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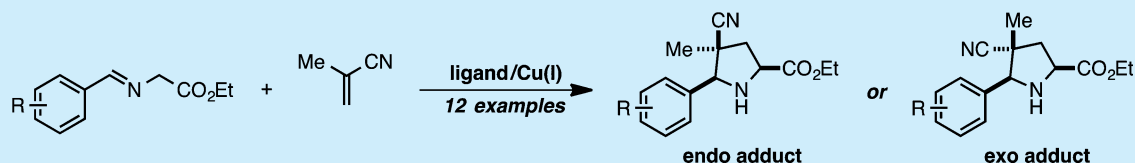
Ligand-Controlled Diastereoselective 1,3-Dipolar Cycloadditions of Azomethine Ylides with Methacrylonitrile

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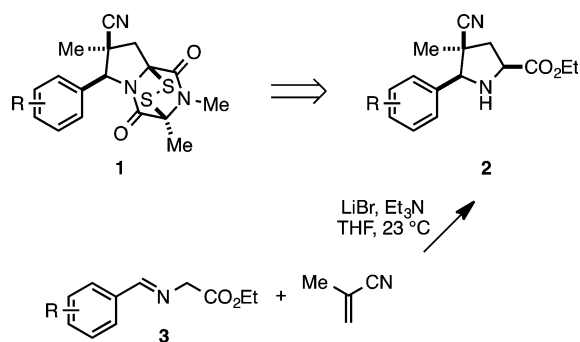
S Supporting Information



ABSTRACT: Copper-catalyzed reactions of glycine ester arylimines and methacrylonitrile provide selective access to either the endo or exo pyrrolidine cycloadducts. DFT calculations have elucidated the origins of ligand-controlled diastereoselectivity.

We recently reported that analogues **1** of epidithiodioxopiperazine (ETP) alkaloids exhibit promising activity against both solid and blood tumors in vitro and that a lead member of this series having a methylenedioxyphenyl-5-yl substituent suppresses tumor growth in mouse xenograft models of melanoma and lung cancer.¹ Pyrrolidine 2-carboxylates **2**, which are pivotal intermediates in the synthesis of **1**, were prepared by 1,3-dipolar cycloadditions of azomethine ylides derived from glycine imines **3** with methacrylonitrile.² Using the commonly employed conditions of Tsuge (Scheme 1),^{2b} endo cycloadducts **2** were formed with 2:1–10:1

Scheme 1. Dipolar Cycloaddition Step in the Synthesis of Antitumor ETP Alkaloid Analogues 1



diastereoselectivity. Although the construction of 2-pyrrolidine esters by 1,3-dipolar cycloadditions is well-developed, with many advances in metal and enantioselective catalysis having been recorded, cycloadditions in which the dipolarophile is activated by a nitrile rather than an ester substituent are much less common.³ For example, prior to our disclosure,¹ there was only one report⁴ of a 1,3-dipolar cycloaddition of an azomethine ylide derived from a glycine imine and methacrylonitrile.^{5,6} As substituted pyrrolidines are structural

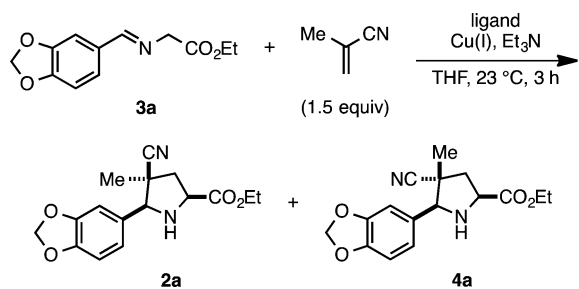
motifs in many bioactive natural products⁷ and synthetic pharmaceuticals,⁸ and nitriles are important pharmacophores,⁹ we chose to examine metal catalysis of cycloadditions of the type illustrated in Scheme 1. We report herein salient features of these investigations, which discovered that either the endo or exo cycloadduct can be formed with high selectivity by changing only the ligand of a Cu(I) catalyst. Computational studies that shed light on the origin of the observed diastereoselectivities are also reported.

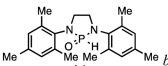
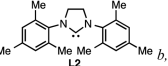
Our studies began by examining copper complexes formed from Cu(MeCN)₄BF₄ in the reaction of imine **3a** and methacrylonitrile (Table 1), because several examples of copper-catalyzed cycloadditions of azomethine ylides with nitrile-containing dipolarophiles had been reported by the Carretero group¹⁰ and others.^{6e,j,k} We initially investigated a variety of ligand types. Reactions using Ph₃P or tricyclohexylphosphine (Cy₃P) afforded pyrrolidine products in high yield; however, only the reaction with Cy₃P was diastereoselective giving the exo cycloadduct **4a** with 9:1 selectivity (entry 2). In contrast, the reaction using 1,2-bis(diphenylphosphino)ethane (dppe) as the ligand resulted in 88:12 diastereoselectivity favoring the endo cycloadduct **2a** (entry 3). Endo stereoselectivity was improved to 50:1 by using tris(2,2,2-trifluoroethyl) phosphite [P(OCH₂CF₃)₃] as the ligand (entry 4). The HASPO ligand **L1** provided the endo cycloadduct **2a** with modest stereoselectivity; however, the yield of this reaction was low (entry 5). The P,N-ligand DavePhos (2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl) resulted in a 41:59 mixture of cycloadducts in a high yield of 85% (entry 6). The use of the NHC ligand **L2** or 1,10-phenanthroline resulted in no reaction (entries 7, 8).

Three ligands—P(OCH₂CF₃)₃, Cy₃P, and DavePhos—were selected to test the generality of the ligand effects observed in

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Table 1. Investigation of Ligands for the Cu(I)-Catalyzed Reaction of Imine **3a** and Methacrylonitrile^a











entry	ligand	yield (%) ^e	dr (endo:exo) ^f
1	Ph ₃ P ^b	86	32:68
2	Cy ₃ P ^b	90	10:90
3	dppf ^c	71	88:12
4	P(OCH ₂ CF ₃) ₃ ^b	74	98:2
5		19	84:16
6	DavePhos ^c	85	41:59
7		0	nd
8	1,10-phenanthroline ^c	0	nd

^aReactions were performed using imine **3a** (0.20 mmol), methacrylonitrile (0.30 mmol), Cu(MeCN)₄BF₄ (10 mol %), and Et₃N (0.12 mmol) at a concentration of 0.20 M in THF. ^bThe reactions were conducted using 22 mol % of the ligand. ^cThe reactions with bidentate ligands were performed using 11 mol % of the ligand. ^dLigand **L2** was generated from the corresponding HBF₄ by stirring with 1.1 equiv of potassium *tert*-butoxide for 10 min before adding Cu(MeCN)₄BF₄. ^eGC yields using 1,3,5-trimethoxybenzene as external standard. ^fRatios were determined by GC-FID analysis. nd = not determined.

our initial survey.¹¹ As summarized in **Table 2**, good yields and very high diastereoselectivities (>94:6) favoring formation of the endo cycloadducts were observed for eight aryl imine substrates in Cu-catalyzed cycloadditions using P(OCH₂CF₃)₃ (initial imine concentration of 0.6 M, 5 h reaction time).^{12,13} The sole exception was the 3-pyridinyl substrate, which reacted with slightly lower diastereoselectivity and in poor yield.¹⁴ Exo cycloadducts were accessed in high stereoselectivity (>86:14) and good yield in similar reactions using Cy₃P (imine concentration of 1 M, reaction time 1 h).¹⁵ As in our preliminary survey, Cu-catalyzed cycloadditions using DavePhos were nonstereoselective. Yields of isolated products and stereoselectivities were similar in reactions conducted on a larger scale (entries 1, 2, 10, 11, 19, 20, 25, and 26).

The origins of the ligand-controlled diastereoselectivity were studied through DFT calculations, using a truncated model of imine **3** and methacrylonitrile. B3LYP-D3/SDD-6-311+G(d,p) energies from B3LYP geometries are given here.¹⁶ Extensive conformational searching has been performed to find the most stable conformer. With the P(OCH₂CF₃)₃ ligand, the computation results show that the endo transition state, **T5S**, is 0.9 kcal/mol more stable than the exo transition state, **T56**. This is consistent with the experimental diastereoselectivity (entry 4, **Table 1**). In **T5S**, the negative electrostatic potential (ESP) region of methacrylonitrile (N terminal) is proximal to

Table 2. Investigation of Ligands for the Cu(I)-Catalyzed Reaction of Imines **3** and Methacrylonitrile^a

entry	imine aryl group	ligand	GC yield ^e (isolated) ^f	dr (endo:exo) ^g
1		P(OCH ₂ CF ₃) ₃ ^b	88% (79%)	96:4 (94:6) ^h
2		Cy ₃ P ^c	97% (82%)	9:91 (11:89) ^h
3		DavePhos ^d	95%	39:61
4		P(OCH ₂ CF ₃) ₃ ^b	58%	94:6
5		Cy ₃ P ^c	>99%	12:88
6		DavePhos ^d	96%	35:65
7		P(OCH ₂ CF ₃) ₃ ^b	91%	94:6
8		Cy ₃ P ^c	93%	9:91
9		DavePhos ^d	93%	40:60
10		P(OCH ₂ CF ₃) ₃ ^b	76% (76%)	98:2 (96:4) ^h
11		Cy ₃ P ^c	97% (83%)	11:89 (12:88) ^h
12		DavePhos ^d	94%	38:62
13		P(OCH ₂ CF ₃) ₃ ^b	14%	86:14
14		Cy ₃ P ^c	52%	12:88
15		DavePhos ^d	46%	49:51
16		P(OCH ₂ CF ₃) ₃ ^b	84%	96:4
17		Cy ₃ P ^c	>99%	12:88
18		DavePhos ^d	>99%	41:59
19		P(OCH ₂ CF ₃) ₃ ^b	88% (74%)	96:4 (96:4) ^h
20		Cy ₃ P ^c	92% (78%)	14:86 (15:85) ^h
21		DavePhos ^d	98%	47:53
22		P(OCH ₂ CF ₃) ₃ ^b	78%	96:4
23		Cy ₃ P ^c	95%	12:88
24		DavePhos ^d	98%	56:44
25		P(OCH ₂ CF ₃) ₃ ^b	91% (74%)	98:2 (96:4) ^h
26		Cy ₃ P ^c	>99% (76%)	14:86 (15:85) ^h
27		DavePhos ^d	>99%	61:39

^aReactions were performed using imine **3** (0.20 mmol), methacrylonitrile (0.22 mmol), and Cu(MeCN)₄BF₄ (5 mol %) at the indicated concentration in THF. ^bReactions run at 0.6 M for 5 h using 11 mol % ligand. ^cReactions run at 1.0 M for 1 h using 11 mol % ligand. ^dReactions run at 0.4 M for 3 h using 5.5 mol % ligand. ^eGC yields determined using 1,3,5-trimethoxybenzene as an internal standard (average of two experiments). ^fIsolated yields from reactions run on a 0.5 mmol scale. ^gRatios determined by GC-FID analysis (average of two experiments). ^hRatios of isolated products.

the ESP-positive region of the phosphite ligand (ligand methylene group),¹⁷ as highlighted in Figure 1, and the

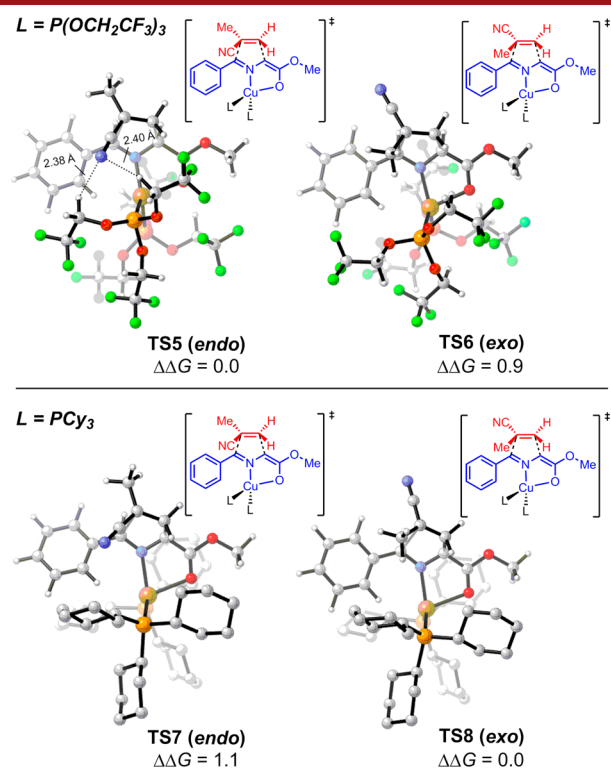
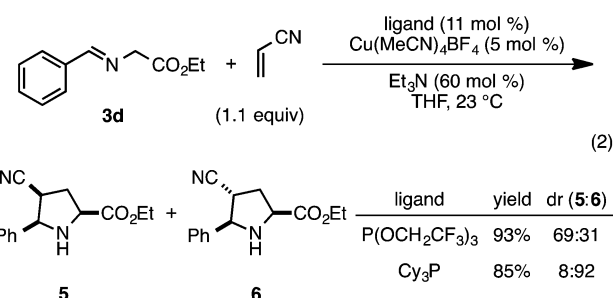
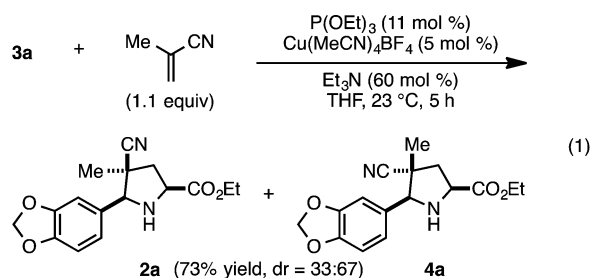


Figure 1. Structures and relative Gibbs free energies of transition states of copper-catalyzed cycloaddition between model azomethine ylide and methacrylonitrile (Gibbs free energies are in kcal/mol; the hydrogens of the Cy_3P ligands are omitted for clarity).

electrostatic interaction stabilizes this endo transition state, leading to the diastereoselectivity. With the Cy_3P ligand, this electrostatic stabilization no longer exists, and the steric repulsions favor the exo transition state. The nitrile group of methacrylonitrile has greater repulsion of the Cy_3P ligand as compared to the methyl group. Therefore, the exo transition state, **TS8**, is 1.1 kcal/mol more stable than the endo transition state, **TS7**, and the diastereoselectivity is reversed.

Two additional observations are consistent with the computational model proposed in Figure 1. The stabilizing electrostatic interactions between the nitrile nitrogen and $P(OCH_2CF_3)_3$ in endo transition structure **TS5** would not be expected if a less electron-deficient phosphite ligand was employed. This prediction is confirmed by the reaction of imine **3a** with methacrylonitrile using triethyl phosphite as the ligand, which proceeded nonstereoselectively to give the exo and endo cycloadducts **4a** and **2a** in a 2:1 ratio (eq 1). In addition, endo stereoselection in the reaction of acrylonitrile with imine **3d** using $P(OCH_2CF_3)_3$ as the ligand occurred with eroded endo stereoselectivity (dr = 69:31, eq 2) compared to cycloaddition with methacrylonitrile under identical conditions. The lack of substitution at the α -position of acrylonitrile results in exo transition structure **TS6** being less disfavored. As would be expected, high exo stereoselectivity was seen in this reaction using Cy_3P as the ligand (eq 2).

In conclusion, by changing only the nature of a phosphorus ligand, 1,3-dipolar cycloaddition reactions of glycine ester arylimines and methacrylonitrile provide either the endo or exo cycloadduct with high diastereoselectivity. These reactions



provide the first diastereoselective access to cyano-substituted pyrrolidines of this type. The DFT transition state structures that rationalize the observed selectivity trends provide a basis for future studies to render such reactions enantioselective.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03171.

Experimental procedures, characterization data for new compounds, supplementary computational results, computational details, Cartesian coordinates and Gibbs free energies of the calculated structures (PDF)

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Notes

The authors declare no competing financial interest.

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(11) During our investigation, Carretero and coworkers reported that a switch in diastereoselectivity could be accomplished using two different biaryl phosphine ligands in Cu-catalyzed azomethine ylide cycloadditions to 1,3-dienes; see: González-Esguevillas, M.; Pascual-Escudero, A.; Adrio, J.; Carretero, J. C. *Chem. - Eur. J.* **2015**, *21*, 4561.

(12) The relative configurations of pyrrolidine products were assigned as described in ref 1 and are supported by 2D ¹H NMR (see the [Supporting Information](#) for details).

(13) Optimization experiments that defined the preferred solvent and reaction concentration for each catalyst can be found in the [Supporting Information](#).

(14) Yields of products **2e** and **4e** were increased when a higher catalyst loading of 10 mol % was used. The pyridinyl substituent undoubtedly reduces catalyst activity, as the addition of 1 equiv of pyridine to the reaction reported in [Table 2](#), entry 10 resulted in <5% formation of cycloadduct **2d**.

(15) Whereas the use of 5.5 mol % of P(OCH₂CF₃)₃ and Cy₃P resulted in the formation of an effective catalyst, the use of 11 mol % resulted in increased catalyst solubility and elevated yields.

(16) (a) Computational details and references are included in the [Supporting Information](#). (b) For a related DFT study, see: Wang, M.; Wang, C.-J.; Lin, Z. *Organometallics* **2012**, *31*, 7870.

(17) ESP diagrams of methacrylonitrile and the copper complex in **TSS** are included in the [Supporting Information](#).