Cycloaddition

Scalable Synthesis of Piperazines Enabled by Visible-Light Irradiation and Aluminum Organometallics

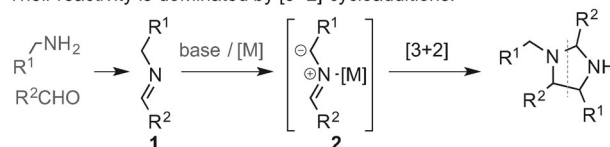*Samuel Suárez-Pantiga, Kilian Colas, Magnus J. Johansson, and Abraham Mendoza**

Dedicated to Professor José Barluenga

Abstract: The development of more active C−H oxidation catalysts has inspired a rapid, scalable, and stereoselective assembly of multifunctional piperazines through a [3+3] coupling of azomethine ylides. A combination of visible-light irradiation and aluminum organometallics is essential to promote this transformation, which introduces visible-light photochemistry of main-group organometallics and sets the basis for new and promising catalysts.
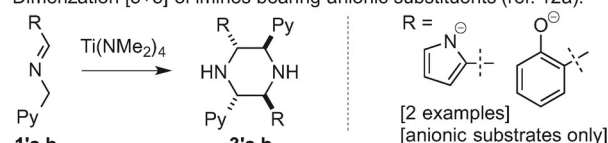
The aggregation of homogeneous catalysts in solution is an obscure phenomenon whose influence is rarely addressed in catalytic studies, thus leading to off-cycle catalyst depletion and/or mechanistic misinterpretation.[1] Deactivation of some important oxidation catalysts are linked to oligomerization,[2] which we aim to address using new piperazine ligands. Piperazines decorated with pyridine (and related) substituents are analogues of pyridylamine ligands relevant to water oxidation,[3] epoxidation of olefins,[4] and C−H oxidation of alkanes.[5] Although these heterocycles are ubiquitous in inorganic chemistry,[6] medicinal chemistry,[7] and natural products,[7a,8] at the onset of our work only long syntheses with problems regarding stereocontrol could be foreseen towards piperazines functionalized at all carbon positions.[6–8] This challenge inspired the direct intermolecular photoreaction, reported herein, to prepare polyfunctional piperazines in one stereoselective and scalable transformation, thus using readily available modular precursors and a unique conceptual basis.

Imines (**1**) are versatile compounds which can be easily synthesized from libraries of simple aldehydes and amines
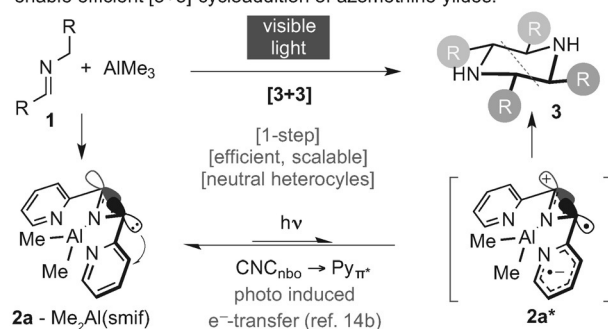
[*] Dr. S. Suárez-Pantiga, K. Colas, Dr. A. Mendoza
Department of Organic Chemistry and Berzelii EXSELENT Center for Porous Materials, Stockholm University
Arrhenius Laboratory, 10691 Stockholm (Sweden)
E-mail: abraham.mendoza@su.se
Homepage: http://www.organ.su.se/am/

Dr. M. J. Johansson
Innovative Medicines, Cardiovascular and Metabolic Diseases, Medicinal Chemistry, AstraZeneca R&D
Pepparedsleden 1, 43183 Mölndal (Sweden)

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201505608.

Scheme 1. Visible light reroutes the native reactivity of aluminum azomethine ylides.

(Scheme 1a). Upon treatment with a base and a chelating metal, imines (**1**) can generate powerful azomethine ylide intermediates (**2**), which dimerize through a [3+2] cycloaddition in the absence of an electron-deficient dipolarophile.[9] We envisioned that rerouting the reactivity of azomethine ylides into a [3+3] cycloaddition[10] would be the ideal strategy to access carbon-functionalized piperazines in one step. At the onset of this work, this process had rarely been documented,[11] often only as a minor side-reaction.[12] The feasibility of our approach is partly supported by the reports of the groups of Gibson[12b] and Xia-Li[12a] on the dimerization of titanium complexes derived from the imines **1′a,b**, which bear anionic substituents (Scheme 1b).[12a,g] Unfortunately, in-house experimentation aimed at extending this chemistry to substrates with the desired neutral substituents proved fruitless (see the Supporting Information),[13] probably because of an insufficient driving force and/or fast retro-cycloaddition.[14]

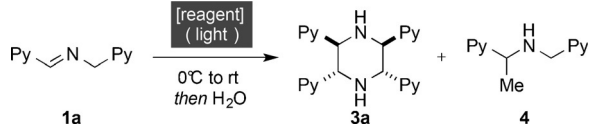Azomethine ylides bearing pyridine substituents (smifs)[14e] have been extensively studied in transition-metal

complexes[14a–c] and are reported to absorb visible light, thus stimulating charge transfer from the aza-allyl anion to the pyridine ring (2a→2a*; Scheme 1c).[14c, 15] We reasoned that intramolecular photostimulated electron transfer[16,17] could generate a key ylide diradical state, capable of circumventing the problematic ground-state [3+3] cycloaddition.[18] Herein, we report an original combination of visible-light irradiation and an aluminum organometallic promoter which enables a practical and scalable synthesis of polyfunctional piperazines through a [3+3] dimerization reaction. The process allows access to carbon-functionalized piperazine products in one step, with complete stereoselectivity, and through a redox-neutral[19] and strategic [3+3] disconnection.[18] The two C−C bonds in the ring are created in the same transformation, as opposed to traditional piperazine syntheses, based on multistep sequences of cyclization and reduction reactions (ketopiperazine,[20] pyrazine reduction[21] or intramolecular aza-pinacol coupling).[22] Using the best combination of these methods, a piperazine product like 3a (see Table 1) would take no less than four steps in the making (even longer for more elaborated substituents or unsymmetrical analogs),[22a, 23] thus discouraging its exploration in catalysis.

Our study focused on aluminum reagents, inspired by a report in which small traces of the piperazine 3a were detected, using a related amine substrate.[12c,d] Initially, we tested our photochemical hypothesis on the imine 1a using a cold white fluorescent bulb (Table 1). Having in mind that high-energy diradical species could be generated in this process, we took special precautions to remove oxygen from the system. While aluminum amides, alkoxides, and aromatic organometallics were proven ineffective (entries 1–3), Me3Al

in toluene produced the desired product 3a in moderate yield (entry 4). The main competitive by-product was the amine 4, which stems from methyl transfer to the imine carbon atom in 1a. Gratifyingly, this by-product is minimized when using tetrahydrofuran as the solvent (entry 5). Different light sources were screened (entries 5–7), among which white LEDs were optimal in performance and reproducibility [(89±3)% yield, $N = 9$]. Relevant control experiments revealed that extensive over-irradiation has only a moderate deleterious effect (entry 8), whereas deoxygenation is far more crucial (entry 9). Visible-light irradiation is essential to observe the desired reactivity (entry 10), and pleasingly supports our original hypothesis.

Additional control experiments demonstrate that this reaction is initiated by the formation of a Me2Al(smif) complex (2a) accelerated by visible-light irradiation and characteristic of the organoaluminum manifold.[13] Me3Al is superior to any other Lewis acid or organometallic we have employed thus far (see Table S1 in the Supporting Information),[13] thereby taking a double role in this process by acting as a base and a [Me2Al]+ source. The acid-base reaction between 1a and Me3Al can be monitored by NMR spectroscopy, thus allowing characterization of 2a and the detection of methane as by-product (Scheme 2a).[25] The formation of 2a is also observed by using a mixture of Li(smif) 2b and Me2AlCl, which upon light irradiation evolves to the piperazine 3a in 65% yield. Nevertheless, no 3a is detected when either Me2AlCl or light irradiation is removed from this system, thus highlighting the essential role of both visible light and the [Me2Al]+ fragment on this reaction. The UV-VIS spectrum of 2a (Scheme 2b) presents strong absorptions at $\lambda = 394$ and 570 nm, and are within the range of the intraligand bands (CNC$_{nbo}$→Py$_{\pi*}$) observed by Wolczanski and co-workers in transition-metal smif complexes [$\lambda = (420\pm40)$ and (590 ± 30) nm].[14b,c,15] We have also monitored the

***Table 1:*** Optimization of the dimerization of 1a with aluminum reagents.[a]

Entry	Reagent	Solvent[b]	Light	Yield [%][c] 3a	4
1	[Al(NR2)3]2[d]	toluene	CFL[e]	0	0
2	Al(OtBu)3	toluene	CFL[e]	0	0
3	AlPh3	toluene	CFL[e]	0	0
4	AlMe3	toluene	CFL[e]	56	15
5	AlMe3	THF	CFL[e]	60	2
6	AlMe3	THF	W[g]	58	2
7	AlMe3	THF	LED[h]	89	3
8	AlMe3	THF	LED[h]	74[i]	2[i]
9	AlMe3	THF	LED[h]	11[f]	23[f]
10	AlMe3	THF	none	11	3

[a] Reaction conditions: imine 1a (0.2 mmol), Me3Al (0.2 mmol), solvent (0.2 mL), 0°C to RT, 4 h. [b] Degassed by three freeze-pump-thaw cycles. [c] Yields determined by 1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [d] NR2 = pyrrolidin-1-yl.[24] [e] Cold fluorescent bulb 20W (1230 lm). [f] Solvent not degassed. [g] Tungsten filament bulb 100 W. [h] 14.4 W cold white LED strip (1100 lm). [i] Reaction time 24 h. CFL=compact fluorescent light, LED=light-emitting diode, THF=tetrahydrofuran.
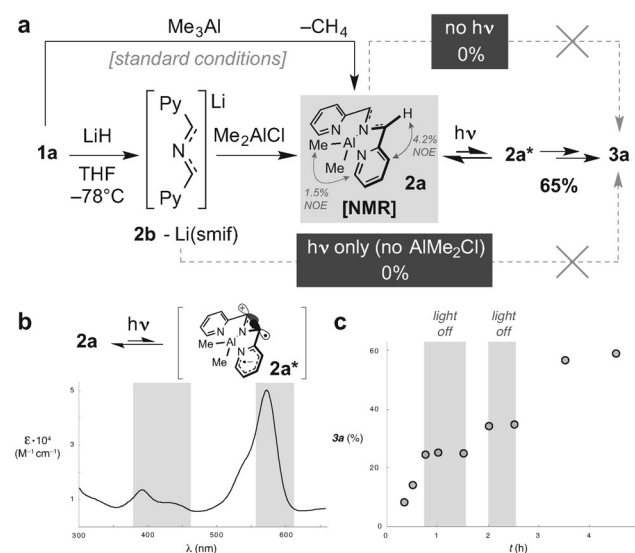
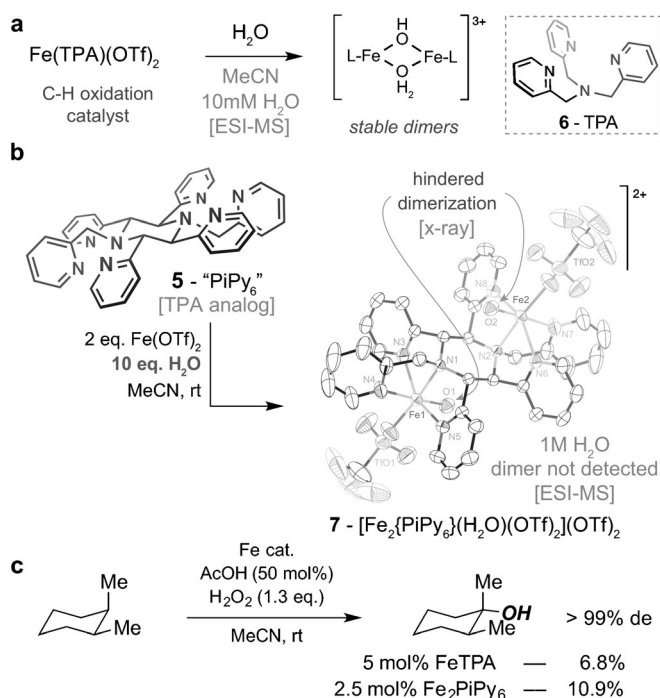***Scheme 2.*** a) Characterization of 2a and evolution to the piperazine 3a: light and [Me2Al]+ are essential. b) UV-VIS spectrum of 2a, featuring intraligand charge-transfer transitions.[14b] c) Formation of 3a is clearly accelerated by visible light.
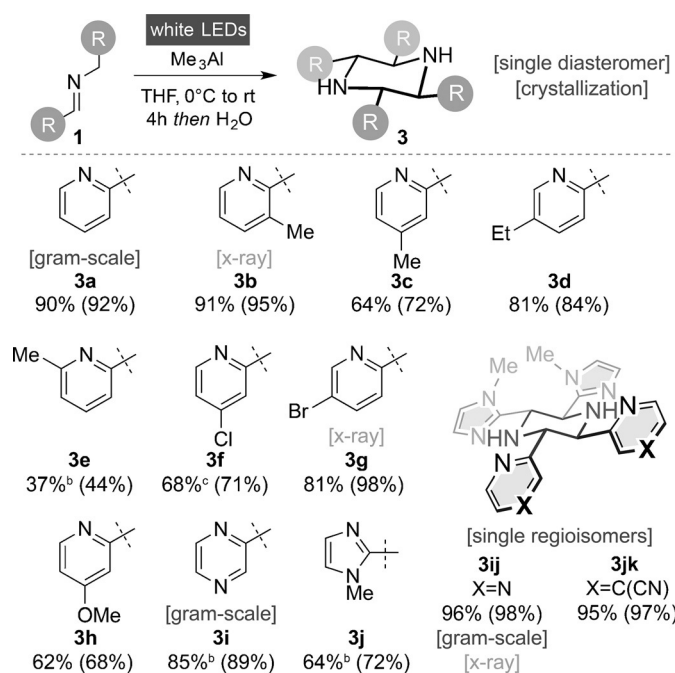
Scheme 3. Scalable synthesis of piperazines. [a] Yield of isolated product is reported. The yield of the crude reaction mixture was determined by ^1H NMR spectroscopy and is given within parentheses. See the Supporting Information. [b] Reaction time 20 h. [c] Reaction time 16 h.

Scheme 4. a) Iron pyridylamine complexes dimerize readily in the presence of trace amounts of water. b) The dinuclear Fe_2PiPy_6 complex **7** is monomeric at high water concentrations. c) **7** is more active than FeTPA in stereoretentive C−H oxidation of alkanes with aqueous H_2O_2. Tf = trifluoromethanesulfonyl.

reaction in the presence and absence of visible light (Scheme 2c), thus observing a clear relationship between light irradiation periods and the formation of **3a**. All these results are fully consistent with the excited diradical intermediate **2a***, which we reasonably propose.[26]

Using the optimal reaction conditions, we explored the reactivity of this system with the aim of developing ligands with diverse stereoelectronic properties (Scheme 3). First, it was found that alkyl groups are tolerated in all four available positions on the pyridine ring (**3a–e**). The efficiencies are satisfactory with the notable exception of the 6-methyl-substituted product **3e**, thus suggesting that a strong inter-action between aluminum and the heterocycle occurs in the course of the reaction (observed by NMR spectroscopy; Scheme 2a). Electron-deficient (halogens or nitrile) and electron-donating (alkoxy) groups are incorporated into the piperazine products **3f–h,jk**. Other heterocyclic substituents were investigated to explore the limits of this reaction and obtain ligands with substantially different properties. While pyridine is ubiquitous in related bibliography,[12a–c,14a] we were delighted to observe that other π-deficient (pyrazine: **3i,ij**) and π-excessive (imidazole: **3j,ij,jk**) heterocyclic substituents are seamlessly incorporated into our system. Remarkably, unsymmetrical imines bearing pyridine, pyrazine, and imidazole substituents are also excellent substrates, thus giving rise to **3ij,jk**, which feature opposite regioselectivity[27] to the ones found in previous systems (Scheme 1).[9,12a,b] We find this regioselectivity suggestive of a distinct mechanism operating in this reaction. In all cases one diastereoisomer is detected in the crude reaction mixture and the products are efficiently isolated by direct recrystallization.

All these features make this method amenable for scale-up, which we demonstrate for **3a** (2.27 g, 72 % yield), **3i** (1.22 g, 64 % yield), and **3ij** (1.15 g, 91 % yield). By taking advantage of their crystallinity, the structures of **3b,g,ij** have been confirmed using X-ray diffraction analysis.[28]

Diastereomerically pure piperazines (**3**), are rigid ana-logues of relevant pyridylamine ligands like **6** (TPA; Scheme 4a), which has led to important catalysts for water oxidation,[3] epoxidation of olefins,[4] and C−H oxidation of alkanes.[5] Iron pyridylamine catalysts suffer from a fast deactivation in the presence of water (coming from aqueous H_2O_2), thus forming stable oxo-bridged dimers (Scheme 4a).[2] Therefore new catalysts which exhibit a superior tolerance to water would minimize the main deactivation pathway.[2] With gram quantities of **3a** in hand, we elaborated it to the densely functionalized ligand **5** (PiPy₆; Scheme 4b), which is closely related to **6**. Aiming to discern the effect of the piperazine nucleus on the dimerization of iron catalysts, we treated **5** with $Fe(OTf)_2$ and excess water. We were delighted to observe the formation of the dinuclear mono-meric complex **7** (confirmed by X-ray diffraction analysis),[28] lacking the intermetallic oxo bridges (Fe-O-Fe) which are commonly found in FeTPA hydrates.[2a,29] A preliminary study revealed that unlike FeTPA, the oxo-briged dimeric species derived from **7**, were not detected in solution, even at high concentrations of water. As a result, the catalytic perfor-mance of **7** is superior to the parent FeTPA in a challenging alkane C−H oxidation reaction (Scheme 4c).[5] The complex **7** is an active catalyst that performs metal-centered (non-Fenton) stereoretentive oxidation using aqueous H_2O_2, with

a 60% increased activity compared to that of FeTPA. Taking advantage of the basic difference between FeTPA and **7** (which we believe is a consequence of its dinuclear design), we plan to develop more elaborated (and active) catalysts for this[5] and other oxidation reactions[3,4] based on the singular, rigid, three-dimensional topology defined by the densely functionalized piperazines which are now available.[14a,c]

In summary, we have developed a scalable and stereoselective synthesis of polar piperazine compounds through a [3+3] cycloaddition of azomethine ylides. This way, densely functionalized piperazines become available in one step from readily available imine starting materials. The visible-light photoinduced electron transfer of aluminum organometallics, introduced herein, has been demonstrated to be essential for this transformation and has the potential to unveil other practical reactions with unique selectivity profiles in the future. This reaction gives access to new relevant ligands in meaningful quantities and is of strategic importance to further developments in catalysis. An in-depth understanding of this reaction and further application of the concepts and products presented herein are being documented in our laboratories and will be reported in due course.

Experimental Section

A vial was charged under argon atmosphere with a solution of imine **1** (0.2 mmol, 1.0 equiv) in freshly *degassed* anhydrous THF (0.2 mL). The solution was cooled down to 0–4 °C and AlMe₃ (1.0 equiv) was added dropwise under white LED irradiation and further stirred for 4–24 h, as specified. Then, the reaction mixture was quenched by careful addition of deionized water, CHCl₃, and NaOH (see the Supporting Information for details). The solids were filtered off, the filtrate concentrated in vacuo, and purified by recrystallization, to obtain pure piperazine **3**.

Acknowledgements

Keywords: aluminum · cycloaddition · heterocycles · oxidation · photochemistry

[1] a) D. Weber, M. R. Gagne, *Chem. Sci.* **2013**, *4*, 335–338; b) R. D. Baxter, D. Sale, K. M. Engle, J.-Q. Yu, D. G. Blackmond, *J. Am. Chem. Soc.* **2012**, *134*, 4600–4606; c) A. Kina, H. Iwamura, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 3904–3905; d) T. Rosner, J. Le Bars, A. Pfaltz, D. G. Blackmond, *J. Am. Chem. Soc.* **2001**, *123*, 1848–1855; e) L. P. C. Nielsen, C. P. Stevenson, D. G. Blackmond, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 1360–1362.

[2] a) I. V. Korendovych, S. V. Kryatov, W. M. Reiff, E. V. Rybak-Akimova, *Inorg. Chem.* **2005**, *44*, 8656–8658; b) N. A. Vermeulen, M. S. Chen, M. C. White, *Tetrahedron* **2009**, *65*, 3078–3084; c) L. Gómez, M. Canta, D. Font, I. Prat, X. Ribas, M. Costas, *J. Org. Chem.* **2013**, *78*, 1421–1433; d) L. Gómez, I. Garcia-Bosch, A. Company, J. Benet-Buchholz, A. Polo, X. Sala, X. Ribas, M. Costas, *Angew. Chem. Int. Ed.* **2009**, *48*, 5720–5723; *Angew. Chem.* **2009**, *121*, 5830–5833; e) V. A. Yazerski, P. Spannring, D. Gatineau, C. H. M. Woerde, S. M. Wieclawska, M. Lutz, H. Kleijn, R. J. M. Klein Gebbink, *Org. Biomol. Chem.* **2014**, *12*, 2062–2070.

[3] H.-Y. Wang, E. Mijangos, S. Ott, A. Thapper, *Angew. Chem. Int. Ed.* **2014**, *53*, 14499–14502; *Angew. Chem.* **2014**, *126*, 14727–14730.

[4] a) K. Chen, M. Costas, J. Kim, A. K. Tipton, L. Que, *J. Am. Chem. Soc.* **2002**, *124*, 3026–3035; b) M. Fujita, M. Costas, L. Que, *J. Am. Chem. Soc.* **2003**, *125*, 9912–9913; c) W. N. Oloo, K. K. Meier, Y. Wang, S. Shaik, E. Munck, L. Que, *Nat. Commun.* **2014**, *5*, 3046; d) Y. Zang, J. Kim, Y. Dong, E. C. Wilkinson, E. H. Appelman, L. Que, *J. Am. Chem. Soc.* **1997**, *119*, 4197–4205.

[5] a) K. Chen, L. Que, Jr., *Chem. Commun.* **1999**, 1375–1376; b) K. Chen, L. Que, *J. Am. Chem. Soc.* **2001**, *123*, 6327–6337.

[6] a) S. L. Hancock, M. F. Mahon, M. D. Jones, *Dalton Trans.* **2011**, *40*, 2033–2037; b) Z. Zhang, X. Xu, S. Sun, Y. Yao, Y. Zhang, Q. Shen, *Chem. Commun.* **2009**, 7414–7416; c) A. R. Paital, D. Mandal, X. Huang, J. Li, G. Aromí, D. Ray, *Dalton Trans.* **2009**, 1352–1362; d) G. D. Fallon, K. S. Murray, B. Spethmann, J. K. Yandell, J. H. Hodgkin, B. C. Loft, *J. Chem. Soc. Chem. Commun.* **1984**, 1561–1563.

[7] a) A. D. Borthwick, *Chem. Rev.* **2012**, *112*, 3641–3716; b) M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361; c) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930; d) R. M. Esnouf, J. Ren, A. L. Hopkins, C. K. Ross, E. Y. Jones, D. K. Stammers, D. I. Stuart, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 3984–3989; e) J. R. Tagat, R. W. Steensma, S. W. McCombie, D. V. Nazareno, S.-I. Lin, B. R. Neustadt, K. Cox, S. Xu, L. Wojcik, M. G. Murray, N. Vantuno, B. M. Baroudy, J. M. Strizki, *J. Med. Chem.* **2001**, *44*, 3343–3346.

[8] a) N. K. Garg, R. Sarpong, B. M. Stoltz, *J. Am. Chem. Soc.* **2002**, *124*, 13179–13184; b) K. C. Nicolaou, S. Totokotsopoulos, D. Giguere, Y. P. Sun, D. Sarlah, *J. Am. Chem. Soc.* **2011**, *133*, 8150–8153; c) H. Wang, S. E. Reisman, *Angew. Chem. Int. Ed.* **2014**, *53*, 6206–6210; *Angew. Chem.* **2014**, *126*, 6320–6324; d) J. A. Codelli, A. L. Puchlopek, S. E. Reisman, *J. Am. Chem. Soc.* **2012**, *134*, 1930–1933; e) E. J. Corey, D. Y. Gin, R. S. Kania, *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203.

[9] E. Erkizia, E. Aldaba, Y. Vara, A. Arrieta, H. Gornitzka, F. P. Cossio, *ARKIVOC* **2005**, *2005*, 189–199.

[10] a) H. Guo, H. Liu, F.-L. Zhu, R. Na, H. Jiang, Y. Wu, L. Zhang, Z. Li, H. Yu, B. Wang, Y. Xiao, X.-P. Hu, M. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 12641–12645; *Angew. Chem.* **2013**, *125*, 12873–12877; b) Z.-L. He, H.-L. Teng, C.-J. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2934–2938; *Angew. Chem.* **2013**, *125*, 3006–3010; c) M. Potowski, J. O. Bauer, C. Strohmann, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2012**, *51*, 9512–9516; *Angew. Chem.* **2012**, *124*, 9650–9654; d) C. Yuan, H. Liu, Z. Gao, L. Zhou, Y. Feng, Y. Xiao, H. Guo, *Org. Lett.* **2015**, *17*, 26–29; e) F. Shi, R.-Y. Zhu, W. Dai, C.-S. Wang, S.-J. Tu, *Chem. Eur. J.* **2014**, *20*, 2597–2604.

[11] R. Huisgen, K. Niklas, *Heterocycles* **1984**, *22*, 21–26.

[12] a) Z. Chen, J. Wu, Y. Chen, L. Li, Y. Xia, Y. Li, W. Liu, T. Lei, L. Yang, D. Gao, W. Li, *Organometallics* **2012**, *31*, 6005–6013; b) R. Cariou, V. C. Gibson, A. K. Tomov, A. J. P. White, *J. Organomet. Chem.* **2009**, *694*, 703–716; c) S. J. Trepanier, S. Wang, *Can. J. Chem.* **1996**, *74*, 2032–2040; d) Wang and co-

workers isolated **3a**, as a minor compound from a related amine. They stated explicitly that "independent synthesis of this compound has not been successful"; e) M. Westerhausen, T. Bollwein, P. Mayer, H. Piotrowski, A. Pfitzner, *Z. Anorg. Allg. Chem.* **2002**, *628*, 1425–1432; f) W. H. Pearson, D. P. Szura, M. J. Postich, *J. Am. Chem. Soc.* **1992**, *114*, 1329–1345; g) Two examples of free piperazines in milligram quantities are reported by Xia-Li (Ref. [12a]). Free piperazines are not reported in Gibson's contribution (Ref. [12b]).

[13] We have also experimented with a plethora of other common Lewis acids and bases without success (see Table S1 in the Supporting Information).

[14] a) B. A. Frazier, P. T. Wolczanski, E. B. Lobkovsky, T. R. Cundari, *J. Am. Chem. Soc.* **2009**, *131*, 3428–3429; b) B. A. Frazier, E. R. Bartholomew, P. T. Wolczanski, S. DeBeer, M. Santiago-Berrios, H. D. Abruna, E. B. Lobkovsky, S. C. Bart, S. Mossin, K. Meyer, T. R. Cundari, *Inorg. Chem.* **2011**, *50*, 12414–12436; c) B. A. Frazier, V. A. Williams, P. T. Wolczanski, S. C. Bart, K. Meyer, T. R. Cundari, E. B. Lobkovsky, *Inorg. Chem.* **2013**, *52*, 3295–3312; d) Fe-smif complexes by Wolczanski and co-workers exist in equilibrium with piperazine dinuclear species (Ref. [14a]), which is shifted to the latter only in the solid state. This behavior (and potential iron contamination) makes this approach unsuitable for the preparation of the free ligands; e) smif = 1,3-di-(2-pyridyl)-2-azaallyl.

[15] The UV-VIS spectra of smif complexes were assigned to charge-transfer transitions from CNC non-bonding orbitals to the heterocycle π^* (CNC{nbo}→Py{π^*}), with a small MLCT contribution.

[16] a) D. Ravelli, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2013**, *42*, 97–113; b) M. Fagnoni, D. Dondi, D. Ravelli, A. Albini, *Chem. Rev.* **2007**, *107*, 2725–2756; c) J. O. Bunte, J. Mattay, M. Oelgemöller in *Synthetic Organic Photochemistry* (Eds.: J. Mattay, A. Griesbeck), CRC, Boca Raton, FL, **2004**, pp. 269–297.

[17] For recent examples, see: a) E. Arceo, I. D. Jurberg, A. Alvarez-Fernandez, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750–756; b) E. Arceo, A. Bahamonde, G. Bergonzini, P. Melchiorre, *Chem. Sci.* **2014**, *5*, 2438–2442; c) M. Silvi, E. Arceo, I. D. Jurberg, C. Cassani, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 6120–6123; d) J. W. Beatty, C. R. Stephenson, *J. Am. Chem. Soc.* **2014**, *136*, 10270–10273; e) D. Hager, D. W. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 16986–16989; f) H.-Q. Do, S. Bachman, A. C. Bissember, J. C. Peters, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*,

2162–2167; g) H. Huo, X. Shen, C. Wang, L. Zhang, P. Rose, L.-A. Chen, K. Harms, M. Marsch, G. Hilt, E. Meggers, *Nature* **2014**, *515*, 100–103; h) J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon, *Science* **2014**, *344*, 392–396.

[18] a) X. Xu, M. P. Doyle, *Acc. Chem. Res.* **2014**, *47*, 1396–1405; b) J. P. A. Harrity, O. Provoost, *Org. Biomol. Chem.* **2005**, *3*, 1349–1358.

[19] a) N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 2854–2867; *Angew. Chem.* **2009**, *121*, 2896–2910.

[20] a) S. Kojima, T. Chabayashi, Y. Umeda, A. Iwamoto, K. Tanabe, K. Ohkata, *Heterocycles* **2008**, *75*, 1493–1501; b) Y. Du, C. J. Creighton, B. V. Falcone, M. H. Parker, D. A. Gauthier, A. B. Reitz, *Tetrahedron Lett.* **2007**, *48*, 6767–6770; c) M. E. Jung, J. C. Rohloff, *J. Org. Chem.* **1985**, *50*, 4909–4913.

[21] a) P. Kukula, R. Prins, *J. Catal.* **2002**, *208*, 404–411; b) G. Lunn, *J. Org. Chem.* **1987**, *52*, 1043–1046; c) F. Y. Miyake, K. Yakushijin, D. A. Horne, *Org. Lett.* **2000**, *2*, 3185–3187.

[22] a) G. J. Mercer, M. S. Sigman, *Org. Lett.* **2003**, *5*, 1591–1594; b) T. Shono, N. Kise, E. Shirakawa, H. Matsumoto, E. Okazaki, *J. Org. Chem.* **1991**, *56*, 3063–3067.

[23] S. Karlsson, J. Lindberg, H. Sörensen, *Org. Process Res. Dev.* **2013**, *17*, 1552–1560.

[24] V. Passarelli, G. Carta, G. Rossetto, P. Zanella, *Dalton Trans.* **2003**, 1284–1291.

[25] The NMR data (including NOE interactions) clearly support the existence of **2a** as a tricoordinated, symmetrical pincer complex in solution. This structure may be responsible for the complete all-equatorial diastereoselectivity observed in this reaction.

[26] A sluggish reaction occurs in the dark, and may resemble the diradical ground-state character of the smif anion; see Ref. [14b].

[27] We found that unsymmetrical imines derived from pyridines lead to two regioisomers of the piperazine product.

[28] CCDC 1052437 (**3b**), 1052438 (**3g**), 1053734 (**3ij**), and 1052436 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[29] a) E. C. Wilkinson, Y. Dong, L. Que, *J. Am. Chem. Soc.* **1994**, *116*, 8394–8395; b) T. Kojima, R. A. Leising, S. Yan, L. Que, *J. Am. Chem. Soc.* **1993**, *115*, 11328–11335.