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Chemical Innovation through Ligand Total Synthesis

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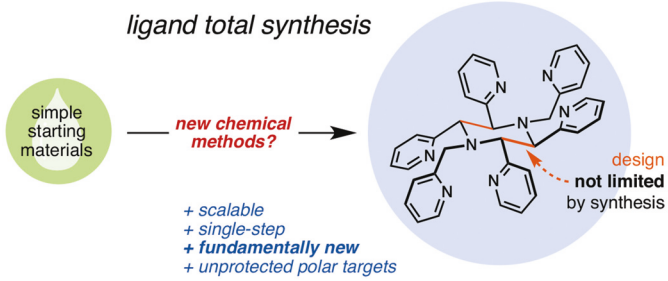
Dedicated to Prof. Shū Kobayashi



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Abstract Natural products are an abundant source of synthetic challenges that foster crucial breakthroughs in organic chemistry. Despite the superior complexity of these targets, ligand total synthesis can inspire solutions to unsolved chemical problems and provide access to creative catalyst designs. This Synpacts article presents a comparative analysis of natural and ligand total synthesis to provide a context for our recent research and motivate the importance of future undertakings in this area.

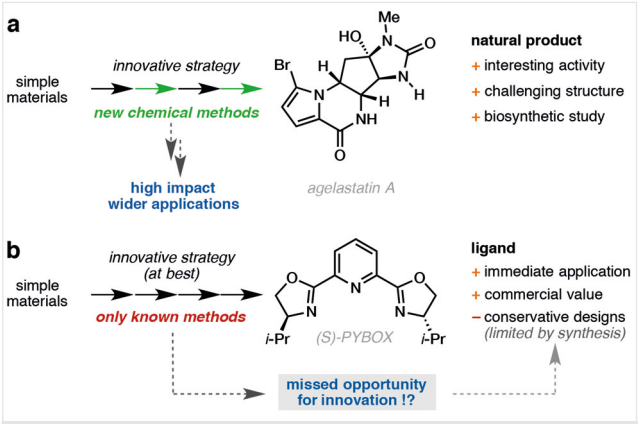
Key words total synthesis, catalysis, ligands, cycloaddition, aluminum, photochemistry

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 University 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

Organic synthesis is fundamentally contributing to the technological development of mankind, thus shaping the future of our society. It has enabled the discovery, supply, and exploitation of both natural and non-natural molecules that build the basis of our survival and comfort.[1] However, the total synthesis of products of natural origin is clearly leading at the forefront of synthetic chemistry.[2] Epic campaigns targeting complex compounds have repeatedly revealed the limitations of the best chemical methods available and have thus inspired the invention of new reactions (Scheme 1, a).[3] In this regard, the pursue of complex natural products has been a main driving force for ground-breaking innovation in synthetic organic chemistry. Recent emphasis on ideality,[4] scalability,[5] automatization,[4b,6] and the integration of C–H functionalization logics into retrosynthetic planning[7] have pushed the discovery of new reactivity even further. These chemical advances are arguably the most important legacy of total synthesis, as they fundamentally transform our perception of complexity and push the boundaries of organic chemistry and other sciences.

'The greatest challenges in synthesis […] provoke the chemist into dramatic action. In such circumstances, one should not bemoan the inability of existing chemistry to accomplish a desired transformation but rather rejoice at opportunity to discover its answer!' – Baran, Shenvi & O'Malley (2009)[3a]



Scheme 1 (a) Natural product total synthesis – continuous inspiration for new chemical reactions; (b) ligand total synthesis – a largely overlooked opportunity for chemical innovation.

While the invention of new tailored reactions is actively pursued in the total synthesis of natural products, the production of artificial compounds still largely relies on elegant applications of previously known methods (Scheme 1, b). In this Synpacts article we set out to illustrate this paradigm giving representative examples from both realms. Within this framework, our research aims to close the quality gap between the total synthesis of natural and non-natural compounds through the invention and exploration of new reactions that streamline access to interesting artificial molecules.

2 Ligands as Artificial Total Synthesis Targets

Ligand total synthesis bears immense potential to inspire fundamental advances with immediate value. The invention of direct methods to transform widely available precursors into complex ligands might pave the way to new explorations in catalysis way beyond traditional or popular motifs. Ligands are generally designed to be simple and accessible in a modular way. This synthetic criterion prioritizes easily accessible ligand classes over competing new designs that emanate from mechanistic (rather than purely synthetic) considerations. In the light of established synthetic methods, structurally complex ligands are often deemed impractical by the non-academic community and they are many times prematurely (and regrettably) discarded in academic research. However, the perception of complexity is only the result of a fatal series of underlying chemical problems, whose solutions may reveal new concepts and technologies with broader applications. Artificial ligands – unlike natural products – are not restricted by the dogmas of biosynthesis and unveil a distinct collection of meaningful synthetic challenges that shall become a new driving force for discovery. Thus, it is up to the synthetic community to tackle the fundamental challenges posed by ligand design, thus emulate the success stories of natural product total synthesis as a powerful stimulus for chemical innovation.[8]

The invention of conceptually new reactions for ligand synthesis is a major creative opportunity, whose motivation exceeds the production of commercial catalysts. Simplifying – or enabling – the synthesis of hardly accessible ligands is important to encourage hypothesis-driven explorations in catalysis and is essential for them to be adopted by the wider community. This ideal situation will only come true by devising succinct and robust syntheses based on practical building blocks and strategic reactions. *These are common features in the best total syntheses of natural products, which cope with complexity through the invention of new powerful methodologies. By adapting these standards to the total synthesis of ligands, we spot a major opportunity to foster innovation in organic chemistry and contribute to shaping the future evolution of catalysis.*[9]

3 Natural Product Total Synthesis: The Inspiration of Relevant New Methods

The synthesis of unique natural products offers the chance of solving fundamental problems in organic chemistry. Establishing an efficient and potentially scalable access to these daunting targets encourages bold – sometimes even artistic – retrosynthetic disconnections that would otherwise remain unexplored.[4a,5,7a,b] Beyond structural assignment and pharmaceutical testing, the main contribution of natural product total synthesis arises from the methods invented *en route* to the target. Some recent syntheses that tactically rely on the invention of new reactions are highlighted in Figure 1.

The unusual reactivity of cycloalkynes has been explored in recent years inspired by intricate natural products. The synthesis of *guanacastepenes N* and *O*[10] by Carreira introduced the insertion of cyclohexynes to promote annulative ring-expansion cascades[11] and motivated further studies on this unique disconnection.[12] Likewise, the synthesis of some strained members of the *welwitindolinone* family by Garg has inspired the development of enolate additions onto indolyne species.[13] This strategy has been further applied to the synthesis of other alkaloids[14] and has been extended to pyridynes.[15] Further research on complex alkaloids like *aspidophylline A*[16] also resulted in the invention of the interrupted Fischer indolization that is now widely applied.[17]

Terpenoid and polyketide natural products are a continuous source of inspiration for new methods. Fañanás and Rodríguez devised a robust and scalable total synthesis of scarce *berkelic acid* motivated by its medicinal properties.[18] The efficient assembly of the delicate spiroketal core required the invention of new ways to generate exocyclic enol ethers through carbophilic alkyne activation, a basic con-

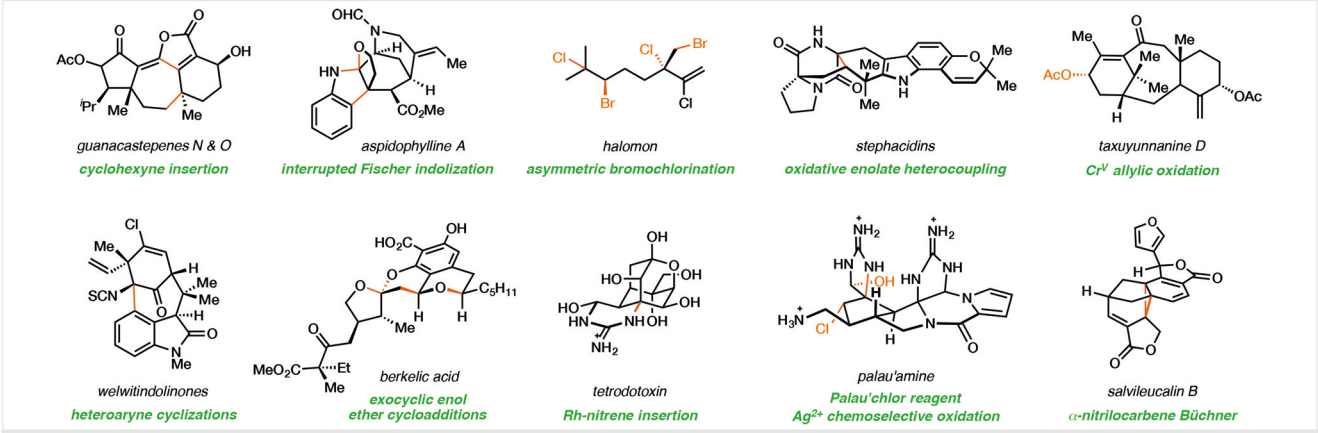


Figure 1 Selected examples of new chemical methods (in red) inspired by recent total syntheses of natural products

cept with many other applications.[19] Following the recent interest in polyhalogenated natural products,[20] Burns developed an elegant approach towards *halomon*.[21] To access this unusual chiral compound, a chemo-, regio-, and enantioselective bromochlorination method was invented,[21] which also streamlined access to related natural products.[22]

Baran greatly simplified the synthesis of *stephacidin A* through the identification of a key bridgehead C–C bond in the backbone.[23] The formation of this strategic bond required the development of oxidative enolate heterocoupling,[23,24] which was widely applicable and built the basis for other variants of the original protocol.[25] Likewise, a difficult C–N bridgehead bond in *tetrodotoxin* benefited from the rhodium-catalyzed nitrene insertion led by Du Bois.[26] This approach proved to be essential for his stunning syntheses of *saxitoxin*[27] and *gonyautoxin 3*,[28] but also evolved in other nitrene-transfer methods towards *manzacidins A* and *C*,[29] and *agelastatin A*.[30]

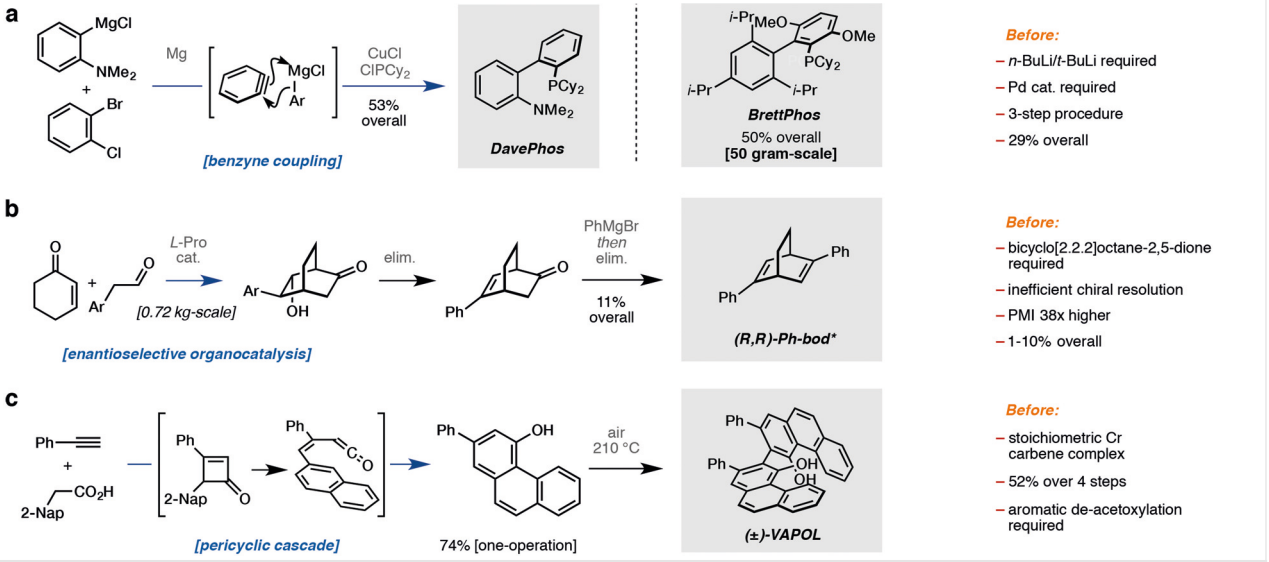
The structural features of complex natural products have also been the origin of new interesting reagents. A key chlorospirocylization *en route* to *palau'amine*,[31] led Baran to develop the chlorination reagent palau'chlor[32] and to find a new application for silver picolinate.[33] Both of these reagents were unique and superior to other popular alternatives and can now be widely applied to other challenging oxidations.[32,33] Similarly, a tough allylic oxidation towards the Taxol® intermediate *taxuyunnanine D* revealed the mild reactivity displayed by an unusual chromium(V) reagent that is now commercialized.[34] Apart from the discovery of novel reagents, the unique structures of natural products also enable the identification of privileged substrates for otherwise problematic reactions. A great recent example is Reisman's synthesis of *salvileucalin B*, whose furanone substructure inspired the exploration of α-diazo-β-ketonitriles in arene cyclopropanation.[35] Again, this methodology was later utilized to provide general access to other arene cyclopropanes lacking the furanone motif.[36]

4 Selected Syntheses of Important Ligands

Ligands are certainly compounds of commercial interest, which are normally involved in the production of valuable goods. For this reason, the syntheses of ligands with important applications are often thoroughly optimized, mostly conserving the same initial strategy. In this Synpacts article we highlight some selected examples whose original route was strategically re-designed (Scheme 2). While none of these syntheses rely on fundamentally new reactions, they do showcase the importance and potential of using innovative tactics in the production of ligands. Despite the elegant tailoring of pre-existing methods to prepare ligands such as *P*-stereogenic phosphines,[37] porphyrins,[38] rotaxanes,[39] and ferrocenes,[40] we are unaware of any ligand synthesis that is based on a new disconnection enabled by a conceptually new reaction – in contrast to the big number of natural product total syntheses that are enabled by new synthetic technologies (*cf.* Figure 1).

Buchwald biaryl ligands are state-of-the-art in palladium cross-coupling[41] and display unique properties in gold catalysis.[42] The original route to prepare electron-rich biaryl phosphines involved a three-step, two-operation, and low-yielding process based on a Suzuki–Miyaura coupling.[43] The situation changed dramatically when a classic benzyne strategy was implemented to build the biaryl system (DavePhos, Scheme 2, a).[44] This allowed to install the C–C bond and the phosphane simultaneously, while avoiding the use of organolithium reagents and palladium catalysts, thus reducing the unit operations and increasing the overall yield. Such a superior approach is now the standard strategy that is used to produce the most advanced ligands in the family (see BrettPhos, Scheme 2, a).[45]

During the last decade, chiral dienes emerged as privileged ligands for enantioselective catalysis.[46] The original routes to the ligand Ph-bod* all started from a bicyclic diketone and involved a low-yielding resolution using a chiral hydrazide or preparative HPLC on a chiral phase.[47] To over-



Scheme 2 Innovative ligand syntheses benefiting from previously known disconnections

come these drawbacks, an enantioselective approach based on a known organocatalytic transformation was implemented in kilogram scale (Scheme 2, b).[48] The product was then further elaborated over three steps to yield (*R*,*R*)-Ph-bod* reducing the costs significantly and improving the product mass intensity (PMI, kg of product/kg of reagents)[49] dramatically.

Although practical on small scale, the initial synthesis of VAPOL required the synthesis of an expensive Fischer carbene complex and a subsequent aromatic de-acetoxylation.[50] To address these limitations, a pericyclic cascade was adapted (Scheme 2, c), which used cheap standard reagents and strategically avoided the deoxygenation step.[51] It involved a ketene [2+2] cycloaddition with phenylacetylene, followed by two electrocyclic reactions, thus allowing efficient access to racemic VAPOL in two operations and high yield.

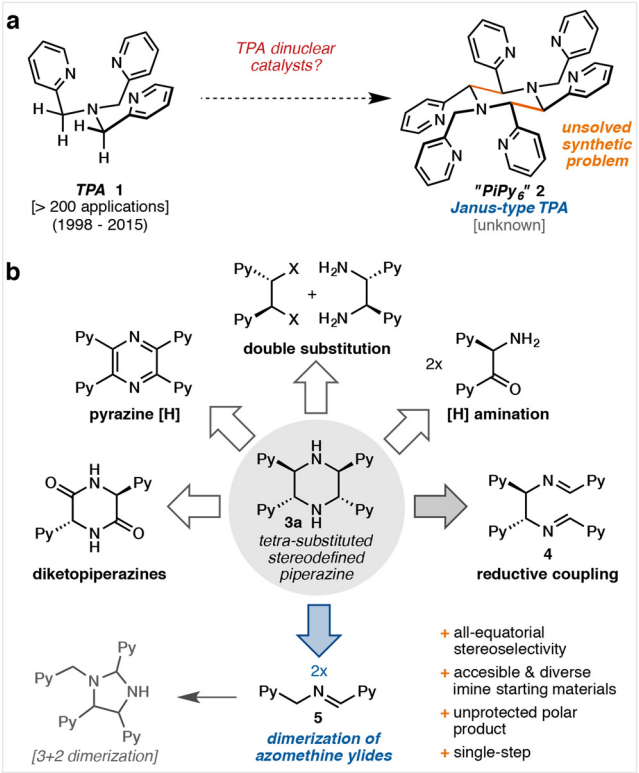
In stark contrast to natural products, the above examples (Scheme 2) clearly reveal that ligand synthesis has so far not been perceived as a playground for innovative chemistry but an area to expand, fine-tune, and validate methodologies that serve previously known disconnections.

5 Total Synthesis of the Ligand $PiPy_6$: The Invention of a New Organometallic Photoreaction

Tris(pyridine-2-ylmethyl)amine (TPA, **1**, Scheme 3, a) is a privileged ligand found in more than 1000 metal complexes with various applications, one being the C–H hydroxylation of unactivated hydrocarbons.[52] Our group aims to understand and address the deactivation pathways of non-heme iron catalysts in these oxidations. Thus, we became interested in a Janus-type analogue of TPA that we termed '$PiPy_6$' (**2**, Scheme 3, a).[9] The design of $PiPy_6$ intended to create a rigid, electronically insulated, and symmetric environment by using a minimally complex ligand (only differing in two hydrogen atoms with the parent TPA). In the case of iron-catalyzed C–H oxidations, we expected this design to translate into a dinuclear catalyst displaying an enhanced tolerance to water and higher performance.[9]

Despite the great amount of work on TPA ligands, at the onset of our research $PiPy_6$ (**2**) remained to be an unknown compound. The most feasible route towards $PiPy_6$ would require *N*-alkylation of the key precursor **3a** (Scheme 3, b), a stereodefined tetrasubstituted piperazine. Although piperazines are ubiquitous in the design of medicinal compounds, we were surprised to find the methods available unsuitable to prepare densely functionalized analogues. Possible retrosynthetic analyses of tetrasubstituted piperazines implied tedious routes involving non-strategic manipulations and widely inaccessible starting materials (Scheme 3, b). Using the best methods available, the most feasible route to **3a** would imply no less than four steps – with even longer sequences for more complex analogues – by using the reductive coupling of diimine **4** as the key reaction to set the desired stereochemistry.[53]

In contrast, the most logical disconnection of the key piperazine **3a** is clearly across both C–C bonds. In the forward sense it implies a [3+3] dimerization of azomethine ylides, which would be easily accessible from imines **5** using simple aldehydes and amines. However, these ylides are known to dimerize through a [3+2] process instead.[54] Thus, re-routing the reactivity of azomethine ylides constituted

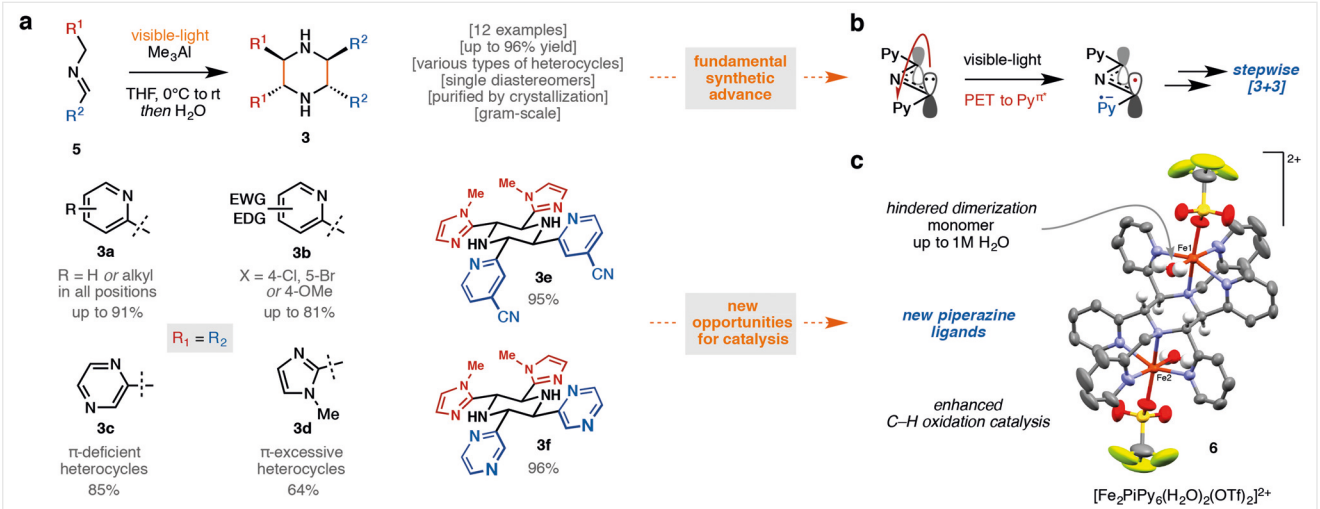


Scheme 3 (a) $PiPy_6$: a Janus-type TPA ligand hiding a fundamental challenge; (b) piperazines: unsuitable disconnections of **3** and our logic new approach.

an attractive challenge with fundamental implications beyond the synthesis of $PiPy_6$. *This situation is similar to countless natural products whose efficient syntheses required the invention of new key reactions.*

In our initial communication,[9] we have reported a solution to the preparative [3+3] synthesis of piperazines. We discovered that combining heterocyclic imines **5** with Me_3Al and visible light produced the desired piperazines **3** as single diastereoisomers (Scheme 4, a). This reaction furnishes products incorporating various heterocycles with different steric and electronic properties. Thus, various pyridines **3a**,**b** and other π-deficient **3c** and π-excessive heterocycles **3d** are well tolerated. Surprisingly, unsymmetrical imines combining electron-rich and electron-poor heterocycles give rise to even more complex piperazine derivatives **3e**,**f** as single regio- and stereoisomers. All these products are crystalline compounds that can be isolated directly from the crude reaction mixture without chromatography. The newly established synthesis thus stands out for its efficiency, selectivity, and practicality. All these features enable scalable production of new piperazine building blocks with tailor-made stereoelectronic properties ready to be further diversified upon *N*-alkylation.

This method is far from being an incremental extension of known reactions. In our view, it demonstrates the potential of ligand targets to unveil methodological gaps. In a fundamental sense, this reaction introduced a solution to the [3+3] dimerization of azomethine ylides.[55,56a] The latter is a challenging eight-electron cycloaddition that is formally forbidden in the ground state. Our solution takes advantage of the desired heterocyclic functionality and exploits its acceptor character to promote the cycloaddition using low-energy light (Scheme 4, b). The strong visible absorption of related azomethine–ylide complexes was known due to fascinating studies by Wolczanski,[56] but it was never exploited in a synthetic sense before our work in the area. Moreover, from a conceptual point of view this reaction introduced the combination of visible light with main-group organometallics in autosensitized reactions. We foresee that many more interesting reactions will emanate from this concept



Scheme 4 The total synthesis of the ligand $PiPy_6$ inspired the development of a new reaction and enabled explorations in C–H oxidation catalysis

in the future. Our extensive screening of organometallic promoters showcases the unique reactivity of the aluminum dialkyl fragment, which we are currently applying to address other unsolved synthetic challenges.

We designed this method to access a family of ligands, following synthetic logics that modestly mimic the retrosynthetic planning of elegant natural product total syntheses. As much as the synthesis of bioactive natural compounds allows further medicinal studies, ligand total synthesis will enable new explorations in catalysis. In our case, the dinuclear iron complex of the novel $PiPy_6$ ligand exhibited an exceptional tolerance to water (Scheme 4, c).[9] Fe_2PiPy_6 (**6**) is a monomeric species at concentrations of water two orders of magnitude superior to the critical dimerization concentration of the parent FeTPA. It also features enhanced C–H oxidation activity, which necessarily emanates from its unique piperazine backbone. We are now actively exploring the potential of piperazine and related ligands based on the principles that inspired $PiPy_6$.

6 Conclusions

Natural product total synthesis is arguably the best vehicle for innovation and discovery in synthetic chemistry. Its prevalence is beyond doubt and is likely a result of the superior structural complexity of natural compounds, as compared to those designed by mankind. However, natural products are constructed by a diverse, yet finite, series of biosynthetic motifs. Artificial compounds, such as complex ligands, certainly offer a distinct set of synthetic problems that foster innovation to advance the methodological and tactical toolkit of modern organic chemistry. Nonetheless, ligand synthesis has so far mainly profited from the elegant utilization of known organic reactions. Our recent report[9] is, to the best of our knowledge, the first exception to this rule. We consider ligand total synthesis as a fertile and underexploited field to nurture new synthetic concepts and technologies. The invention of new methods to form strategic bonds does transform our perception of modularity, accessibility, and complexity altogether. Beyond the sustainable supply of expensive catalysts, ligand total synthesis also offers an opportunity to explore new designs beyond the dogma and tradition of coordination chemistry and catalysis.

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References

(1) Keasling, J. D.; Mendoza, A.; Baran, P. S. *Nature (London, U.K.)* **2012**, *492*, 188.
(2) (a) Keding, S. J.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11937. (b) Nicolaou, K. C.; Snyder, S. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11929. (c) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943. (d) Nicolaou, K. C.; Hale, C. R. H.; Nilewski, C.; Ioannidou, H. A. *Chem. Soc. Rev.* **2012**, *41*, 5185. (e) Ball, P. *Nature (London, U.K.)* **2015**, *528*, 327.
(3) (a) Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530. (b) Nicolaou, K. C.; Baran, P. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 2678. (c) Nicolaou, K. C.; Hale, C. R. H. *Natl. Sci. Rev. U.S.A.* **2014**, *1*, 233.
(4) (a) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657. (b) Balieu, S.; Hallett, G. E.; Burns, M.; Bootwicha, T.; Studley, J.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 4398.
(5) (a) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854. (b) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193.
(6) (a) Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature (London, U.K.)* **2015**, *520*, 329. (b) Li, J.; Ballmer, S. G.; Gillis, E. P.; Fujii, S.; Schmidt, M. J.; Palazzolo, A. M.; Lehmann, J. W.; Morehouse, G. F.; Burke, M. D. *Science* **2015**, *347*, 1221. (c) Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature (London, U.K.)* **2014**, *513*, 183.
(7) (a) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (b) Davies, H. M. L.; Manning, J. R. *Nature (London, U.K.)* **2008**, *451*, 417. (c) Chen, D. Y. K.; Youn, S. W. *Chem. Eur. J.* **2012**, *18*, 9452.
(8) (a) Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R.; Myers, A. G. *Science* **2005**, *308*, 395. (b) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241. (c) Ledford, H. *Nature (London, U.K.)* **2010**, *468*, 608. (d) Jørgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878.
(9) Suárez-Pantiga, S.; Colas, K.; Johansson, M. J.; Mendoza, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 14094; and references cited therein.
(10) (a) Gampe, C. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 2962. (b) Gampe, C. M.; Carreira, E. M. *Chem. Eur. J.* **2012**, *18*, 15761.
(11) Gampe, C. M.; Boulos, S.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 4092.
(12) Gampe, C. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3766.
(13) (a) Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797. (b) Huters, A. D.; Styduhar, E. D.; Garg, N. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 3758.
(14) (a) Styduhar, E. D.; Huters, A. D.; Weires, N. A.; Garg, N. K. *Angew. Chem. Int. Ed.* **2013**, *52*, 12422. (b) Goetz, A. E.; Silberstein, A. L.; Corsello, M. A.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 3036.
(15) Goetz, A. E.; Garg, N. K. *Nat. Chem.* **2013**, *5*, 54.
(16) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877.

(17) (a) Moreno, J.; Picazo, E.; Morrill, L. A.; Smith, J. M.; Garg, N. K. *J. Am. Chem. Soc.* **2016**, *138*, 1162. (b) Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458.
(18) Fañanás, F. J.; Mendoza, A.; Arto, T.; Temelli, B.; Rodríguez, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 4930.
(19) (a) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7044. (b) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Chem. Eur. J.* **2008**, *14*, 10892. (c) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 1644. (d) Barluenga, J.; Calleja, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Chem. Eur. J.* **2010**, *16*, 7110.
(20) Nilewski, C.; Geisser, R. W.; Carreira, E. M. *Nature (London, U.K.)* **2009**, *457*, 573.
(21) Bucher, C.; Deans, R. M.; Burns, N. Z. *J. Am. Chem. Soc.* **2015**, *137*, 12784.
(22) Hu, D. X.; Seidl, F. J.; Bucher, C.; Burns, N. Z. *J. Am. Chem. Soc.* **2015**, *137*, 3795.
(23) (a) Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 606. (b) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678.
(24) Baran, P. S.; DeMartino, M. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 7083.
(25) (a) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546. (b) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (c) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568.
(26) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.
(27) Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964.
(28) Mulcahy, J. V.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 12630.
(29) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950.
(30) Wehn, P. M.; Du Bois, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3802.
(31) (a) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 1095. (b) Su, S.; Rodriguez, R. A.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 13922.
(32) Rodriguez, R. A.; Pan, C.-M.; Yabe, Y.; Kawamata, Y.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 6908.
(33) Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 16490.
(34) Wilde, N. C.; Isomura, M.; Mendoza, A.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4909.
(35) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774.
(36) Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7304.
(37) (a) Gatineau, D.; Giordano, L.; Buono, G. *J. Am. Chem. Soc.* **2011**, *133*, 10728. (b) León, T.; Riera, A.; Verdaguer, X. *J. Am. Chem. Soc.* **2011**, *133*, 5740. (c) Huang, Y.; Li, Y.; Leung, P.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2014**, *136*, 4865. (d) Du, Z.-J.; Guan, J.; Wu, G.-J.; Xu, P.; Gao, L.-X.; Han, F.-S. *J. Am. Chem. Soc.* **2015**, *137*, 632. (e) Han, Z. S.; Zhang, L.; Xu, Y.; Sieber, J. D.; Marsini, M. A.; Li, Z.; Reeves, J. T.; Fandrick, K. R.; Patel, N. D.; Desrosiers, J.-N.; Qu, B.; Chen, A.; Rudzinski, D. M.; Samankumara, L. P.; Ma, S.; Grinberg, N.; Roschangar, F.; Yee, N. K.; Wang, G.; Song, J. J.; Senanayake, C. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 5474. (f) Chan, V. S.; Chiu, M.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6021.
(38) Senge, M. O. *Acc. Chem. Res.* **2005**, *38*, 733.
(39) Lewis, J. E. M.; Bordoli, R. J.; Denis, M.; Fletcher, C. J.; Galli, M.; Neal, E. A.; Rochette, E. M.; Goldup, S. M. *Chem. Sci.* **2016**, *7*, 3154.
(40) Gao, D.-W.; Gu, Q.; You, S.-L. *J. Am. Chem. Soc.* **2016**, *138*, 2544.
(41) (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.
(42) (a) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326.
(43) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.
(44) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334.
(45) Hoshiya, N.; Buchwald, S. L. *Adv. Synth. Catal.* **2012**, *354*, 2031.
(46) (a) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4482. (b) Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *Synlett* **2011**, 1345. (c) Feng, X.; Du, H. *Asian J. Org. Chem.* **2012**, *1*, 204.
(47) (a) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (b) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503.
(48) Abele, S.; Inauen, R.; Spielvogel, D.; Moessner, C. *J. Org. Chem.* **2012**, *77*, 4765.
(49) Jimenez-Gonzalez, C.; Ponder, C. S.; Broxterman, Q. B.; Manley, J. B. *Org. Process Res. Dev.* **2011**, *15*, 912.
(50) Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S.-M.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392.
(51) Ding, Z.; Osminski, W. E. G.; Ren, H.; Wulff, W. D. *Org. Process Res. Dev.* **2011**, *15*, 1089.
(52) Blackman, A. G. *Eur. J. Inorg. Chem.* **2008**, 2633.
(53) (a) Mercer, G. J.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 1591. (b) Karlsson, S.; Lindberg, J.; Sörensen, H. *Org. Process Res. Dev.* **2013**, *17*, 1552.
(54) Erkizia, E.; Aldaba, E.; Vara, Y.; Arrieta, A.; Gornitzka, H.; Cossio, F. P. *ARKIVOC* **2005**, *(ix)*, 189.
(55) This process had been documented only rarely before our work, see: (a) Chen, Z.; Wu, J.; Chen, Y.; Li, L.; Xia, Y.; Li, Y.; Liu, W.; Lei, T.; Yang, L.; Gao, D.; Li, W. *Organometallics* **2012**, *31*, 6005. (b) Cariou, R.; Gibson, V. C.; Tomov, A. K.; White, A. J. P. *J. Organomet. Chem.* **2009**, *694*, 703. (c) Trepanier, S. J.; Wang, S. *Can. J. Chem.* **1996**, *74*, 2032. (d) Westerhausen, M.; Bollwein, T.; Mayer, P.; Piotrowski, H.; Pfitzner, A. *Z. Anorg. Allg. Chem.* **2002**, *628*, 1425. (e) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329. (f) Huisgen, R.; Niklas, K. *Heterocycles* **1984**, *22*, 21. (g) Guerra, P. V.; Yaylayan, V. A. *Agric. Food Chem.* **2010**, *58*, 12523.
(56) (a) Frazier, B. A.; Wolczanski, P. T.; Lobkovsky, E. B.; Cundari, T. R. *J. Am. Chem. Soc.* **2009**, *131*, 3428. (b) Frazier, B. A.; Williams, V. A.; Wolczanski, P. T.; Bart, S. C.; Meyer, K.; Cundari, T. R.; Lobkovsky, E. B. *Inorg. Chem.* **2013**, *52*, 3295. (c) Frazier, B. A.; Bartholomew, E. R.; Wolczanski, P. T.; DeBeer, S.; Santiago-Berrios, M.; Abruna, H. D.; Lobkovsky, E. B.; Bart, S. C.; Mossin, S.; Meyer, K.; Cundari, T. R. *Inorg. Chem.* **2011**, *50*, 12414.