<http://www.diva-portal.org>

Postprint

This is the accepted version of a paper published in *Synthesis (Stuttgart)*. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the original published paper (version of record):

Otero-Fraga, J., Montesinos-Magraner, M., Mendoza, A. (2017)
Perspectives on Intermolecular Azomethine Ylide [3+2] Cycloadditions with Non-Electrophilic Olefins
Synthesis (Stuttgart), 49(4): 802-809
<https://doi.org/10.1055/s-0036-1588662>

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

Permanent link to this version:

<http://urn.kb.se/resolve?urn=urn:nbn:se:su:diva-141374>

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

Jorge Otero-Fraga^{a,*}

Marc Montesinos-Magraner^{a,†}

Abraham Mendoza^{a,*}

^a Department of Organic Chemistry and Berzelii EXSELENT Center for Porous Materials Stockholm University, Arrhenius Laboratory 106 91 Stockholm (Sweden)

[†] The authors contributed equally

abraham.mendoza@su.se

Dedicated to Prof. Paul Knochel

Received:
Accepted:
Published online:
DOI:

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.

- 1 Introduction
- 2 State-of-the-art using electron-poor olefins
- 3 Research on activated non-electrophilic olefins
- 4 Extracted generalities
- 5 Conclusions and outlook

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

reactions.⁴ Interestingly, still today a vast portion of abundant olefin classes have eluded to participate in this chemistry, thus pointing to unsolved fundamental challenges that we illustrate in this account.

Scheme 1 Scope of this review.

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

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 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 have expanded its features over decades. These advances have been scrutinized in a consistent stream of seminal reviews.⁴ In these revisions, 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.

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, -pyridines as well as azalactones and silylmethylimines have produced 2- and 2,5-functionalized pyrrolidines. Various olefins have also demonstrated to participate in these cycloadditions, however they always contain one (or more) electron-withdrawing group(s). For example, various acrylate derivatives, nitroalkenes, vinylsulfones 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 the 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 Zhang⁸ and Jørgensen⁹ 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 Waldmann²³ 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} Au¹⁶ or Ni²¹ 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, 12c, 23b, 23c} (with Cu), *TF-biphampfos*,^{19a, 19b} and *segphos*^{12b, 17b, 17c} (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, 18c} Following the pioneering research by Vicario²⁴ and Gong,²⁵ enantioselective organocatalysis has also contributed to expand the scope of this reaction taking advantage of various classes of organocatalysts^{4d, 4g} such as pyrrolidines,²⁴ phosphoric acids²⁵ or (thio)ureas.²⁶

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

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.

Aromatic olefins

In 1970, Kauffmann pioneered the [3+2] cycloaddition between an aromatic imine and olefins bearing aromatic substituents (Scheme 3, a).²⁷ In this paper it was introduced the key concept of using lithium 2-aza-allyl anions as highly reactive analogs 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*-chloro amines and KO^tBu 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 $sp^2 \rightarrow sp^3$ re-hybridization and the aromatization of the naphthalene moiety. However, even when counting with 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 step-wise 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-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 enantiospecific [3+2] cycloaddition on a non-electrophilic olefin reported to date (Scheme 3, d).³³ In a single example, he could demonstrate efficient chirality transfer from a prolinol auxiliary built into the structure of the 2-aza-allyl anion.

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

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 step-wise mechanism operating when using these conjugated systems.^{35, 36b}

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 allyl-silanes. Among those, vinyl-silanes have found a broader range of applications providing with additional activation and enabling downstream manipulations (Tamao-Fleming oxidation).^{31b} The high regioselectivity that characterizes 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 (Ph₂P), and arsenic (Ph₂As) (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 in 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 analogs to promote the reaction due to insufficient electronegativity. For example, the reaction with olefins bearing substituents containing tellurium (PhTe), antimony (Ph₂Sb), tin (Ph₃Sn) or lead (Ph₃Pb) 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.*

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.*

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

As a result, non-strained unactivated olefins do not participate in intermolecular cycloadditions either. Only *un-stabilized 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 been met yet. Simple olefins whether linear or cyclic (i.e. 1-hexene or cyclohexene) have been declared unreactive in 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.

Extracted generalities

Kinetic barrier to non-electrophilic olefins

The intimate mechanism of various azomethine ylide [3+2] cycloadditions have been the subject of several computational studies.⁴² Indications of both concerted and step-wise mechanisms have been found both experimentally and computationally depending on the system studied. However, in most cases the resulting products can be rationalized invoking simple frontier molecular orbital reasoning (Scheme 7).^{31a} The HOMO of the 2-aza-allyl anion 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 On the contrary less electrophilic olefins bearing higher energy LUMOs and a larger HOMO-LUMO gap, reasonably result in decreased reactivity.

Scheme 7 Molecular orbital interactions define the viable activation barriers.

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 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 of the reports that have been discussed in the sections above.^{27b, 29, 40}

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

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 with more energetic HOMOs that can lower the activation barrier of this process (Scheme 8, b). However, the generation of lithium amide products seem 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 counter-cation 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.

Acknowledgment

The authors gratefully acknowledge the scientific committee of the Bürgenstock Conference and the Swiss Chemical Society for a JSP fellowship (AM) and the invitation to contribute to this special issue. Unrestricted support from the personnel of the Dept. of Organic Chemistry and the Dept. of Materials and Environmental Chemistry (SU) is deeply appreciated. Financial support for this work has been provided by the Swedish Research Council (Vetenskapsrådet, 2012-2969), the Swedish Innovation Agency (VINNOVA), the Marie Curie Actions (631159), the Carl Trygger Foundation (fellowship to JO), the Berzelii Center EXSELENT, AstraZeneca AB and Stockholm University.

References

- (1) (a) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471; (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713; (d) Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869; (e) Albrecht, L.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2014**, *20*, 358; (f) Meninno, S.; Lattanzi, A. *Chem. Commun.* **2013**, *49*, 3821; (g) Buchner, E. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 2637; (h) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 7876; (i) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248; (j) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.
- (2) (a) Cho, B. T. *Chem. Soc. Rev.* **2009**, *38*, 443; (b) Vargas-Caporalí, J.; Juaristi, E. *Synthesis* **2016**, DOI: 10.1055/s-0035-1562793; (c) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
- (3) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783.
- (4) (a) Nájera, C.; Sansano, J. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6272; (b) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484; (c) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784; (d) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 12434; (e) Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296; (f) Wang, L. J.; Tang, Y., In *Comprehensive Organic Synthesis II*, Ed. 2; Elsevier: Amsterdam, **2014**; (g) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366.
- (5) (a) Suárez-Pantiga, S.; Colas, K.; Johansson, M. J.; Mendoza, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 14094; (b) Mendoza, A.; Colas, K.; Suárez-Pantiga, S.; Götz, D. C. G.; Johansson, M. J. *Synlett* **2016**, *27*, 1753.
- (6) (a) Filippone, S.; Maroto, E. E.; Martín-Domech, A.; Suarez, M.; Martín, N. *Nat. Chem.* **2009**, *1*, 578; (b) Maroto, E. E.; de Cózar, A.; Filippone, S.; Martín-Domech, Á.; Suarez, M.; Cossío, F. P.; Martín, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 6060; (c) Sawai, K.; Takano, Y.; Izquierdo, M.; Filippone, S.; Martín, N.; Slanina, Z.; Mizorogi, N.; Waelchli, M.; Tsuchiya, T.; Akasaka, T.; Nagase, S. *J. Am. Chem. Soc.* **2011**, *133*, 17746.
- (7) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817.
- (8) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400.
- (9) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4236.
- (10) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174.
- (11) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 5971.
- (12) (a) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394; (b) López-Pérez, A.; Adrio, J.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 340; (c) Hernández-Toribio, J.; Padilla, S.; Adrio, J.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2012**, *51*, 8854.
- (13) Zeng, W.; Zhou, Y. G. *Org. Lett.* **2005**, *7*, 5055.
- (14) Yan, X. X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X. L.; Wu, Y. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1979.
- (15) Zeng, W.; Chen, G. Y.; Zhou, Y. G.; Li, Y. X. *J. Am. Chem. Soc.* **2007**, *129*, 750.
- (16) (a) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638; (b) Melhado, A. D.; Amarante, G. W.; Wang, Z. J.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 3517.
- (17) (a) Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364; (b) Yamashita, Y.; Guo, X. X.; Takashita, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 3262; (c) Yamashita, Y.; Imaizumi, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 4893.
- (18) (a) Nájera, C.; Retamosa, M. d. G.; Sansano, J. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 6055; (b) Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Wu, F.-L. *Tetrahedron: Asymmetry* **2010**, *21*, 1184. (c) Castelló, L. M.; Nájera, C.; Sansano, J. M.; Larrañaga, O.; de Cózar, A.; Cossío, F. P. *Org. Lett.* **2013**, *15*, 2902. (d) Nájera, C.; de Gracia Retamosa, M.; Sansano, J. M. *Org. Lett.* **2007**, *9*, 4025.
- (19) (a) Wang, C. J.; Liang, G.; Xue, Z. Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250; (b) Xue, Z.-Y.; Liu, T.-L.; Lu, Z.; Huang, H.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2010**, *46*, 1727; (c) Li, Q.-H.; Liu, T.-L.; Wei, L.; Zhou, X.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2013**, *49*, 9642.
- (20) Oura, I.; Shimizu, K.; Ogata, K.; Fukuzawa, S. I. *Org. Lett.* **2010**, *12*, 1752.
- (21) Arai, T.; Yokoyama, N.; Mishiro, A.; Sato, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 7895.
- (22) Zhang, C.; Yu, S. B.; Hu, X. P.; Wang, D. Y.; Zheng, Z. *Org. Lett.* **2010**, *12*, 5542.
- (23) (a) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schürmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735; (b) Potowski, M.; Schürmann, M.;

- Preut, H.; Antonchick, A. P.; Waldmann, H. *Nat. Chem. Biol.* **2012**, *8*, 428; (c) Narayan, R.; Bauer, J. O.; Strohmman, C.; Antonchick, A. P.; Waldmann, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 12892; (d) Vidadala, S. R.; Golz, C.; Strohmman, C.; Daniliuc, C. G.; Waldmann, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 651.
- (24) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168.
- (25) (a) Chen, X. H.; Zhang, W. Q.; Gong, L. Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652; (b) Chen, X. H.; Wei, Q.; Luo, S. W.; Xiao, H.; Gong, L. Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819.
- (26) (a) Liu, Y. K.; Liu, H.; Du, W.; Yue, L.; Chen, Y. C. *Chem. Eur. J.* **2008**, *14*, 9873; (b) Sun, W.; Zhu, G.; Wu, C.; Li, G.; Hong, L.; Wang, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8633.
- (27) (a) Kauffmann, T.; Berg, H.; Köppelmann, E. *Angew. Chem.* **1970**, *82*, 396; (b) Kauffmann, T. *Angew. Chem. Int. Ed.* **1974**, *13*, 627.
- (28) Pandiancherri, S.; Lupton, D. W. *Tetrahedron Lett.* **2011**, *52*, 671.
- (29) Kauffmann, T.; Habersaat, K.; Koeppelmann, E. *Chem. Ber.* **1977**, *110*, 638.
- (30) Tsuge, O.; Kanemasa, S.; Hatada, A.; Matsuda, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2537.
- (31) (a) Pearson, W. H.; Stevens, E. P. *J. Org. Chem.* **1998**, *63*, 9812; (b) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329.
- (32) (a) Pearson, W. H.; Lian, B. W. *Angew. Chem. Int. Ed.* **1998**, *37*, 1724; (b) Pearson, W. H. *Pure Appl. Chem.* **2002**, *74*; (c) Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903.
- (33) Pearson, W. H.; Stevens, E. P.; Aponick, A. *Tetrahedron Lett.* **2001**, *42*, 7361.
- (34) (a) Kauffmann, T.; Eidenschink, R. *Angew. Chem.* **1971**, *83*, 794; (b) Kauffmann, T.; Eidenschink, R. *Chem. Ber.* **1977**, *110*, 645.
- (35) Pearson, W. H.; Mans, D. M.; Kampf, J. W. *J. Org. Chem.* **2004**, *69*, 1235.
- (36) (a) Bower, D. J.; Howden, M. E. H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 672; (b) Pearson, W. H.; Mans, D. M.; Kampf, J. W. *Org. Lett.* **2002**, *4*, 3099.
- (37) Popowski, E. *Z. Chem.* **1974**, *14*, 360.
- (38) (a) Kauffmann, T.; Ahlers, H.; Hamsen, A.; Schulz, H.; Tilhard, H. J.; Vahrenhorst, A. *Angew. Chem. Int. Ed.* **1977**, *89*, 107; (b) Kauffmann, T.; Ahlers, H.; Echsler, K. J.; Schulz, H.; Tilhard, H. J. *Chem. Ber.* **1985**, *118*, 4496.
- (39) Pearson, W. H.; Mi, Y.; Lee, I. Y.; Stoy, P. *J. Am. Chem. Soc.* **2001**, *123*, 6724.
- (40) Pearson, W. H.; Walters, M. A.; Oswell, K. D. *J. Am. Chem. Soc.* **1986**, *108*, 2769.
- (41) Kamata, K.; Terashima, M. *Heterocycles* **1980**, *14*, 205.
- (42) (a) Neumann, F.; Lambert, C.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1998**, *120*, 3357; (b) Freeman, F.; Dang, P.; Huang, A. C.; MacK, A.; Wald, K. *Tetrahedron Lett.* **2005**, *46*, 1993; (c) Kuznetsov, M. L. *Russ. Chem. Rev.* **2006**, *75*, 935.
- (43) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.
- (44) (a) Kauffmann, T.; Eidenschink, R. *Angew. Chem. Int. Ed.* **1973**, *85*, 583; (b) Kauffmann, T.; Eidenschink, R. *Chem. Ber.* **1977**, *110*, 651; (c) Kauffmann, T.; Busch, A.; Habersaat, K.; Koeppelmann, E. *Chem. Ber.* **1983**, *116*, 492.

Biosketches

Dr. Abraham Mendoza was born and raised in Gijón, a city in the beautiful coast of Asturias (Spain). He obtained his BSc and PhD degrees in Chemistry (2009) at the Univ. of Oviedo with Profs. J. Barluenga, F. J. Fañanás and F. Rodríguez. He 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 Univ. 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.