ORGANIC LETTERS

2010
Vol. 12, No. 24
5608−5611

N-(2-Pyridylmethyl)imines as Azomethine Precursors in Catalytic Asymmetric [3 + 2] Cycloadditions

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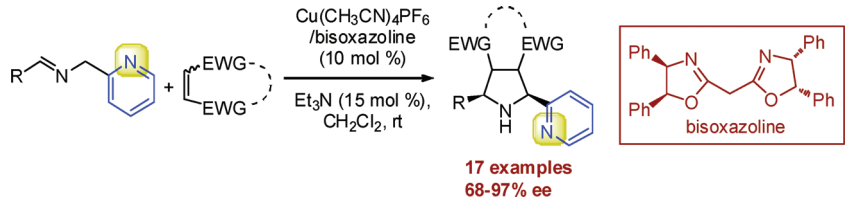
Received September 7, 2010

ABSTRACT



An efficient Cu(I)-catalyzed asymmetric [3 + 2] cycloaddition of *N*-(2-pyridylmethyl) imines has been developed. In the presence of a $Cu(CH_3CN)_4PF_6$/bisoxazoline catalyst system, high levels of enantioselectivity (up to 97% *ee*) and moderate to high exo selectivity were achieved with a wide variety of substituted dipolarophiles, including maleimides, fumarates, fumarodinitrile, enones, and nitroalkenes. The reaction with unsymmetrically substituted dipolarophiles is completely regioselective.

In recent years, the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides has witnessed an explosive growth,[1] to become nowadays a very powerful and atom-economical methodology for the enantioselective synthesis of pyrrolidines.[2] In addition to efficient protocols using Zn, Ag, Cu, Ni, and Ca chiral complexes,[3] several organocatalytic asymmetric methods have been recently reported.[4] Despite this huge progress, some important scope limitations still remain, especially with regard to the substitution at the azomethine precursor. By far, most catatytic asymmetric procedures, both metal-catalyzed and organocatalytic approaches, deal with the use of α-iminoesters. To the best of our knowledge, the only two general exceptions to this trend have been recently reported by Kobayashi et al. and our group using α-iminophosphonates[5a] and α-iminonitriles,[5b] respectively, in asymmetric Ag-catalyzed [3 + 2] cycloadditions.

The great efficiency of α-iminoesters as azomethine precursors relies on the high acidity at the enolizable Cα position and the formation of a rigid five membered *N*,*O*-bidentate metalated azomethine. We envisaged that a suitable coordinating nitrogen heterocycle, such as the 2-pyridyl group, could also provide sufficient activation and an appropriate discriminating environment to promote the asymmetric cycloaddition via formation of a five membered *N*,*N*-bidentate metalated azomethine[6] (Scheme 1). A scattered example of the intramolecular version of this process has been previously reported using Ag-PHOX complexes.[7] Herein we describe a protocol for the intermolecular catalytic asymmetric [3 + 2] cycloaddition of *N*-(2-pyridylmethyl)imines with a variety of activated olefins. The resulting 2-pyridyl pyrrolidine adducts hold a great potential as chiral *N*,*N*-ligands and organocatalysts.[8]

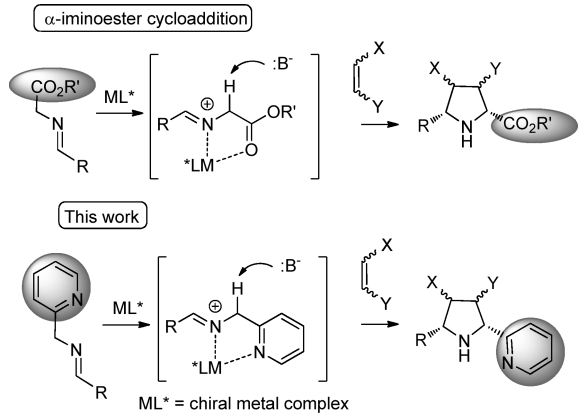
As model reaction we chose the cycloaddition of the pyridyl imine **1a** with *N*-methyl maleimide. After screening various Cu, Ag and Zn metal sources and a variety of chiral ligands, the combination of copper salts and bisoxazoline

(1) For pioneering references, see: (a) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401. (b) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. J.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236–4238.

(2) For recent reviews, see: (a) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (b) Pellisier, H. *Tetrahedron* **2007**, *63*, 3235–3285. (c) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484–4517. (d) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272–6276.

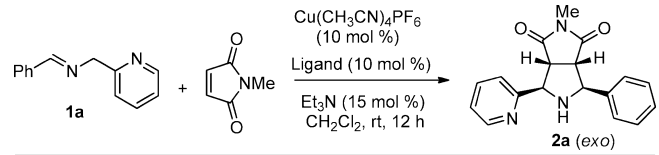
10.1021/ol102605q
Published on Web 11/15/2010

Scheme 1



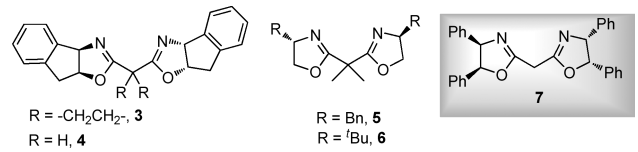
ligands provided the best results[9] (Table 1). The reaction using $Cu(OTf)_2$ and ligand **3** (10 mol %) as catalyst system, in the presence of Et_3N as base (CH_2Cl_2, rt), afforded a mixture of *exo*/*endo* pyrrolidines **2a** with low yield and enantioselectivity (entry 1). Better enantioselectivities were obtained with bisoxazolines **5** and **7**, albeit with poor diastereoselectivity (entries 2 and 3). In contrast, a Cu(I) salt such as $Cu(CH_3CN)_4PF_6$ proved to be highly *exo* diastereoselective, especially in combination with bisoxazoline ligands **4**, **6** and **7** (entries 6−8). Pleasingly, a nearly complete diastereoselectivity and very high enantioselectivity (97% *ee*) was achieved with the tetraphenyl bisoxazoline **7** (85% yield, entry 8). The cycloaddition can be also performed using a lower catalyst loading (3−5 mol % of $Cu(CH_3CN)_4PF_6$ and ligand **7**), albeit with a significant erosion of the enantioselectivity (entry 9).

Table 1. Reaction Conditions for the Model Reaction



entry	metal source	L*	exo/endo[a]	yield(%)[b]	ee (exo)(%)[c]
1	$Cu(OTf)_2$	**3**	34/66	30	51
2	$Cu(OTf)_2$	**5**	40/60	45	77
3	$Cu(OTf)_2$	**7**	65/35	60	95
4	$CuPF_6$[d]	**3**	66/34	68	20
5	$CuPF_6$[d]	**5**	75/25	72	6
6	$CuPF_6$[d]	**4**	>98/<2	70	40
7	$CuPF_6$[d]	**6**	>98/<2	62	50
8	$CuPF_6$[d]	**7**	>98/<2	85	97
9	$CuPF_6$[d]	**7**	>98/<2	76[e] (66)[f]	91[e] (88)[f]

[a] Determined by ^1H NMR. [b] Isolated yield. [c] Determined by HPLC. [d] $CuPF_6 = Cu(CH_3CN)_4PF_6$. [e] 5 mol % of catalyst. [f] 3 mol % of catalyst.



Interestingly, no reaction was observed under the optimal conditions shown in entry 8 when the phenyl, 3-pyridyl or 4-pyridyl substituted imines (**1b**−**d**) were used instead of **1a**, proving the key role of the 2-pyridyl unit as efficient activating group in the formation of the metalated azomethine intermediate[10] (Scheme 2).

Given the high reactivity of the phenyl imine **1a**, we next examined the scope of this asymmetric transformation with regard to the substitution at the imine[11] (Table 2). In all cases only the exo isomer was isolated (62−86% yield) and an excellent enantiocontrol was achieved from aryl and heteroaryl substituted imines regardless of the nature of the substituents (89−97% ee, entries 1−7). As expected, the

(3) For selected recent references, Cu-catalysts, see: (a) Robles-Machín, R.; González-Esguevillas, M.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2010**, *75*, 233–236. (b) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338–5339. (c) Kim, H. Y.; Shih, H.-Y.; Knabe, W. E.; Oh, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7420–7423. (d) Filippone, S.; Maroto, E. E.; Martín-Domenech, A.; Suarez, M.; Martín, N. *Nature Chem.* **2009**, *1*, 578–582. (e) Hernandez-Toribio, J.; Gómez Arrayás, R.; Martín-Matute, B.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 393–396. (f) López-Pérez, A.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 340–343. (g) López-Pérez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 10084–10085. (h) Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250–17251. (i) Fukuzawa, S.-I.; Oki, H. *Org. Lett.* **2008**, *10*, 1747–1750. (j) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979–1983. Ag-catalysts: (k) Shimizu, K.; Ogata, K.; Fukuzawa, S.-i. *Tetrahedron Lett.* **2010**, *51*, 5068–5070. (l) Oura, I.; Shimizu, K.; Ogata, K.; Fukuzawa, S.-i. *Org. Lett.* **2010**, *12*, 1752–1755. (m) Xue, Z.-Y.; Liu, T.-L.; Lu, Z.; Huang, H.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2010**, *46*, 1727–1729. (n) Yu, S.-B.; Hu, X.-P.; Deng, J.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *Tetrahedron: Asymmetry* **2009**, *20*, 621–625. (o) Wang, C.-J.; Xue, Z.-Y.; Liang, G.; Zhou, L. *Chem. Commun.* **2009**, 2905–2907. (p) Nájera, C.; de Gracia Retamosa, M.; Sansano, J. M.; de Cozar, J. M.; Cossío, F. P. *Tetrahedron: Asymmetry* **2008**, *19*, 2913–2933. (q) Nájera, C.; de Gracia Retamosa, M.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6055–6058. Zn-catalysts (r) Dogan, O.; Koyuncu, H.; Garner, P.; Bulut, A.; Youngs, W. J.; Panzner, M. *Org. Lett.* **2006**, *8*, 4687–4690. Ni-catalysts (s) Arai, T.; Yokoyama, N.; Mishiro, A.; Sato, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7895–7898. (t) Shi, J.-W.; Zhao, M.-X.; Lei, Z.-Y.; Shi, M. *J. Org. Chem.* **2008**, *73*, 305–308. Ca-catalysts (u) Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13321–13332.

(4) For selected organocatalytic asymmetric versions of this reaction, see: (a) Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. *Chem.—Eur. J.* **2008**, *14*, 9873–9877. (b) Xue, M.-X.; Zhang, X.-M.; Gong, L.-Z. *Synlett* **2008**, 691–694. (c) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652–5654. (d) Ibrahem, I.; Ríos, R.; Vesely, J.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 6252–6257. (e) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168–5170. (f) Alemparte, C.; Blay, G.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 4569–4572.

(5) (a) Yamashita, Y.; Guo, X.-X.; Takashita, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 3262–3263. (b) Robles-Machín, R.; Alonso, I.; Adrio, J.; Carretero, J. C. *Chem.—Eur. J.* **2010**, *16*, 5286–5291.

(6) For the non asymmetric thermal 1,3-dipolar cycloaddition of *N*-(2-pyridylmethyl)imines, see: Grigg, R.; Donegan, G.; Gunaratne, H. Q. N.; Kennedy, D. A.; Malone, J. F.; Sridharan, V.; Thianatanagul, S. *Tetrahedron* **1989**, *45*, 1723–1746.

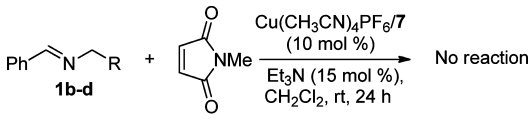
(7) Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, 1431–1436.

(8) See for example: (a) Xu, D.-Z.; Shi, S.; Wang, Y. *Eur. J. Org. Chem.* **2009**, 4848–4853. (b) Comba, P.; Lang, C.; Lopez de Laorden, C.; Muruganantham, A.; Rajaraman, G.; Wadepohl, H.; Zajaczkowski, M. *Chem.—Eur. J.* **2008**, *14*, 5313–5328. (c) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsui, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559. (d) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 320–321.

(9) See Supporting Information for catalyst optimization studies.

(10) For a recent example on the use of the 2-pyridine unit as activating group in asymmetric metal catalyzed reactions, see: Rupnicki, L.; Saxena, A.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 10386–10387.

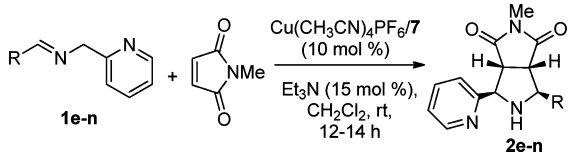
Scheme 2



R = Ph, **1b**; R = 3-pyridyl, **1c**; R = 4-pyridyl, **1d**

2-pyridyl imine **1l** afforded the meso compound **2l** in 90% yield (entry 8). Interestingly, challenging substrates such as α,β-unsaturated (entry 9) and alkyl substituted imines (entry 10) proved also to be suitable partners in the cycloaddition, albeit with a lower enantioselectivity (68−74% ee). The absolute and relative configuration of pyrrolidine *exo*-**2g** was unequivocally established by X-ray diffraction.[12]

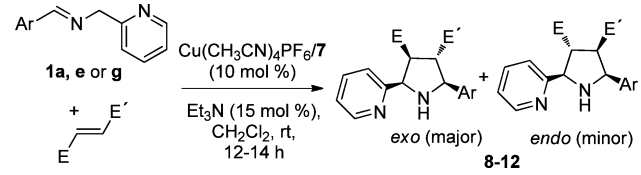
Table 2. Catalytic Asymmetric [3 + 2] Cycloaddition of 2-Pyridyl Imines **1e**−**n** with *N*-Methyl Maleimide

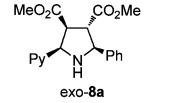
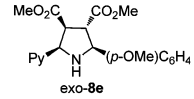
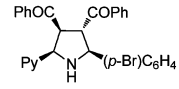
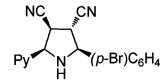
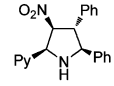
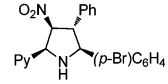
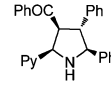


entry	R	product	yield (%)[a]	ee (%)[b]
1	(*p*-OMe)C_6H_4	**2e**	78	90
2	(*m*-Me)C_6H_4	**2f**	83	94
3	(*p*-Br)C_6H_4	**2g**	86	92
4	(*o*-F)C_6H_4	**2h**	78	94
5	(*p*-NO_2)C_6H_4	**2i**	62	97
6	2-Thienyl	**2j**	83	95
7	2-Furyl	**2k**	72	89
8	2-pyridyl	**2l**	90	–
9	Ph−CH=CH	**2m**	78	68
10	Cy	**2n**	79	74

[a] Isolated yield. [b] Determined by HPLC.

Table 3. Reaction with other Dipolarophiles



entry	product	*exo*/*endo*[a]	yield *exo* (%)[b]	*ee* *exo* (%)[c]
1	 exo-**8a**	77/23	60	82(90)[d]
2	 exo-**8e**	77/23	58	91
3	 exo-**9g**	75/25	63	72(93)[d]
4	 exo-**10g**	50/50	45	87(97)[d]
5	 exo-**11a**	63/37	53	96
6	 exo-**11g**	63/37	57	86(96)[d]
7	 exo-**12a**	>98/<2	77	92

[a] Determined by ^{1}H NMR in the crude mixture. [b] Isolated yield of pure exo adduct after silica gel chromatography. [c] *ee* of exo adduct determined by HPLC. [d] *ee* of exo adduct after recrystallization.

To extend the synthetic scope of this procedure, a wide variety of trans substituted dipolarophiles were next explored in the cycloaddition of imines **1** under the optimal Cu-catalyzed reaction conditions (Table 3). The reactions of diactivated symmetrical dipolarophiles such as dimethyl fumarate, dibenzoylethylene, and fumarodinitrile, occurred with a moderate exoselectivity[13] (45−63% yield in isolated exo isomer) and good enantioselectivities ranging from 72% to 91% ee (entries 1−4). Interestingly, the ee of the major pyrrolidine exo adduct can be further enhanced to very high levels by simple recrystallization (Table 3, values in parentheses).

Gratifyingly, the reaction with unsymmetrically substituted alkenes such as nitroalkenes[14] and enones[15] (adducts **11** and **12**) was completely regioselective, leading to the regioisomer having the activating group contiguous to the pyridyl unit

(11) Typical procedure for asymmetric [3 + 2] cycloadditions: (3a*S*, 4*S*, 6*R*, 6a*R*)-2-methyl-4-phenyl-6-(2-pyridyl)-octahydropyrrolo[3,4-c]pyrrole-1,3-dione (*exo*-**2a**): To a solution of bisoxazoline ligand **7** (12.4 mg, 0.027 mmol) and $Cu(CH_3CN)_4PF_6$ (10.1 mg, 0.027 mmol) and Et_3N (5.3 μL, 0.041 mmol) in CH_2Cl_2 (0.5 mL), under nitrogen atmosphere, at room temperature, a solution of imine **1a** (79.4 mg, 0.41 mmol) in CH_2Cl_2 (0.5 mL) and *N*-methylmaleimide (30.0 mg, 0.27 mmol) in CH_2Cl_2 (0.5 mL) were successively added. The mixture was stirred overnight and filtered through a plug of Celite with the aid of CH_2Cl_2 (5.0 mL). The organic layer was washed with NH_3 5% (aq) (2 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated. The resulting residue was purified by silica gel flash chromatography (hexane-EtOAc 1:2) to afford *exo*-**2a** (70.5 mg, 85%, white solid).

(12) See Supporting Information for details of the X-ray structure of *exo*-**2g**, *exo*-**10g**, and *exo*-**11g**. CCDC 784831, CCDC 784832, and CCDC 784833 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(13) By analogy with the 1,3-dipolar cycloaddition of α-iminoesters, *exo* refers to the pyrrolidine adduct with *trans* stereochemistry at C2−C3.

(14) For catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with nitroalkenes, see: refs 3b and 3j.

(15) For the use of enones as dipolarophiles, see refs 3e and 3l.

(1,2-disubstitution). The cycloaddition of (*E*)-β-nitrostyrene took place with moderate exo selectivity and high enantioselectivity (entries 5 and 6, 96% and 86% *ee*, respectively), whereas the reaction with *trans*-chalcone led only to the exo isomer, also with high enantioselectivity (92% *ee*, entry 7). It is interesting to note that the regioselectivity of the cycloaddition with *N*-(2-pyridylmethyl)imines is opposite to that observed in the reaction with the usual α-iminoesters, which provide the pyrrolidine adducts with 1,3-disubstitution between the ester moiety and the activating group at the dipolarophile. The absolute and relative configuration of the bromine-containing pyrrolidines *exo*-**10g** and *exo*-**11g** was unequivocally established by X-ray diffraction.[12]

In summary, we have described that *N*-(2-pyridylmethyl)imines can be used as efficient azomethine precursors in catalytic asymmetric [3 + 2] cycloadditions. Employing $Cu(CH_3CN)_4PF_6$/bisoxazoline **7** as a chiral catalyst system, high enantioselectivities (up to 97% *ee*) and moderate to high *exo*-selectivities have been accomplished for a wide variety of dipolarophiles under mild reaction conditions. The extension of this enantioselective Cu-catalyzed 1,3-dipolar cycloaddition to other heterocycle containing azomethine ylides is underway.

Acknowledgment. This work is dedicated to Professor Carmen Nájera on the occasion of her 60th birthday. Financial support from the Ministerio de Ciencia e Innovación (MICINN, project CTQ2009-07791), Consejería de Educación de la Comunidad de Madrid (programme AVANCAT; S2009/PPQ-1634) and Universidad Autónoma de Madrid/Comunidad de Madrid (UAM/CAM project CCG08-UAM/PPQ-4454) is greatly appreciated. S.P. thanks the MICINN for a predoctoral contract.

Supporting Information Available: Experimental procedures, characterization data for new compounds, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102605Q