Asymmetric Catalysis

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Highly Enantioselective Catalytic [6+3] Cycloadditions of Azomethine Ylides**

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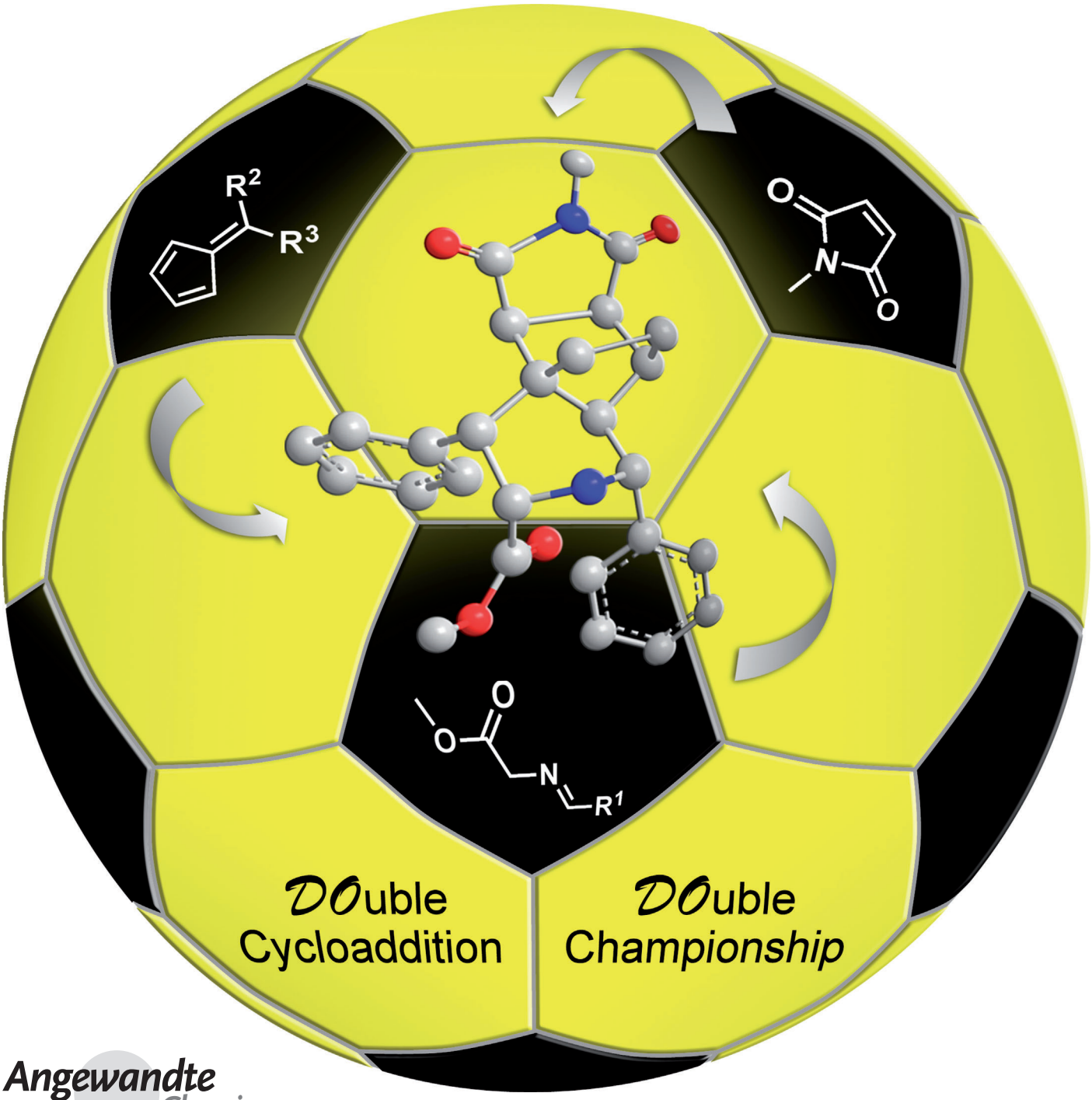
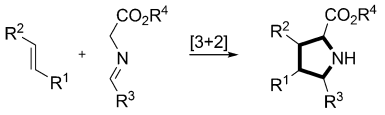
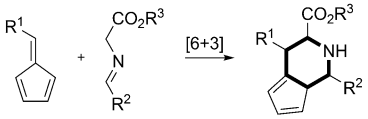


Stereocontrolled cycloaddition reactions give efficient access to bioactive[1] cyclic molecules[2,3] through concerted formation of two bonds and several stereocenters in one step. In particular, the reaction of activated alkenes with azomethine ylides derived from amino acids and aldehydes is a powerful method for the highly stereoselective synthesis of substituted pyrrolidines [Eq. (1)][3–5] bearing up to four stereogenic



(1)

centers. In contrast, catalytic enantioselective higher-order cycloadditions have been explored in only a few cases.[6] Recently, a related approach to racemic pentasubstituted piperidines that employed azomethine ylides in a [6+3] cycloaddition was reported by Hong et al. [Eq. (2)].[7] Herein,

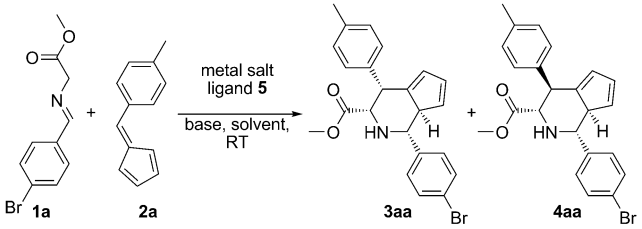


(2)

we report the first catalytic enantioselective [6+3] cycloaddition of azomethine ylides with fulvenes to provide piperidine derivatives having four stereocenters with high regio- and enantioselectivity.[8] We demonstrate that the enantioselective [6+3] cycloaddition can be combined with a [4+2] cycloaddition in one pot to yield complex annulated piperidines with eight stereocenters.

To establish the method we investigated the [6+3] cycloaddition of azomethine ylide **1a** with fulvene **2a** in detail. Use of substoichiometric amounts of copper(I) salt in the presence of a stereodirecting ligand and base, led to formation of two diastereomeric [6+3] cycloaddition products, **3aa** and **4aa** (Table 1). [3+2] cycloaddition products or regioisomeric

Table 1: Screen of reaction conditions.[a]

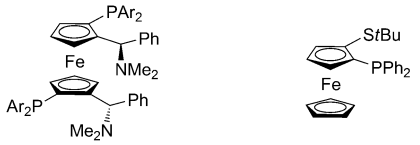


Entry	Catalyst	5	Solvent	t [h]	d.r.[b]	Yield [%][c]	ee [%][d]
1	$[Cu(CH_3CN)_4]PF_6$	**5a**	toluene	23	56:44	38	52
2	$[Cu(CH_3CN)_4]PF_6$	**5b**	toluene	23	70:30	45	88
3	$[Cu(CH_3CN)_4]PF_6$	**5c**	toluene	20	60:40	51	15
4	$[Cu(CH_3CN)_4]PF_6$	**5d**	toluene	20	50:50	35	22
5	$[Cu(CH_3CN)_4]PF_6$	**5e**	toluene	48	n.d.	trace	n.d.
6	$[Cu(CH_3CN)_4]PF_6$	**5f**	toluene	4	81:19	63	90
7	$[Cu(CH_3CN)_4]BF_4$	**5f**	toluene	0.5	87:13	70	93
8	CuOTf·PhMe	**5f**	toluene	6	62:38	42	93
9	AgOAc	**5f**	toluene	4	55:20[e]	53	68
10	CF_3COAg	**5f**	toluene	4	46:22[e]	43	62
11	$AgOSO_2CF_3$	**5f**	toluene	4	49:17[e]	32	68
12	$AgSbF_6$	**5f**	toluene	4	46:14[e]	42	70
13	$[Cu(CH_3CN)_4]BF_4$	**5f**	THF	0.5	75:25	72	91
14	$[Cu(CH_3CN)_4]BF_4$	**5f**	CH_2Cl_2	0.5	71:29	67	88
15	$[Cu(CH_3CN)_4]BF_4$	**5f**	$CHCl_3$	0.5	86:14	76	93
16	$[Cu(CH_3CN)_4]BF_4$	**5f**	Et_2O	0.5	78:22	72	94
17	$[Cu(CH_3CN)_4]BF_4$	**5f**	1,4-dioxane	0.5	87:13	80	92
18[f]	$[Cu(CH_3CN)_4]BF_4$	**5f**	1,4-dioxane	0.5	83:17	75	92
19[g]	$[Cu(CH_3CN)_4]BF_4$	**5f**	1,4-dioxane	1	81:19	71	91
20[h]	$[Cu(CH_3CN)_4]BF_4$	**5f**	1,4-dioxane	5	n.d.	trace	n.d.

[a] Reaction conditions: chiral ligand **5** (5 mol%), catalyst (5 mol%), Et_3N (1 equiv), glycine ester imine **1a** (1 equiv, 0.10 mmol), and derivative of fulvene **2a** (1.5 equiv) in solvent (0.1 M) at ambient temperature. [b] Determined by ^1H NMR spectroscopy. [c] Yield of isolated pure major diastereomer **3aa** after chromatography on silica gel. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Additionally 20–30% of undefined isomers were formed. [f] Using 3 mol% of catalyst and ligand **5f**. [g] Using 2 mol% of catalyst and ligand **5f**. [h] Using 1 mol% of catalyst and ligand **5f**. n.d. = not determined.

5a, Ar = phenyl
5b, Ar = 3,5-dimethylphenyl

5c



5d, Ar = *o*-tolyl
5e, Ar = 3,5-bis(trifluoromethyl)phenyl

5f

[6+3] cycloaddition products were not detected. Initial investigations to establish an enantioselective cycloaddition involved the use of commercially available chiral ligands with $[Cu(CH_3CN)_4]PF_6$ (5 mol%) in toluene (Table 1, entries 1–6). Application of chiral P,P-ligands, such as paracyclophanes **5a** and **5b**, led to product **3aa** with low diastereoselectivity but with moderate to good enantioselectivity (Table 1, entries 1–

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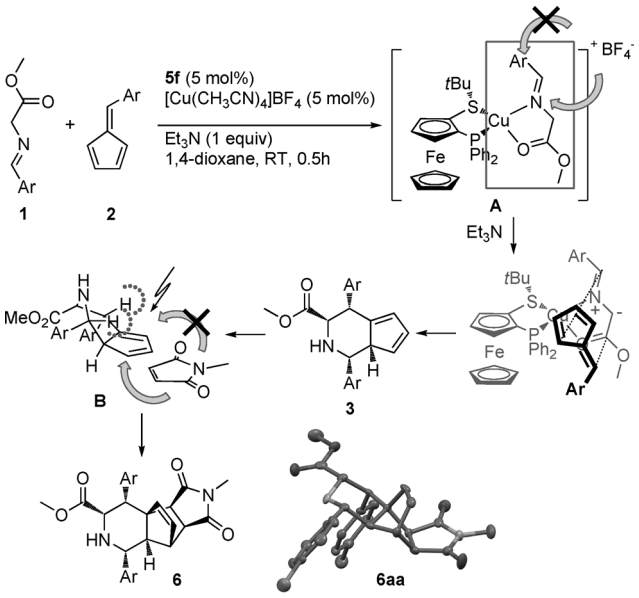
2). Likewise, chiral P,N-ferrocene ligands **5c** and **5e** did not induce high enantioselectivity (Table 1, entries 3–5). However, gratifyingly, use of the S,P-ferrocenyl ligand (*R*)-Fesulphos[9] (**5f**; Table 1, entry 6) led to significantly improved diastereo- and enantioselectivity. Subsequently, various sources of copper(I) and silver(I) were screened as catalysts (Table 1, entries 7–12). In the presence of Cu^+ catalysts higher yields and enantioselectivity for **3aa** were achieved whereas the use of Ag^+ led to the formation of four diastereomers. The best catalyst for the cycloaddition was $[Cu(CH_3CN)_4]BF_4$ (Table 1, entry 7). Exploration of various solvents resulted in moderate differences in enantioselectivity (88–94%) and yield (67–80%) for **3aa** (Table 1, entries 7, 13–17). The highest yield (80%) for the major diastereomer **3aa** was reached in 1,4-dioxane (Table 1, entry 17). Application of *N*,*N*-diisopropylethylamine instead of triethylamine led to a decrease of diastereoselectivity, and the use of 1,8-diazabicycloundec-7-ene resulted in a lower yield of the [6+3] cycloadduct. Remarkably, catalyst loading can be reduced to 2% without loss of enantioselectivity of **3aa** (Table 1, entries 17–20). However, we observed a decrease of yield and diastereoselectivity depending on the amount of chiral complex employed. Based on these results, we chose to use 5 mol% of $[Cu(CH_3CN)_4]BF_4$ as catalyst, 5 mol% of (*R*)-Fesulphos (**5f**) as chiral ligand, and Et_3N (1 equiv) as base in 1,4-dioxane at ambient temperature (Table 1, entry 17) for the subsequent experiments.

The initial products of the [6+3] cycloadditions are only moderately stable, therefore we investigated further synthetic transformations of the highly reactive cyclopentadiene functionality of the [6+3] cycloadduct **3aa**.[10] Compound **3aa** reacted smoothly with *N*-methylmaleimide at ambient temperature to yield Diels–Alder adduct **6aa** in good yield (Table 2, entry 1). Only one diastereomer of the [4+2] cycloadduct was detected, and the Diels–Alder reaction proceeded with complete conservation of enantiomeric purity of the chiral diene. The reaction has considerable substrate scope, and various activated dienophiles reacted with similar efficiency (Table 2, entries 2–4). The absolute configuration of the [6+3] cycloaddition product **3aa** and of the resulting Diels–Alder adduct were unambiguously determined by crystal structure analysis of compound **6aa** (Scheme 1).

To rationalize the steric course of the reaction we propose the formation of intermediate complex **A** (Scheme 1). In this arrangement the copper is coordinated by both the chiral

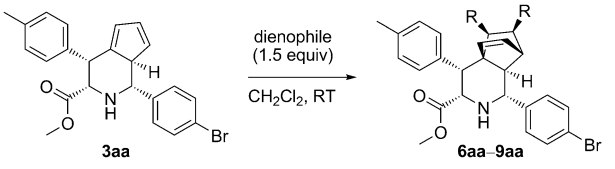


Scheme 1. Proposed intermediates and transition states for the formation of **6** by enantioselective [6+3] cycloaddition and subsequent Diels–Alder reaction. ORTEP plot of **6aa** with the thermal ellipsoids shown at 50% probability.[11]

ligand **5f** and the glycine ester imine **1** in a tetrahedral arrangement. This proposal is in agreement with previous findings of Carretero and co-workers that were based on NOE experiments indicating interactions between the *tert*-butyl group of ligand **5f** and the aromatic ring of glycine ester imine **1**.[9e] Deprotonation of complex **A** by the base results in formation of the azomethine ylide, which undergoes 1,3-dipolar cycloaddition with fulvene **2**. The attack takes place from the less-hindered face, that is, in this case, from the front to avoid unfavorable interactions with the bulky *tert*-butyl group. The subsequent Diels–Alder reaction proceeds via the favored *exo*-transition state (**B**) and yields the [4+2] cycloaddition product **6** with high selectivity. To investigate whether the [6+3] cycloaddition and the Diels–Alder reaction could be combined in a one-pot sequence, the reaction of α-iminoester **1a** with fulvene **2a** was initiated by treatment with (*R*)-Fesulphos **5f** and $[Cu(CH_3CN)_4]BF_4$ in the presence of base in 1,4-dioxane at ambient temperature, and after 30 minutes *N*-methylmaleimide was added. Gratifyingly, the desired cycloadduct **6aa** bearing eight stereocenters was obtained with an enantioselectivity of 92% in a combined yield of 70% over two steps (Table 3, entry 1).

Encouraged by this result, we investigated the scope of the [6+3]/[4+2] cycloaddition one-pot sequence using various glycine ester imines **1** and fulvenes **2** (Table 3). Regardless of the electronic properties of the substituents on glycine ester

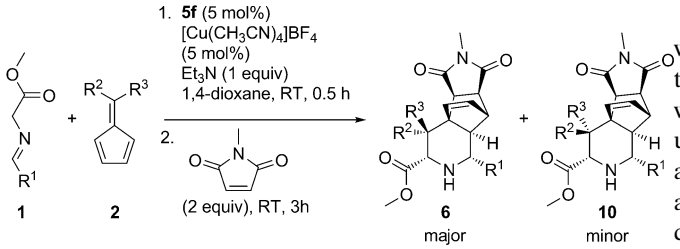
Table 2: Diels–Alder reaction of [6+3] cycloaddition product **3aa** with various dienophiles.[a]

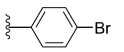
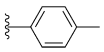
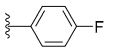
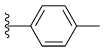
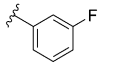
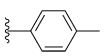
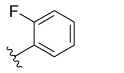
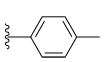
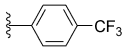
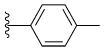
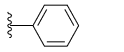
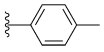
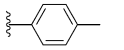
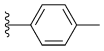
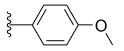
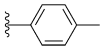
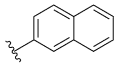
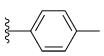
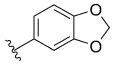
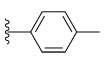
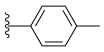
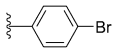
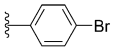
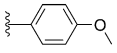
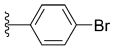
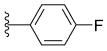
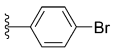
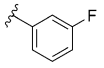
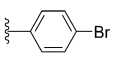
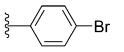
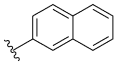
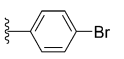
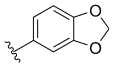
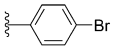
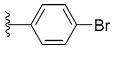


Entry	Product	Dienophile	*t* [h]	*exo*/*endo*	Yield [%][b]
1	**6aa**	*N*-methylmaleimide	2	>95:5	72
2	**7aa**	maleic anhydride	3	>95:5	79
3	**8aa**	Benzoquinone	5	>95:5	68
4	**9aa**	naphthalene-1,4-dione	5	>95:5	70

[a] Reaction conditions: [6+3] cycloaddition product **3aa** (1 equiv, 0.10 mmol), and dienophile (1.5 equiv, 0.15 mmol) in CH_2Cl_2 (0.1 M) at ambient temperature. [b] Yield of isolated product after column chromatography on silica gel.

Table 3: Scope of the one-pot catalytic enantioselective [6+3] cycloaddition/Diels–Alder reaction sequence.[a]



Entry	6	R^1	R^2	R^3	d.r.[b]	Yield [%][c]	*ee* [%][d]
1	**6aa**			H	87:13	70	92 (55)
2	**6ba**			H	87:13	72	92 (54)
3	**6ca**			H	83:17	69	89
4	**6da**			H	75:25	58	94
5	**6ea**			H	87:13	68	93
6	**6fa**			H	87:13	55	89
7	**6ga**			H	80:20	53	91
8	**6ha**			H	80:20	46	91
9	**6ia**			H	83:17	62	91 (45)
10	**6ja**			H	83:17	58	87
11[e]	**6ka**			H	n.d.	< 5	n.d.
12	**6ab**			H	87:13	80	93
13	**6ac**			H	87:13	80	94
14	**6ad**			H	87:13	75	94
15	**6ae**			H	83:17	65	92
16	**6af**			H	80:20	62	94
17	**6ag**			H	83:17	79	92
18	**6ah**			H	83:13	75	97
19[e]	**6ai**			H	80:20	73	36
20[e]	**6aj**		Me	Me	> 95:5	96	60

[a] Reaction conditions: chiral ligand **5f**, catalyst, base, α-iminoester **1** (1 equiv), and fulvene **2** (1.5 equiv) in 1,4-dioxane (0.1 M) at ambient temperature, then *N*-methylmaleimide (2 equiv). [b] Determined by ^{1}H NMR spectroscopy after the [6+3] cycloaddition. [c] Yields of the isolated pure major diastereomer after column chromatography. [d] Determined by HPLC analysis on chiral phase. The *ee* of minor isomer **10** is given in brackets. [e] Using 10 mol% of catalyst and ligand **5f**.

imines **1**, the products were obtained with enantioselectivities of 87–94% *ee* (Table 3, entries 1–10).

α-Iminoesters with aryl substituents having electron-withdrawing groups, such as fluorine and trifluoromethyl, in the *para* position (Table 3, entries 2 and 5) gave the products with slightly higher diastereoselectivity and higher yields than unsubstituted 1,3-dipoles (Table 3, entry 6) and imines having aryl substituents with electron-donating substituents, such as a methyl- or a methoxy group (Table 3, entries 7 and 8). The diastereoselectivity of the cycloaddition depends on the position of the substituents on the aromatic ring, and was lower for *ortho*-substituted than *para*-substituted phenyl derivatives (Table 3, entries 2–4). Sterically demanding groups are also tolerated leading to preparatively viable yields and enantioselectivities (Table 3, entries 9 and 10). Use of an α-iminoester obtained from 3-methylbutanal did not lead to formation of the desired product (Table 3, entry 11).

To further explore the scope of the one-pot sequence, a series of substituted fulvenes, which are readily available by condensation of cyclopentadiene with various aldehydes, was examined (Table 3, entries 12–20). Regardless of their electronic and steric properties, the substituents have no major influence on the yield. However, the position of the substituent on the aromatic ring does influence the stereoselectivity. The diastereoselectivity of the [6+3] cycloaddition is lower when there is an *ortho* substituent than when there is a *para* substituent but the enantiodifferentiation is not effected (Table 3, entries 14–16). The cycloadducts obtained from the different fulvenes **2** were obtained in viable yields (62–96%) and with high enantioselectivities (up to 97%). Alkyl-substituted fulvenes react smoothly giving the corresponding products in good to excellent yields, but with low enantioselectivity (Table 3, entries 19–20). The minor isomers **10** are formed with lower enantioselectivity (Table 3, entries 1, 2, 9).

In conclusion, we have reported the first catalytic enantioselective [6+3] cycloaddition of azomethine ylides with fulvenes to provide piperidine derivatives with four stereocenters with high regio- and enantioselectivity.[8] This enantioselective [6+3] cycloaddition was combined with a [4+2] cycloaddition in one pot to yield complex annulated piperidines with eight stereocenters.

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[1] a) K. Kumar, H. Waldmann, *Angew. Chem.* **2009**, *121*, 3272–3290; *Angew. Chem. Int. Ed.* **2009**, *48*, 3224–3242; b) M. Kaiser, S. Wetzel, K. Kumar, H. Waldmann, *Cell. Mol. Life Sci.* **2008**, *65*, 1186–1201; c) R. S. Bon, H. Waldmann, *Acc. Chem. Res.* **2010**, *43*, 1103–1114; d) S. Wetzel, R. S. Bon, K. Kumar, H. Waldmann, *Angew. Chem.* **2011**, *123*, 10990–11018; *Angew. Chem. Int. Ed.* **2011**, *50*, 10800–10826.

[2] For reviews, see a) H. Pellissier, *Tetrahedron* **2012**, *68*, 2197–2232; b) A. Sakakura, K. Ishihara, *Chem. Soc. Rev.* **2011**, *40*, 163–172; c) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 189–218;

d) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703 – 4832; e) G. Domínguez, J. Pérez-Castells, *Chem. Soc. Rev.* **2011**, *40*, 3430 – 3444; f) H. Pellissier, *Tetrahedron* **2010**, *66*, 1509 – 1555; g) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Soc. Rev.* **2010**, *39*, 783 – 816; h) S. Perreault, T. Rovis, *Chem. Soc. Rev.* **2009**, *38*, 3149 – 3159; i) H. Pellissier, *Tetrahedron* **2009**, *65*, 2839 – 2877; j) P. Wessig, G. Muller, *Chem. Rev.* **2008**, *108*, 2051 – 2063; k) S. Reymond, J. Cossy, *Chem. Rev.* **2008**, *108*, 5359 – 5406; l) T. Shibata, *Adv. Synth. Catal.* **2006**, *348*, 2328 – 2336; m) M. Harmata, *Adv. Synth. Catal.* **2006**, *348*, 2297 – 2306; n) R. P. Hsung, A. V. Kurdyumov, N. Sydorenko, *Eur. J. Org. Chem.* **2004**, 23 – 44; o) E. J. Corey, *Angew. Chem.* **2002**, *114*, 1724 – 1741; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650 – 1667.

[3] For reviews, see a) J. Adrio, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6784 – 6794; b) C. Nájera, J. M. Sansano, M. Yus, *J. Braz. Chem. Soc.* **2010**, *21*, 377 – 412; c) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887 – 2902; d) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235 – 3285; e) V. Nair, T. D. Suja, *Tetrahedron* **2007**, *63*, 12247 – 12275; f) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484 – 4517; g) C. Nájera, J. M. Sansano, *Angew. Chem.* **2005**, *117*, 6428 – 6432; *Angew. Chem. Int. Ed.* **2005**, *44*, 6272 – 6276; h) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765 – 2809.

[4] For selected recent examples on [3+2] cycloadditions of azomethine ylides, see: a) E. Conde, D. Bello, A. de Cózar, M. Sánchez, M. A. Vázquez, F. P. Cossío, *Chem. Sci.* **2012**, *3*, 1486 – 1491; b) M. González-Esguevillas, J. Adrio, J. C. Carretero, *Chem. Commun.* **2012**, *48*, 2149 – 2151; c) T.-L. Liu, Z.-L. He, Q.-H. Li, H.-Y. Tao, C.-J. Wang, *Adv. Synth. Catal.* **2011**, *353*, 1713 – 1719; d) Y. Yamashita, T. Imaizumi, S. Kobayashi, *Angew. Chem.* **2011**, *123*, 4995 – 4998; *Angew. Chem. Int. Ed.* **2011**, *50*, 4893 – 4896; e) Q.-H. Li, M.-C. Tong, J. Li, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2011**, *47*, 11110 – 11112; f) T.-L. Liu, Z.-L. He, C.-J. Wang, *Chem. Commun.* **2011**, *47*, 9600 – 9602; g) H.-L. Teng, H. Huang, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2011**, *47*, 5494 – 5496; h) T.-L. Liu, Z.-L. He, H.-Y. Tao, Y.-P. Cai, C.-J. Wang, *Chem. Commun.* **2011**, *47*, 2616 – 2618; i) T. Arai, N. Yokoyama, A. Mishiro, H. Sato, *Angew. Chem.* **2010**, *122*, 8067 – 8070; *Angew. Chem. Int. Ed.* **2010**, *49*, 7895 – 7898; j) Z.-Y. Xue, T.-L. Liu, Z. Lu, H. Huang, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2010**, *46*, 1727 – 1729; k) T. Arai, A. Mishiro, N. Yokoyama, K. Suzuki, H. Sato, *J. Am. Chem. Soc.* **2010**, *132*, 5338 – 5339; l) I. Oura, K. Shimizu, K. Ogata, S.-i. Fukuzawa, *Org. Lett.* **2010**, *12*, 1752 – 1755; m) C. Zhang, S.-B. Yu, X.-P. Hu, D.-Y. Wang, Z. Zheng, *Org. Lett.* **2010**, *12*, 5542 – 5545.

[5] For examples from our group, see a) M. Potowski, M. Schurmann, H. Preut, A. P. Antonchick, H. Waldmann, *Nat. Chem. Biol.* **2012**, *8*, 428 – 430; b) A. P. Antonchick, H. Schuster, H. Bruss, M. Schurmann, H. Preut, D. Rauh, H. Waldmann, *Tetrahedron* **2011**, *67*, 10195 – 10202; c) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schurmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735 – 740; d) H. Waldmann, E. Blaser, M. Jansen, H. P. Letschert, *Chem. Eur. J.* **1995**, *1*, 150 – 154; e) H. Waldmann, E. Blaser, M. Jansen, H. P. Letschert, *Angew. Chem.* **1994**, *106*, 717 – 719; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 683 – 685.

[6] a) Y. Hayashi, H. Gotoh, M. Honma, K. Sankar, I. Kumar, H. Ishikawa, K. Konno, H. Yui, S. Tsuzuki, T. Uchimaru, *J. Am. Chem. Soc.* **2011**, *133*, 20175 – 20185; b) B. M. Trost, P. J. McDougall, O. Hartmann, P. T. Wathen, *J. Am. Chem. Soc.* **2008**, *130*, 14960 – 14961; c) R. Shintani, M. Murakami, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 12356 – 12357; d) R. P. Reddy, H. M. L. Davies, *J. Am. Chem. Soc.* **2007**, *129*, 10312 – 10313; e) M. Harmata, S. K. Ghosh, X. C. Hong, S. Wacharasindhu, P. Kirchhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2058 – 2059; for review, see f) P. A. Inglesby, P. A. Evans, *Chem. Soc. Rev.* **2010**, *39*, 2791 – 2805; g) Z. X. Yu, Y. Wang, Y. Y. Wang, *Chem. Asian J.* **2010**, *5*, 1072 – 1088.

[7] B. C. Hong, A. K. Gupta, M. F. Wu, J. H. Liao, G. H. Lee, *Org. Lett.* **2003**, *5*, 1689 – 1692.

[8] Functionalized piperidines are important building blocks in organic synthesis and the development of novel methods for their synthesis is in high demand: a) M. S. M. Pearson, M. Mathe-Allainmat, V. Fargeas, J. Lebreton, *Eur. J. Org. Chem.* **2005**, 2159 – 2191; b) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701 – 1729; c) P. M. Weintraub, J. S. Sabol, J. A. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953 – 2989; d) F. X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693 – 3712; e) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435 – 446; f) S. Laschat, T. Dickner, *Synthesis* **2000**, 1781 – 1813.

[9] a) J. Priego, O. G. Mancheno, S. Cabrera, R. G. Arrayas, T. Llamas, J. C. Carretero, *Chem. Commun.* **2002**, 2512 – 2513; b) O. G. Mancheño, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2004**, *126*, 456 – 457; c) S. Cabrera, R. G. Arrayas, J. C. Carretero, *Angew. Chem.* **2004**, *116*, 4034 – 4037; *Angew. Chem. Int. Ed.* **2004**, *43*, 3944 – 3947; d) S. Cabrera, R. G. Arrayas, J. C. Carretero, *J. Am. Chem. Soc.* **2005**, *127*, 16394 – 16395; e) S. Cabrera, R. G. Arrayas, B. Martin-Matute, F. P. Cossio, J. C. Carretero, *Tetrahedron* **2007**, *63*, 6587 – 6602; and references [5a] and [5b].

[10] The products of the [6+3] cycloadditions are unstable during storage at low temperature owing to isomerization and dimerization. The products of the subsequent cycloaddition are considerably more stable.

[11] CCDC 885432 (**6aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

