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Perspectives on Intermolecular Azomethine Ylide [3+2] Cycloadditions with Non-Electrophilic Olefins

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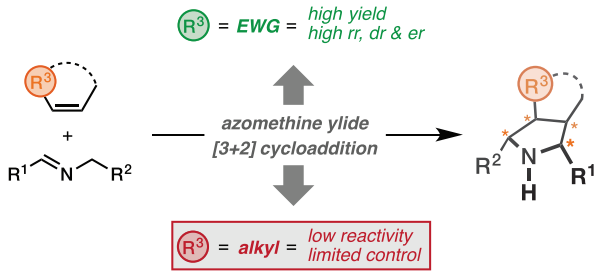
Dedicated to Prof. Paul Knochel.



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Abstract Our interest in the synthesis of compact nitrogen heterocycles from abundant sources has motivated a critical analysis of the status in azomethine ylide chemistry. Despite the outstanding developments in catalytic enantioselective [3+2] cycloadditions, these are still limited to electron-poor olefins. Only a few examples can be found in the literature that report on cycloadditions using non-electrophilic alkenes and those are compiled herein. With this account we aim to extract lessons and challenges that will inspire future breakthroughs in this area.

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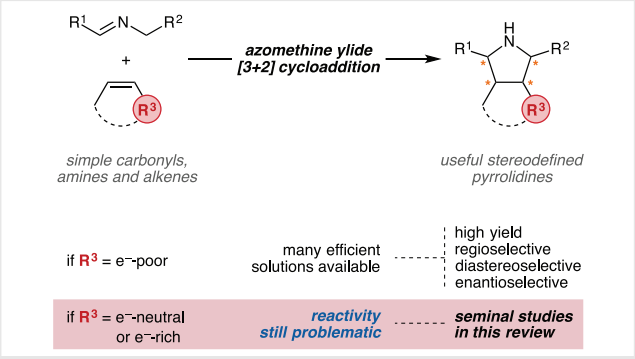
Key words heterocycles, pyrrolidines, anionic cycloaddition, azomethine ylide, catalysis

Dr. Abraham Mendoza was born and raised in Gijón, a city in the beautiful coast of Asturias (Spain). He obtained his B.Sc. and Ph.D. degrees in Chemistry (2009) at the Univ. of Oviedo with Profs. J. Barluenga, F. J. Fañanás, and F. Rodríguez. He was awarded a Fulbright Fellowship (2010–2012) to join Prof. P. S. Baran at The Scripps Research Institute and then returned to Europe as a Marie Curie Fellow (2012–2013) at the University of Cambridge with Prof. M. J. Gaunt. In late 2013, he started his independent career at Stockholm University as a Junior Researcher of the Swedish Research Council and became a member of the Berzelii EXSELENT Center on Porous Materials. His group is currently pursuing scalable and automatic synthetic methods involving C–H functionalization, oxidative coupling, and main-group organometallic photochemistry.

1 Introduction

Pyrrolidines are ubiquitous heterocycles with unique properties, which make them essential both in natural and artificial molecules alike. In organic synthesis, these heterocycles have been central in the development of fundamental carbonyl chemistry and have given birth, for example, to potent organocatalysts,[1] oxazaborolidine Lewis acids,[2] and important ligand classes.[3] As a result, synthetic methods to access pyrrolidines from abundant sources are instrumental to explorations across disciplines. The most direct and strategic way of assembling densely functionalized pyrrolidines is the [3+2] cycloaddition between imines and alkenes (Scheme 1).[4] The abundance and modularity of these starting materials enable succinct routes to new diverse pyrrolidines otherwise unavailable. As a result, sustained efforts over time have been invested to advance these reactions.[4] Interestingly, still today a vast portion of abundant olefin classes have eluded participation in this chemistry, thus pointing to unsolved fundamental challenges that we illustrate in this account.

The deprotonation of imines is the most common source of azomethine ylide intermediates in [3+2] dipolar cycloadditions with olefins.[4] This reaction is remarkable as



Scheme 1 Scope of this review

it generates two carbon–carbon bonds and possibly four stereocenters in a single transformation. Not surprisingly, this process has attracted the attention of leading research groups worldwide, which has expanded its features over decades. These advances have been scrutinized in a consistent stream of seminal reviews.[4] In these articles, it becomes evident that electron-deficient alkenes are the most widely studied class of substrates, which often produce high chemical yields in a regio-, diastereo-, and enantioselective fashion.

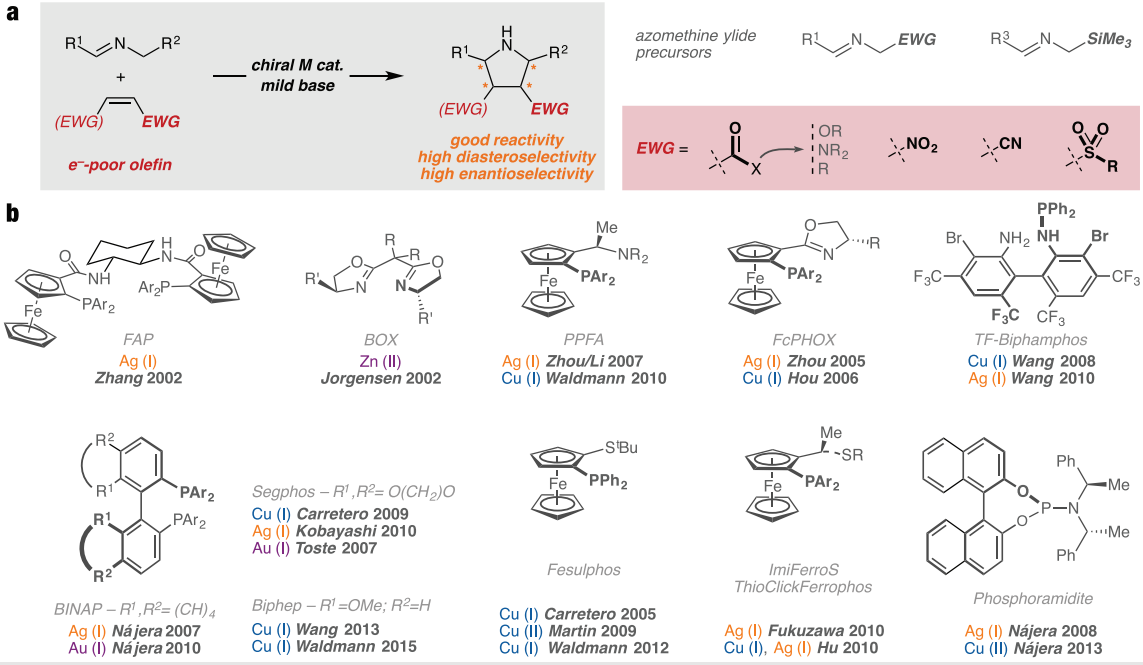
Beyond these outstanding developments, *the focus of this account is to compile the relatively rare precedents in which non-electrophilic alkenes have participated in azomethine ylide [3+2] cycloadditions.* If this challenge would be met, the synthesis of otherwise inaccessible nitrogen heterocycles (i.e., new ligands) would be available in one step from ubiquitous sources.[5] On the occasion of the 51st Bürgenstock Conference on Stereochemistry, hereby is presented an analysis of the scholarly literature at the reactivity frontier of these cycloadditions that ventures to inspire future research in this area.

2 State-of-the-Art Using Electron-Poor Olefins

The importance of pyrrolidines has motivated intense research efforts directed to broaden as much as possible the scope of asymmetric azomethine ylide [3+2] cycloadditions (Scheme 2, a).[4] As such, dipole sources such as α-imino esters, nitriles, phosphonates and pyridines, as well as azalactones and silylmethylimines, have produced 2- and 2,5-functionalized pyrrolidines. Various olefins have also been demonstrated to participate in these cycloadditions, however they always contain one (or more) electron-withdrawing group(s). For example, various acrylate derivatives, nitroalkenes, vinyl sulfones, or acrylonitriles have commonly been employed. These electron-poor functions have defined the pyrrolidine 3,4-substituents that can be accessed through this disconnection. This trend has only been challenged by studies on cycloaddition with non-coordinating fullerene dipolarophiles (activated).[6] Despite these limitations, great progress has been made in this area after the breakthrough by Allway and Grigg in 1991 using stoichiometric Co and Mn ephedrine complexes.[7] The first catalytic enantioselective [3+2] cycloadditions were reported independently by Zhang[8] and Jørgensen[9] in 2002 (Scheme 2, b). Since then, countless contributions by Schreiber,[10] Carreira,[11] Carretero,[12] Zhou,[13] Hou,[14] Li,[15] Toste,[16] Kobayashi,[17] Nájera,[18] Wang,[19] Fukuzawa,[20] Arai,[21] Hu/Zheng,[22] Waldmann,[23] and others have continuously pushed the limits of this chemistry. Comprehensive reviews have compiled these efforts, evidencing the dominance of Cu and Ag catalysts.[4] However, other metals, such as Zn,[9] Ca,[17a] Au,[16] or Ni,[21] have also been proved instrumental in some scenarios. A wide variety of chiral ligands based on *P,S*-, *P,N*-, or *P,P*-bidentate designs have been developed over the years with the aim to push the scope and selectivity of these cycloadditions even further. This way, ligands like *Biphep*,[19c,23d] *Fesulphos*,[6,12a,c,23b,c] (with Cu), *TF-Biphamphos*,[19a,b] and *Segphos*[12b,17b,c] (with both Cu and Ag) have been particularly successful. More recently, bis-phosphine ligands of the *Segphos*[16] and *BINAP*[18b] families have been used to generate highly effective dinuclear Au catalysts. Monodentate phosphoramidite ligands have also provided excellent enantioselectivities.[18a,c] Following the pioneering research by Vicario[24] and Gong,[25] enantioselective organocatalysis has also contributed to expand the scope of this reaction taking advantage of various classes of organocatalysts[4d,g] such as pyrrolidines,[24] phosphoric acids,[25] or (thio)ureas.[26]

3 Research on Activated Non-Electrophilic Olefins

Beyond doubt, electron-poor olefins prevail in [3+2] cycloadditions. The promise of extending this direct and strategic transformation to any type of olefin has motivated pioneering research to overcome this fundamental reactivity barrier. Thus far, only lithium 2-aza-allyl anions (ionic azomethine ylides) have been competent in the cycloaddition with some types of non-electrophilic olefins. As it will be discussed below, all the olefin classes that have been demonstrated in intermolecular [3+2] reactions still require some sort of activation. The α-olefins are the only subclass of unactivated alkenes that have been demonstrated in this chemistry, however only in intramolecular reactions so far. In this section, we venerate the seminal reports on this chemistry by classifying these contributions based on the type of olefin that was used as substrate.

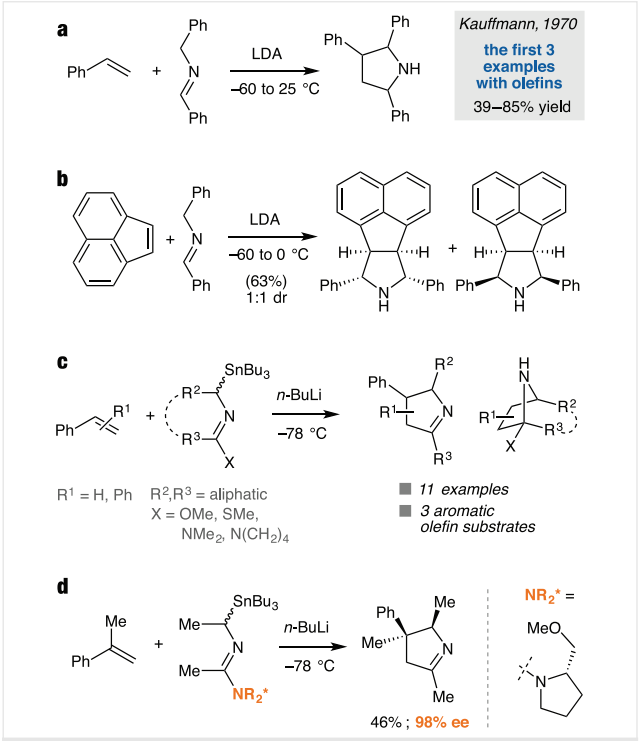


Scheme 2 Current landscape in azomethine ylide [3+2] cycloaddition chemistry: (a) substrates and (b) enantioselective metal catalysts

3.1 Aromatic Olefins

In 1970, Kauffmann pioneered the [3+2] cycloaddition between an aromatic imine and olefins bearing aromatic substituents (Scheme 3, a).[27] *This paper introduced the key concept of using lithium 2-aza-allyl anions as highly reactive analogues of azomethine ylides.* Using this approach, it was possible to synthesize densely functionalized pyrrolidines (without electron-withdrawing substituents in the 3,4-positions) in a single operation for the first time. However, this remarkable intermolecular reaction could only incorporate olefins bearing aromatic substituents, like styrenes and stilbenes. Recently, a different approach to similar pyrrolidine products has been reported using a mixture of *N*-chloroamines and KO*t*-Bu as imine surrogates.[28] Acenaphthylene is an extreme example of an aromatic alkene due to its ring-strain and substantial antiaromatic character. Upon cycloaddition, this system benefits from the $sp^2 \rightarrow sp^3$ rehybridization and the aromatization of the naphthalene moiety. However, even when counting these additional driving forces, the cycloaddition between acenaphthylene and a model 2-aza-allyl anion was found to be reversible and poorly stereoselective (Scheme 3, b).[29] Both facts are suggestive of the adverse thermodynamics and low-energy stepwise pathways that may be operating in 2-aza-allyl lithium cycloadditions.

While Kauffmann used hindered bases to deprotonate *N*-benzylimines,[27a] a different approach was necessary to access less stabilized 2-aza-allyl anions. Tsuge introduced *N*-silylmethylimines as viable sources of these intermediates.[30] However, the transmetalation process developed by Pearson using alkyltin-functionalized imines proved to be significantly more general (Scheme 3, c).[31] This way, the 2-

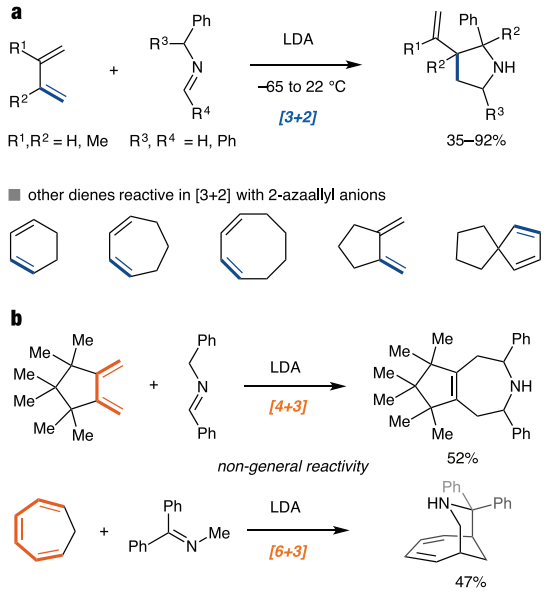


Scheme 3 Reactivity of 2-aza-allyl anions with aromatic olefins

aza-allyl anion chemistry could be extended to aliphatic and hetero-functionalized imines. On the olefin side, mainly styrenes and stilbenes were again limiting the scope of this reaction. Still, an intramolecular variant was successfully applied in several total syntheses of alkaloids.[32] Remarkably, when hetero-functionalized 2-aza-allyl anions were used, the stereochemistry of the olefin was not transferred into the products indicating again that stepwise pathways could be operating.[31a] Still, Pearson's approach was suitable to deliver the only example of an enantiospecific [3+2] cycloaddition on a non-electrophilic olefin reported to date (Scheme 3, d);[33] he demonstrated efficient chirality transfer from a prolinol auxiliary built into the structure of the 2-aza-allyl anion.

3.2 Polyenes

Building on the initial success with aromatic olefins, Kauffmann explored the reactivity with dienes, observing a clear preference for the [3+2] manifold over other possible higher-order cycloadditions (Scheme 4, a). This way, the 1,3-diene moiety behaved as a vinyl-activated olefin, which consequently gave access to vinyl-decorated pyrrolidines.[34] This reactivity was further extended to other cyclic diene substrates, using both deprotonation and tin transmetalation as the source of 2-aza-allyl anion intermediates.[35]

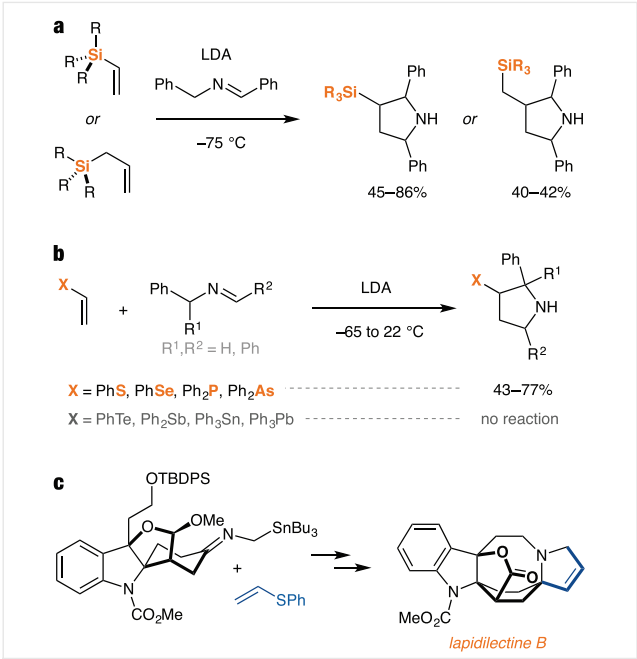


Scheme 4 Reactivity of 2-aza-allyl anions with dienes and polyenes

In this context, higher-order cycloadditions have only rarely been documented. On dienes, only a densely functionalized specimen was found to react with the 2-aza-allyl anion through a [4+3] cycloaddition (Scheme 4, b).[35] The reactivity of cycloheptatriene in this chemistry is rather capricious leading to [6+3] cycloadducts in some instances.[35,36] The formation of [3+2] and carbolithiation co-products is suggestive of a competitive stepwise mechanism operating when using these conjugated systems.[35,36b]

3.3 Hetero-Substituted Olefins

Popowski was the first to introduce unsaturated silanes as viable substrates in [3+2] cycloadditions with 2-aza-allyl anions (Scheme 5, a).[37] The beneficial activation provided by the organosilicon group has been observed in both vinyl- and allylsilanes. Among these, vinylsilanes have found a broader range of applications due to the special activation and the enabling downstream manipulations possible with the silicon group (Tamao–Fleming oxidation).[31b] The high regioselectivity that characterize the cycloaddition of vinylsilanes can be predicted based on the charge distribution calculations (LUMO has the largest coefficient in the β-carbon), further supporting the predictive value of the frontier molecular orbital model in this chemistry.[31a]



Scheme 5 Reactivity of 2-aza-allyl anions with olefins that are activated by hetero-substituents

Olefins bearing a soft hetero-substituent have proven over the years privileged activated substrates in [3+2] cycloadditions. The intermolecular reaction was firstly discovered by Kauffmann using olefins with substituents containing sulfur (PhS), selenium (PhSe), phosphorus (Ph_2P), and arsenic (Ph_2As) (Scheme 5, b).[38] After the cycloaddition, these groups could be removed or used as handles in further manipulations. The special reactivity of vinyl sulfides has been exploited in several creative total synthesis of natural products by Pearson.[31b,32] Although these approaches

are mostly based on intramolecular reactions, the synthesis of *lapidilectine B* (Scheme 5, c) is based on a key intermolecular cycloaddition.[39] The smooth reactivity of hetero-substituted olefins was rationalized based on their inductively electron-withdrawing character (and inefficient electron-donation to the π-system of the olefin).[38a] This argument is consistent with the inability of heavier analogues to promote the reaction due to insufficient electronegativity. For example, the reaction with olefins bearing substituents containing tellurium (PhTe), antimony (Ph_2Sb), tin (Ph_3Sn), or lead (Ph_3Pb) failed to produce [3+2] cycloadducts to any practical extent.[38b] *So far, simple enol ethers and enamines have not been reported to participate in analogous 2-aza-allyl anion [3+2] cycloadditions, probably due to an excessive electron-rich character.*

3.4 Rare Examples with Alkyl-Substituted Olefins: Norbornadiene and Tethered α-Olefins

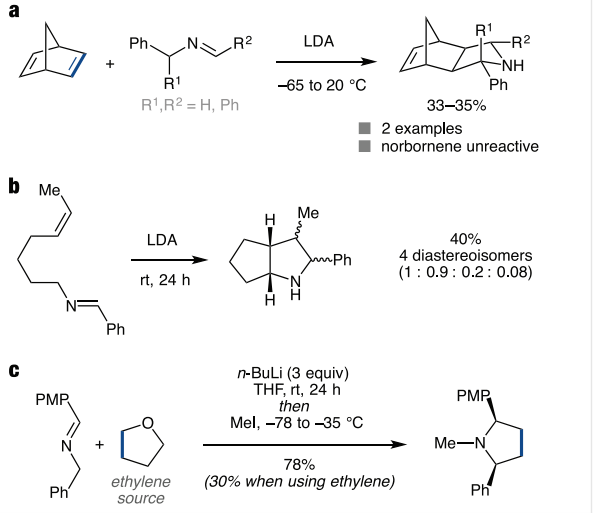
Unlike other cycloadditions, the use of strained olefins in this context has been reported only rarely and is illustrative of the special kinetic and thermodynamic barriers of this reaction. Norbornadiene is thus far the only strained olefin that has been reported to participate in the cycloaddition with 2-aza-allyl anions, and this occurred only in low yield (Scheme 6, a).[27b] Remarkably the related norbornene olefin has been explicitly declared unreactive in various papers and compilations.[31,32c] *Therefore, strained olefins are surprisingly outside the range of viability for azomethine ylide [3+2] cycloadditions, which is suggestive of the special requirements of these transformations.*

As a result, non-strained unactivated olefins do not participate in intermolecular cycloadditions either. Only *unstabilized 2-aza-allyl anions* have been trapped *intramolecularly* by *unhindered alkyl-substituted olefins* (Scheme 6, b).[40] Despite these restrictions, Pearson found these cycloadditions instrumental for the synthesis of various fused alkaloid natural products.[32c] *The fundamental challenge of using unactivated olefins in intermolecular azomethine ylide cycloadditions has not yet been met. Simple olefins whether linear or cyclic (i.e., hex-1-ene or cyclohexene) have been declared unreactive on various occasions.*[27b,31b,32c] The only exception we are aware of is a single report on the cycloaddition of ethylene, which was intriguingly required to be generated from the fragmentation of tetrahydrofuran for efficient coupling (Scheme 6, c).[41] Beyond this isolated example, a general solution to the intermolecular [3+2] cycloaddition with unactivated olefins awaits to be uncovered. This solution has an obvious potential in the synthesis of densely functionalized pyrrolidines in one operation from modular sources. The promise of using abundant (even natural) alkenes, aldehydes, and amines to access important heterocycles supports the importance of further undertakings in this area.

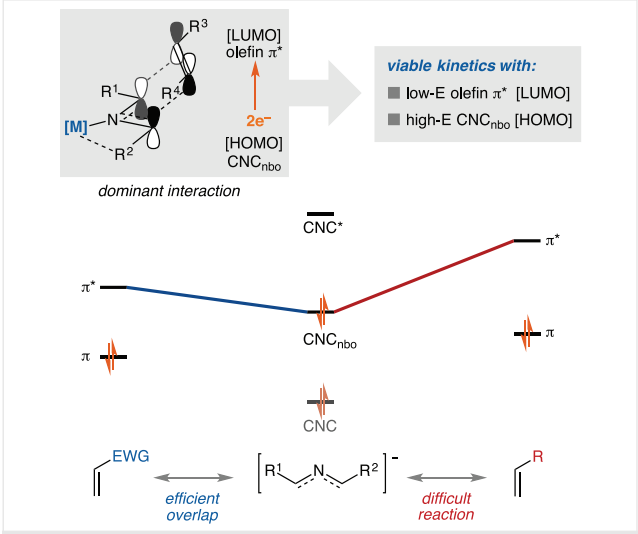
4 Extracted Generalities

4.1 Kinetic Barrier to Non-Electrophilic Olefins

The intimate mechanism of various azomethine ylide [3+2] cycloadditions has been the subject of several computational studies.[42] Indications of both concerted and stepwise mechanisms have been found both experimentally and computationally depending on the system studied. However, in most cases the resulting products can be rationalized by invoking simple frontier molecular orbital reasoning (Scheme 7).[31a] The HOMO of the 2-aza-allyl anion



Scheme 6 Precedents of the reaction of 2-aza-allyl anions with alkyl-substituted olefins and ethylene

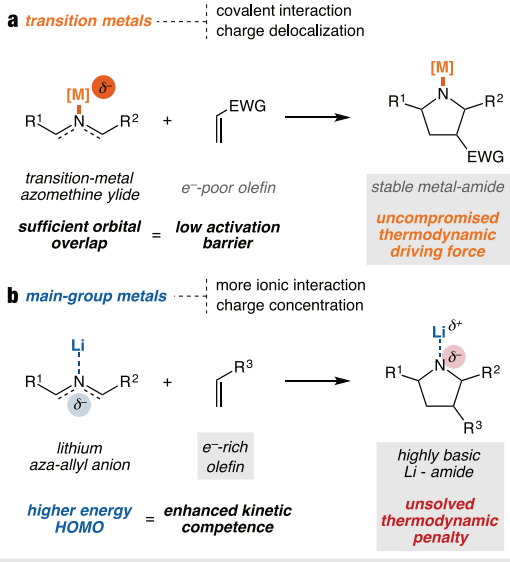


Scheme 7 Molecular orbital interactions define the viable activation barriers

resides in a formally non-bonding orbital bearing a node in the central nitrogen atom (CNC_{nbo}). The dominant symmetry-allowed orbital interaction with the olefin (see Scheme 7, grey box) occurs between the HOMO of the ylide (CNC_{nbo}) and the LUMO of the olefin (π*).[43] With this simple model, the supremacy of electron-deficient olefins in this cycloaddition is easily rationalized. These alkenes have a LUMO of low energy to best overlap with the HOMO in the 2-aza-allyl anion. This model is also consistent with the extensive reactivity reported with heterocumulenes as electrophilic dipolarophiles.[44] For example, nitriles, iso(thio)cyanates, carbodiimides, or carbon disulfide have been reported to react efficiently in [3+2] cycloadditions with 2-aza-allyl anions.[44] In contrast, less electrophilic olefins bearing higher energy LUMOs and a larger HOMO–LUMO gap, reasonably result in decreased reactivity.

4.2 Charge Concentration: An Unsolved Thermodynamic Penalty

Beyond the favorable orbital interactions that may stabilize the transition state in these reactions (and thus the kinetics), the concentration of charge in the products impose an additional thermodynamic penalty (Scheme 8). The negative charge that is delocalized across the CNC system gets concentrated in the nitrogen atom, as a result of the formation of the two new σ-C–C bonds. The immediate product of this reaction is a metal amide, a strong base whose formation decreases the thermodynamic driving force of the process. This fundamental penalty has been alleviated in most catalytic systems by delocalizing the charge on a suitable transition-metal fragment and further



Scheme 8 Fundamental difference in thermodynamic driving force between reactions mediated by transition metals and main group metals

coupling with a subsequent acid-base equilibrium. Transition-metal amides are known to be less basic than their main group analogues. Notably, excellent substrates for other cycloadditions like, for example, norbornene (which benefit from the release of strain) are not effective in this chemistry.[31,32c] This fact is suggestive of the severely adverse thermodynamics of 2-aza-allyl anion cycloadditions, which has hampered further extension to simple alkyl-substituted olefins so far. In fact, the cycloreversion has been documented in several reports that have been discussed in the sections above.[27b,29,40]

5 Conclusions and Outlook

When using electron-deficient olefins, the [3+2] cycloaddition with imines has been found to be very useful in the assembly of pyrrolidine heterocycles.[4] These reactions are normally mediated by transition-metal catalysts that stabilize the putative azomethine ylide and assist in the stabilization of the resulting nitrogen anion (Scheme 8, a). However, this approach has not been successful in cycloadditions with electron-neutral or electron-rich olefins. This is probably due to inefficient orbital overlap with stabilized azomethine ylides.

In the seminal studies compiled in this account, lithium 2-aza-allyl anions have been found instrumental to push forward the reactivity frontier of this chemistry by engaging aromatic or hetero-substituted olefins in intermolecular couplings. These reactive 2-aza-allyl anions provide more energetic HOMOs that can lower the activation barrier of this process (Scheme 8, b). However, the generation of lithium amide products seems to thermodynamically disfavor the reaction and even results in cycloreversion equilibria.

Therefore, the challenge of engaging electron-neutral or electron-rich olefins in this chemistry seem to require that: (1) high-energy electron density is available in the 2-aza-allyl anion, to minimize the activation barrier; and (2) stabilization of the nitrogen anion to warrant favorable thermodynamics. These requirements may be met through a careful engineering of the countercation of the 2-aza-allyl anion intermediate, an approach that is being actively pursued in our group at the moment. Our future contributions aim to provide the first general entry to powerful pyrrolidine products by answering this long-standing fundamental challenge.

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