ORGANIC LETTERS

2004
Vol. 6, No. 13
2253−2256

Role of Noncovalent Interactions in the Enantioselective Reduction of Aromatic Ketimines with Trichlorosilane

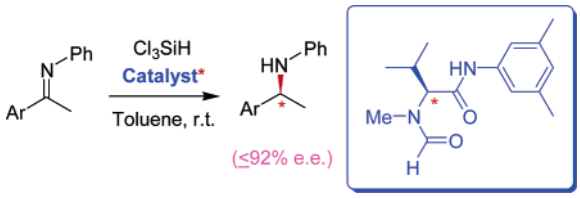
Andrei V. Malkov,* Andrea Mariani, Kenneth N. MacDougall, and Pavel Kočovský*

Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, U.K.

amalkov@chem.gla.ac.uk; pavelk@chem.gla.ac.uk

Received April 28, 2004

ABSTRACT

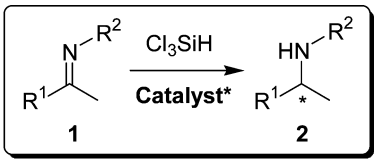


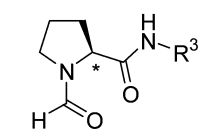
Asymmetric reduction of ketimines 1 with trichlorosilane can be catalyzed by a new *N*-methyl L-valine derived Lewis basic organocatalyst, such as 4d, with high enantioselectivity. The structure–reactivity investigation suggests hydrogen bonding and arene–arene interactions between the catalyst and the incoming imine as the main factor determining the enantiofacial selectivity.

The recipe for successful asymmetric catalysis includes a delicate mix of various factors, such as catalyst structure and loading, solvent, temperature, etc. Often, even minor changes to any of these characteristics can produce a dramatic effect on the stereochemical outcome of the reaction.[1] Among the methods designed to enhance enantioselectivity through structural variations, chiral relay represents an emerging new strategy where a conformationally flexible group, appropriately placed, effectively conveys the chiral information to the reaction center.[2] We have recently developed new *N*-methyl amino acid derived amidophoshine ligands and demonstrated that the conformational bias, imposed by the tertiary amide group, led to high enantioselectivity in the Cu(I)-catalyzed conjugate addition of Et_2Zn to α,β-enones.[3] Our *N*-methyl valine derived ligands proved superior to those prepared from proline, showing that the rigid cyclic framework of proline may not always be an advantage.[3]

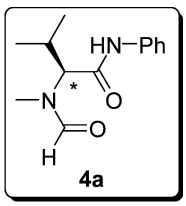
In search for an extension of this principle to other applications, we turned our attention to imine reduction (Scheme 1), which gives rise to chiral amines that are

Scheme 1. Asymmetric Reduction of Ketimines





3a, R^3 = Ph
3b, R^3 = 1-Naphthyl



common intermediates in the synthesis of pharmaceutical drugs and agrochemicals. Current methods for asymmetric reduction of imines, such as transition-metal-catalyzed high-pressure hydrogenation,[4,5] hydrosilylation,[4,6] or transfer

(1) For recent overviews, see (a) Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3418. (b) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532. (c) Fagnow, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26.

(2) For a recent review on chiral relay effect, see: (a) Corminboeuf, O.; Quaranta, L.; Renaud, P.; Liu, M.; Jasperse, C. P.; Sibi, M. P. *Chem. Eur. J.* **2003**, *9*, 28. For a recent contribution, see: (b) Sibi, M. P.; Zhang, R.; Manyem, S. *J. Am. Chem. Soc.* **2003**, *125*, 9306.

(3) Malkov, A. V.; Hand, J. B.; Kočovský, P. *Chem. Commun.* **2003**, 1948.

10.1021/ol049213+ CCC: $27.50 © 2004 American Chemical Society
Published on Web 05/27/2004

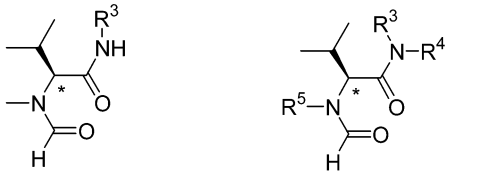
hydrogenation,[7] are tainted by the problem of metal leaching, so that development of an organocatalytic protocol appears to be an attractive alternative. Because Cl_3SiH can be activated by Lewis bases (R_3N, DMF, MeCN, etc.) to effect hydrosilylation of imines,[8] we set out to design a suitable chiral Lewis basic catalyst.[9,10] While this work was in progress, Matsumura reported on the asymmetric reduction of imines **1** with Cl_3SiH, catalyzed by the L-proline-derived formamides (*S*)-**3a**,**b** (10−20 mol %) with ≤66% ee (Scheme 1; Table 1, entries 1 and 2).[11] This work represented a great opportunity to test our chiral relay principle by replacing the cyclic proline framework with the more flexible *N*-methyl valine unit. To this end, diamides (*S*)-**4**,**5** were synthesized, which can be regarded as chiral analogues of DMF (Scheme 2).

Table 1. Reduction of Ketimines **1a**−**k** with Trichlorosilane, Catalyzed by (*S*)-**3a**,**b** and (*S*)-**4a**[a]

entry	imine	R^1, R^2	cat.	solvent	yield (%)[b]	**2**, % ee[c] (config)[d]
1	**1a**	Ph, Ph	**3a**	CH_2Cl_2	91	55 (*R*)[e]
2	**1a**	Ph, Ph	**3b**	CH_2Cl_2	52	66 (*R*)[e]
3	**1a**	Ph, Ph	**4a**	CH_2Cl_2	68	79 (*S*)
4	**1a**	Ph, Ph	**4a**	$CHCl_3$	79	86 (*S*)
5	**1a**	Ph, Ph	**4a**	MeCN	65	30 (*S*)
6	**1b**	4-$MeOC_6H_4$, Ph	**4a**	CH_2Cl_2	62	76 (*S*)
7	**1b**	4-$MeOC_6H_4$, Ph	**4a**	$CHCl_3$	57	80 (*S*)
8	**1c**	4-$CF_3C_6H_4$, Ph	**4a**	$CHCl_3$	43	87 (*S*)
9	**1d**	4-$NO_2C_6H_4$, Ph	**4a**	$CHCl_3$	30	85 (*S*)
10	**1e**	2-naphth, Ph	**4a**	CH_2Cl_2	69	80 (*S*)
11	**1e**	2-naphth, Ph	**4a**	$CHCl_3$	50	87 (*S*)
12	**1f**	*c*-C_6H_{11}, Ph	**4a**	$CHCl_3$	80	37 (*S*)
13	**1g**	Ph, 4-$MeOC_6H_4$	**4a**	$CHCl_3$	96	85 (*S*)
14	**1h**	Ph, 2-$MeOC_6H_4$	**4a**	CH_2Cl_2	36	22 (*S*)
15	**1i**	Ph, *c*-C_6H_{11}	**4a**	$CHCl_3$	50	<5
16	**1j**	Ph, *n*-Bu	**4a**	$CHCl_3$	60	<5
17	**1k**	Ph, CH_2Ph	**3a**	CH_2Cl_2	97	55 (*R*)[e]
18	**1k**	Ph, CH_2Ph	**4a**	$CHCl_3$	46	8

[a] The reaction was carried out at 0.5 mmol scale with 1.5 equiv of Cl_3SiH and 10 mol % of the catalyst at room temperature for 16 h. [b] Isolated yield. [c] Determined by chiral HPLC or GC. [d] Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see Supporting Information) and/or by HPLC/GC via comparison with authentic samples; configuration of **2d** is assumed to be (*S*) in analogy with the rest of the series. [e] Reference 11.

Scheme 2. Optimization of Catalyst Structure



4a, R^3 = Ph
4b, R^3 = 4-$MeOC_6H_4$
4c, R^3 = 3,5-$(MeO)_2C_6H_3$
4d, R^3 = 3,5-$Me_2C_6H_3$
4e, R^3 = 3,5-$(CF_3)_2C_6H_3$
4f, R^3 = 3,5-$Cl_2C_6H_3$

5a, R^3 = *n*-Bu, R^4 = H, R^5 = Me
5b, R^3 = Ph, R^4 = R^5= Me
5c, R^3 = 3,5-$(MeO)_2C_6H_3$; R^4 = R^5= H

Ketimines **1a**−**k** were reduced with Cl_3SiH in the presence of catalyst (*S*)-**4a** (10 mol %) (Table 1). Imine **1a** afforded **2a** in 79% ee (entry 3), and the product had the configuration opposite to that reported by Matsumura,[11] though the configuration of the catalyst was identical! However, reduction of **1k**, catalyzed by (*S*)-**4a**, gave nearly racemic product (entry 18), while with (*S*)-**3a** the corresponding amine **2k** was obtained in 55% ee (entry 17; cf. entry 1). These results suggest that the enantiodifferentiation mechanisms for proline- and valine-derived catalysts are different. In the catalysis by **3a**, the emphasis in the proposed transition state, accounting for the stereochemistry observed, was given to the steric repulsion by placing the bulky anilide group of the catalyst and the aromatic groups of the substrate away from each other,[11] which seemed to agree with the same level of enantioselectivity obtained for the reduction of ketimines **1a** and **1k**. However, in the case of catalyst **4a**, dramatic difference in selectivities observed for **1a** and **1k** suggests that electronic interactions between the catalyst and the substrate may become a key factor.

Recently, we have shown that arene−arene interactions can have a key impact on the reactivity and enantioselectivity in organocatalysis,[12] which prompted us to probe the extent of noncovalent interactions involved in the reduction of imines. First, the nature of the solvent was assessed. Switching from CH_2Cl_2 to $CHCl_3$ in the reduction of **1a** resulted in further increase of enantioselectivity (from 79%

(4) (a) Morrison, J. D. *Asymmetric Synthesis*; Academic: New York, 1983; Vol 2. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, 1994. (c) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; J. Wiley and Sons: New York, 2000. (d) James, B. R. *Catal. Today* **1997**, *37*, 209. (e) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(5) For recent reports on catalytic hydrogenation (with Ir, Rh, and Ru), see refs 4b−d and the following: (a) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425. (b) Jiang, X. B.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Andrien, J. G. O.; Boogers, J. A. F.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 1503. (c) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195. (d) Okuda, J.; Verch, S.; Stürmer, R.; Spaniol, T. S. *J. Organomet. Chem.* **2000**, *605*, 55. For Ru-catalyzed transfer hydrogenation, see: (e) Samec, J. S. M.; Bäckvall, J. E. *Chem. Eur. J.* **2002**, *8*, 2955.

(6) (a) Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1998**, *63*, 6344. (b) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1103. (c) Vedejs, E.; Trapencieris, P.; Suna, E. *J. Org. Chem.* **1999**, *64*. 6724. (d) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713. (e) Nishikori, H.; Yoshihara, R.; Hosomi, A. *Synlett* **2003**, 561. (f) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2228.

(7) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472.

(8) (a) Benkeser, R. A.; Snyder, D. *J. Organomet. Chem.* **1982**, *225*, 107. (b) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407.

(9) For an overview, see: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. For a recent contribution, see: (b) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 9659 and references therein.

(10) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977.

(11) (a) Iwasaki, F.; Omonura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525. For a related reduction of ketones, see: (b) Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, *40*, 7507.

(12) Malkov, A. V., Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674.

to 86% ee; entries 3 and 4), whereas MeCN proved unsuitable (entry 5).[13] This behavior suggests $\pi-\pi$ interactions of the arene systems of the catalyst and the substrate.[14]

The role of the individual aromatic nuclei both in the ketimine **1** and in the catalyst **4** were then investigated to find the scope of the reaction and shed light on the origin of the asymmetric induction. The electron-rich imine **1b** exhibited enantioselectivity marginally lower than that of **1a** (entries 6 and 7), and electron-poor imines **1c**,**d** showed enhanced asymmetric induction (entries 8 and 9). 2-Naphthyl-imine **1e** reacted in the same way as **1a** (entries 10 and 11), but the cyclohexyl analogue **1f** showed a significantly reduced enantioselectivity, although in the latter case the overall result was affected by rather fast, noncatalytic background reaction (entry 12).

Variation of the imine *N*-substituent (R^2) had a more dramatic effect. Thus, whereas the *p*-methoxy imine **1g** gave high conversion and enantioselectivity (entry 13), its *o*-isomer **1h** was much less efficient (entry 14), demonstrating the steric effect. By contrast, imines **1i**,**j**, derived from nonaromatic amines, afforded practically racemic products (entries 15 and 16), indicating the crucial role of the *N*-aryl moiety of the ketimine for asymmetric induction.[15]

Lower temperature led to an increased enantioselectivity, as shown for imines **1a** and **1f** and catalyst **4a** (Table 2, entries 1 and 2; cf. Table 1, entries 4 and 12), partly as a result of suppressing the background reaction, which is particularly strong for **1f**.

The role of the amide functionality in the catalyst was elucidated with the aid of amides **4a**−**f** and **5a**−**c**. No reaction was observed with *n*-butyl amide **5a** (Table 2, entry 24), confirming the importance of the aromatic system in this position. Tertiary amide **5b**, lacking the NH group, proved to be a sluggish catalyst (entry 25), suggesting that a hydrogen bonding between the NH group of the catalyst and the imine nitrogen may also play a role in the transition state. Furthermore, removing the *N*-Me group from the formamide part, as in catalyst **5c**, proved to be detrimental to enantioselectivity (entry 26; cf. entry 7), showing the importance of the *N*-Me for the chiral relay.[3]

A set of anilides **4a**−**f** was employed to shed light on the nature of the aromatic interactions between the anilide part of the catalyst and the substrate.[16] Catalyst **4b** with a donor group was found to be slightly less efficient with imines **1a**,**e**, compared to **4a** (Table 2, entries 3−5). An additional methoxy substituent (**4c**) led to a further decrease in selectivity (entries 6−8). 3,5-Dimethylphenylamide **4d** generally gave higher yields and slightly better selectivity than the parent phenylamide **4a** (entries 9−15). By contrast, a significantly reduced efficacy was observed for the electron-poor 3,5-bis(trifluoromethyl)- and 3,5-dichloroanalogues **4e** and **4f** (entries 21−23).

Table 2. Reduction of Ketimines **1a**−**l** with Trichlorosilane, Catalyzed by **4a**−**f** and **5a**−**c**[a]

entry	imine	R^1, R^2	cat	solvent	yield (%)[b]	**2**, % ee[c] (config)[d]
1[e]	**1a**	Ph, Ph	**4a**	$CHCl_3$	49	92 (*S*)
2[e]	**1f**	*c*-C_6H_{11}, Ph	**4a**	$CHCl_3$	53	59 (*S*)
3	**1a**	Ph, Ph	**4b**	CH_2Cl_2	62	70 (*S*)
4	**1a**	Ph, Ph	**4b**	$CHCl_3$	62	85 (*S*)
5	**1e**	2-naphth, Ph	**4b**	CH_2Cl_2	53	66 (*S*)
6	**1a**	Ph, Ph	**4c**	$CHCl_3$	81	82 (*S*)
7	**1c**	4-$CF_3C_6H_4$, Ph	**4c**	$CHCl_3$	94	77 (*S*)
8	**1g**	Ph, 4-$MeOC_6H_4$	**4c**	$CHCl_3$	82	79 (S)
9	**1a**	Ph, Ph	**4d**	$CHCl_3$	70	89 (*S*)
10[e]	**1a**	Ph, Ph	**4d**	$CHCl_3$	94	92 (*S*)
11	**1b**	4-$MeOC_6H_4$, Ph	**4d**	$CHCl_3$	62	87 (*S*)
12	**1c**	4-$CF_3C_6H_4$, Ph	**4d**	$CHCl_3$	88	87 (*S*)
13[e]	**1c**	4-$CF_3C_6H_4$, Ph	**4d**	$CHCl_3$	95	89 (*S*)
14	**1g**	Ph, 4-$MeOC_6H_4$	**4d**	$CHCl_3$	79	86 (*S*)
15[e]	**1g**	Ph, 4-$MeOC_6H_4$	**4d**	$CHCl_3$	85	90 (*S*)
16	**1a**	Ph, Ph	**4d**	Tol	81	92 (*S*)
17	**1b**	4-$MeOC_6H_4$, Ph	**4d**	Tol	86	85 (*S*)
18	**1c**	4-$CF_3C_6H_4$, Ph	**4d**	Tol	86	89 (*S*)
19	**1g**	Ph, 4-$MeOC_6H_4$	**4d**	Tol	85	91 (*S*)
20	**1l**	2-MeC_6H_4, Ph	**4d**	Tol	90	92 (*S*)
21	**1a**	Ph, Ph	**4e**	$CHCl_3$	88	53 (*S*)
22	**1c**	4-$CF_3C_6H_4$, Ph	**4e**	$CHCl_3$	92	69 (*S*)
23	**1a**	Ph, Ph	**4f**	$CHCl_3$	35	56 (*S*)
24	**1a**	Ph, Ph	**5a**	$CHCl_3$	0	
25	**1a**	Ph, Ph	**5b**	$CHCl_3$	23	7 (*S*)
26	**1c**	4-$CF_3C_6H_4$, Ph	**5c**	$CHCl_3$	84	35 (*S*)

[a] The reaction was carried out at 0.5 mmol scale with 1.5 equiv of Cl_3SiH and 10 mol % of the catalyst at room temperature unless stated otherwise, 16 h. [b] Isolated yield. [c] Determined by chiral HPLC or GC. [d] Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see Supporting Information) and/or by HPLC/GC via comparison with authentic samples; configuration of **2d** and **2l** is assumed to be (*S*) in analogy with the rest of the series. [e] The reaction was carried out at −20 °C.

The activation of trichlorosilane is likely to proceed via a bidentate coordination with the catalyst through the formamide and anilide carbonyls.[17] In the series of catalysts **4a**−**f**, the Lewis basicity of the formamide moiety remained constant, while the substituents in the arylamide part should affect its donor properties. Apparently, catalysts **4e**,**f**, with electron-withdrawing groups in the aromatic ring, are less efficient in chelation to the weakly Lewis acidic trichlorosilane. Therefore, despite their increased capability of π-stacking,[18] moderate enantioselectivity was obtained. In the electron-rich anilides **4b**,**c**, the chelating ability is not compromised but in this case the $\pi-\pi$ interactions with the

(13) In the absence of the catalyst, the conversion after 24 h at room temperature in CH_2Cl_2 and $CHCl_3$ was <5%, and ~10% in MeCN.

(14) Note that chloroform has been shown to be the solvent that most strongly stabilizes the arene−arene interactions: Breault, G. A.; Hunter, C. A.; Mayers, P. C. *J. Am. Chem. Soc.* **1998**, *120*, 3402.

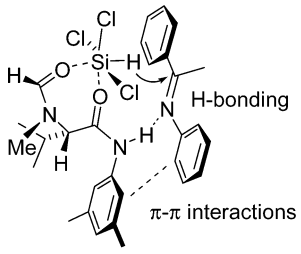
(15) While imines **1a**−**e**,**g**,**h**,**j**,**k** all exists as pure (*E*)-isomers, NMR spectra of **1f**,**i**,**l** indicate 11:1, 14:1, and 3:1 (*E*/*Z*)-mixtures, respectively.

(16) This strategy is commonly used in design of chiral selectors in chiral chromatography: Pirkle, W. H.; Koscho, M. E. *J. Chromatogr. A* **1999**, *840*, 151.

(17) In the ^{13}C NMR spectrum of a 1:1 mixture of **4d** and $HSiCl_3$, shifts of ~0.1 and 0.2 ppm were observed for the corresponding signals of formamide and anilide carbonyls relative to free **4d**. The methyl groups in the aromatic ring became nonequivalent, indicating a weak bidentate coordination. Furthermore, replacing the formamide unit proved fruitless: Thus, no reaction was observed for the -N(Me)CO_2CF_3 and -N(Me)CO_2-(*t*-Bu) analogues of **4a** and for the acetamide congener of **3a**.[11b]

substrate are weaker.[19] Finally, 3,5-dimethylphenylamide **4d** represents a perfect balance of electronic properties, which results in good reactivity and enantioselectivity.

On the basis of the available experimental data we suggest structure **A** (Figure 1) as a transition state in the reduction



A

Figure 1. Proposed transition state.

of *N*-arylimines, which incorporates both hydrogen bonding and π-stacking as key elements.

(18) (a) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc*. **1990**, *112*, 5525. (b) Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 651. (c) Waters, M. L. *Curr. Opin. Chem. Biol.* **2002**, *6*, 736. (d) Castellano, R. K.; Diederich, F.; Meyer, E. A. *Angew. Chem., Int. Ed*. **2003**, *42*, 1210.

(19) The alternative edge-to-face C−H/π interactions, which are normally favored by electron-rich aromatic donors,[18] would dictate the formation of a different transition state, which may result in lower enantioselectivity.

A possible involvement of hydrogen bonding prompted us to employ toluene as an environmentally friendly replacement for chlorinated solvents. Although toluene is not regarded as an ideal solvent when $\pi-\pi$ interactions are involved, the results presented in Table 2 (entries 16−20) show that, in this reaction, it is actually the solvent of choice: the level of selectivity attained in toluene at room temperature matched those in chloroform at −20 °C.

In conclusion, we have designed new L-valine-derived catalysts **4**, which effect reduction of *N*-aryl ketimines **1** with Cl_3SiH to afford secondary amines **2**. The observed enantioselectivity (≤92% ee) of this organocatalytic protocol matches the level of the transition-metal-catalyzed methods,[5] with **4d** being the champion catalyst and toluene the solvent of choice. Arene−arene interactions and hydrogen bonding between the catalyst and the substrate appear to be the key factors in the enantiodifferentiation process.

Acknowledgment. We thank the University of Rome "La Sapienza" for a fellowship to A.M. and the University of Glasgow for a fellowship to K.N.McD. and additional support.

Supporting Information Available: General experimental methods, synthesis of ligands **4** and **5**, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049213+