

Cycloaddition

Highly Enantioselective Intramolecular 1,3-Dipolar Cycloaddition: A Route to Piperidino-Pyrrolizidines**

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Abstract: Enantioselective catalytic intermolecular 1,3-dipolar cycloadditions are powerful methods for the synthesis of heterocycles. In contrast, intramolecular enantioselective 1,3-dipolar cycloadditions are virtually unexplored. A highly enantioselective synthesis of natural-product-inspired pyrrolidino-piperidines by means of an intramolecular 1,3-dipolar cycloaddition with azomethine ylides is now reported. The method has a wide scope and yields the desired cycloadducts with four tertiary stereogenic centers with up to 99% *ee*. Combining the enantioselective catalytic intramolecular 1,3-dipolar cycloaddition with a subsequent diastereoselective intermolecular 1,3-dipolar cycloaddition yielded complex piperidino-pyrrolizidines with very high stereoselectivity in a one-pot tandem reaction.

Biology-oriented synthesis (BIOS) employs biological relevance as the key parameter for the design and synthesis of compound collections enriched by bioactive molecules. For BIOS in particular, the scaffolds of natural product classes selected in evolution serve as biologically prevalidated “privileged” starting points in chemical structure space.^[1] The compounds in natural-product-inspired collections are often structurally complex and rich in stereogenic centers. Therefore, the development of efficient methods for their enantioselective synthesis is at the heart of BIOS.^[2]

Intermolecular enantioselective catalytic dipolar cycloadditions employing azomethine ylides lead to substituted pyrrolidines and currently receive substantial interest.^[3] In contrast, intramolecular 1,3-dipolar cycloadditions in general and with azomethine ylides in particular, which hold the promise to give efficient access to annulated polycyclic ring systems, have rarely succumbed to enantioselective catalysis.^[4]

The 2,3-pyrrolidino-3,4-piperidine (4,7-diazabicyclo-[4.3.0]nonane) scaffold is an integral part of the underlying structure of numerous alkaloids endowed with diverse bioactivities, including anti-tumor, antibiotic, and insecticidal activity (Figure 1).^[5] Despite this importance, only very few methods for the synthesis of this scaffold have been reported,^[6] and an enantioselective method is lacking entirely.

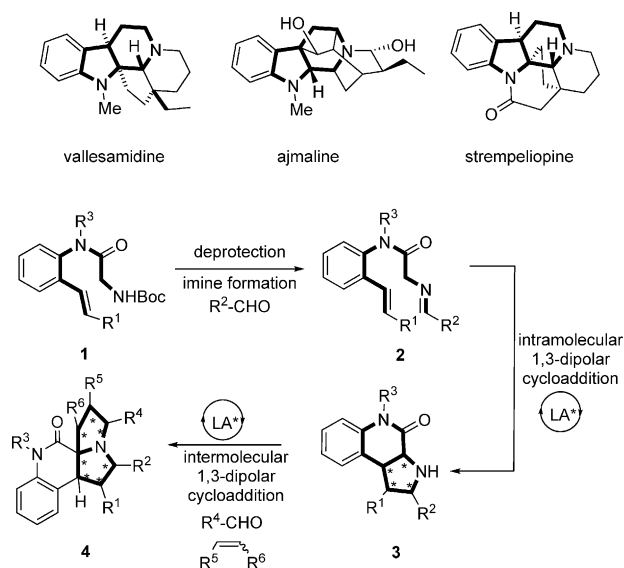


Figure 1. Structures of representative natural products incorporating the 2,3-pyrrolidino-3,4-piperidine scaffold and strategy for the synthesis of the scaffold by means of enantioselective catalytic intramolecular 1,3-dipolar cycloaddition.

Herein, we report the development of a highly enantioselective synthesis of pyrrolidino-piperidine scaffold **3** by means of an intramolecular 1,3-dipolar cycloaddition. The method has a wide scope and yields the desired cycloadducts with four tertiary stereogenic centers with up to 99% *ee*. Combining the enantioselective catalytic intramolecular 1,3-dipolar cycloaddition with a subsequent stereoselective intermolecular 1,3-dipolar cycloaddition yielded complex piperidino-pyrrolizidines in a one-pot reaction sequence.

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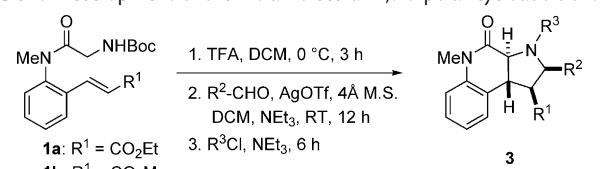
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For the synthesis of the desired annulated heterocycle class, we envisioned that azomethine ylides generated in situ from Schiff bases **2**, which are derived from glycine *N*-aryl amides, would add to the double bond attached to the aryl group in a 1,3-dipolar cycloaddition, and that this reaction could be carried out in an enantioselective fashion in the presence of a chiral Lewis acid catalyst (Figure 1).^[7]

To establish the reaction sequence, Boc-protected glycine *N*-aryl amides **1** were deprotected (Table 1) and converted into the corresponding imines in situ. Treatment of the Schiff

Table 1: Development of the intramolecular 1,3-dipolar cycloaddition.^[a]



Entry	Product	R ¹	R ²	R ³	Yield [%]
1 ^[b]	3a	CO ₂ Me	Ph	H	88
2	3b	CO ₂ Et	Ph	CO ₂ Me	88
3	3c	CO ₂ Et	<i>m</i> -FC ₆ H ₄	CO ₂ Me	78
4	3d	CO ₂ Et	3-thiophenyl	CO ₂ Me	76
5	3e	CO ₂ Et	<i>p</i> -BrC ₆ H ₄	CO ₂ Me	87
6	3f	CO ₂ Me	Ph	CO ₂ Et	71
7	3g	CO ₂ Me	<i>m</i> -FC ₆ H ₄	CO ₂ Et	79
8	3h	CO ₂ Me	<i>p</i> -MeOC ₆ H ₄	CO ₂ Et	73
9	3i	CO ₂ Me	3-thiophenyl	CO ₂ Et	75

[a] Reaction conditions: **1** (0.12 mmol) and TFA (1.2 mmol) were used for the deprotection. Then, aldehyde (0.12 mmol), Et₃N (0.24 mmol), AgOTf (5 mol%), and activated 4 Å M.S. powder in DCM as the solvent (2 mL). In all cases, a d.r. of >20:1 was observed. [b] Without acylation with methyl chloroformate. Boc = *tert*-butoxycarbonyl, DCM = dichloromethane, M.S. = molecular sieves, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

base with different Ag and Cu catalysts revealed that the best results were obtained with AgOTf in the presence of NEt₃ and molecular sieves in DCM at room temperature (see the Supporting Information, Table S1 for details). Under these conditions, *trans* cycloadducts **3** were formed in viable yields and as single diastereomers with >20:1 diastereoselectivity. The initial cycloadducts are moderately stable, and *N*-acylation at the pyrrolidine nitrogen atom increases their stability.

The results shown in Table 1 demonstrate that aromatic aldehydes with either electron-withdrawing or -donating substituents and heteroaromatic aldehydes can successfully be employed in the transformation. As in the case of intermolecular 1,3-dipolar cycloadditions with azomethine ylides,^[6,7] imines derived from aliphatic aldehydes did not give the cycloadducts. To obtain high yields, an electron-withdrawing substituent R¹ is required. When R¹ was a phenyl or an alkyl group, cycloadduct formation was not observed.

Initial attempts to develop an enantioselective catalytic sequential one-pot synthesis revealed that under the conditions described above, enantioselectivity was low and not reproducible. These problems were overcome by isolation of

the Schiff base and subsequent separate cycloaddition. Screening different Ag and Cu salts and chiral ligands revealed that in general, Cu salts yielded better results, and that [Cu(MeCN)₄]BF₄ was the best catalyst. Among several mono- or bidentate phosphine ligands (see Figure S1 and Table S2 for details), 3,4,5-(MeO)₃Ph-MeOBIPHEP gave the best results in terms of both yield and enantioselectivity. Notably, ligands that were effective in intermolecular 1,3-dipolar cycloadditions^[6,7] with azomethine ylides gave inferior results in the intramolecular reactions (see Figure S1). A screen of different solvents, temperatures, and bases showed that the reactions are best performed in diethyl ether at room temperature and in the presence of NEt₃ as the base. Variation of the electron-withdrawing olefin substituent R¹ identified the cyano group as being superior to an ester (Table 2, entries 1 and 2).

Investigating the scope of the enantioselective intramolecular 1,3-dipolar cycloaddition under the identified reaction conditions (Table 2) revealed that 1) irrespective of the electronic nature of the aldehydes employed, the reactions proceeded with high diastereoselectivity and with preparatively viable yields and that 2) the enantioselectivity is controlled by electronic factors. Thus, in the presence of an unsubstituted phenyl group or electron-donating substituents at the phenyl group or in the presence of electron-rich heteroaromatic rings, *ee* values of 95 to 99% were achieved (Table 2, entries 3, 7–17). The introduction of electron-withdrawing substituents, such as NO₂, F, or Br, led to lower enantioselectivities (entries 4–6), but with a *para*-iodophenyl substituent, the *ee* value reached 97% again (Table 2, entry 15). 3) The amide substituent R³ could be varied, and the enantioselectivity remained high (entries 3, 7–9, 22). However, this does not apply in all cases (see entry 21). 4) Replacement of the nitrile group by an ester group leads to reduced enantioselectivity (entries 19–21). As the *N*-unmasked cycloadducts are only moderately stable, they may subsequently be *N*-acylated in a separate step (entries 10–17).

The absolute configuration of the products was unambiguously ascertained through crystal-structure analysis of cycloadduct **3x** (see Figure 2 and the Supporting Information). To explain the stereochemical outcome of the cycloaddition, we propose that in analogy to earlier observations,^[8] Cu⁺ coordinates the bidentate phosphine ligand and the Schiff base in a tetrahedral arrangement (see Figure 2). Deprotonation of the Schiff base generates the azomethine ylide and initiates the cycloaddition. Owing to the steric requirements of the intramolecular cycloaddition, in the reactive conformation, the amide must be *cis*-configured, such that the olefin can approach the dipole. The dipolarophile approaches the dipole in an *endo* transition state to minimize steric interactions and strain. The attack of the electron-poor olefin preferably occurs from the front. Facial differentiation is achieved by means of the alkoxy-substituted aryl substituents on the phosphines (Figure 2). Upon attack from the back of the dipole, the cyanovinyl group would face unfavorable interactions with the aryl group pointing towards the back. Owing to the ligand stereochemistry established by the atropisomeric bis(phosphine), the second aryl group of this

Table 2: Scope of the catalytic enantioselective intramolecular 1,3-dipolar cycloaddition reaction.^[a]

Entry	Product	R ¹	R ²	R ³	R ⁴	Yield [%] ^[b]	ee [%] ^[c]
1	3j	CO ₂ Et	Ph	Me	H	75	82
2	3k	CN	Ph	Me	H	82	93
3	3l	CN	<i>p</i> -MeOC ₆ H ₄	Me	H	78	95
4	3m	CN	<i>p</i> -NO ₂ C ₆ H ₄	Me	H	71	13
5	3n	CN	<i>p</i> -FC ₆ H ₄	Me	H	75	73
6	3o	CN	<i>p</i> -BrC ₆ H ₄	Me	H	78	83
7	3p	CN	3-furanyl	Me	H	54	96
8	3q	CN	3-thiophenyl	Me	H	50	95
9	3r	CN	Ph	H	H	80	98
10	3s	CN	Ph	H	CO ₂ Me	75	98
11	3t	CN	<i>p</i> -MeOC ₆ H ₄	CO ₂ Me	CO ₂ Me	76	98
12	3u	CN	<i>p</i> -MeC ₆ H ₄	CO ₂ Me	CO ₂ Me	78	98
13	3v	CN	<i>m</i> -MeC ₆ H ₄	CO ₂ Me	CO ₂ Me	73	97
14	3w	CN	<i>o</i> -MeC ₆ H ₄	CO ₂ Me	CO ₂ Me	75	98
15	3x	CN	<i>p</i> -IC ₆ H ₄	CO ₂ Me	CO ₂ Me	79	97
16	3y	CN	3-furanyl	H	CO ₂ Me	63	98
17	3z	CN	3-thiophenyl	H	CO ₂ Me	75	99
18	3aa	CO ₂ Bn	Ph	Me	H	69	74
19	3ab	CO ₂ Et	Ph	Bn	H	65	62
20	3ac	CO ₂ Bn	Ph	Bn	H	35	63
21	3ad	CN	Ph	Bn	H	57	80
22	3ae	CN	<i>p</i> -MeC ₆ H ₄	Bn	H	75	95

[a] Reaction conditions: **1** (0.12 mmol) and TFA (1.2 mmol) were used for the deprotection. Aldehyde (0.12 mmol) and DIPEA (0.24 mmol) were used for imine formation. Then, catalyst (5 mol%), ligand (5 mol%, Ar = 3,4,5-(MeO)₃C₆H₂), base (0.12 mmol), and activated 4 Å M.S. powder in Et₂O (2 mL). [b] Yields of isolated products after column chromatography. For **3s–3z**, yields and ee values were determined after separate N-acylation of the initial cycloadducts. Under the optimized reaction conditions, all products were obtained with > 20:1 d.r. [c] Determined by HPLC analysis on a chiral stationary phase. DIPEA = diisopropylethylamine.

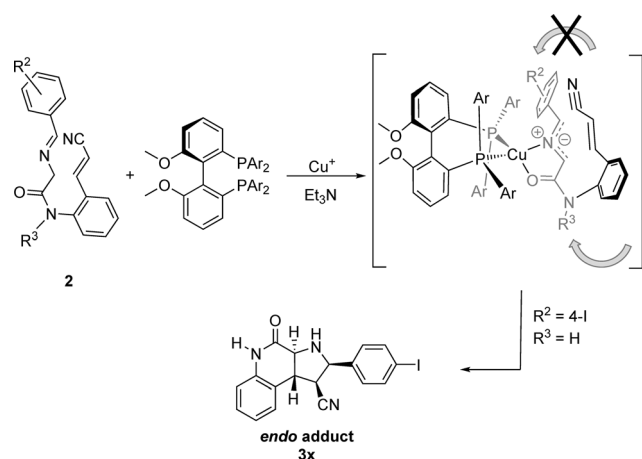


Figure 2. Proposed mechanism and rationalization of the stereoselectivity observed in the enantioselective intramolecular cycloaddition reaction. Ar = 3,4,5-(MeO)₃C₆H₂.

phosphine points downwards such that in the shown orientation of the dipole, steric interactions are minimized.

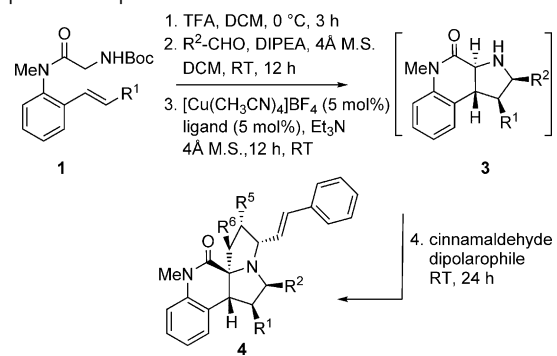
Cycloadducts **3** (R⁴ = H) can in principle be regarded as cyclic N-alkylated amino acid amides. We envisioned that treatment of these secondary amines with an aldehyde would give rise to an iminium intermediate, which could be deprotonated to yield a new azomethine ylide, which in turn could undergo a further 1,3-dipolar cycloaddition with a reactive dienophile. If orchestrated correctly, a tandem sequence of intra- and intermolecular cycloadditions would become feasible. Orienting experiments employing primary cycloadduct **3k**, cinnamaldehyde, and methyl acrylate in the presence of 5 mol% of AgOAc and NEt₃ were indeed successful, and a tandem sequence employing the conditions established for the enantioselective transformation could also be developed (Table 3). When cinnamaldehyde and methyl acrylate were added after completion of the first enantioselective cycloaddition, the desired pyrrolizidine adduct **4a** was obtained in 60% overall yield after four individual steps and with the same enantiomeric excess as previously recorded for the primary cycloadduct. When the racemic primary cycloadduct was treated with aldehyde, acrylate, and the chiral catalyst, no enantioselectivity was induced indicating that the stereoselectivity for the whole sequence is determined in the first cycloaddition step and that the second cycloaddition is highly diastereoselective.

The absolute configuration of the double cycloadducts was determined by means of careful analysis of their NMR spectra by analogy to related syntheses and through crystal-structure analysis of cycloadduct **4d** (see the Supporting Information).^[9]

For the cycloadducts obtained from *trans* olefins such as nitrostyrene, interactions identified through nuclear Overhauser effect (NOE) spectra indicate that the benzylic proton originating from the former double bond of the dipolarophile is in proximity to the proton next to the nitrile group. Likewise, NOE signal enhancements were determined for the proton in the α -position to the nitro group and the allylic proton originating from the cinnamaldehyde. This result indicates that the second cycloaddition passes through an *endo* transition state with *trans*- and, by analogy, monosubstituted dipolarophiles (Figure 3). We assume that the second cycloaddition reaction is a concerted process; however, a stepwise mechanism cannot be ruled out completely.

The tandem sequence displayed a very appreciable substrate scope, and the substituents in both the first and the second dipolarophile could be widely varied. Notably, the introduction of disubstituted olefins in the second cycloaddition step in a one-pot procedure yielded annulated pyrrolizidines with seven contiguous stereogenic centers, including a quaternary carbon atom. Thus *trans*-cinnamaldehyde and β -nitrostyrene yielded fully substituted pyrrolizidines **4b** and **4c**, respectively, in appreciable yields (Table 3,

Table 3: Enantioselective synthesis of piperidino-pyrrolizidines by tandem intra- and intermolecular 1,3-dipolar cycloadditions in a sequential one-pot reaction.^[a]



Entry	Product	R ¹	R ²	R ⁵	R ⁶	Yield [%] ^[b]
1	4a	CN	Ph	CO ₂ Me	H	60
2	4b	CN	Ph	CHO	Ph	47
3	4c	CN	Ph	NO ₂	Ph	45
4	4d ^[c]	CN	Ph	CO ₂ Me	CO ₂ Me	52
5	4e	CN	<i>p</i> -MeC ₆ H ₄	CO ₂ Me	H	57
6	4f	CN	<i>p</i> -MeOC ₆ H ₄	CO ₂ Me	H	70
7	4g	CN	3-thiophenyl	CO ₂ Me	H	50
8	4h	CN	<i>m</i> -MeC ₆ H ₄	CO ₂ Me	H	58
9	4i	CO ₂ Et	Ph	CO ₂ Me	H	50

[a] Reaction conditions: **1** (0.12 mmol) and TFA (1.2 mmol) were used for the deprotection. Aldehyde (0.12 mmol) and DIPEA (0.24 mmol) were used for imine formation. Then, catalyst (5 mol%), ligand (5 mol%), base (0.12 mmol), and activated 4 Å M.S. powder in Et₂O/THF (5:1) as the solvent (2.5 mL). Aldehyde (0.12 mmol), Et₃N (0.12 mmol), and the dipolarophile (0.60 mmol) were used for the second cycloaddition. [b] Yields of isolated products after column chromatography. [c] The substituents R⁶ and R⁵ are in a *cis* arrangement.

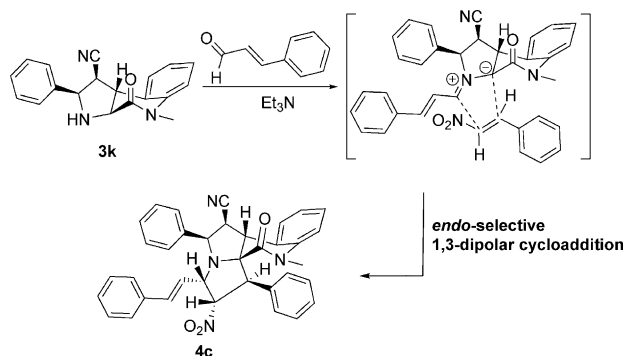


Figure 3. Models for possible transition states to rationalize the stereoselectivity of the second cycloaddition reaction.

entries 2 and 3). Likewise, the *cis* dipolarophile dimethyl maleate smoothly underwent the cycloaddition to yield the corresponding complex pyrrolizidine **4d** (entry 4). Furthermore, the structure of the aromatic aldehydes tolerated different substitution patterns to yield the corresponding cycloadducts in viable yields (entries 5–8). Finally, also the olefin substituent R¹ could be varied (entry 9). Pyrrolizidines are core structures of numerous chiral natural-product-

inspired heterocycles and are of interest in their own right. For example, they define the scaffolds of glycosidase inhibitors, which have been the subject of numerous investigations.^[10]

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- [1] a) M. Kaiser, S. Wetzel, K. Kumar, H. Waldmann, *Cell. Mol. Life Sci.* **2008**, *65*, 1186–1201; b) S. Wetzel, R. S. Bon, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 10800–10826; *Angew. Chem.* **2011**, *123*, 10990–11018; c) H. van Hattum, H. Waldmann, *J. Am. Chem. Soc.* **2014**, *136*, 11853–11859; d) R. S. Bon, H. Waldmann, *Acc. Chem. Res.* **2010**, *43*, 1103–1114.
- [2] a) K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 3224–3242; *Angew. Chem.* **2009**, *121*, 3272–3290; b) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schurmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735–740; c) R. Narayan, J. O. Bauer, C. Strohmman, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 12892–12896; *Angew. Chem.* **2013**, *125*, 13130–13134; d) H. Takayama, Z.-J. Jia, L. Kremer, J. O. Bauer, C. Strohmman, S. Ziegler, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 12404–12408; *Angew. Chem.* **2013**, *125*, 12630–12634; e) P.-Y. Dakas, J. A. Parga, S. Höing, H. R. Schöler, J. Sterneckert, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 9576–9581; *Angew. Chem.* **2013**, *125*, 9755–9760; f) T. Voigt, C. Gerding-Reimers, T. N. T. Tuyen, S. Bergmann, H. Lachance, B. Scholermann, A. Brockmeyer, P. Janning, S. Ziegler, H. Waldmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 410–414; *Angew. Chem.* **2013**, *125*, 428–432; g) H. Dücker, V. Pries, V. Khedkar, S. Menninger, H. Bruss, A. W. Bird, Z. Maliga, A. Brockmeyer, P. Janning, A. Hyman, S. Grimme, M. Schurmann, H. Preut, K. Hubel, S. Ziegler, K. Kumar, H. Waldmann, *Nat. Chem. Biol.* **2012**, *8*, 179–184.
- [3] a) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick, H. Waldmann, *Acc. Chem. Res.* **2014**, *47*, 1296–1310; b) M. Potowski, M. Schurmann, H. Preut, A. P. Antonchick, H. Waldmann, *Nat. Chem. Biol.* **2012**, *8*, 428–430; c) C. Chen, X. Li, S. L. Schreiber, *J. Am. Chem. Soc.* **2003**, *125*, 10174–10175; d) A. S. Gothelf, K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 4236–4238; *Angew. Chem.* **2002**, *114*, 4410–4412; e) J. M. Longmire, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401.
- [4] For enantioselective catalytic intramolecular cycloadditions with azomethine ylides, see: a) R. Stohler, F. Wahl, A. Pfaltz, *Synthesis* **2005**, 1431–1436; b) N. Li, J. Song, X.-F. Tu, L. Bin, X.-H. Chen, L.-Z. Gong, *Org. Biomol. Chem.* **2010**, *8*, 2016–2019; for an enantioselective catalytic 1,3-dipolar cycloaddition with acylhydrazones, see: c) S. Kobayashi, H. Shimizu, Y. Yamashita, H. Ishitani, J. Kobayashi, *J. Am. Chem. Soc.* **2002**, *124*, 13678–13679.
- [5] a) K. M. Witherup, W. R. Richard, A. C. Graham, A. M. Bernard, M. J. Salvatore, W. C. Lumma, P. S. Anderson, S. M. Pitzberger, S. L. Varga, *J. Am. Chem. Soc.* **1995**, *117*, 6682–6685; b) S. Hong, J. Yang, S. M. Weinreb, *J. Org. Chem.* **2006**, *71*, 2078–2089; c) V. Caprioli, G. Cimino, A. D. Giulio, A. Madaio, G. Scognamiglio, E. Trivellone, *Comp. Biochem. Physiol. Part B* **1992**, *103*, 293–296.
- [6] a) M. A. Marx, A.-L. Grillot, C. T. Louer, K. A. Beaver, P. A. Bartlett, *J. Am. Chem. Soc.* **1997**, *119*, 6153–6167; b) Y. He, H.

- Mahmud, B. R. Wayland, H. V. R. Dias, C. J. Lovely, *Tetrahedron Lett.* **2002**, 43, 1171–1174.
- [7] M. Potowski, J. O. Bauer, C. Strohmman, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2012**, 51, 9512–9516; *Angew. Chem.* **2012**, 124, 9650–9654.
- [8] M. Potowski, A. P. Antonchick, H. Waldmann, *Chem. Commun.* **2013**, 49, 7800–7802.
- [9] D. Lim, J. A. Codelli, S. E. Reisman, *Chem. Sci.* **2013**, 4, 650–654.
- [10] N. Asano, K. Ikeda, M. Kasahara, Y. Arai, H. Kizu, *J. Nat. Prod.* **2004**, 67, 846–850.
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