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The Preparation and Utility of Bis(sulfinyl)imidoamidine Ligands for the Copper-Catalyzed Diels−Alder Reaction

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The design and preparation of a novel class of ligands based on the sulfinyl imine functionality is described. In particular, an efficient and modular synthesis of bis(sulfinyl)imidoamidine (siam) ligands is reported. The versatility of the synthetic sequence is demonstrated by the preparation of various analogues to explore the effect of substitution about the ligand framework on catalytic activity. The utility of the siam ligands in asymmetric catalysis is demonstrated in the Cu(II)-catalyzed Diels−Alder reaction where highly enantio- and diastereoselective reactions are reported for a range of *N*-acyloxazolidinone dienophile and diene substrate combinations. Of particular note is the efficiency of these asymmetric catalysts for reactions involving challenging and relatively unreactive acyclic diene substrates. Finally, structural data are provided for several ligands as well as metal−ligand complexes.

Introduction

The field of asymmetric catalysis has produced remarkable results, allowing the preparation of chiral, nonracemic products for a variety of transformations.[1] While great strides have been made in the field, the development of new chiral ligands to accelerate and direct Lewis acid catalyzed reactions continues to be an area of intense scrutiny. The most effective ligands are based upon a small number of successful templates (Figure 1). The chiral influence of these "privileged" ligand classes is typically derived from either naturally occurring chiral sources such as amino acids (**1**, **2**) or tartaric acid (**3**, **4**), or from synthetically accessible chiral scaffolds (**5**, **6**). While these ligands afford highly effective catalysts, the limited number of accessible chiral motifs often restricts the design of new ligands. Furthermore, even for classical reactions such as the Diels−Alder cycloaddition, unmet challenges remain with regard to issues of reactivity and selectivity for challenging substrates. Herein, we describe the design of a new class of modular ligands based on the sulfinyl imine functionality, and the application of these ligands toward the asymmetric Diels−Alder reaction.

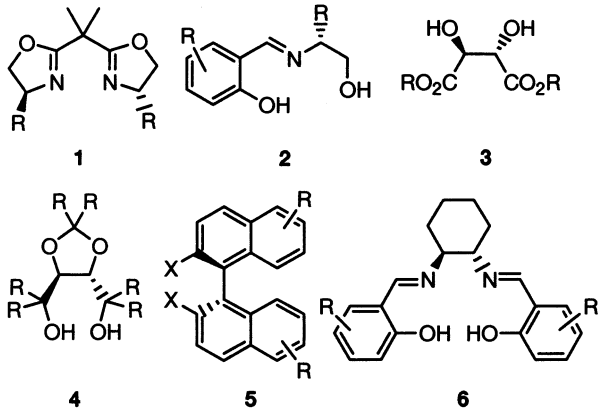
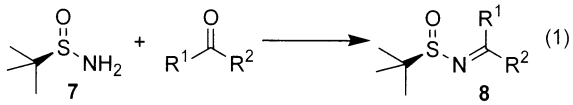


FIGURE 1. Examples of privileged ligand structures.

Discussion

Sulfinyl Imine Ligands. Our research into the viability of ligands incorporating the chiral *N*-sulfinyl imine functionality was prompted by its many appealing characteristics. The enantiopure *N*-*tert*-butanesulfinyl imine functionality is readily prepared by the direct condensation of *N*-*tert*-butanesulfinamide **7** with aldehydes or ketones to afford sulfinyl imines **8**.[2] Both enantiomers of **7** are available commercially and are easily prepared



on greater than mole scale.[3] Imines **8** are bench stable compounds that serve as versatile intermediates for the

(1) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. J., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York; 1999.

(2) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278−1284.

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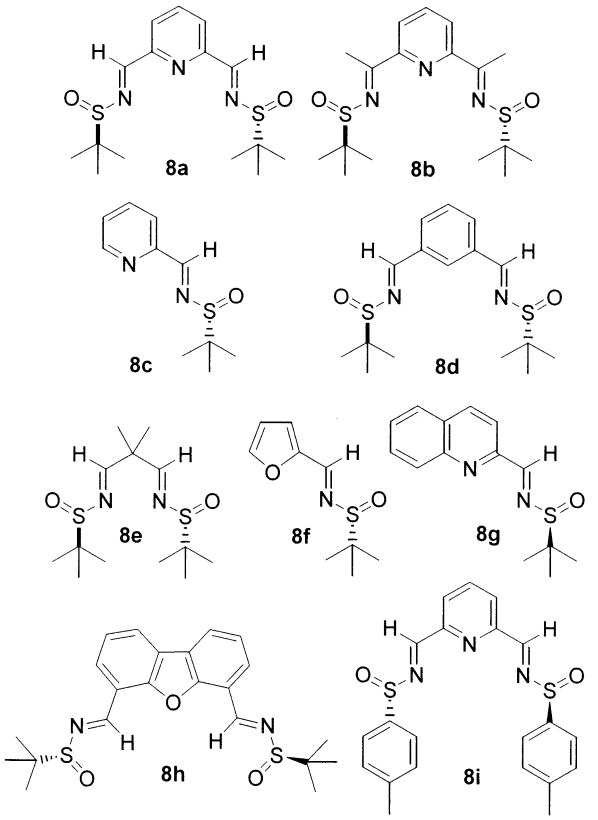
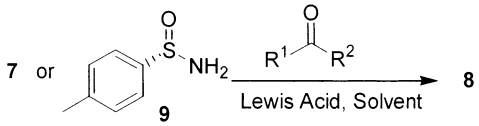
construction of enantiopure amine derivatives.[4] Additionally, when employed as ligands, imines **8** have the potential to coordinate metals through the sulfur, oxygen, or nitrogen atoms, further enhancing the flexibility of this ligand class.[5] Despite these intriguing attributes, at the time we began our studies, no research had been published with regard to the sulfinyl imine functional group in asymmetric catalysis.[5,6]

Ligand Synthesis. Our initial efforts to develop sulfinyl-based ligands were focused primarily on *N*-*tert*-butanesulfinyl imines since they can be prepared by the Lewis acid-catalyzed condensation of **7** and a variety of aldehydes and ketones. Several ligands were designed in direct analogy to highly successful bisoxazoline ligands (**8a**,**b**,**e**,**h**,**i**).[7] Additionally, we desired to prepare a variety



of other C_2-symmetric and non-C_2-symmetric *tert*-butanesulfinyl imine ligands (**8c**,**d**,**f**,**g**). For the preparation of sulfinyl imines, excess $CuSO_4$ is typically employed as a Lewis acid catalyst and water scavenger for aldehyde precursors, while $Ti(OEt)_4$ is the reagent of choice for ketones.[2] However, for the preparation of the sterically congested compound **8e** or the electronically deactivated imine **8f**, $CuSO_4$ was not effective in promoting the formation of the desired sulfinyl imines. For these less reactive substrates and for sulfinyl ketimine **8b**, $Ti(OEt)_4$ was found to be the optimal catalyst (Table 1). To investigate the importance of steric and electronic effects of the sulfinyl substituent, *p*-toluenesulfinyl imine **8i** was also prepared. Sulfinyl imines of this type are readily available from the corresponding (*S*)-*p*-toluenesulfinamide **9**.[8]

TABLE 1. The Preparation of Ligands 8



product	Lewis acid	solvent	time (h)	temp (°C)	yield (%)
8a	$CuSO_4$	CH_2Cl_2	4	22	74
8b	$Ti(OEt)_4$	THF	4	75	58
8c	$CuSO_4$	CH_2Cl_2	1	22	95
8d	$CuSO_4$	CH_2Cl_2	18	22	98
8e	$CuSO_4$	CH_2Cl_2	24	40	no reaction
8e	$Ti(OEt)_4$	THF	3	22	34
8f	$CuSO_4$	CH_2Cl_2	24	22	40
8f	$Ti(OEt)_4$	THF	4	22	82
8g	$CuSO_4$	CH_2Cl_2	3	22	98
8h	$CuSO_4$	CH_2Cl_2	36	22	69
8i	$CuSO_4$	CH_2Cl_2	1	22	68

The Diels−Alder reaction of cyclopentadiene and *N*-acryloyloxazolidinone **10a** was chosen for an initial screen because it has served as a benchmark for the development of several Lewis acid catalysts (Table 2).[1] While many metal complexes of ligands **8a** and **8e** were initially investigated, including $Zn(OTf)_2$, $Zn(SbF_6)_2$, CuOTf, MgI_2, $MgBr_2$, $Co(ClO_4)_2$, FeI_3, $Yb(OTf)_3$, $Co(ClO_4)$, $Sn(OTf)_2$, and $Ni(ClO_4)_2$, all imparted dramatically inferior selectivity and/or reactivity in comparison to the $Cu(OTf)_2$-catalyzed reactions. Therefore, $Cu(OTf)_2$ was utilized as the sole Lewis acid for screening the full set of ligands **8**.

A number of ligands catalyzed the desired transformation with moderate enantioselectivity. In general, C_2-symmetric ligands were preferable to their nonsymmetric counterparts (entry 1 vs entry 3). Sulfinyl imines derived from ketones were found to be less selective than those derived from aldehydes (entry 1 vs entry 2). Ligand **8i**, incorporating the *p*-tolyl substituent at sulfur, was less selective than the corresponding *tert*-butyl derivative **8a** (entry 9 vs 1). Interestingly, although ligand **8i** has the opposite configuration at sulfur, it delivers **11a** with the same absolute configuration. Finally, ligands that do not incorporate an additional binding element (entries 4 and

(3) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011−8019.

(4) (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913−9914. (b) Tang, T.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12−13. (c) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883−8904. (d) Borg, G.; Chino, M.; Ellman, J. A. *Tetrahedron Lett.* **2001**, *42*, 1433−1436. (e) Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127−10128

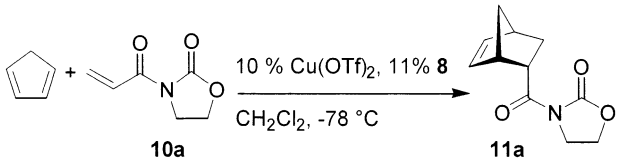
(5) (a) Owens, T. D.; Hollander, F. J.; Oliver, A. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 1539−1540. (b) A Rh(I) sulfinyl amidine complex has been isolated and shown to bind through the sulfinyl sulfur and nitrogen atoms. Souers, A. J.; Owens, T. D.; Oliver, A. G.; Hollander, F. J.; Ellman, J. A. *Inorg. Chem.* **2001**, *40*, 5299−5301.

(6) Other catalysts based on chirality solely at sulfur have been developed. (a) Khiar, N.; Fernandez, I.; Alcudia, F. *Tetrahedron Lett.* **1993**, *34*, 123−126. (b) Tokunoh, R.; Sodeoka, M.; Aoe, K.; Shibasaki, M. *Tetrahedron Lett.* **1995**, *44*, 8035−8038. (c) Bolm, C.; Kaugmann, D.; Zehnder, M.; Neuburger, M. A. *Tetrahedron Lett.* **1996**, *37*, 3985−3988. (d) Hiroi, K.; Suzuki, Y.; Kawagishi, R. *Tetrahedron Lett.* **1999**, *40*, 715−718. (e) Bolm, C.; Simic, O. *J. Am. Chem. Soc.* **2001**, *123*, 3830−3831. (f) Harmata, M.; Ghosh, S. K. *Org. Lett.* **2001**, *3*, 3321−3323.

(7) (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335 and references therein. (b) Nishiyama, H.; Sakagucki, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846−848. (c) Kanemasa, S.; Oderatoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074−3088.

(8) The (*S*)-*p*-toluenesulfinamide can be prepared in a single step from Andersen's reagent. Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, T. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403−1406.

TABLE 2. Diels–Alder Reaction with Sulfinyl Imine Ligands



entry	ligand	temp (°C)/time (h)	yield (%)	ee (%)[a]	dr
1	**8a**	−78/6	69	72 (*R*)	94/6
2	**8b**	−78/6	24	9 (*R*)	94/6
3	**8c**	−78/6	70	32 (*S*)	90/10
4	**8d**	−78/6	68	53 (*S*)	93/7
5	**8e**	−78/6	91	<5 (*S*)	93/7
6	**8f**	−78/6	13	40 (*S*)	95/5
7	**8g**	−78/6	72	12 (*R*)	90/10
8	**8h**	−78/6	46	37 (*R*)	97/3
9	**8i**	−78/6	39	37 (*R*)	95/5

[a] The absolute configuration refers to the stereochemistry at the 2-position of **11a**. The ee was determined by chiral HPLC.

FIGURE 2. Geometry of ligand **8a** in the solid state.

5) afforded **11a** in lower selectivity than ligand **8a**, in which the sulfinyl imine units are bridged by a pyridine ring. Presumably, in the absence of an additional binding element, coordination of both sulfinyl imine substituents to produce a highly organized complex is disfavored.

X-ray Analysis of Ligands 8a and 8b. Analysis of the X-ray crystal structures of ligands **8a** and **8b** reveals that significant conformational changes are required for coordination of both sulfinyl imine groups (Figure 2). Ligand **8a** is found to adopt an approximately synperiplanar (*s-cis*) configuration for the C=N−S=O unit in the solid state, with the S=O bond nearly planar with the C=N bond (dihedral angle=17°). While crystal packing forces are relevant, coplanar geometry is also expected to be an energetic minimum based on theoretical calculations of related sulfinyl imines.[9] Rigidity about the N−S bond of the *N*-sulfinyl imine moiety is presumably important for successful chirality transfer using this directing group and for ligand preorganization in asymmetric catalysis.

Sulfinyl ketimine **8b** is found to adopt a similar, extended geometry in the solid state (Figure 3). Interestingly, while **8b** also adopts a roughly *s-cis* configuration, the greater deviation from planarity (O=S−N=C dihedral angle = 34°) coincides with diminished enantioselectivity relative to **8a**. Most importantly, neither ligand **8a** nor **8b** adopts the proper geometry in the solid state required for tridentate binding.

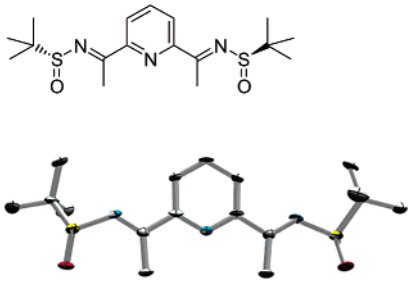


FIGURE 3. Geometry of ligand **8b** in the solid state.

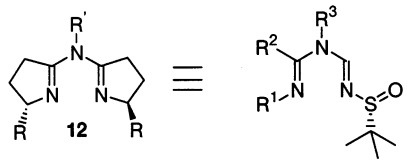
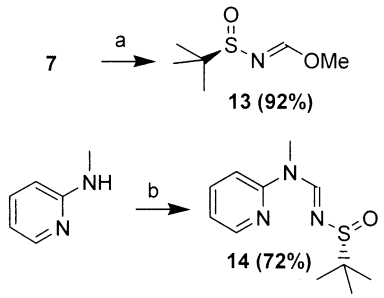


FIGURE 4. Pfaltz' aza-semicorrin **12** and a general sulfinyl imidoamidine ligand.

SCHEME 1[a]



[a] Conditions: (a) $HC(OMe)_3$, cat. *p*-TsOH, 100 °C, 3 h; (b) BuLi, THF, −78 °C, 1 h, then **13**, rt, 1 h.

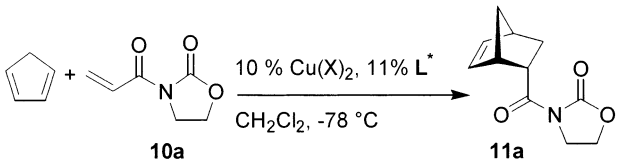
Second-Generation Ligands: Sulfinyl Imidoamidines (siam). In comparison to bisoxazoline ligands, the sulfinyl imine nitrogen is less Lewis basic and presumably coordinates more weakly to copper. Given that conformational changes are necessary for tridentate binding of ligands **8a** and **8b** through the sulfinyl nitrogen, we sought to design a catalyst system that would provide a more strongly chelating *N*-sulfinyl binding element. Pfaltz and co-workers have shown that imidoamidines of the general structure **12** (aza-semicorrins) are valuable ligands for asymmetric catalysis.[10] Sulfinyl imine ligands with this architecture might provide a more rigid scaffold while increasing the coordinating ability of the sulfinyl imine moiety (Figure 4).

Synthesis of Sulfinyl Imidoamidine (siam) Ligands. Heating **7** in refluxing trimethyl orthoformate with catalytic *p*-TsOH cleanly afforded *O*-methyl-*N*-*tert*-butanesulfinyl imidate **13** in 92% yield. From this intermediate, the nonsymmetric ligand **14** incorporating a pyridyl-binding element was prepared in a single step from 2-methylaminopyridine (Scheme 1). When this ligand was employed in the $Cu(OTf)_2$-catalyzed Diels–Alder reaction, promising selectivity was observed (Table 3). We were hopeful that a C_2-symmetric variant would

(9) (a) Tietze, L. F.; Schuffenhuer, A. *Eur. J. Org. Chem.* **1998**, *1998*, 1629−1637. (b) Bharatam, P. V.; Uppal, P.; Kaur, A.; Kaur, D. *J. Chem. Soc., Perkin Trans. 2* **2000**, 43−50.

(10) (a) Pfaltz, A. *Synlett* **1999**, 835−842 and references therein. (b) More recently Reiser has prepared analogous aza-bis(oxazolines). Glos, M.; Reiser, R. *Org. Lett.* **2000**, *2*, 2045−2048.

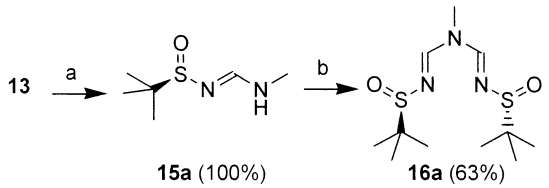
TABLE 3. Imidoamidine Catalyzed Diels–Alder Reactions



entry	ligand	metal	time (h)	yield (%)	ee (%)[a]	dr[b]
1	**14**	$Cu(OTf)_2$	6	45	62	93:7
2	**16a**	$Cu(OTf)_2$	6	nr		
3	**14**	$Cu(SbF_6)_2$	6	92	56	95:5
4	**16a**	$Cu(SbF_6)_2$	0.1	96	98	>99:1

[a] Determined by chiral HPLC. [b] Determined by ^{1}H NMR.

SCHEME 2[a]



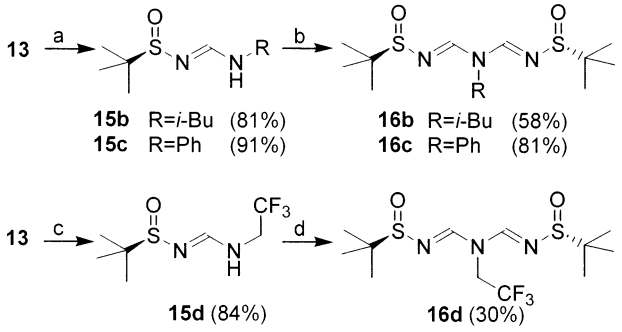
[a] Conditions: (a) $MeNH_2$/MeOH, rt, 12 h; (b) KH, THF, 0 °C, 30 min, then **13**, 1 h.

improve the selectivity. Ligand **16a** was therefore prepared in two steps from **7** (Scheme 2). Addition of methylamine to **13** afforded the *N*-sulfinyl amidine **15a** in quantitative yield. Following deprotonation, **15a** adds to a second equivalent of **13** to afford the symmetric bis(sulfinyl)imidoamidine (siam) **16a** (3 steps, 58% overall yield). In contrast to results for ligand **14**, the catalyst prepared from $Cu(OTf)_2$ and ligand **16a** was completely unreactive at −78 °C. However, the use of the less coordinating SbF_6 counterion produced an extremely reactive and selective catalyst (entry 4).[11]

Synthesis of Modified siam Ligands. The importance of different substituents on the sulfinyl imidoamidine (siam) framework was investigated next. Ligands containing various substituents at the internal nitrogen were prepared by first adding amines into sulfinyl imidate **13** to afford the corresponding sulfinyl amidines **15b**–**d** (Scheme 3). While most additions were complete within minutes at room temperature, the electron-poor trifluoroethylamine added more slowly. Compound **13** was heated in neat trifluoroethylamine at 60 °C in a pressure tube to obtain good conversion to **15d** in a reasonable amount of time. Amidines **15b** and **15c** were deprotonated with BuLi and then **13** was added to afford the bis(sulfinyl)imidoamidines **16b** and **16c** in 58% and 81% yields, respectively. The preparation of the electron-poor ligand **16d** required modified conditions. Heating amidine **15d** with **13** in refluxing THF in the presence of a slight excess of K_2CO_3 (1.2 equiv) afforded the desired ligand **16d** in 30% yield after 24 h.

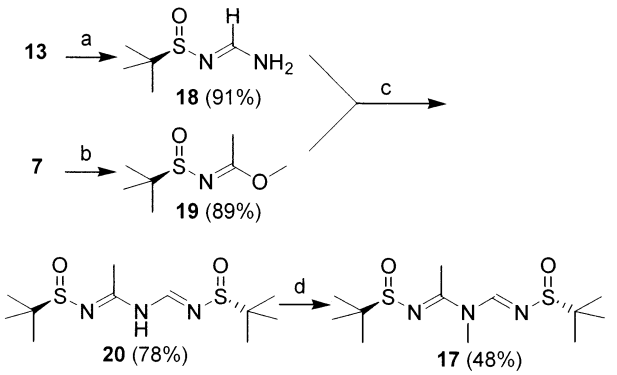
Preparation of ligand **17** incorporating substitution at the sp^2-carbon was next explored (Scheme 4). Amidine **18** was prepared by addition of ammonia in EtOH to

SCHEME 3[a]



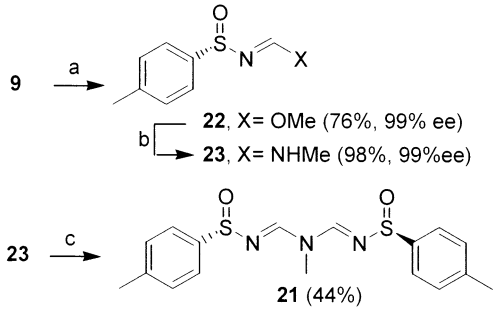
[a] Conditions: (a) RNH_2 (10 equiv), THF, rt, 1 h; (b) BuLi, THF, −78 °C, then **13**, rt, 1 h. (c) $CF_3CH_2NH_2$ (15 equiv), 60 °C, 2 h; (d) K_2CO_3, **13**, THF, 65 °C, 24 h.

SCHEME 4[a]



[a] Conditions: (a) NH_3/EtOH, rt, 12 h; (b) $CH_3C(OMe)_3$, cat. *p*-TsOH, 110 °C, 3 h; (c) KH, THF; (d) KH, THF, rt, 15 min, then MeI, rt, 12 h.

SCHEME 5[a]



[a] Conditions: (a) cat. *p*-TsOH, THF, $HC(OMe)_3$, rt, 3 h; (b) $MeNH_2$/MeOH; (c) K_2CO_3, **22**, THF, 60 °C, 12 h.

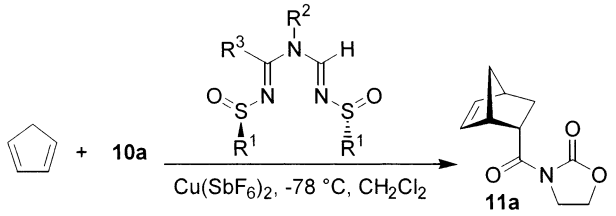
imidate **13**. Deprotonation with KH was followed by the addition of imidate **19** to afford the nonsymmetric imidoamidine **20** in 78% yield. Deprotonation of **20** was followed by the addition of 5.0 equiv of MeI to afford **17** in 48% yield.[12]

Finally, to investigate the importance of the substituent on sulfur, ligand **21** was prepared beginning with *p*-toluenesulfinamide **9** (Scheme 5). In contrast to the preparation of *tert*-butanesulfinyl imidate **14a**, heating

(11) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798–800.

(12) Addition of methylamine to **18** followed by deprotonation and addition to imidate **13** did not provide the desired product **17**.

TABLE 4. Influence of Substitution on siam Ligands



entry	ligand[a]	R^1	R^2	R^3	dr[b]	ee[c]
1	**16b**	*t*-Bu	*i*-Bu	H	99:1	97
2	**16c**	*t*-Bu	Bn	H	99:1	96
3	**16d**	*t*-Bu	CH_2CF_3	H	99:1	98
4	**17**	*t*-Bu	Me	Me	99:1	60
5	**21**	*p*-tol	Me	H	94:6	32

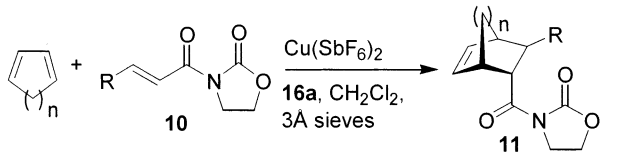
[a] All reactions were run with 10 mol % $CuCl_2$, 20 mol % $AgSbF_6$, 11 mol % ligand, and 3 Å mol sieves. [b] Determined by ^{1}H NMR. [c] Determined by HPLC.

9 in neat trimethyl orthoformate with catalytic *p*-TsOH afforded only a 17% yield of **22**. The major product of the reaction was racemic methyl *p*-tolylsulfinate.[13] More importantly, the sulfinyl imidate was obtained with only 70% ee. The increased electrophilicity of the sulfur center of **9** relative to **7** parallels the reactivity trend observed for sulfinyl imines **8**.[14] Fortunately, running the reaction in THF at a 0.2 M concentration suppressed the formation of the methyl sulfinate byproduct, affording the desired imidate in 78% yield and with >99% ee. From imidate **22**, the preparation of the sulfinyl amidine **23** and bis(sulfinyl)imidoamidine **21** was straightforward.

Catalysis with Modified siam Ligands. With the new ligands in hand, the effect of permutations of the siam framework was studied (Table 4). Substitution on the internal nitrogen (R^2) is well tolerated and produces catalysts that maintain high selectivities (entries 1 and 2). The ability to incorporate substitution at this position has important implications with regard to preparation of a support-bound ligand.[15] Importantly, the ability to modify the electronic properties of the ligand by substitution at this position (**16d**, entry 3) would prove beneficial for less reactive systems (vide infra). In contrast, ligand **17** was found to provide very poor selectivity for the Diels−Alder reaction. The use of the *p*-toluenesulfinyl-derived ligand **21** afforded **11a** with dramatically reduced enantioselectivity in comparison to the corresponding *tert*-butyl derivative **16a**.

Substrate Scope: Dienophiles. The $Cu(SbF_6)_2$−siam catalyst system was then tested with a series of substituted dienophiles (Table 5). Selectivities remained high for imides derived from crotonic acid (**10b**), cinnamic acid (**10c**), and fumaric acid (**10d**) (entries 2−4), even at the higher temperatures required for the less reactive substrates. Importantly, the efficiency of the catalyst system permits catalyst loading levels as low as 1% for

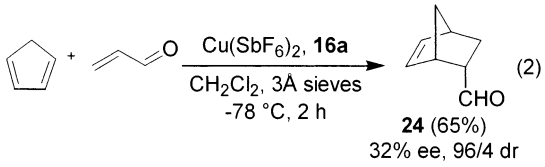
TABLE 5. Substrate Generality in the Diels−Alder Reaction Using Ligand 16a[a]



entry	n	substrate (R =)	adduct	% cat.[a]	time (h)	temp (°C)	yield (%)	ee (%)[b]	dr[c]
1	1	H (**10a**)	**11a**	10	0.1	−78	96	98	99:1
2	1	CH_3 (**10b**)	**11b**	10	8	−40	76	97	98:2
3	1	Ph (**10c**)	**11c**	10	16	0	58	94	95:5
4	1	CO_2Et (**10d**)	**11d**	10	2	−78	85	96	97:3
5[d]	1	H (**10a**)	**11a**	1	8	−78	95	98	99:1
6	2	H (**10a**)	**11e**	10	16	0	50	90	98:2

[a] Reactions were run with 10 mol % $CuCl_2$, 20 mol % $AgSbF_6$, and 11 mol % **16a**. [b] Determined by chiral HPLC or GC (see experimental data, Supporting Inforamtion). [c] Determined by ^{1}H NMR. [d] Reaction run with 1.0 mol % $CuCl_2$, 2.0 mol % $AgSbF_6$, and 1.1 mol % **16a**.

reactions with cyclopentadiene (entry 5). Furthermore, the high reactivity of the system allows for the use of much less reactive dienes such as cyclohexadiene (entry 6). The importance of the bidentate activation of the dienophile is highlighted by the failure of acrolein to undergo the Diels−Alder reaction with high selectivity (eq 2).



Substrate Scope: Acyclic Substrates. Although few asymmetric catalysts are effective for less reactive dienes, the success of the Diels−Alder reaction with cyclohexadiene encouraged us to investigate acyclic substrates (Table 6). Utilizing the Cu(II)−siam catalyst, isoprene and 2,3-dimethylbutadiene both react with **10a** to afford the Diels−Alder product in high yield and with excellent enantioselectivity (entries 1 and 2). It is worth noting that for these particular substrates, the bisoxazolines are much less selective (∼60−65% ee).[16] Incorporation of substituents at the terminal position of the diene, however, resulted in greatly diminished selectivity and reactivity as seen for the reaction of piperylene (entry 3). Interestingly, substitution at the terminal position of the diene is tolerated when used in conjunction with different bidentate dienophiles (vide infra). The selectivity of the catalyst system is sensitive to the size of substituents on the 2-position of the diene. For example, while high reactivity is maintained for 2-phenylbutadiene, selectivity is poor (entry 4). The presence of the bulky TBDPS ether results in both lower reactivity and lower selectivity (entry 5).

Another challenging set of Diels−Alder substrates involves the combination of acyclic dienes and substituted dienophiles (eq 3).[17] As expected for this substrate

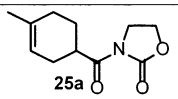
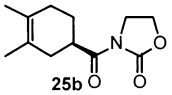
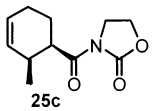
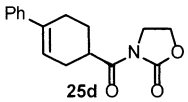
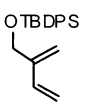
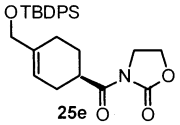
(13) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977−5985.

(14) For the addition of Grignard reagents into *p*-toluenesulfinyl imines, attack at sulfur competes with attack at the carbon−nitrogen double bond. Moreau, P.; Essiz, M.; Merour, J.; Bouzard, D. *Tetrahedron: Asymmetry* **1997**, *8*, 591−594. Attack at sulfur is not observed for *tert*-butanesulfinyl imines. See ref 4a.

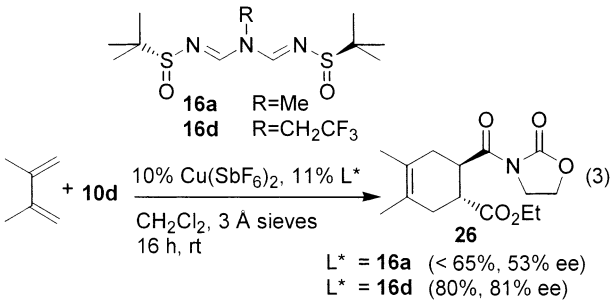
(15) For a review of support bound catalysts for asymmetric synthesis see: Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637−4662. See also ref 10b.

(16) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582−7594.

TABLE 6. $Cu(SbF_6)_2$–16a-Catalyzed Diels–Alder Reactions of 10a with Acyclic Dienes

entry	diene	product	time (h)	temp (°C)	Yield (%)	dr	ee (%)
1		 **25a**	16	rt	83	-	93
2		 **25b**	16	0	96	-	92
3		 **25c**	16	rt	18	2.0:1.0:0.4[a]	41[b]
4		 **25d**	2	rt	87	-	45
5		 **25e**	16	rt	33	-	62

[a] Refers to ratio of 1,2-*endo*; other regioisomers. Determined by NMR. [b] ee of major isomer.



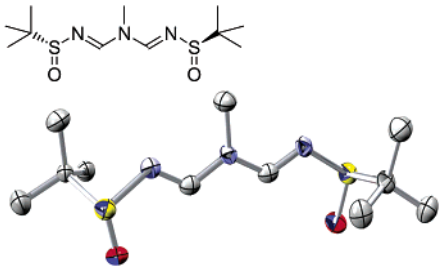
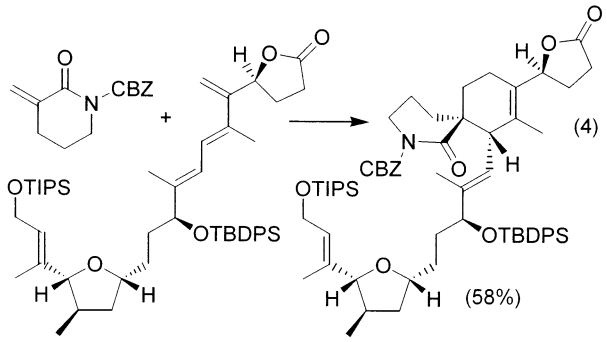


FIGURE 5. Crystal structure for siam ligand **16a**.

combination, the reaction was extremely sluggish with ligand **16a** and only the activated diene derived from ethyl fumarate (**10d**) was found to be sufficiently reactive, producing **26** with 53% ee and in less than 65% yield. For this particular reaction, the increased reactivity of the siam ligand derived from trifluoroethylamine (**16d**) was necessary to obtain good selectivity and complete conversion to product.

Substrate Scope: Complex Substrate. Perhaps the most challenging test for asymmetric catalysts lies in their application to complex molecule synthesis.[18] Recently, Murai, Ishihara, and co-workers utilized the $Cu(SbF_6)_2$–siam catalyst system for Diels–Alder reactions of CBZ-protected-α-methylene lactam dienophiles in elegant studies toward the synthesis of the spirocyclic core of gymnodimine (eq 4).[19] In this transformation only a single Diels–Alder product was observed and was isolated in 58% yield. Although bidentate dienophiles are necessary (eq 2), this example demonstrates that asymmetric catalysis is not restricted to *N*-acyl-oxazolidinone-based dienophiles. Furthermore, for this transformation, substitution at the terminal position of the diene does not negatively impact selectivity (Table 6, entry 3).



Mechanistic Considerations. While Cu(II) is known to coordinate well to nitrogen, there remained the possibility of alternative binding modes with the sulfinyl group (via sulfur or oxygen). Additionally, a crystal structure of **16a** was obtained that revealed a nearly linear arrangement along the axis of the imidoamidine with the sulfinyl groups adopting an *s-cis* conformation (Figure 5). In comparison to the structures of sulfinyl imines **8a** and **8b**, the C=N–S=O dihedral angle is even closer to planarity.[20] Once again, for chelation via the imido-nitrogens, a conformational change would be necessary.

(17) (a) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345. (b) Ghosh, A. K.; Cho, H.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *39*, 3687–3691.

(18) Nicolau, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698.

(19) (a) Tsujimoto, T.; Ishihara, J.; Horie, M.; Murai, A. *Synlett* **2002**, 399–402. (b) Ishihara, J.; Horie, M.; Shimada, Y.; Tojo, S.; Murai, A. *Synlett* **2002**, 403–406.

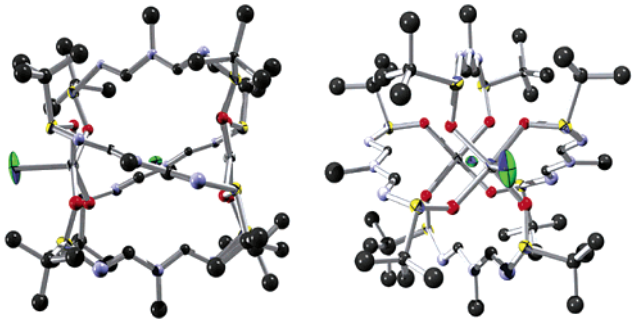


FIGURE 6. X-ray structure of Cu_2(**16a**)$_4$ M_2L_4-helicate **27** (2 views). The $Cu_2Cl_6^{2-}$ counterion was omitted for clarity. Color legend: sulfur, yellow; oxygen, red; chlorine, green.

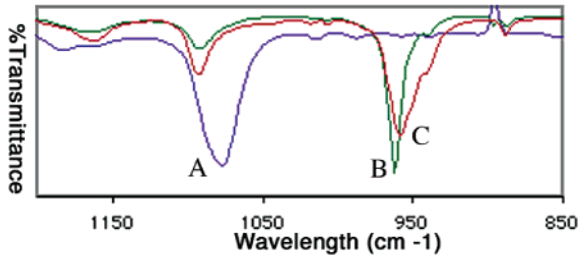


FIGURE 7. IR overlay of **16a** in solution (A), $Cu(SbF_6)_2$·(**16a**) in the solid state (B), and $Cu(SbF_6)_2$·(**16a**) in solution (C).

X-ray Structure of a Cu(II)−siam Complex. After much effort, a crystalline $CuCl_2$−siam complex (**27**) was obtained that was suitable for X-ray crystallographic studies. Somewhat surprisingly, the complex crystallized as a dimeric species in which each of four siam ligands coordinate two copper atoms via the sulfinyl oxygen. Interestingly, complex **27** (Figure 6) exists as an M_2L_4 helicate, with each ligand maintaining a linear geometry and making a quarter turn between the two Cu atoms.[21] This represents only the second reported M_2L_4 quadruple-stranded helicate and the first example in which the chiral information is introduced by the ligand. An uncoordinated chloride counterion exists within the cage of the helicate. A second chloride ion and a Cu_2Cl_6 counterion occupy the axial coordination sites of the Cu(II) complex. Notably, a crystal structure of a $Cu(SbF)_2$−siam complex was obtained and showed the same binding mode as **27**, however the resolution was poor.

The solid-state structure proved invaluable for determining the predominant binding mode of ligand **16a** in solution. In both the crystalline $Cu(SbF_6)_2$−siam complex and a freshly prepared solution of the $Cu(SbF_6)_2$−siam catalyst in CH_2Cl_2, the sulfinyl S=O stretch shifts to longer wavelengths (969 cm^{-1} vs 1077 cm^{-1} in the free ligand, Figure 7). A shift to longer wavelengths also occurs with oxygen binding of sulfoxide ligands to Cu(II) species.[22] The addition of imide **10a** after preparation of the catalyst does not alter the sulfinyl S=O stretch,

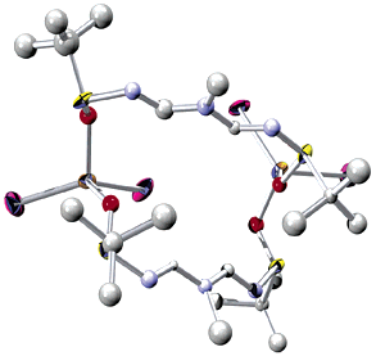


FIGURE 8. Crystal structure of Zn_2I_4(**16a**)$_2$ complex **28**. Color legend: sulfur, yellow; oxygen, red; iodine, purple.

suggesting that the primary metal species in solution remains oxygen bound even in the presence of the coordinating dienophile.

The propensity for ligand **16a** to form dimeric complexes via the sulfinyl oxygen coordination is not limited to Cu(II) complexes. When ligand **16a** is stirred with ZnI_2, complex **28** is obtained (Figure 8). The geometry about Zn is tetrahedral with the iodide counterions occupying the other coordination sites. A similar helical twist is also observed when viewed along the axis of the two zinc atoms.

While we do not currently have a mechanistic rationalization of the observed stereochemical induction for siam-catalyzed reactions, several observations are relevant. First of all, in contrast to the bisoxazoline catalyst systems, the presence of a 2-fold excess of ligand relative to copper does not inhibit the reaction rate.[23] Second, while not dramatic, the reaction of cyclopentadiene and imide **10a** (eq 5) exhibits nonlinearity[24] with regard to ligand enantiopurity (Figure 9), proving that other species besides a simple monomeric species are present under the reaction conditions. Furthermore, analysis of the catalyst mixture by mass spectrometry after 1 h of stirring shows the presence of several monomeric and dimeric species, including CuL_2, Cu_2L_2, CuL_3, and Cu_2L_3.[25]

Careful catalyst preparation is critical to the success of the Cu(II)−siam catalyst system. Typically, 11 mol % of **16a** is stirred together with 10 mol % of $CuCl_2$ and 20 mol % of $AgSbF_6$ in the presence of 3 Å molecular sieves at room temperature for 1 h prior to addition of the imide and diene.[26] Shorter catalyst aging times (10 min) are acceptable, but if the catalyst is aged longer (8h) the reaction rate drops dramatically and nearly racemic products are obtained! Furthermore, when imide **10a** was present during the catalyst aging period, no catalytic activity was observed for the reaction of **10a** and cyclopentadiene.

Constrained Ligand. While IR and X-ray studies demonstrate that the predominant ligand species in the

(20) The ligand crystallizes as a pair of molecules in the asymmetric unit. The dihedral angles are 9.0° and 9.7° for one molecule and 4.4° and 15.6° in the other. See Supporting Information for crystallographic data.

(21) (a) Albrecht, M. *Chem. Rev.* **2001**, *101*, 3457−3497. (b) One other M_2L_4-helicate has been characterized. McMorran, D. A.; Steel, P. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 3295−3297.

(22) Huang, Z.; Liao, D.; Zhang, R.; Zhang, X.; Huang, T.; Wang, H. *Polyhedron* **1996**, *15*, 981−984.

(23) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−661.

(24) Kagan, H. B. *Synlett* **2001**, 888−899.

(25) Electrospray ionization in MeCN showed diagnostic isotopic distributions consistent with the presence of the above species (see Supporting Information).

(26) While not strictly necessary, better and more reproducible results were found when molecular sieves were added to the reaction mixture. For example, compound **25b** is produced in only 69% ee in the absence of molecular sieves.

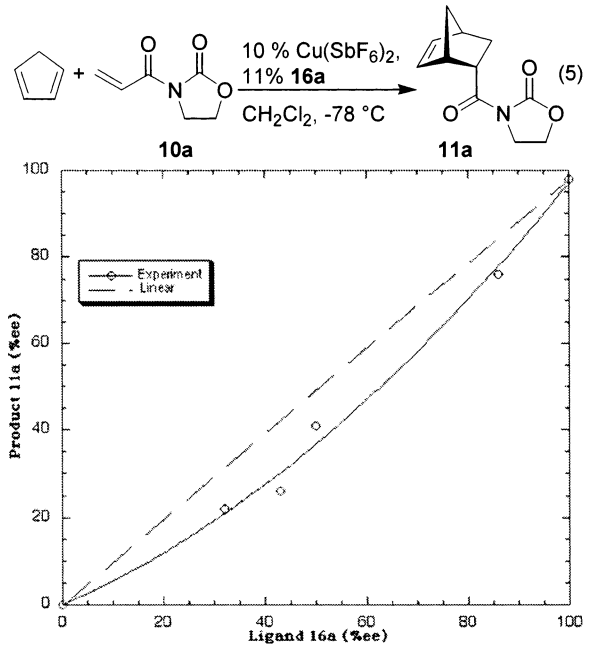
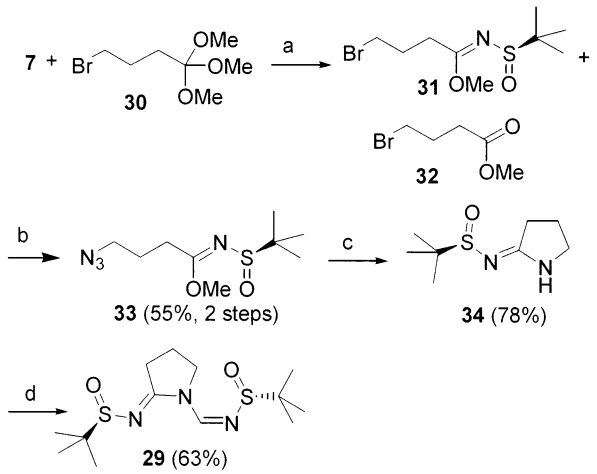


FIGURE 9. Graph of product enantioselectivity vs ligand **16a** enantioselectivity.

reaction mixture are oxygen-bound Cu complexes, there remains the possibility that nitrogen-bound complexes are responsible for catalysis. If this is the case, constrained ligands such as **29** should be effective because the ligand geometry favors coordination through nitrogen. Furthermore, the ligand constraints would prohibit the dimeric bonding pattern found in Cu(II)−siam complexes. Ortho ester **30** was reacted with **7** and $MgSO_4$ to afford an inseparable mixture of imidate **31** and ester **32** (Scheme 6). Azide displacement of the product mixture with NaN_3 afforded the desired azide **33** in 55% overall yield from **7**. Upon heating **33** with triphenylphosphine and Et_3N, cyclic amidine **34** was obtained in 78% yield. Finally, **34** was heated with **13** and K_2CO_3 in THF to afford ligand **29** in four overall steps. The constrained ligand **29** efficiently catalyzed the reaction of cyclopentadiene and imide **10a** but afforded the product with low selectivity (96:04 dr, 45% ee). Interestingly, use of ligand **17**, which incorporates the same substitution pattern minus any cyclic constraints, provided similarly poor levels of induction and reactivity (Table 4, entry 4). While a mechanistic model is not currently available to explain this, it appears that any substitution at the amidino-sp^2-carbon is deleterious to the selectivity of the reaction.

SCHEME 6[a]



[a] Conditions: (a) THF, $MgSO_4$; (b) NaN_3, DMF, NaI; (c) Ph_3P, THF, H_2O; (d) K_2CO_3, THF, **13**, reflux.

Conclusion

The sulfinylimidoamidine (siam) ligands coordinate to $Cu(SbF_6)_2$ to afford active and selective catalysts for the Diels−Alder reaction employing a variety of substrates. These ligands are readily synthesized in only three steps and present a highly modular class of ligands. Studies of the crystallographic and solution structures of these compounds point to a unique coordination of the sulfinyl oxygen to both Cu and Zn species. Importantly, ligands **16** impart high selectivity for the Diels−Alder reaction of a variety of challenging substrates including the relatively unreactive acyclic dienes.

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Supporting Information Available: Experimental Procedures, spectral data for all new compounds, and mass spectrometric and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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