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## NATURAL PRODUCT INSPIRED ENANTIOSELECTIVE SYNTHESIS OF HEXAHYDRO-AZA-PENTALENONES

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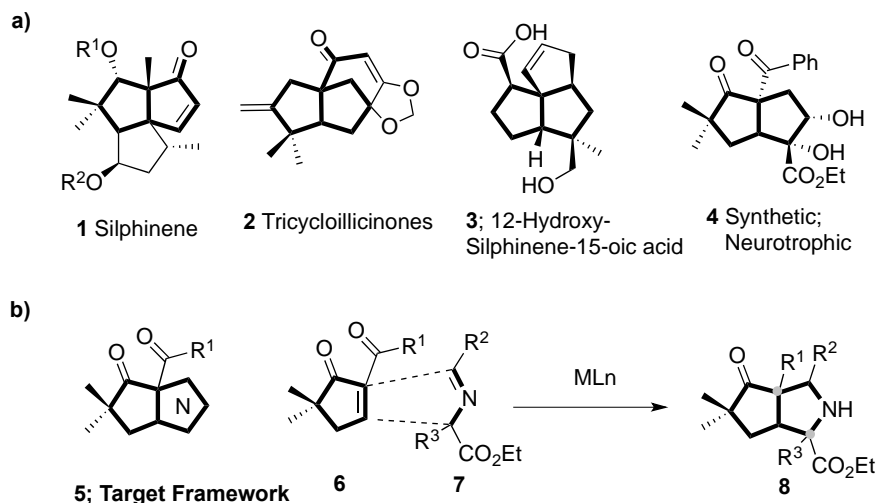
**Abstract** - An asymmetric synthesis of structurally complex hexahydro-azapentalenones embodying four consecutive stereogenic centers including two quaternary centers, one of which is an *all-carbon-quaternary* center, was developed with an enantioselective [3+2] cycloaddition reaction of azomethine ylides and substituted cyclopentenones.

The tool box of organic synthesis gives efficient access to numerous heterocyclic frameworks aiming either at a given target compound class or as a consequence of developing a synthetic methodology. However, only recently it was realized that all these synthetic small molecules represent merely a fraction of the possible frameworks that may populate the vast chemical space.<sup>1,2</sup> Thus, the immense potential of unrealized chemical space remains untapped in diverse applications. Very recently, stereoselective syntheses routes to novel and biologically relevant molecular frameworks have been targeted that can be used to build focused compound collections.<sup>2,3</sup> Natural products that are bestowed with interesting biological activities are a rich source of structural information that can be exploited to generate compound collections.<sup>4</sup> In this sense, we reported a collection of small molecules inspired by a sesquiterpenoid class of natural products (**1-3**, Scheme 1a) that was aimed to identify novel neurotrophic small molecules.<sup>5</sup> Among the most active of these molecules were compounds embodying the pentalenone scaffold, a 5,5-carbocyclic ring system. For instance, compound **4** at the conc. of 1 μM induced 20% increase in neurite outgrowth in primary neurons as compared to the positive control brain derived neurotrophic factor. In order to further exploit the biological relevance of this scaffold class as well as to induce more drug-like character to this class of molecules, we envisioned to generate a compound collection based on the azapentalenone scaffold (**5**, Scheme 1b).

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Dedicated to Prof. Lutz F. Tietze on the occasion of his 75<sup>th</sup> birthday

Here we describe an asymmetric synthesis of a collection of structurally complex aza-pentalenones embodying four consecutive stereogenic centers including two quaternary centers, one of which is an *all-carbon-quaternary* center, by employing a [3+2] cycloaddition reaction of azomethine ylides derived from  $\alpha$ -imonoesters (**7**) with doubly activated cyclopentenones (**6**).

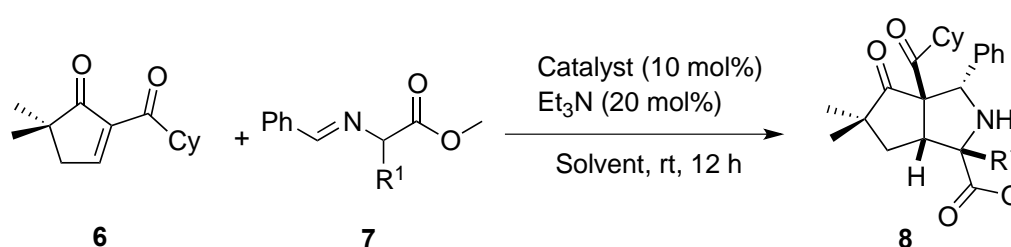


**Scheme 1.** a) Natural and bioactive small molecules (**1-4**) with pentalenone and related ring-system; b) target scaffold (**5**) and a synthetic plan for an enantioselective synthesis of hexahydro-aza-pentalenones (**8**).

The asymmetric [3+2] cycloaddition reaction of azomethine ylides with electron-deficient olefins remains one of the most efficient strategies to build enantiomerically pure pyrrolidines, present in many natural products and other synthetic biologically active molecules.<sup>6</sup> Since the first asymmetric reaction reported in 2002,<sup>7</sup> many powerful chiral metal catalysts and organocatalysts have been developed and applied successfully.<sup>8,9</sup> The cycloaddition reaction often proceeds with high enantio-/diastereoselectivity with a range of electron-poor dipolarophiles, like  $\alpha,\beta$ -unsaturated esters, maleimides, nitroalkenes, vinyl sulfones, and fullerene. However, only in few cases were cyclic enones were investigated in this asymmetric dipolar cycloaddition reaction. Among the successful catalytic complexes that could provide asymmetric [3+2] cycloaddition reactions with unsubstituted 2-cyclopentenone were a CuI-Fesulphos complex as well as a chiral Ag(I)/phosphoramidite complex that led to *endo*-cycloadducts with high enantioselectivity.<sup>10</sup> The asymmetric [3+2] cycloaddition reaction of azomethine ylides has also been used to form pyrrolidine rings in the synthesis of various complex natural product derivatives as well as natural product inspired compounds.<sup>11</sup> One of these cases focused on the asymmetric one-pot tandem synthesis of structurally complex molecular architectures by two consecutive asymmetric [3+2] cycloaddition reactions of azomethine ylides to *p*-benzoquinone employing (*R*)-Fesulphos and Cu(MeCN)<sub>4</sub>BF<sub>4</sub>.<sup>12</sup> In our synthetic strategy targeting the aza-pentalenone scaffold (**5**, Scheme 1), we

planned to employ the  $\alpha,\alpha$ -dimethyl-cyclopentenone (**6**) with an appending substituted ketone moiety as dipolarophile in asymmetric [3+2] cycloadditions reaction with azomethine ylides (Scheme 1b). Though the use of highly substituted cyclopentenones in this reaction is challenging, a successful execution would generate a three dimensionally complex bicyclic pyrrolidine scaffold supporting four consecutive stereogenic centers with two quaternary centers, one of which would be an *all-carbon-quaternary* center (Scheme 1b).

**Table 1.** Optimization studies of the [3+2] cycloaddition of  $\alpha$ -iminoester (**7**) and cyclopentenone (**6**)



Entry	R <sup>1</sup>	Catalyst	Solvent	Yield <b>8</b> (%) <sup>a</sup>
1.	H	AgOAc	DCM	mix. products
2.	Me	AgOAc	DCM	<b>8a</b> (65)
3.	Me	AgOAc	THF	<b>8a</b> (49)
4.	Me	Cu(MeCN) <sub>4</sub> BF <sub>4</sub>	DCM	<b>8a</b> (78)
5.	Me	Cu(MeCN) <sub>4</sub> BF <sub>4</sub>	THF	<b>8a</b> (42)
6.	Ph	Cu(MeCN) <sub>4</sub> BF <sub>4</sub>	DCM	NR
7.	Bn	Cu(MeCN) <sub>4</sub> BF <sub>4</sub>	DCM	<b>8b</b> (91)

a: isolated yields.

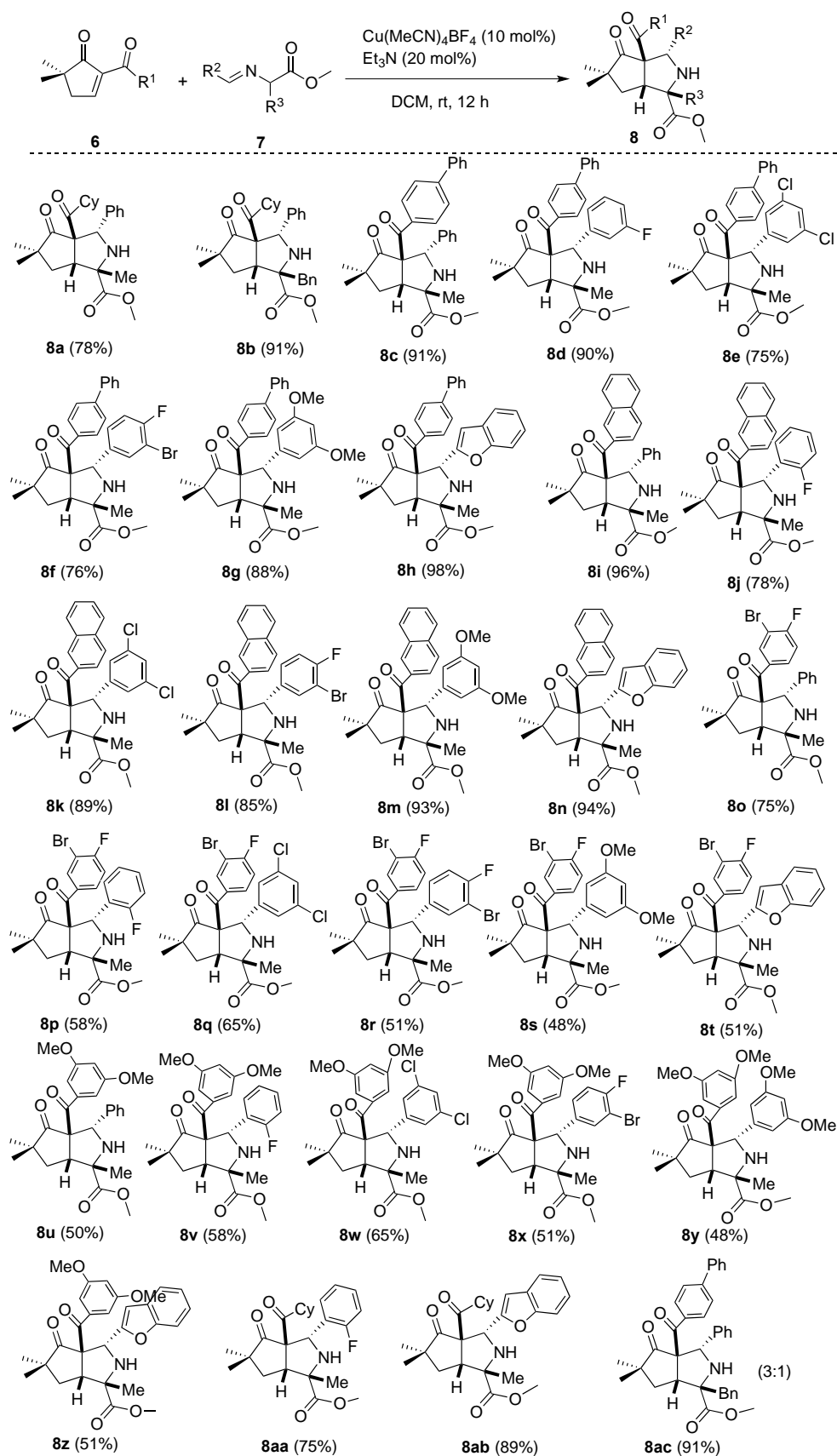
The bis-activated cyclopentenones (**6**)<sup>5</sup> and the  $\alpha$ -iminoesters (**7**)<sup>12</sup> were prepared as reported before. Cyclohexyl substituted cyclopentenone **6a** was used for optimization of the reaction conditions with  $\alpha$ -iminoesters (**7**). Employing 10 mol% of silver acetate as catalyst in the cycloaddition reaction between **6a** and **7a** (R<sup>1</sup> = H) in dichloromethane (DCM) led to an inseparable mixture of different compounds (Entry 1, Table 1). Employing the methyl substituted precursor **7b** (R<sup>1</sup> = Me) under these reaction conditions led to exclusive formation of a single diastereoisomer of the desired [3+2] cycloadducts **8a** (Entry 2, Table 1). Changing the solvent to tetrahydrofuran (THF) decreased the yield of **8a** substantially (Entry 3, Table 1). Interestingly, the Cu(I) complex Cu(MeCN)<sub>4</sub>BF<sub>4</sub> as catalyst afforded **8a** as single product in very high yield (Entry 4, Table 1). The same reaction in tetrahydrofuran (THF) as solvent was less efficient (Entry

5). Encouraged by the successful execution of the dipolar cycloaddition between cyclopentenone **6a** and the alanine derived azomethine ylide, we further employed a phenyl glycine derived substrate **7c** ( $R^1 = \text{Ph}$ ) as azomethine ylide source. However, no reaction was observed under the optimized reaction condition (Entry 6, Table 1). To our pleasure however, the benzylglycine derived substrate **7d** ( $R^1 = \text{Bn}$ ) did provide the desired cycloadducts **8b** in excellent yield and as single diastereoisomer (Entry 7, Table 1).

In order to access aza-pentalenone scaffold based and highly substituted bicyclic molecules (**8**), differently substituted cyclopentenones (**6**) as well as  $\alpha$ -iminoesters (**7**) were employed under the optimized reaction condition. To this end, a solution of tetrakis(acetonitrile)copper(I) tetrafluoroborate (10 mol%, 30  $\mu\text{mol}$ ),  $\alpha$ -iminoester **7** (1.1 equiv., 0.33 mmol) and  $\text{Et}_3\text{N}$  (20 mol%, 60  $\mu\text{mol}$ ) in DCM was added cyclopentenone **6** (1 equiv., 0.30 mmol). The mixture was allowed to stir at ambient temperature for 12 h and the solvent was removed *in vacuo*. The cycloadducts were purified by column chromatography on silica gel (EtOAc/petroleum ether) to afford pure products.

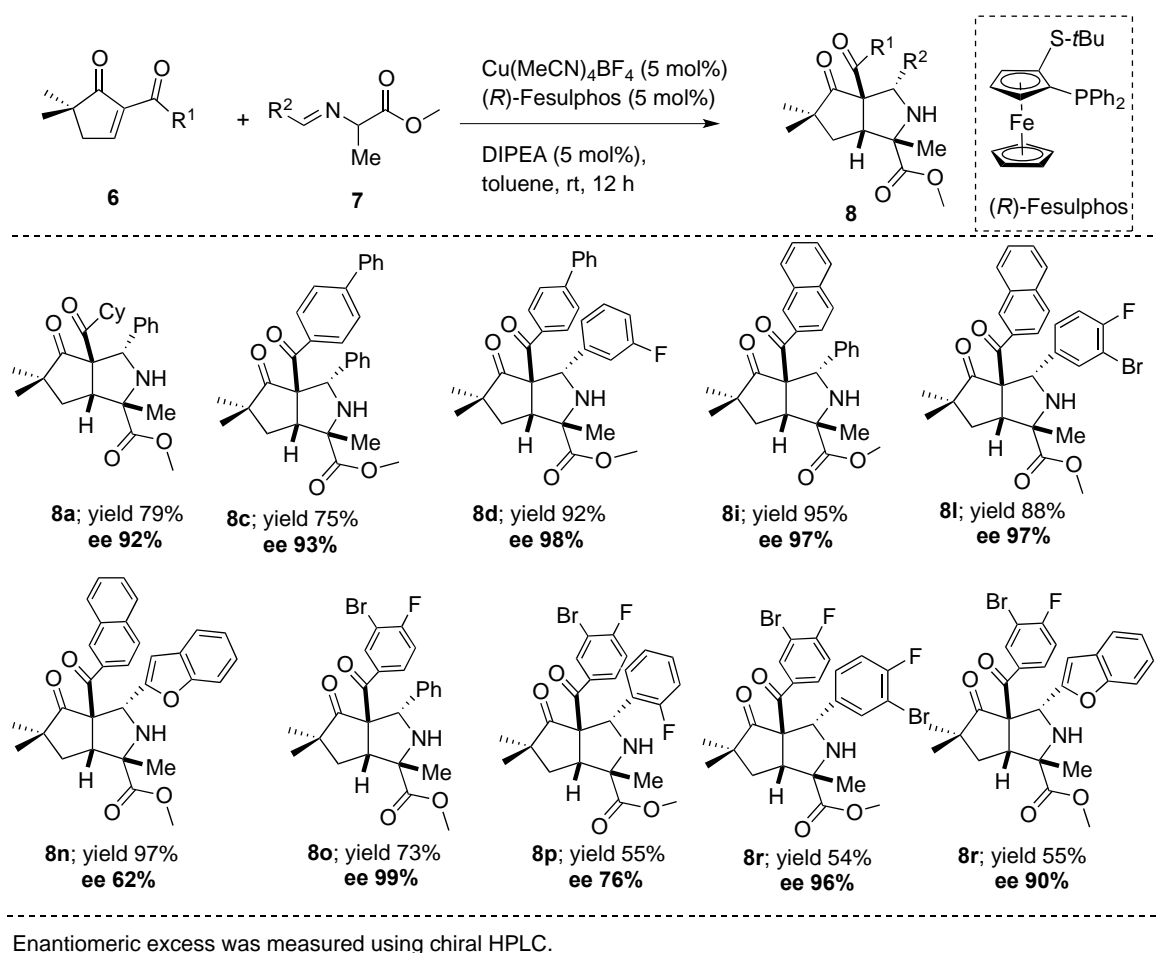
The cycloaddition tolerated differently substituted ketones on the cyclopentenone **6** as well as different aromatic groups on the imine part of  $\alpha$ -iminoesters **7<sup>1</sup>** (Scheme 2) and afforded the corresponding cycloadducts in high yields and with excellent stereoselectivities. Both electron-rich as well as electron-poor aromatic rings on the ketone and imine functions were successfully incorporated into the desired aza-pentalenone scaffold in a completely stereoselective manner. The  $\alpha$ -iminoester derived from benzofuran-2-carbaldehyde was also successfully employed in this cycloaddition and afforded the corresponding adducts in high yields (Scheme 2). Reaction of phenylalanine derived  $\alpha$ -iminoesters ( $R^3 = \text{Bn}$ , Scheme 2) with **6a** yielded the desired cycloadduct (**8b**) with equal efficiency, however, in another case (**8ac**, Scheme 2) the diastereoselectivity was compromised.

The majority of the reported [3+2] cycloaddition reactions between cyclic enones and azomethine ylides proceed with preferred or exclusive formation of *endo* cycloadducts.<sup>10-12</sup> We believe that cyclopentenone **6** supporting two electron-withdrawing groups would strongly favor an *endo*-transition state in order to avoid the steric clash between bulky aromatic groups on the imine as well as on the ketone and thereby leading exclusively to *endo*-adducts (**8**).



**Scheme 2.** Stereoselective [3+2] cycloaddition of  $\alpha$ -iminoesters (**7**) and cyclopentenones (**6**)

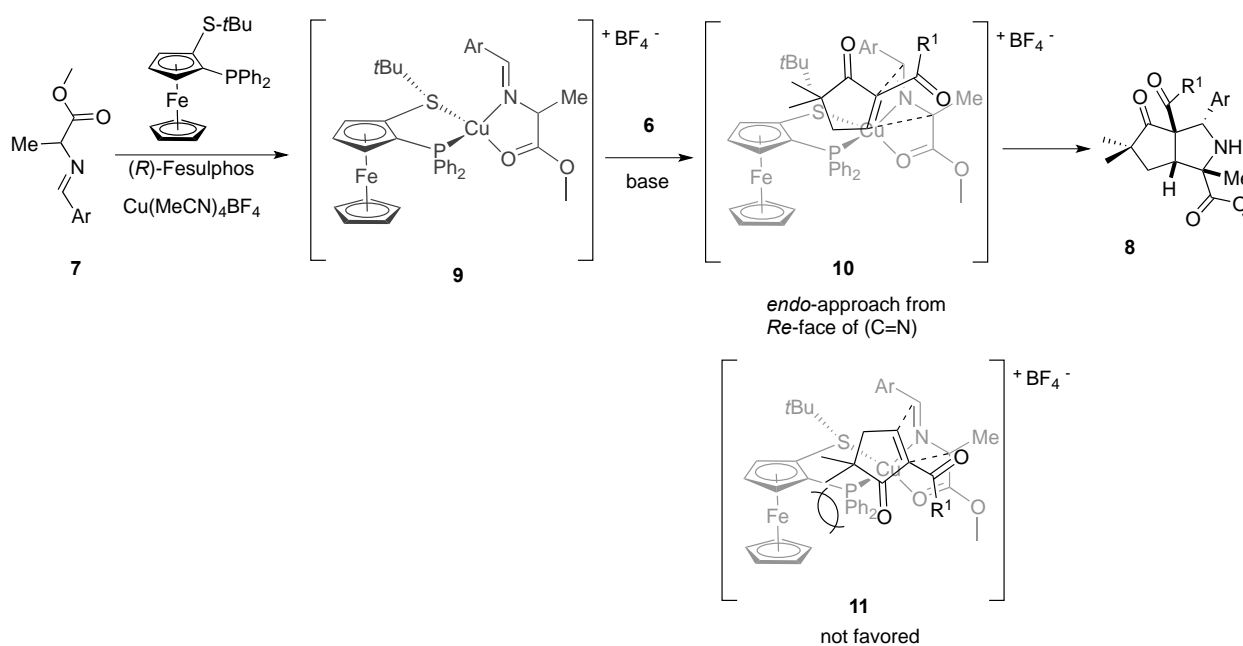
Fortunately, the reaction conditions developed in our earlier exploration of dipolar cycloaddition reactions of azomethine ylides was also applicable to cyclopentenones (**6**). We were therefore encouraged to directly employ the asymmetric reaction conditions developed earlier for asymmetric dipolar cycloaddition of azomethine ylide and *p*-benzoquinones.<sup>12</sup> Thus, employing 5 mol% each of the most effective ligand (*R*)-Fesulphos, Cu(MeCN)<sub>4</sub>BF<sub>4</sub> salt and diisopropylethylamine (DIPEA) in the dipolar cycloaddition reactions of alanine derived azomethine ylides (**7**) with cyclic enones (**6**) led to the formation of cycloadducts **8** as single diastereomers in high yield and with very good to excellent enantioselectivity. Aza-pentalenones supporting differently substituted aromatic groups on the  $\alpha$ -keto moiety as well as next to amino function were generated in high yields. Except for a few cases (**8n**, **8p**), excellent enantioselectivities were observed for the cycloadducts formed (Scheme 3).



**Scheme 3.** Enantioselective catalytic [3+2] cycloaddition reaction affording aza-pentalenones (**8**)

Mechanistically, the stereochemical outcome of the asymmetric cycloaddition between iminoesters (**7**) and cyclopentenones (**6**) is influenced by steric interactions. A tetrahedral complex **9** is formed between the alanine derived  $\alpha$ -iminoester (**7**), Cu(MeCN)<sub>4</sub>BF<sub>4</sub> and the bidentate chiral ligand (*R*)-Fesulphos

(Scheme 4). Deprotonation of the iminoester forms the azomethine ylide that undergoes cycloaddition reaction with cyclopentenone (**6**). The dipolarophile approaches from *Re*-face (with respect to C=N) of the ylide to avoid the steric interaction of its dimethyl substituents with the tertiary butyl group (**10**) and thereby affords the *endo*-cycloadduct (**8**, Scheme 4). The other possible *endo*-approach in **11** is not favored due to the steric repulsion between the bulk of alkyl cyclopentenone and the diphenyl rings of the ligand (Scheme 4).



**Scheme 4.** Stereochemical model

In conclusion, we have developed an efficient synthetic access to an aza-pentalenone scaffold based small molecule collection by employing the [3+2] cycloaddition reaction between azomethine ylides derived from  $\alpha$ -iminoesters and highly substituted and bis-activated cyclopentenones. The reaction provided a series of cycloadducts as diastereomerically pure single isomers in high yields. An asymmetric version of this reaction was realized using a catalytic complex of  $\text{Cu}(\text{MeCN})_4\text{BF}_4$  and *(R)*-Fesulphos and afforded the desired products in high yields and with excellent enantioselectivities.

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## REFERENCES AND NOTES

1. A. H. Lipkus, Q. Yuan, K. A. Lucas, S. A. Funk, W. F. Bartelt III, R. J. Schenck, and A. J. Trippe, *J. Org. Chem.*, 2008, **73**, 4443.
2. (a) A. A. Shelat and R. K. Guy, *Nat. Chem. Biol.*, 2007, **3**, 442; (b) S. Dandapani and L. A. Marcaurelle, *Nat. Chem. Biol.*, 2010, **6**, 861.
3. (a) T. J. Maimone and P. S. Baran, *Nat. Chem. Biol.*, 2007, **3**, 396; (b) G. Valot, J. Garcia, V. Duplan, C. Serba, S. Barluenga, and N. Winssinger, *Angew. Chem. Int. Ed.*, 2012, **51**, 5391; (c) R. J. Rafferty, R. W. Hicklin, K. A. Maloof, and P. J. Hergenrother, *Angew. Chem. Int. Ed.*, 2014, **53**, 220.
4. D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2012, **75**, 311.
5. P.-Y. Dakas, J. A. Parga, S. Höing, H. R. Schöler, J. Sternecker, K. Kumar, and H. Waldmann, *Angew. Chem. Int. Ed.*, 2013, **52**, 9576.
6. (a) S. G. Pyne, A. S. Davis, N. J. Gates, J. P. Hartley, K. B. Lindsay, T. Machan, and M. Tang, *Synlett*, 2004, 2670; (b) L. M. Harwood and R. J. Vickers, In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*, ed. by A. Padwa and W. Pearson, Wiley & Sons, New York, 2002.
7. (a) J. M. Longmire, B. Wang, and X. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 13400; (b) A. S. Gothelf, K. V. Gothelf, R. G. Hazell, and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2002, **41**, 4236.
8. Recent reviews on catalytic asymmetric 1,3-dipolar cycloadditions: (a) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick, and H. Waldmann, *Acc. Chem. Res.*, 2014, **47**, 1296; (b) B. Engels and M. Christl, *Angew. Chem. Int. Ed.*, 2009, **48**, 7968; (c) L. M. Stanley and M. P. Sibi, *Chem. Rev.*, 2008, **108**, 2887; (d) M. Álvarez-Corral, M. Muñoz-Dorado, and I. Rodríguez-García, *Chem. Rev.*, 2008, **108**, 3174; (e) M. Naodovic and H. Yamamoto, *Chem. Rev.*, 2008, **108**, 3132.
9. For recent examples on Cu and Ag catalysts: (a) R. Robles-Machin, M. González-Esguevillas, J. Adrio, and J. C. Carretero, *J. Org. Chem.*, 2010, **75**, 233; (b) A. López-Pèrez, J. Adrio, and J. C. Carretero, *Angew. Chem. Int. Ed.*, 2009, **48**, 340; (c) A. López-Pèrez, J. Adrio, and J. C. Carretero, *J. Am. Chem. Soc.*, 2008, **130**, 10084; (d) C.-J. Wang, G. Liang, Z.-Y. Xue, and F. Gao *J. Am. Chem. Soc.*, 2008, **130**, 17250; (e) T. Llamas, A. Ramón Gómez, and J. C. Carretero, *Synthesis* 2007, 950; (f) Y. Yamashita, X.-X. Guo, R. Takashita, and S. Kobayashi, *J. Am. Chem. Soc.*, 2010, **132**, 3262; (g) Z.-Y. Xie, T.-L. Liu, Z. Lu, H. Huang, H.-Y. Tao, and C.-J. Wang, *Chem. Commun.*, 2010, **46**, 1727; (h) R. Robles-Machín, I. Alonso, J. Adrio, and J. C. Carretero, *Chem. Eur. J.*, 2010, **16**, 5286.
10. (a) J. Hernández-Toribio, R. G. Arrayás, B. Martín-Matute, and J. C. Carretero, *Org Lett.*, 2009, **11**, 393; (b) C. Zhang, S.-B. Yu, X.-P. Hu, D.-Y. Wang, and Z. Zheng, *Org. Lett.*, 2010, **12**, 5542; (c) M. R. Chaulagain and Z. D. Aron, *J. Org. Chem.*, 2010, **75**, 8271.

11. (a) M. Potowski, C. Golz, C. Strohmann, A. P. Antonchick, and H. Waldmann, [Bioorg. Med. Chem.](#), **2015**, **23**, 2895; (b) M. Potowski, C. Merten, A. P. Antonchick, and H. Waldmann, [Chem. Eur. J.](#), **2015**, **21**, 4913; (c) R. Narayan, J. O. Bauer, C. Strohmann, A. P. Antonchick, and H. Waldmann, [Angew. Chem. Int. Ed.](#), **2013**, **52**, 12892; (d) H. Takayama, Z.-J. Jia, L. Kremer, J. O. Bauer, C. Strohmann, S. Ziegler, A. P. Antonchick, and H. Waldmann, [Angew. Chem. Int. Ed.](#), **2013**, **52**, 12404; (e) M. Potowski, A. P. Antonchick, and H. Waldmann, [Chem. Commun.](#), **2013**, **49**, 7800; (f) A. P. Antonchick, S. López-Tosco, J. Parga, S. Sievers, M. Schürmann, H. Preut, S. Höing, H. R. Schöler, J. Sternecker, D. Rauh, and H. Waldmann, [Chem. Biol.](#), **2013**, **20**, 500.
12. M. Potowski, M. Schürmann, H. Preut, A. P. Antonchick, and H. Waldmann, [Nat. Chem. Biol.](#), **2012**, **8**, 428.