Organic LETTERS

Letter

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

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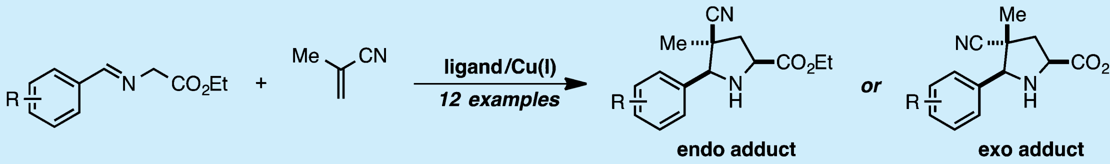
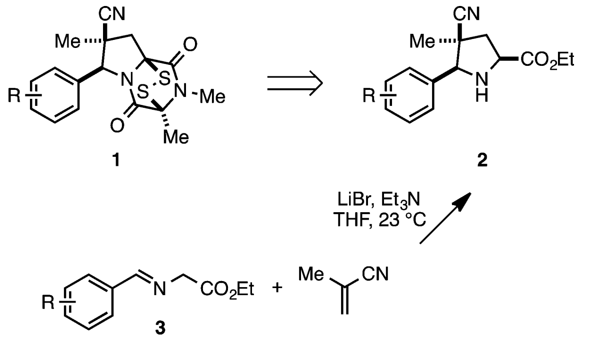
Ⓢ *Supporting Information*



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 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 report[4] 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 products[7] 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.

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



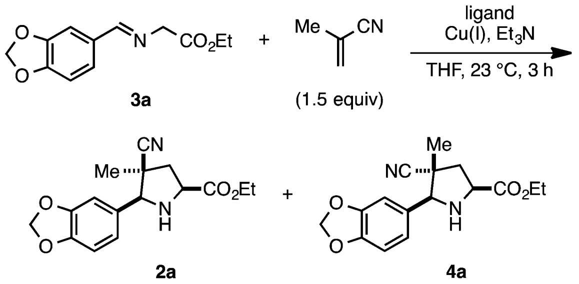
Our studies began by examining copper complexes formed from Cu(MeCN)$_4$BF$_4$ in the reaction of imine **3a** and methacrylonitrile (Table 1), because several examples of copper-catalyzed cycloadditions of azomethine ylides with nitrile-containing dipolarophiles had been reported by the Carretero group[10] and others.[6e,j,k] We initially investigated a variety of ligand types. Reactions using Ph$_3$P or tricyclohexylphosphine (Cy$_3$P) afforded pyrrolidine products in high yield; however, only the reaction with Cy$_3$P 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(OCH$_2$CF$_3$)$_3$] 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).

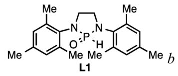
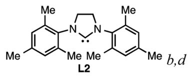
Three ligands—P(OCH$_2$CF$_3$)$_3$, Cy$_3$P, and DavePhos—were selected to test the generality of the ligand effects observed in

Received: November 2, 2015

DOI: 10.1021/acs.orglett.5b03171
Org. Lett. XXXX, XXX, XXX–XXX

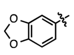
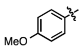
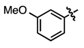
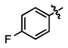
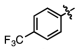
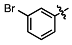
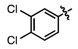
Table 1. Investigation of Ligands for the Cu(I)-Catalyzed Reaction of Imine 3a and Methacrylonitrile[a]



entry	ligand	yield (%)[e]	dr (endo:exo)[f]
1	Ph_3P[b]	86	32:68
2	Cy_3P[b]	90	10:90
3	dppe[c]	71	88:12
4	$P(OCH_2CF_3)_3$[b]	74	98:2
5	 L1 [b]	19	84:16
6	DavePhos[c]	85	41:59
7	 L2 [b,d]	0	nd
8	1,10-phenanthroline[c]	0	nd

[a] Reactions were performed using imine **3a** (0.20 mmol), methacrylonitrile (0.30 mmol), $Cu(MeCN)_4BF_4$ (10 mol %), and Et_3N (0.12 mmol) at a concentration of 0.20 M in THF. [b] The reactions were conducted using 22 mol % of the ligand. [c] The reactions with bidentate ligands were performed using 11 mol % of the ligand. [d] Ligand **L2** was generated from the corresponding HBF_4 by stirring with 1.1 equiv of potassium *tert*-butoxide for 10 min before adding $Cu(MeCN)_4BF_4$. [e] GC yields using 1,3,5-trimethoxybenzene as external standard. [f] Ratios were determined by GC-FID analysis. nd = not determined.

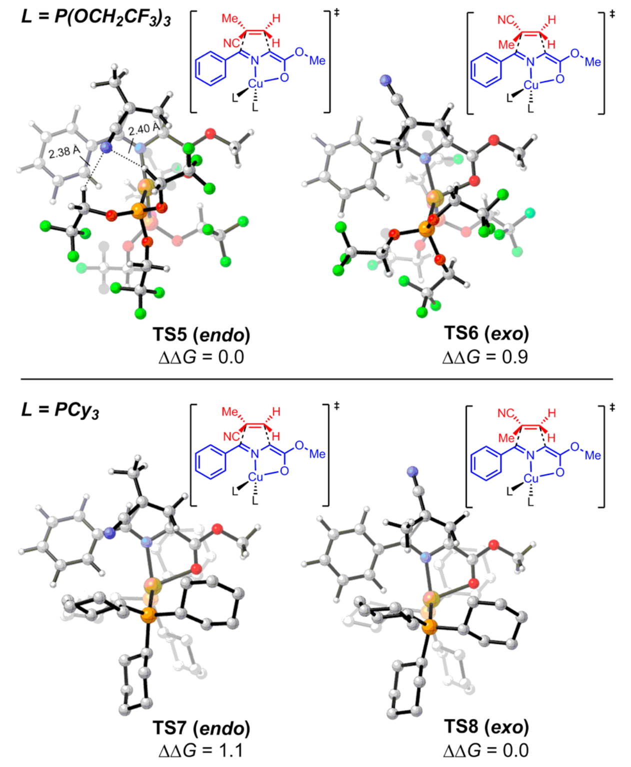
Table 2. Investigation of Ligands for the Cu(I)-Catalyzed Reaction of Imines 3 and Methacrylonitrile[a]

entry	imine aryl group	ligand	GC yield[e] (isolated)[f]	dr (endo:exo)[g]
1	 3a	$P(OCH_2CF_3)_3$[b]	88% (79%)	96:4 (94:6)[h]
2		Cy_3P[c]	97% (82%)	9:91 (11:89)[h]
3		DavePhos[d]	95%	39:61
4	 3b	$P(OCH_2CF_3)_3$[b]	58%	94:6
5		Cy_3P[c]	>99%	12:88
6		DavePhos[d]	96%	35:65
7	 3c	$P(OCH_2CF_3)_3$[b]	91%	94:6
8		Cy_3P[c]	93%	9:91
9		DavePhos[d]	93%	40:60
10	 3d	$P(OCH_2CF_3)_3$[b]	76% (76%)	98:2 (96:4)[h]
11		Cy_3P[c]	97% (83%)	11:89 (12:88)[h]
12		DavePhos[d]	94%	38:62
13	 3e	$P(OCH_2CF_3)_3$[b]	14%	86:14
14		Cy_3P[c]	52%	12:88
15		DavePhos[d]	46%	49:51
16	 3f	$P(OCH_2CF_3)_3$[b]	84%	96:4
17		Cy_3P[c]	>99%	12:88
18		DavePhos[d]	>99%	41:59
19	 3g	$P(OCH_2CF_3)_3$[b]	88% (74%)	96:4 (96:4)[h]
20		Cy_3P[c]	92% (78%)	14:86 (15:85)[h]
21		DavePhos[d]	98%	47:53
22	 3h	$P(OCH_2CF_3)_3$[b]	78%	96:4
23		Cy_3P[c]	95%	12:88
24		DavePhos[d]	98%	56:44
25	 3i	$P(OCH_2CF_3)_3$[b]	91% (74%)	98:2 (96:4)[h]
26		Cy_3P[c]	>99% (76%)	14:86 (15:85)[h]
27		DavePhos[d]	>99%	61:39

[a] Reactions were performed using imine **3** (0.20 mmol), methacrylonitrile (0.22 mmol), and $Cu(MeCN)_4BF_4$ (5 mol %) at the indicated concentration in THF. [b] Reactions run at 0.6 M for 5 h using 11 mol % ligand. [c] Reactions run at 1.0 M for 1 h using 11 mol % ligand. [d] Reactions run at 0.4 M for 3 h using 5.5 mol % ligand. [e] GC yields determined using 1,3,5-trimethoxybenzene as an internal standard (average of two experiments). [f] Isolated yields from reactions run on a 0.5 mmol scale. [g] Ratios determined by GC-FID analysis (average of two experiments). [h] Ratios of isolated products.

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 $P(OCH_2CF_3)_3$ (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 Cy_3P (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 $P(OCH_2CF_3)_3$ ligand, the computation results show that the endo transition state, **TS5**, is 0.9 kcal/mol more stable than the exo transition state, **TS6**. This is consistent with the experimental diastereoselectivity (entry 4, Table 1). In **TS5**, the negative electrostatic potential (ESP) region of methacrylonitrile (N terminal) is proximal to the ESP-positive region of the phosphite ligand (ligand methylene group),[17] as highlighted in Figure 1, and the 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.

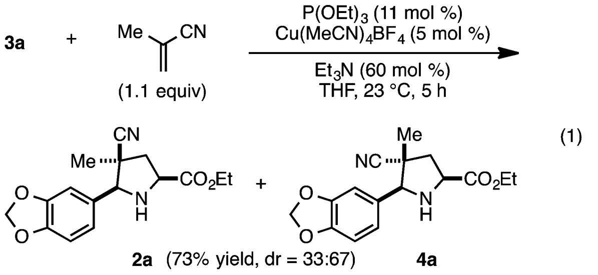


TS5 (*endo*) $\Delta\Delta G = 0.0$ **TS6** (*exo*) $\Delta\Delta G = 0.9$

TS7 (*endo*) $\Delta\Delta G = 1.1$ **TS8** (*exo*) $\Delta\Delta G = 0.0$

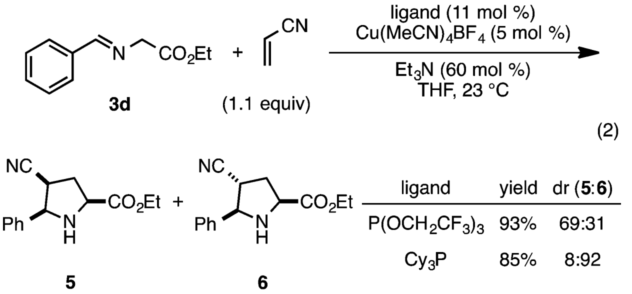
Figure 1. Structures and relative Gibbs free energies of transition states of copper-catalyzed cycloaddition between model azomethine ylide and methacrylonitrile (Gibbs free energies are in kcal/mol; the hydrogens of the Cy_3P ligands are omitted for clarity).

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).



2a (73% yield, dr = 33:67) **4a**

(1)



3d

(2)

5 **6**

ligand	yield	dr (**5**:**6**)
$P(OCH_2CF_3)_3$	93%	69:31
Cy_3P	85%	8:92

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.

■ ACKNOWLEDGMENTS

M.C.W. thanks the National Science Foundation for a graduate fellowship (DGE-1321846) and Professor Vy Dong for routine access to GC-FID instrumentation. We are grateful to the National Science Foundation (CHE-1361104) for financial support of this research. Calculations were performed on the Hoffman2 cluster at UCLA and the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by the NSF (OCI-1053575).

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(10) For Cu-catalyzed reactions of azomethine imines and nitrile-containing dipolarophiles other than acrylonitrile, see: (a) Cabrera, S.; Arrayás, R. G.; Martín-Matute, B.; Cossío, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587. (b) Padilla, S.; Tejero, R.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2010**, *12*, 5608. (c) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (d) Rajkumar, V.; Babu, S. A. *Synlett* **2014**, *25*, 2629.

(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 ^{1}H 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 $P(OCH_2CF_3)_3$ and Cy_3P 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 **TS5** are included in the Supporting Information.