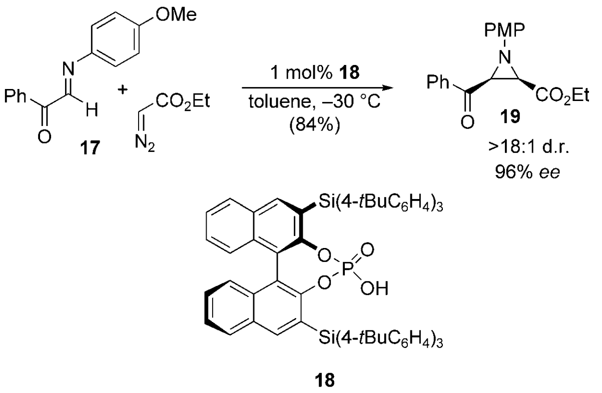
Scheme 4. Bis(carboxylic acid) catalyzed enantioselective Mannich additions with α-diazoalkanes. M.S. = molecular sieves.

As noted before [Scheme 1, Eq. (4) and Scheme 2], diazo ester donors have long been used as precursors to aziridines when using *N*-alkyl imines. In 2008, Maruoka and co-workers reported a Brønsted acid catalyzed enantioselective aziridination using *N*-Boc-protected imines.[33] In the context of the "Mannich" pathway as described above by Terada and co-workers, this selectivity for aziridination is remarkable. Additionally, this development is one of the few enantioselective aziridination reactions based on carbon–carbon bond formation in which the *trans* diastereomer is favored.[34] Good enantioselectivity was observed with high diastereoselection. These additions used an N−H α-diazo amide (**15**) for the first time, and it is notable that these transformations do not suffer from protonative self-decomposition as a result of the embedded N−H bond (Scheme 5). But based solely on the often written mechanism for these reactions (Figure 1), it is not clear why the putative diazonium intermediate evolves to the aziridine product instead of the diazo, as observed in the examples by Terada and co-workers. A possible explanation includes the decreased acidity that might be predicted for the α-diazonium amide **6** (X = NHPh) relative to α-diazonium ester **6** (X = O*t*Bu). Separately, the research groups of Akiyama and Maruoka suggest that the change in diastereoselectivity from *cis* to *trans* may be explained by a favorable hydrogen bond between substrates in the carbon–carbon bond-forming step, wherein the diazoalkane functions as a hydrogen-bond donor to the *N*-Boc-protected carbonyl oxygen atom. Alternatively, and more dramatically, a change in mechanism may be operative, wherein **6** may no longer exist as a discrete intermediate.



Scheme 5. Bis(carboxylic acid) catalyzed enantioselective *trans*-aziridination with α-diazo phenyl amide.

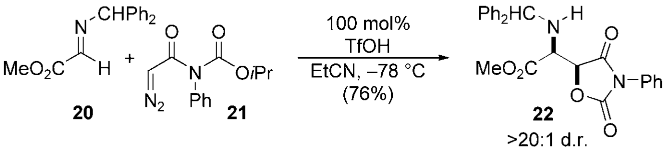
A significant advance was made recently by Akiyama et al.,[35] who reported the only new highly enantioselective aza-Darzens reaction since the seminal work of Wulff and co-workers.[14a,b] The addition of ethyl diazoacetate to electron-deficient aldimines was catalyzed by a chiral nonracemic phosphoric acid in good yield, diastereo-, and enantioselection (Scheme 6). In this brief report it was noted that the structure of the chiral phosphoric acid affected not only enantioselection and the favored antipode of the *cis*-aziridine



Scheme 6. The enantioselective, Brønsted acid catalyzed synthesis of aziridine developed by Akiyama and co-workers. PMP = *p*-methoxyphenyl.

product, but also the degree of formation of the vinylogous carbamate (**10**) that is often a coproduct of poor diazoalkane/imine couplings. Optimization of the reaction provided not only generality among a range of α-keto imines, but also a two-step, one-pot method beginning from the hydrate of the aromatic glyoxal starting material. The sense of enantioselection in this example is worth comment. If diazonium **6** is an intermediate common to the Terada, Maruoka, and Akiyama examples (Scheme 3, Scheme 4, and Scheme 6, respectively), the favored azomethine face is common to the latter two only, despite the use of homochiral catalysts and ostensibly similar aldimines. The reason for this stereochemical divergence is unclear, but exists as a potential tool with which to study mechanism and stereoinduction using catalyst design.

All of these reports manipulate the formation and decomposition of putative diazonium intermediate **6** (Figure 1). Proton loss reforms the diazo functionality, whereas aziridine ring formation by substitution at the diazonium carbon atom provides products in which two stereogenic centers have been created from prochiral imine and diazoalkane substrates. We have reported a new variation to complement these themes, thus providing access to amino alcohol backbones. Use of the novel α-diazo imide **21** in combination with triflic acid and α-keto imines **20** led to α-oxy β-amino acid derivatives (**22**) in good yield (Scheme 7).[36] The diastereoselection for this transformation was typically high (> 20:1) and favored the *syn* diastereomer. In addition to methyl-glyoxylate-derived imine **20**, aryl α-keto aldimines also provided good reactivity and high diastereoselection. Reactivity of alkyl α-keto aldimines remained high, but diastereoselection dropped to 4:1. Aryl aldimines were more sluggish, but provided good yields of isolated product and consistently good diastereoselection at 10:1. The diazoalkane donor **21** functions as a synthetic equivalent to a glycolate anion, and provides a new basis for the development of enantioselective variants. It is not yet clear whether addition product **22** was formed directly from a diazonium intermediate such as **6**, or whether aziridine was formed first, followed by its stereospecific ring opening.



Scheme 7. Addition of diazoimide promoted by Brønsted acid: a diastereoselective *syn*-glycolate Mannich.

2.2. Brønsted Acid Catalyzed Diazoalkane Additions to Carbonyl Groups: "Non-Roskamp" Pathways to C–C Bond Formation

Carbonyl group acceptors are almost entirely unprecedented in diazoalkane/Brønsted acid reports. Reported studies suggests that an inability to control the addition/cyclization (or alternatively, addition/proton loss) pathway relative to addition/migration might be responsible. Among the mainstays of aldehyde homologation is the $SnCl_4$-catalyzed addition of ethyl diazoacetate to aldehydes, which led to β-keto esters as reported first by Holmquist and Roskamp (Figure 2).[37] This reaction is believed to proceed through an addition/hydride migration route. Hossain and co-workers described trends across a range of Lewis acids and Brønsted acids, and revealed that in contrast to the selectivity for β-ketoester provided by $SnCl_4$, many other Lewis acids and $HBF_4{\cdot}OEt_2$ provided either low selectivity, or favored a 3-hydroxy acrylate product.[38]

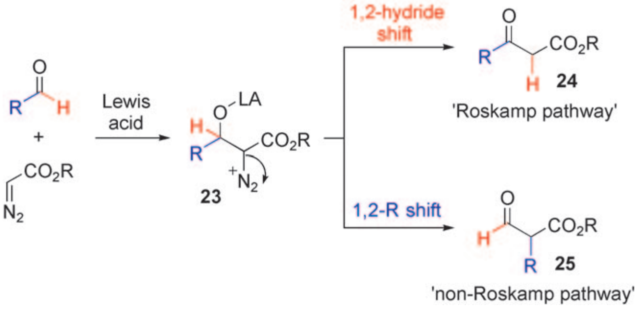
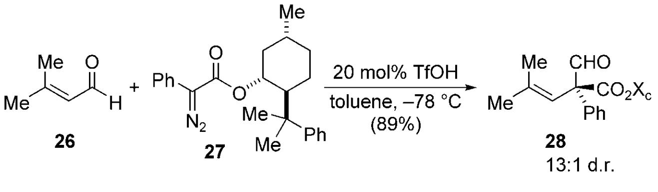


Figure 2. Lewis acid catalyzed addition of diazoester to aldehydes: divergent migration pathways from a common diazonium intermediate. LA = Lewis acid.

Assuming that this reaction proceeds in a stepwise manner, favoring 1,2-hydride migration from the intermediate diazonium ion (Figure 2), reactions that divert to alkyl migration would provide products resulting from a formal insertion pathway. A Brønsted acid promoted, diastereoselective variant was recently developed by Maruoka and co-workers and is depicted in Scheme 8. Within a brief screen of acids, including $BF_3{\cdot}OEt_2$, $MeAlCl_2$, and $TiCl_4$, triflic acid provided the highest yield of isolated product and the greatest preference for aryl group migration when using an aryl aldehyde.[39] Extension to a chiral α-diazo ester derived from (−)-phenyl menthyl (**27**), and the use of toluene allowed the development of a diastereoselective homologation reaction that led to aldehydes of type **28** (Scheme 8). The authors propose a model for stereoselection in which the phenyl ring



Scheme 8. Brønsted acid catalyzed addition to a carbonyl group: diazoalkane insertion with aldehydes. X_c = (−)-phenyl menthyl.

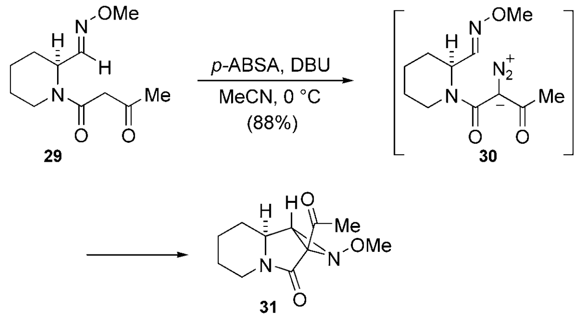
of the chiral auxiliary shields one face of the *s-cis*-diazoester carbon atom, thus leading to the diastereoselective formation of an intermediate diazonium (c.f. **23**). Hence, triflic acid not only provides the proper activation of the aldehyde, but also leads to a subsequent diazonium triflate that fragments smoothly to the β-keto aldehyde product with a high degree of selectivity and efficiency.

Based on the success of Brønsted acid catalyzed aza-Darzens reactions, one might reasonably expect that the synthesis of the Darzens epoxide from diazoacetate would be equally straightforward. Although this is not yet so, progress on this front was reported only recently by Gong and co-workers, who discovered a titanium(IV) binolate Lewis acid that promotes the highly enantioselective addition of an α-diazo acetamide to a broad range of aldehydes to produce the *cis*-epoxide products.[40] Furthermore, the addition of diazoacetate to ketone electrophiles has succumbed only recently through the use of an amino alcohol–zinc(II) complex. Enantioselection was generally moderate, but reached as high as 87 % *ee* for an aliphatic ketone (isopropyl methyl ketone, 20 % yield).[41]

2.3. Mechanism

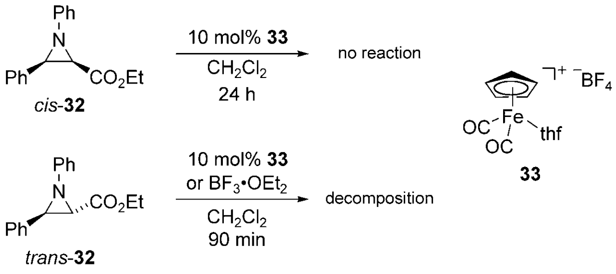
The advances summarized above were made largely despite the general lack of knowledge regarding the exact mechanism of these reactions. Consistent with Lewis acid activation, it is broadly assumed that diazoalkanes undergo addition to the carbon–heteroatom π-bond in the first step, thus leading to α-diazonium intermediates (e.g. **6**). From this common intermediate an aziridine moiety, α-diazo adduct, or rearrangement product (for X = N) can be formed. Whether any of these elementary steps is reversible is not yet known, although some information might be gleaned from studies of similar intermediates formed during Brønsted acid catalyzed decomposition of triazolines.[42] The effect of substrate substituents does appear to have coalesced, consistent with intermediates of type **6**, but exceptions to this behavior (e.g. Scheme 5) do exist, and might reflect the subtle interplay between timing of sequential bond formation, and/or the influence of the diazonium counterion on these relative rates. As noted above, divergent enantioselection and/or product selectivity when using catalysts that appear functionally and structurally similar (c.f. **4**, **12**, **18**) may indicate crossover between divergent mechanistic pathways.

The pathways outlined for Lewis acid catalyzed additions of diazoalkanes to imines are supported in part by the documentation of α-diazo and aziridine products from (thermal) intramolecular reactions. Wright and McMills observed a rapid conversion into aziridine when the intramolecular cyclization involved an oxime moiety (Scheme 9).[43] Under the basic conditions of diazo transfer, tricyclic aziridine **31** was formed in good yield. The intermediate diazo **30** could be characterized spectroscopically, although its rapid cyclization prevented its isolation.



Scheme 9. Spontaneous diazoalkane/oxime cycloaddition. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, *p*-ABSA = *p*-acetamidobenzenesulfonyl azide.

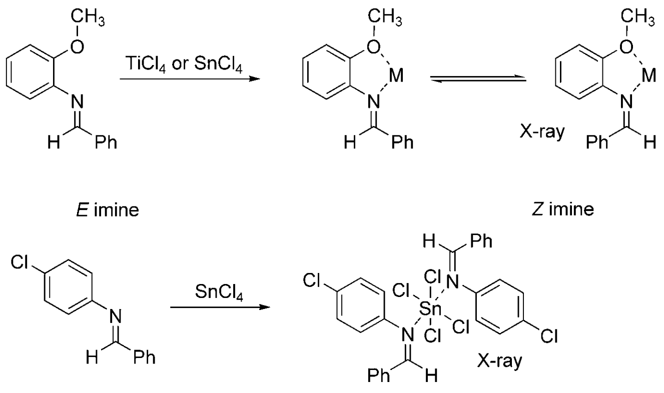
Our understanding of the factors affecting stereoselection is somewhat complicated by the numerous Lewis acid promoted reactions that provide complex product mixtures. Caution was prescribed by Hossain and co-workers when drawing conclusions from (apparent) highly selective, but low yielding, aza-Darzens reactions. A careful study of the reaction between *N*-phenyl benzaldimine and ethyl diazoacetate with the Lewis acid $[CpFe(CO)_2(thf)]BF_4$ (**33**) determined the reaction to be unselective at the aziridination stage (Scheme 10). However, the product mixture suffered from Lewis acid promoted decomposition of the *trans*-aziridine diastereomer (Scheme 10).[44,45] This combination resulted in apparent high *cis*-selectivity in some cases. It is unclear whether Brønsted acid variants suffer a similar sensitivity. Although the common vinylogous amide byproducts (**9**, **10**) can be produced by Brønsted acids, there have not yet been reports of selective aziridine decomposition by Brønsted acid. Moreover, the combined findings of the Maruoka (Scheme 5) and Akiyama (Scheme 6) research groups wherein high yielding, enantioselective *cis*- and *trans*-aziridination reac-



Scheme 10. Selective Lewis acid promoted decomposition of a *trans*-aziridine.

tions were developed, respectively, establishes that the compatibility can be quite high. But with ratios of aziridine/vinylogous amide often at 3–4:1 in these cases, the potential impact of selective catalyst-mediated decomposition of one aziridine diastereomer is not insignificant.

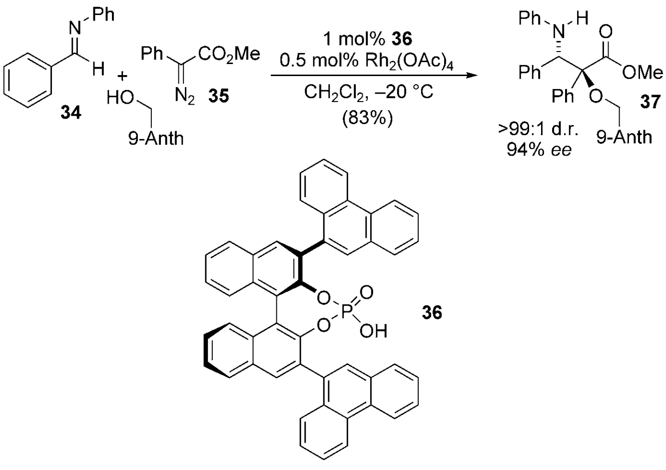
An additional consideration is the azomethine geometry in the catalyst-bound imine—an important prerequisite for the discussion of stereochemical models. Although most aldimines favor, if not exclusively, the *E*-imine geometry in solution,[46] they can isomerize to their *Z*-imine counterparts upon complexation to a Lewis acid. Tin(IV) and titanium(IV) complexes of imines have been crystallized and structurally defined by X-ray crystallography during the course of studies by Jørgensen and co-workers, who investigated the Lewis acid catalyzed aza-Darzens reaction (Scheme 11).[47] These complexes (equimolar Lewis acid/imine) furnished the *cis*-aziridine product upon addition of ethyl diazoacetate. Unfortunately, this level of thoughtful design and experimentation could not be developed into an enantioselective variant, as analogous complexes formed from chiral titanium(IV)–taddol (α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol) provided only racemic aziridine. To date, stereochemical models postulated in the literature for Brønsted acids do not appear to have invoked the imine E→Z isomerization.



Scheme 11. Lewis acid induced geometrical isomerization of aldimines.

2.4. Diazoalkane Activation Using Brønsted Acid Co-catalysis

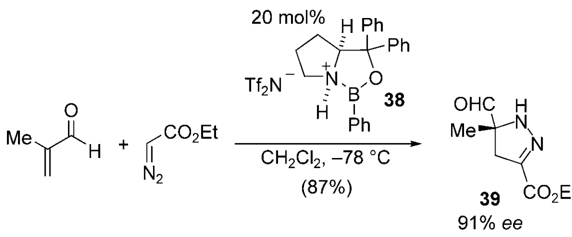
The potential compatibility of Brønsted acids with diazoalkanes has led to the application of multicomponent catalyst systems of transition metal and Brønsted acid to reactions involving diazoalkanes. In an example (Scheme 12) reported by Hu, Gong, and co-workers, rhodium(II) activated a diazoalkane **35**, and the intermediate rhodium carbene first underwent O–H insertion with an alcohol, followed by addition of a (putative) oxonium ylide to a chiral nonracemic iminium salt **34**·**36**.[48] The overall reaction yielded an *anti*-glycolate Mannich product **37** with high diastereo- and enantioselectivity. The level of rate control inherent to this transformation is more remarkable when considering the low concentration of the two catalysts (each < 2 mol %) working cooperatively to activate separate reactants according to the proposed mechanism. Control experiments suggested that the Brønsted acid **36** alone did not promote the reaction. The Brønsted acid strength also appeared to accelerate the carbon–carbon bond-forming pathway relative to O–H and N–H insertion, with stronger acids favoring the former, that can compete when using rhodium(II) alone.[49] It is unclear whether rhodium plays a role during the key stereoselective step.[50]



Scheme 12. Chiral phosphoric acid/rhodium(II) co-catalysis of a diazoalkane–imine addition.

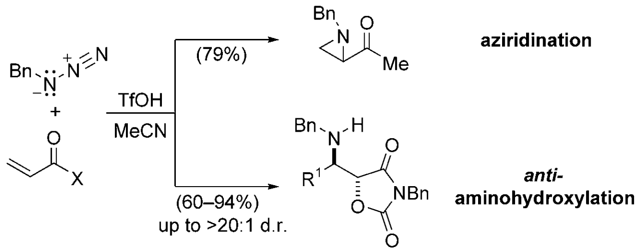
Cooperative Brønsted acid catalysis is not limited to transition metals, and activation of olefins toward diazoalkanes using a chiral Brønsted acid is a very recent accomplishment. In a study just reported, Ryu and co-workers enlisted a Brønsted acid to further activate the (main group) chiral oxazaborolidine Lewis acid (Scheme 13).[51] The authors have discovered that α-substituted enals can be activated by a triflic-acid-activated chiral oxazaborolidine toward α-diazoacetates. For example, methacrolein and ethyl diazoacetate reacted in the presence of catalyst **38** and provided pyrazoline **39** in 95 % *ee* and 86 % yield. Notably, the authors advance a stereochemical model that uses triflimide to activate the boron Lewis acid, and not the enal directly. This study provides evidence that cycloaddition can be more rapid than direct protonation of the diazo ester.

In addition to these new catalyst activation strategies, the recent rapid development of diazoalkane/Brønsted acid reactions suggests that new ylide donors may be ripe for development. By analogy, the azide functional group can be viewed as an "aza-diazoalkane".[52] Indeed, azides are competent donors when Brønsted acids are employed to activate electrophilic olefins. Azides can suffer similar protonative



Scheme 13. Brønsted acid activated Lewis Acid for the enantioselective dipolar cycloaddition of ethyl diazoacetate.

decomposition pathways,[53] and the acid-stimulated rearrangement of electron-rich azides to Schiff bases is the basis for a number of efficient reactions.[54] In 2004, we reported the Brønsted acid promoted azide/olefin route to aziridine derivatives (Scheme 14).[19] Additionally, unsaturated imide substrates bearing a participating oxygen atom yield to formal aminohydroxylation when activated by Brønsted acid toward electron-rich azide compounds (Scheme 14). The potential of this reaction to proceed through a triazoline intermediate has been the subject of more recent studies, and the stability of triazolines in the presence of triflic acid has been shown to be markedly dependent on both temperature and water (or similar Brønsted basic additives).[42]



Scheme 14. Azide/olefin reactions promoted by a Brønsted Acid. Bn = benzyl.

3. Summary and Outlook

This Minireview has enumerated the successes in development of a Brønsted acid promoted diazo additions to azomethine derivatives, but the corresponding additions to carbonyl compounds are absent beyond the aldehyde C–C insertion reaction by Maruoka and co-workers (Scheme 8). The recent finding by Gong and co-workers that a titanium(IV) binolate Lewis acid can promote the Darzens reaction using an α-diazo phenylamide with high enantioselection suggests that this too may change.[40]

The momentum continues to increase for the successful application of Brønsted acids to both known and new reaction types based on diazoalkane reagents. Although developments in this area have been based largely on hypothetical mechanisms, they now provide a basis set with which to answer the question: “Why is proton transfer to a diazoalkane carbon atom slow relative to the observed carbon–carbon/carbon–heteroatom bond formation?”. The answer may ultimately reside in a more critical evaluation of the relationship between a proton’s reactivity and its ligand(s). Also, insofar as Brønsted acids are ostensibly simple hydrogen bond donors, we have an opportunity to refine our understanding and description of the fundamental chemical behavior of the hydrogen bond.[23f]

Mechanistic uncertainties aside, the practitioner of synthetic organic chemistry cares first for the ease with which a large number of diverse, complex small molecules might be available in “one pot” from commercially available materials. It is clear that consideration of putative intermediates **6** remains a fertile ground for the development of new chiral small molecules available from a rather small group of diazo- and azomethine reagents. Awareness and development of diazoalkane reactions promoted by aprotic Lewis acid might assist with prognostication of the field’s future development, as these activating agents do not immediately provide the diazoalkane substrate with a protonative decomposition pathway. The focus of this report is the compatibility of diazoalkanes with Brønsted acid catalysts. However, advances in the understanding of azide compatibility with Brønsted acids,[42] as well as others,[18] suggest that numerous innovative opportunities will soon come to light.

4. Addendum

After submission of this manuscript, Wulff and co-workers[55] presented evidence for a boroxinate-based Brønsted acid derivative of VAPOL ((2,2’-diphenyl-[3,3’-biphenanthrene]-4,4’-diol) as the active catalyst in asymmetric aziridination of imines [Scheme 1, Eq. (4) and Ref. [14]]. Additionally, Hu and co-workers reported a highly diastereoselective synthesis of β-aryl isoserine derivatives using a rhodium-catalyzed three-component reaction of ethyl diazoacetate, water, and aryl imine.[56]

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