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Direct and Stereospecific [3+2] Synthesis of Pyrrolidines from Simple Unactivated Alkenes

Jorge Otero-Fraga,^[a] Samuel Suárez-Pantiga,^[a] Marc Montesinos-Magraner,^[a] Dennis Rhein^[a] and Abraham Mendoza^{*[a]}

This paper is dedicated to Prof. Jan-Erling Bäckvall on the occasion of his 70th birthday.

Abstract: Pyrrolidines are central heterocyclic compounds with endless applications in organic synthesis, metal- and organocatalysis. In particular, their potential as ligands for first-row transition-metal catalysts has inspired a new method to access complex poly-heterocyclic pyrrolidines in one-step from available materials. This fundamental step forward is grounded on the discovery of an essential organoaluminum promoter that engages unactivated and electron-rich olefins in intermolecular [3+2] cycloadditions for the first time.

The discovery of catalysts to enable new, more efficient and more sustainable transformations is a prime objective of our time. To this end, the development of new transition-metal catalysts requires new synthetic methods that can quickly supply diverse and powerful ligands. Recent research targeting ligand synthesis has enabled practical access to important catalysts and contributed with solutions to fundamental synthetic challenges.^[1] In this sense, stereodefined polydentate *N*-donor ligands are particularly demanding due to their nucleophilicity, redox chemistry and their strong binding to transition metals. Unlike common syntheses based on C–N bond-forming reactions,^[2] our group has recently reported an alternative approach based on C–C bond construction.^[1b] Herein, we present a versatile synthesis of poly-heterocyclic pyrrolidines (Scheme 1, a) that is aimed at (1) increasing the coordinative power of the *N*-donor, and (2) enhancing the structural and functional modularity of these ligand scaffolds using diverse alkene precursors. Beyond ligands, pyrrolidines are central heterocycles that are found in medicinal compounds,^[3] photovoltaic devices,^[4] supramolecular assemblies,^[5] and they are also a cornerstone in both metal-^[2c, 6] and organocatalysts^[7] due to the particular nucleophilicity of their pyramidalized *N*-donor.^[7f] The most strategic method to obtain pyrrolidines is the azomethine ylide [3+2] cycloaddition,^[8] albeit still limited to electron-deficient olefins.^[8–10] This fundamental restraint has never been overcome and it is particularly relevant in the synthesis of sturdy ligands with inert backbones, which would require removal and/or manipulation of the enabling electron-withdrawing group. Herein, we report a system that

engages aliphatic and electron-rich olefins in azomethine ylide [3+2] cycloadditions to provide direct access to new pyrrolidine scaffolds in one-step from commercial sources.

Scheme 1. [a] New pyrrolidine ligands require a new cycloaddition method (*this work*). [b] Discovery of organoaluminum activation. [c] Optimization. ^aReaction conditions: imine **1a** (0.1 mmol), reagent (0.2 mmol), olefin **2a** (0.5 mmol), ¹¹ THF (1 mL), 0 °C to 80 °C, 12 h. ^bYields determined by ¹H-NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

We have recently reviewed the current state-of-the-art in azomethine ylide [3+2] cycloadditions involving non-electrophilic olefins.^[8a] Lithium 2-aza-allyl anions (**Li-A**) introduced by Kauffmann^[12] and popularized by Pearson^[13] can engage the least activated olefins thus far, namely styrenes,^[10] vinylsulfides and vinylsilanes.^[8a, 12, 13] These intermolecular reactions often display a modest scope (alkyl and cycloalkyl olefins are unreactive),^[12b, 13] selectivity and even reversibility.^[8a] Preliminary experimentation (Scheme 1, b; top) revealed that imines featuring *N*-heterocycles, are particularly difficult, as it could be expected from the electrophilic character of these heteroaromatics.^[9, 14] For example, *bis*-(2-pyridyl)-imine **1a** and styrene **2a** do not react in the conditions reported by Kauffmann (involving **Li-A**). We believe

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that it is due to slow kinetics and/or a charge-localization enthalpic penalty (**Li-A** $\rightarrow$ **Li-B**)^[15] that has never been fundamentally addressed. We hypothesized that the counter-cation associated with the 2-aza-allyl anion could have a crucial effect at both (1) enabling viable kinetics, by increasing the electron-density on 2-aza-allyl system **A**; and (2) alleviating the thermodynamic balance of the process, by stabilizing the electron-rich metal-amide **B**. Inspired by our recent research,^[1b] we explored the effect of organoaluminum additives, observing that when imine **1a** is deprotonated with LDA and treated with Me₂AlCl, pyrrolidine **3aa** is formed in 58% yield (Scheme 1, b; bottom). This spectacular effect is likely due to the increased electron-rich character of **Me₂Al-A** (faster kinetics than **Li-A**) and the greater stability of **Me₂Al-B** (larger driving force than for **Li-B**). Encouraged by this result, we optimized this system using a challenging aliphatic α -olefin **2b** as model substrate (Scheme 1, c). This class of alkenes have never participated in [3+2] cycloadditions.^[8a] We observed that the lithium anion **Li-A** could not promote the cycloaddition (0% yield), while the Me₂Al-derived anion **Me₂Al-B** furnished the cycloadduct **3ab** (52% yield). Additionally, we found that Me₃Al, which can act as a base and a [Me₂Al]⁺ source,^[1b] is a more efficient activator (67% yield) than LDA/Me₂AlCl. Rigorous deoxygenation and visible-light irradiation were deemed inconsequential (Table S2). These factors were essential in the piperazine synthesis that we reported earlier, thus suggesting a distinct mechanism operating in this case (see also Scheme 4, a-c).^[16] Other alkyl-, aryl-, amido- or alkoxy-aluminum reagents as well as titanium bases and zinc or magnesium organometallics were not effective (Table S2) at promoting this reaction.

With these optimized conditions in hand, we explored the reactivity using commercial olefins of diverse stereoelectronic nature (Scheme 2). Terminal olefins are good substrates that lead to the desired functionalized pyrrolidine products **3aa-aj** with a varied selection of functional groups and sterically-controlled stereoselectivities (Scheme 2, a). Remarkably, electron-rich olefins like butyl vinyl ether and *N*-vinylcarbazole also engage in

this cycloaddition (**3ai,aj**). To the best of our knowledge, these are the first nucleophilic olefins to participate in this reaction.^[8a, 12]

Although electron-deficient olefins are beyond the scope of this report, an acrylate substrate was found to seamlessly engage in this cycloaddition as well (see SI). Products featuring all-carbon quaternary centers **3ak-am** are formed using *gem*-difunctionalized alkenes, including a 1,3-diene (**3am**) and a functionalized methyldiene cyclobutane (**3ak**). In contrast to non-cyclic alkenes, cyclic olefins produce polycyclic pyrrolidines as single diastereoisomers (Scheme 3, b). The stereochemistry of these products (determined by NMR, see SI) could be confirmed in the product **3an** through X-ray diffraction analysis.^[17]

Carbocyclic olefins of various sizes (**3an-ap**), containing fused (**3ar,as,au**) and bridged (**3aq,av**) bicycles, and oxygen (**3ap**) or nitrogen (**3au**) heterocycles are all successful in this reaction. The power of the system to assemble complex frameworks in one step from commercial materials is well exemplified by **3ar**. Its versatility is best showcased by **3av** and **3a₂v**, which are obtained with different ratios of the same materials. Moreover, **3av** is primed for the heterogenization through ring-opening metathesis polymerization (ROMP)^[18] and **3a₂v** leads to interesting C–H oxidation catalysts (Scheme 4, d). To put these results in perspective we should emphasize that even strained^[12b, 13c] and conventional cycloalkanes were specifically declared unreactive in azomethine ylide [3+2] cycloadditions before our work.^[8a, 13a,b]

Importantly, these polar pyrrolidines can be decorated with unprotected amines (**3ac,aj,au**), alcohols (**3ad**), nitriles (**3ae,ak**), ethers (**3af,ai**), ketals (**3ap**), esters (**3at**), silanes (**3ag,ah**) and other olefins (**3am,av**). We have found that the purification of these polar pyrrolidines is understandably best achieved using automatized reverse-phase chromatography. However, if this technique is unavailable or unsuitable, the aluminum amides produced (**Me₂Al-B**; Scheme 1, b) can be conveniently *N*-Boc-protected *in situ*, purified by conventional normal-phase chromatography (**3ah-al,ap,ar,at**) and deprotected quantitatively with standard protocols (for example **3ar**, see SI).^[19]

Scheme 2. Scope of the [3+2] cycloaddition on the olefin. Yields determined by ¹H-NMR using 1,1,2,2-tetrachloroethane as an internal standard. In parenthesis, isolated yield. [†]Isolated as *N*-Boc adduct.

To explore the heterocycles that could be incorporated in the imine side, we chose two symmetrical cyclic alkenes as substrates (Scheme 3). We were pleased to find that unsymmetrical imines containing both π -deficient and π -excessive heterocycles could be efficiently incorporated in this reaction. Heterocycles such as pyrazine (**3bq,bo-eo**), thiazole (**3fo**), furan (**3cq,co**), and thiophene (**3dq**) can be incorporated into the products, which additionally provide an entry into other functional groups through further manipulations. Surprisingly, we found that this system can also accommodate simple aryl substituents (without undergoing *ortho*-metallation; see SI, III.2) including neutral (**3gq**), electron-poor (**3hq**), electron-rich (**3iq-kq**), and even an unprotected phenol (**3jq**). This feature allows to obtain bidentate scaffolds and opens the door for new metallacyclic compounds.^[20] So far, one *N*-donor heterocycle is required to observe any conversion,^[9] which is suggestive of the crucial role of aluminate species in this reaction.

Scheme 3. Scope of the [3+2] cycloaddition with various heterocyclic imine substrates. Reaction conditions: see Scheme 1, c. Yields determined by ¹H-NMR using 1,1,2,2-tetrachloroethane as an internal standard. In parenthesis, data obtained after reverse-phase HPLC purification.¹⁹

The reactivity leap using organoaluminum activators deserves further scrutiny. We challenged the system using stilbenes **2w**, which are primed for step-wise and reversible processes (Scheme 4, a).^[8a, 10] However, *cis*-**2w** and *trans*-**2w** produced stereospecifically the corresponding pyrrolidines *cis*-**3aw** and *trans*-**3aw**, respectively. This feature is suggestive of an irreversible cycloaddition enabled by the enhanced stability of **Me₂Al-B** (Scheme 1, b). To confirm this point, we synthesized the deuterated compound *cis*-**3aw-d₂** (from *cis*-**2w-d₂**, see SI) and exposed it to an excess of *cis*-**2w**, Me₃Al, and prolonged heating, however the cross-over product *cis*-**3aw** (that would stem from a reversible process) was not detected (Scheme 4, b). Mechanisms involving step-wise radical coupling seem unlikely in the light of the efficient formation of **3ax**, featuring Newcomb's cyclopropane probe for picosecond-lived radical intermediates (Scheme 4, c).^[16, 21] The high driving force for ring-opening of this cyclopropane

highly disfavors any open-shell pathway (either in chain or non-chain). Collectively, these experiments support a stereospecific, and irreversible cycloaddition mediated by **Me₂Al-A** (previously characterized).^[1b, 16, 22]

Products **3** are designed to obtain new catalysts. Following our interest in highly-structured complexes for C–H oxidation,^[1b, 23] we sought to preliminarily explore the activity of ligands derived from **3a₂v** (Scheme 4, d). This way, **1a** and norbornadiene **2v** can be coupled using Me₃Al and *N*-alkylated (without isolating **3a₂v**) to deliver the complex ligands **4a,b** in 53–58% overall yield. Compound **4a** is a dinuclear analogue of the venerable ligand TPA (**5**; TPA = *tris*-(2-pyridylmethyl)amine),^[24] and **4b** is the first derivative with differentiated pyridine donors in this class. Unlike TPA, **4a,b** allow to control the individual *trans*-influence of the different *N*-donors around the metal center (Scheme 1, a). Pleasingly, the dinuclear iron catalysts derived from **4a,b** proved to be more active than FeTPA^[23, 24] in the stereoretentive C–H oxidation of the benchmark alkane *cis*-**6**. This illustrates how products **3** can enable explorations in catalysis otherwise impossible, thus adding to their evident potential as precursors of organocatalysts and multidentate phosphoramidites.

Scheme 4. Mechanistic support and practical synthesis of ligands with a promising outlook. [a] See SI for details.

To summarize, herein we put forward organometallic activation as a new concept in azomethine ylide [3+2] cycloadditions and demonstrated its utility to engage several classes of unactivated and electron-rich olefins for the first time. A simple and available organoaluminum promoter enhances the reactivity of heterocyclic imines and provides with sufficient driving force for this challenging reaction to occur. This work sets the fundamental basis for future solutions to this long-standing problem. The method provides direct access to unprotected poly-

heterocyclic pyrrolidines with evident potential to answer fundamental questions in catalysis, thus inviting for further exploration of these scaffolds. The availability of olefins, amines and aldehydes of artificial and natural origin ensures the utility of this method to access new molecules that are empowered by the privileged pyrrolidine core.

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- [1] (a) Mendoza, A.; Colas, K.; Suárez-Pantiga, S.; Götz, D. C. G.; Johansson, M. J., *Synlett* **2016**, 27, 1753; For a selection of recent contributions, see: (b) Suárez-Pantiga, S.; Colas, K.; Johansson, M. J.; Mendoza, A., *Angew. Chem. Int. Ed.* **2015**, 54, 14094; (c) González-Fernández, E.; Nicholls, L. D. M.; Schaaf, L. D.; Farès, C.; Lehmann, C. W.; Alcarazo, M., *J. Am. Chem. Soc.* **2017**, 139, 1428; (d) Ramírez-López, P.; Ros, A.; Romero-Arenas, A.; Iglesias-Sigüenza, J.; Fernández, R.; Lassaletta, J. M., *J. Am. Chem. Soc.* **2016**, 138, 12053; (e) Narute, S.; Parnes, R.; Toste, F. D.; Pappo, D., *J. Am. Chem. Soc.* **2016**, 138, 16553; (f) Sako, M.; Takeuchi, Y.; Tsujihara, T.; Kodaera, J.; Kawano, T.; Takizawa, S.; Sasai, H., *J. Am. Chem. Soc.* **2016**, 138, 11481; (g) Gao, D.-W.; Gu, Q.; You, S.-L., *J. Am. Chem. Soc.* **2016**, 138, 2544; (h) Beaud, R.; Phipps, R. J.; Gaunt, M. J., *J. Am. Chem. Soc.* **2016**, 138, 13183; (i) Li, S.; Zhang, J.-W.; Li, X.-L.; Cheng, D.-J.; Tan, B., *J. Am. Chem. Soc.* **2016**, 138, 16561; (j) Bhat, V.; Wang, S.; Stoltz, B. M.; Virgil, S. C., *J. Am. Chem. Soc.* **2013**, 135, 16829; (k) Zijlstra, H.; León, T.; de Cózar, A.; Guerra, C. F.; Byrom, D.; Riera, A.; Verdager, X.; Bickelhaupt, F. M., *J. Am. Chem. Soc.* **2013**, 135, 4483; (l) Egami, H.; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki, T., *J. Am. Chem. Soc.* **2010**, 132, 13633.
- [2] (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N., *J. Am. Chem. Soc.* **1990**, 112, 2801; (b) Tyeklar, Z.; Jacobson, R. R.; Wei, N.; Murthy, N. N.; Zubieta, J.; Karlin, K. D., *J. Am. Chem. Soc.* **1993**, 115, 2677; (c) Chen, M. S.; White, M. C., *Science* **2007**, 318, 783; (d) Company, A.; Gómez, L.; Güell, M.; Ribas, X.; Luis, J. M.; Que, L.; Costas, M., *J. Am. Chem. Soc.* **2007**, 129, 15766.
- [3] (a) Chen, W.; Zhan, P.; De Clercq, E.; Liu, X., *Current Pharmaceutical Design* **2012**, 18, 100; (b) Vilchis-Reyes, M. A.; Hanessian, S., *Proline Methanologues: Design, Synthesis, Structural Properties, and Applications in Medicinal Chemistry*. Springer, 2015, pp 1-45.
- [4] (a) Filippone, S.; Maroto, E. E.; Martín-Domenech, Á.; Suarez, M.; Martín, N., *Nature Chem.* **2009**, 1, 578; (b) Maroto, E. E.; Filippone, S.; Suárez, M.; Martínez-Álvarez, R.; de Cózar, A.; Cossio, F. P.; Martín, N., *J. Am. Chem. Soc.* **2014**, 136, 705.
- [5] Lim, Y.-b.; Moon, K.-S.; Lee, M., *Chem. Soc. Rev.* **2009**, 38, 925.
- [6] Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y., *Chem. Eur. J.* **2006**, 12, 3636.
- [7] (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) MacMillan, D. W. C., *Nature* **2008**, 455, 304; (d) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A., *Angew. Chem. Int. Ed.* **2015**, 54, 13860; (e) Fu, G. C., *Acc. Chem. Res.* **2004**, 37, 542; (f) Murphy, J. J.; Silvi, M.; Melchiorre, P., *Enamine-Mediated Catalysis (n → π*)*. In *Lewis Base Catalysis in Organic Synthesis*, Wiley-VCH Verlag, 2016, pp 857-902; (g) Miller, S. J., *Acc. Chem. Res.* **2004**, 37, 601.
- [8] (a) Mendoza, A.; Otero-Fraga, J.; Montesinos-Magraner, M., *Synthesis* **2017**, 49, 802; (b) Hashimoto, T.; Maruoka, K., *Chem. Rev.* **2015**, 115, 5366; (c) Adrio, J.; Carretero, J. C., *Chem. Commun.* **2014**, 50, 12434; (d) Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H., *Acc. Chem. Res.* **2014**, 47, 1296; (e) Wang, L. J.; Tang, Y., *Intermolecular 1,3-Dipolar Cycloadditions of Alkenes, Alkynes, and Allenes*. In *Comprehensive Organic Synthesis II (Second Edition)*, Elsevier, 2014, pp 1342-1383; (f) Adrio, J.; Carretero, J. C., *Chem. Commun.* **2011**, 47, 6784; (g) Pandey, G.; Banerjee, P.; Gadre, S. R., *Chem. Rev.* **2006**, 106, 4484; (h) Nájera, C.; Sansano, J. M., *Angew. Chem. Int. Ed.* **2005**, 44, 6272; (i) Pascual-Escudero, A.; de Cózar, A.; Cossio, F. P.; Adrio, J.; Carretero, J. C., *Angew. Chem. Int. Ed.* **2016**, 55, 15334.
- [9] For [3+2] cycloadditions with heterocyclic imines, see: (a) Ponce, A.; Alonso, I.; Adrio, J.; Carretero, J. C., *Chem. Eur. J.* **2016**, 22, 4952; (b) Padilla, S.; Tejero, R.; Adrio, J.; Carretero, J. C., *Org. Lett.* **2010**, 12, 5608.
- [10] Carretero and Cossio have reported [3+2] cycloadditions with electron-deficient styrenes, but styrene itself has been declared unreactive.⁸ⁱ In the seminal study by Kauffmann, the cycloaddition with *cis*-stilbene only proceeded in 21% yield using lithium 2-aza-allyl anions.^{12b}
- [11] If desired, the excess of Me₃Al and the olefin could be reduced to 1 and 2 equiv. respectively with only a minor erosion of efficiency (Table S1). However, in this study a higher excess was used due to the inexpensive nature of these materials.
- [12] (a) Kauffmann, T.; Berg, H.; Köppelmann, E., *Angew. Chem.* **1970**, 82, 396; (b) Kauffmann, T., *Angew. Chem. Int. Ed.* **1974**, 13, 627.
- [13] (a) Pearson, W. H.; Stoy, P., *Synlett* **2003**, 903. (b) Pearson, W. H.; Szura, D. P.; Postich, M. J., *J. Am. Chem. Soc.* **1992**, 114, 1329; (c) Pearson, W. H.; Stevens, E. P., *J. Org. Chem.* **1998**, 63, 9812.
- [14] The 2-aza-allyl anions require a high-energy HOMO to engage the high-energy LUMOs of non-electrophilic alkenes. However, the heterocyclic substituents in the imine lower the energy of the HOMO orbital in the 2-aza-allyl anion, thus increasing the energy gap with the LUMO of non-electrophilic olefins.
- [15] The negative charge delocalized in **Li-A** is concentrated in the N-atom of the putative lithium amide product **Li-B**.
- [16] Unlike our previous open-shell 8e⁻-cycloaddition,^{1b} this is a thermally-allowed 6e⁻ [3+2] reaction likely operating through a closed-shell mechanism (without photo-induced SET and insensitive to traces of O₂). CCDC deposition number 1528080.
- [17] (a) Lafaye, K.; Nicolas, L.; Guérinot, A.; Reymond, S.; Cossy, J., *Org. Lett.* **2014**, 16, 4972; (b) Dijkstra, H. P.; Chuchuryukin, A.; Suijkerbuijk, B. M. J. M.; van Klink, G. P. M.; Mills, A. M.; Spek, A. L.; van Koten, G., *Adv. Synth. Catal.* **2002**, 344, 771.
- [19] *N*-Boc derivatives improve the mass recovery in the purification using conventional normal-phase chromatography. Deprotection is achieved using trifluoroacetic acid in quantitative yield (see SI). *N*-Ts derivatives may also be accessed (**3at-Ts**, see SI).
- [20] Lazareva, A.; Daugulis, O., *Org. Lett.* **2006**, 8, 5211.
- [21] (a) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R., *J. Am. Chem. Soc.* **1992**, 114, 10915; (b) Newcomb, M., *Tetrahedron* **1993**, 49, 1151.
- [22] Carbanionic stepwise carbometallation-type mechanisms seem unlikely as these may lead to β-alkoxy-elimination products with olefins like **2f,i,p**, which have never been detected.
- [23] Olivo, G.; Cussó, O.; Costas, M., *Chem. Asian J.* **2016**, 11, 3148.

[24] (a) Chen, K.; Que, L., *Chem. Commun.* **1999**, 1375; (b) Chen, K.; Que, L., *J. Am. Chem. Soc.* **2001**, *123*, 6327; (c) Blackman, A. G., *Eur. J. Inorg. Chem.* **2008**, 2633; for a recent example, see: (d) Koepke, S. J.; Light,

K. M.; VanNatta, P. E.; Wiley, K. M.; Kleber-Emmons, M. T. *J. Am. Chem. Soc.* **2017**, DOI: 10.1021/jacs.7b03278.

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Trimethylaluminum promotes the first [3+2] azomethine ylide cycloadditions that engage non-electrophilic olefins. This reaction allows the stereoselective combination of abundant feedstocks to access new polar poly-dentate scaffolds for ligand design.

Jorge Otero-Fraga, Samuel Suárez-Pantiga, Marc Montesinos-Magraner, Dennis Rhein and Abraham Mendoza*

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