ORGANIC LETTERS

2011
Vol. 13, No. 3
402−405

Highly Enantioselective Nitrone Cycloadditions with 2-Alkenoyl Pyridine *N*-Oxides Catalyzed by Cu(II)−BOX Complexes

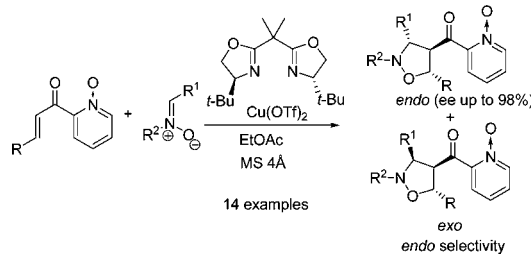
Santiago Barroso,[†] Gonzalo Blay,[*,†] M. Carmen Muñoz,[‡] and José R. Pedro[*,†]

Departament de Química Orgànica, Facultat de Química, Universitat de València, C/Dr. Moliner, 50, E-46100 Burjassot, València, Spain, and Departamento de Física Aplicada, Universidad Politécnica de Valencia, E-46071 Valencia, Spain

gonzalo.blay@uv.es; jose.r.pedro@uv.es

Received November 9, 2010

ABSTRACT



Enantioselective nitrone cycloadditions with 2-alkenoyl pyridine *N*-oxides as dipolarophiles have been reported. The reaction is catalyzed by Cu(II)−BOX complexes to give the expected isoxazolidine products with high diastereo- and enantioselectivity.

The 1,3-dipolar cycloaddition reaction is an important and atom-economic synthetic tool for the preparation of five-membered heterocycles, which are present in a large number of bioactive compounds. Several compounds have been used as 1,3-dipoles in this kind of reaction, nitrones being among the most studied substrates. The isoxazolidine products obtained from these reactions are valuable precursors to biologically active γ-amino acids, γ-aminoalcohols, β-lactams, amino sugars, and alkaloids.[1] In recent years, a number of enantioselective Lewis acid catalyzed nitrone cycloadditions with either electron-deficient (normal-electron demand) or electron-rich alkenes (inverse-electron demand) have been reported,[2] some of them using copper complexes with chiral ligands as catalysts.[3] With respect to the copper-catalyzed nitrone cycloadditions with electron-deficient alkenes, only a limited number of substrates have been successfully used as dipolarophiles. First examples were described by Saito, using 3-(2-alkenoyl)-1,3-oxazolidin-2-ones as chelating dipolarophiles together with bis-imine and BOX complexes.[4]

[†] Universitat de València.
[‡] Universidad Politécnica de Valencia.

(1) (a) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1. (b) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. *2*. (c) Torssell, K. B. G. *Natural Product Chemistry*; VCH: Weinheim, 1988. (d) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2002.

(2) For recent reviews, see: (a) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2001; pp 211−248. (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235–3285. For recent examples, see: (c) Badoiu, A.; Bernardinelli, G.; Kündig, E. P. *Synthesis* **2010**, 2207–2212. (d) Phomkeona, K.; Takemoto, T.; Ishima, Y.; Shibatomi, K.; Iwasa, S.; Nishiyama, H. *Tetrahedron* **2008**, *64*, 1813–1822. (e) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodriguez, R.; Oro, L. A.; Lahoz, F. J.; Balana, A. I.; Tejero, T.; Merino, P. *J. Am. Chem. Soc.* **2005**, *127*, 13386–13398. (f) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431–1434. (g) Iwasa, S.; Maeda, H.; Nishiyama, K.; Tsushima, S.; Tsukamoto, Y.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 8281–8287. (h) Jensen, K. B.; Roberson, M.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 9080–9084.

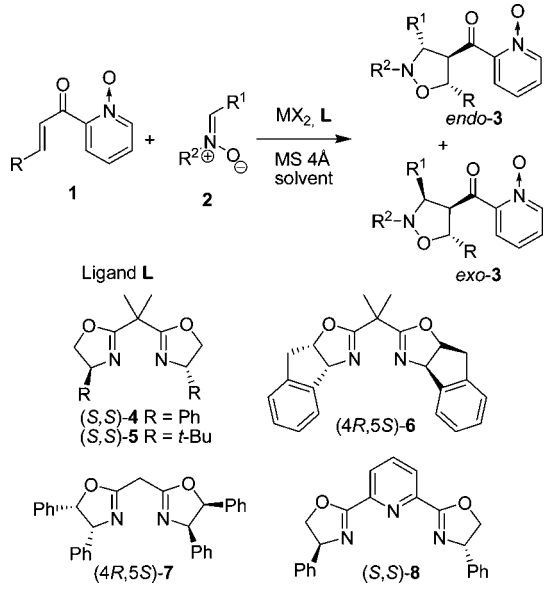
(3) For a recent review on copper-catalyzed 1,3-dipolar cycloadditions, see: Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887–2902.

10.1021/ol102716e
Published on Web 12/22/2010

In these cases, the dipolarophile is able to form a chelate with the metal ion of the chiral complex which is responsible for the high stereoselectivities observed. Other chelating dipolarophiles have been also used as reaction substrates. Thus, Palomo[5] introduced α′-hydroxy enones in BOX−Cu(II)-catalyzed reactions to obtain the *endo* adducts, and Sibi reported the BOX−Cu(II) catalyzed reaction using 1-substituted 2-alkenoyl-5,5-dimethyl-3-pyrazolidones[6] and acyclic alkenoylimides[7] as dipolarophiles, which favored the formation of the corresponding *exo* adducts. Also, very recently Ishihara has described the use of propioloyl- and acryloylpyrazoles as dipolarophiles in nitrone cycloadditions.[8]

Jørgensen introduced the 2-acylpyridine *N*-oxide moiety as a new chelating scaffold for Cu(II)−BOX-catalyzed reactions.[9] Inspired by this work, we developed 2-alkenoylpyridine *N*-oxides as efficient chelating substrates for asymmetric catalysis. We have used these substrates as dienophiles in Diels−Alder reactions[10] and as heterodienes in inverse-electron demand hetero-Diels−Alder reactions.[11] These substrates have also been used by Singh et al. in Mukaiyama−Michael reactions[12] and Friedel−Crafts alkylations.[13] As we and Singh have shown, these substrates are much more reactive and afford higher enantioselectivities in asymmetric Cu(II)−BOX-catalyzed[14] reactions than the corresponding nonoxidized 2-alkenoylpyridines. In this communication we present the use of the 2-alkenoylpyridine *N*-oxides as dipolarophiles for the Cu(II)−BOX-catalyzed 1,3-dipolar cycloaddition reactions with nitrones (Scheme 1).[15]

Scheme 1. Nitrone 1,3-Dipolar Cycloadditions to Alkenoyl Pyridine *N*-Oxides and BOX Ligands Evaluated in This Study



The reaction between cinnamoylpyridine *N*-oxide (**1a**, R = Ph) and nitrone **2a** ($R^1 = R^2 = Ph$) to give **3aa** (R = R^1 = R^2 = Ph) was used for the screening of ligands and conditions (Table 1). Initially, we tested this reaction under the optimized conditions for the Diels−Alder reaction,[9] using $Cu(OTf)_2$ and Ph-BOX ligand (*S*,*S*)-**4**, in dichloromethane (entry 1). To our surprise, low yields of racemic compounds were obtained. The use of $Zn(OTf)_2$ instead of $Cu(OTf)_2$ gave even worse results (entry 2).

Table 1. Optimization of the Reaction of Dipolarophile **1a** (R = Ph) with Nitrone **2a** ($R^1 = R^2 = Ph$): Screening of Ligands[a]

entry	MX_2	L	yield(%)[b]	*endo*/*exo*	ee (%)*endo*[c,d]
1[e]	$Cu(OTf)_2$	(*S*,*S*)-**4**	<10[f]	n.d.	0
2[e]	$Zn(OTf)_2$	(*S*,*S*)-**4**	<5[f]	n.d.	0
3	$Cu(OTf)_2$	(*S*,*S*)-**4**	94	62:38	(*S*)10
5	$Cu(OTf)_2$	(*S*,*S*)-**5**	85	92:8	(*R*)89
4	$Cu(OTf)_2$	(4*R*,5*S*)-**6**	90	80:20	(*S*)59
6	$Cu(OTf)_2$	(4*R*,5*S*)-**7**	79	82:18	0
7	$Cu(OTf)_2$	(*S*,*S*)-**8**	86	85:15	0

[a] All experiments were carried out under nitrogen: **1a** (0.25 mmol), **2a** (0.3 mmol), MX_2 (0.025 mmol, 10 mol %), **L** (0.025 mmol, 10 mol %), MS 4 Å (100 mg), CH_2Cl_2 (1.5 mL), rt, 5 h. [b] Purified by flash chromatography. [c] Determined by HPLC on a Chiralcel OD-H column. [d] The absolute configuration of the carbon α to carbonyl is in parentheses. [e] No MS were used. [f] Yield after 24 h.

Then, we tested the use of additives. It has been described that the addition of molecular sieves significantly influences the results of 1,3-dipolar cycloadditions.[16] Effectively, when we carried out the reaction in the presence of 4 Å molecular sieves (400 mg/mmol **1a**), the reaction was complete in 5 h, providing a 62:38 *endo*/*exo* mixture of diastereomers in 94% yield, although in only 10% ee for the *endo* diastereomer. Encouraged by this result, we tested different BOX ligands **5**−**8**, and to our delight, ligand (*S*,*S*)-**5** afforded the desired compound **3aa** with 89% ee and high diatereoselectivity (*endo*/*exo* 92:8). Ligands (*S*,*S*)-**4** and (*S*,*S*)-**5** afforded opposite enantiomers in a similar way as it has been observed in other Cu(II)-catalyzed reactions with these ligands.[13] Ligand (4*R*,5*S*)-**7**, bearing an unsubstituted central methylene, and the pyBOX ligand (*S*,*S*)-**8** gave racemic mixtures. Further optimization with ligand (*S*,*S*)-**5** was achieved by changing solvents and the amounts of MS (Table 2). Both nitromethane and EtOAc performed better than other solvents in terms of diastereo- and enantioselectivity, although EtOAc gave a better yield (entry 5). The type of MS was also tested although it did not show a very important effect (entries 5−7): 4 Å MS gave better diastereoselectivities than 3 and 5 Å MS, although with 3 Å MS a slightly better enantiose-

(4) (a) Saito, T.; Yamada, Y.; Miyazaki, S.; Otani, T. *Tetrahedron Lett.* **2004**, *45*, 9585–9587. (b) Saito, T.; Yamada, Y.; Miyazaki, S.; Otani, T. *Tetrahedron Lett.* **2004**, *45*, 9581–9584. See also: (c) Desimoni, G.; Faita, G.; Toscanini, M.; Boiocchi, M. *Chem.—Eur. J.* **2009**, *15*, 9674–9677.

(5) Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; Lopez, R.; Gonzalez, A.; Linden, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6187–6190.

(6) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718–719.

(7) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagaran, N.; Jasperse, C. P. *Org. Lett.* **2005**, *7*, 2349–2352.

(8) Sakakura, A.; Hori, H.; Fushimi, M.; Ishihara, K. *J. Am. Chem. Soc.* **2010**, *132*, 15550–15552.

(9) (a) Landa, A.; Minnkilä, A.; Blay, G.; Jørgensen, K. A. *Chem.—Eur. J.* **2006**, *12*, 3472–3483. (b) Landa, A.; Richter, B.; Johansen, R. L.; Minkkilä, A.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 240–245.

(10) Barroso, S.; Blay, G.; Pedro, J. R. *Org. Lett.* **2007**, *9*, 1983–1986.

Table 2. Optimization of the Reaction of Dipolarophile **1a** (R = Ph) with Nitrone **2a** ($R^1 = R^2 = Ph$) Using Ligand (*S*,*S*)-**5**: Effect of Solvent and MS[a]

entry	solvent	MS (Å/mg)	time (h)	yield (%)[b]	*endo*/*exo*[c]	ee (%)[d] *endo*/*exo*
1	CH_2Cl_2	4/100	5	85	92:8	89/12
2	Toluene	4/100	5.5	85	87:13	85/18
3	CH_3NO_2	4/100	5	86	93:7	92/28
4	CH_3CN	4/100	29	20	79:21	78/32
5	EtOAc	4/100	5	100	94:6	92/9
6	EtOAc	3/100	5	81	89:11	96/33
7	EtOAc	5/100	5	92	86:14	91/32
8	EtOAc	4/50	21	97	90:10	95/36
9	EtOAc	4/200	21	86	91:9	93/17
10	EtOAc	4/75	10	94	94:6	95/61
11[e]	EtOAc	4/75	24	96	91:9	98/41

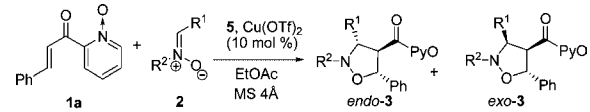
[a] All experiments were carried out under nitrogen: **1a** (0.25 mmol), **2a** (0.3 mmol), $Cu(OTf)_2$ (0.025 mmol), (*S*,*S*)-**5** (0.025 mmol), MS, solvent (1.5 mL), rt. [b] Purified by flash chromatography. [c] Determined by ^1H NMR. [d] Determined by HPLC on a Chiralcel OD-H column. [e] Reaction carried out at 0 °C.

lectivity was obtained. However, it was possible to arrive at a compromise between diastereo- and enantioselectivity by adjusting the amount of 4 Å MS to 300 mg/mmol of dipolarophile (entry 10). The ee could be slightly increased by carrying out the reaction at 0 °C, although this required a longer reaction time (entry 11) and the diastereoselectivity was lower.

With these optimized conditions in hand, we investigated the scope of the reaction. First, we studied the reaction of alkenoyl pyridine *N*-oxide **1a** (R = Ph) as a dipolarophile with different nitrones (Table 3). In general, *N*-phenyl nitrones (entries 1−5) gave better results than *N*-methyl or *N*-benzyl nitrones (entries 6 and 7). *N*-Phenyl nitrones derived from aromatic aldehydes gave the corresponding cycloadducts with good yields as well as diastereo- (near 9:1 favoring the *endo* isomer) and enantioselectivities (above 90% ee), except in the case of nitrone **1d** derived from *p*-nitrobenzaldehyde that reacted with low yield, although with good stereoselectivity. However, nitrone **1e**, derived from alicyclic cyclohexancarbaldehyde was poorly reactive and gave cycloadduct **3ae** with fair diastereoselectivity but only 60% ee.

Then, we performed the reaction of differently substituted dipolarophiles **1** with nitrone **2a** ($R^1 = R^2 = Ph$). The results are gathered in Table 4. The R group on the double bond of the dipolarophile **1** was amenable to variation. When R was

Table 3. 1,3-Dipolar Cycloadditions of 2-Alkenoyl Pyridine *N*-Oxide **1a** (R = Ph) with Nitrones **2a**−**g** Using Ligand (*S*,*S*)-**5**[a]

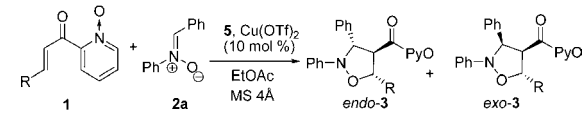


PyO = pyridin-2-yl *N*-oxide

entry	**2**	R^1	R^2	time (h)	**3**	yield (%)[b]	*endo*/*exo*[c]	(%)[d] *endo*/*exo*
1	**a**	Ph	Ph	10	**aa**	94	94:6	95/61
2	**b**	4-$MeOC_6H_4$	Ph	24	**ab**	77	86:14	90/42
3	**c**	4-BrC_6H_4	Ph	24	**ac**	81	91:9	94/45
4	**d**	4-$NO_2C_6H_4$	Ph	48	**ad**	36	94:6	89/79
5	**e**	cyclohexyl	Ph	24	**ae**	16	74:26	60/29
6	**f**	Ph	Me	48	**af**	59	66:34	88/78
7	**g**	Ph	Bn	48	**ag**	62	61:39	80/75

[a] All experiments were carried out under nitrogen: **1a** (0.25 mmol), **2a** (0.3 mmol), $Cu(OTf)_2$ (0.025 mmol, 10 mol %), (*S*,*S*)-**5** (0.025 mmol, 10 mol %), MS 4 Å (75 mg), EtOAc (1.5 mL), rt. [b] Purified by flash chromatography. [c] Determined by ^1H NMR. [d] Determined by HPLC on chiral stationary phase columns.

Table 4. 1,3-Dipolar Cycloadditions of 2-Alkenoyl Pyridine *N*-Oxides **1a**−**h** with Nitrone **2a** ($R^1 = R^2 = Ph$) Using Ligand (*S*,*S*)-**5**[a]



PyO = pyridin-2-yl *N*-oxide

entry	**1**	R	time (h)	**3**	yield (%)[b]	*endo*/*exo*[c]	ee (%)[d] *endo*/*exo*
1	**a**	Ph	10	**aa**	94	94:6	95/61
2	**b**	4-$MeOC_6H_4$	24	**ba**	69	93:7	96/nd
3	**c**	4-BrC_6H_4	10	**ca**	82	90:10	96/22
4	**d**	4-$NO_2C_6H_4$	1.5	**da**	56	87:13	96/21
5	**e**	2-furyl	24	**ea**	43	>99:1	95/−
6	**f**	2-thienyl	24	**fa**	68	94:6	91/nd
7	**g**	(*E*)-PhCH=CH-	24	**ga**	52	93:7	93/33
8	**h**	*t*-Bu	1	**ha**	98	92:8	86/45
9[e]	**a**	Ph	24	**aa**	100	90:10	92/35

[a] All experiments were carried out under nitrogen: **1a** (0.25 mmol), **2a** (0.3 mmol), $Cu(OTf)_2$ (0.025 mmol, 10 mol %), (*S*,*S*)-**5** (0.025 mmol, 10 mol %), MS 4 Å (75 mg), EtOAc (1.5 mL), rt. [b] Purified by flash chromatography. [c] Determined by ^1H NMR. [d] Determined by HPLC on chiral stationary phase columns. [e] **1a** (3.0 mmol), **2a** (2.5 mmol), $Cu(OTf)_2$ (0.125 mmol, 5% mol), **5** (0.125 mmol, 5 mol %), MS 4 Å (750 mg), EtOAc (7 mL), rt.

a substituted phenyl group, high diastereoselectivities (near 9:1 favoring the *endo* cycloadduct) and enantiomeric excesses (above 95% ee for the *endo* diastereomer) were obtained, regardless of the electronic nature of the substituent; again, the 4-nitrophenyl derivative gave the corresponding cycloadduct only in moderate yield. R can be also a five-membered heterocyle (entries 5 and 6). In these cases the reaction was a little bit slow. The furyl-containing compound **1f** afforded

(11) Barroso, S.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Adv. Synth. Catal.* **2009**, *351*, 107–111.
(12) Singh, P. K.; Singh, V. K. *Org. Lett.* **2008**, *10*, 4121–4124.
(13) Singh, P. K.; Singh, V. K. *Org. Lett.* **2010**, *12*, 80–83.
(14) For a review on BOX-catalyzed reactions, see: Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651.
(15) A few days after the submission of our manuscript we noticed a related paper by Faita describing one example of this reaction: Livieri, A.; Boiocchi, M.; Desimoni, G.; Faita, G. *Chem.—Eur. J.*, DOI: 10.1002/chem.201002017.
(16) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483–5488.

the highest diastereoselectivity, although the yield dropped considerably. Similar results were obtained with compound **1g** bearing an alkene. Dipolarophile **1h**, bearing a bulky *tert*-butyl group, showed a very high reactivity and gave cycloadduct **3ah** with good yield, fair diastereoselectivity, and 86% ee. Experiments also showed that the amount of catalyst can be reduced to as low as 5 mol %, and the reaction scaled up at least ten times without noticeable effect on the yield and stereoselectivity (entry 9).

Suitable crystals for X-ray analysis of compound *endo*-**3fa** could be obtained upon crystallization from EtOAc, which allowed establishing the absolute stereochemistry for this compound (Figure 1). For the remaining cycloadducts,

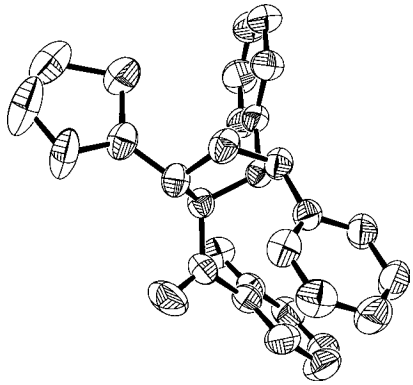


Figure 1. ORTEP plot for the X-ray structure of compound **3fa**. Flack parameter 0.1(12).

the absolute configuration was assigned on the assumption of a uniform stereochemical mechanistic pathway.

The stereochemistry of the products indicates the preference of the nitrone to approach the dipolarophile from the α-*re* face of the double bond. Following previous studies[13] on BOX−Cu(II) catalyzed reactions, we suggest that a distorted square-planar complex is formed by the dipolarophile **1**, ligand **5**, and metal center, with the dipolarophile coordinating to two positions of the copper ion, with the carbonyl and *N*-oxide moieties. The dipolarophile would adopt the more stable s-*cis* conformation, and in this way the approach of the nitrone from the α-*si* face of the double bond would be hampered by one of the *tert*-butyl groups (left) of the ligand. On the other hand, the *endo* approach would minimize the interactions between the R^1 group of the nitrone and the other *tert*-butyl group (right) of the ligand. This model is in good agreement with the recent findings by Faita,[15] who has isolated a complex of compound **1a**, $Cu(OTf)_2$, and a related bis-oxazoline ligand having an elongated square-bipyramidal structure, with two triflate anions occupying the axial positions. Since it is not clear whether these two anions are present also in solution, and for clarity, we have omitted them in Figure 2.

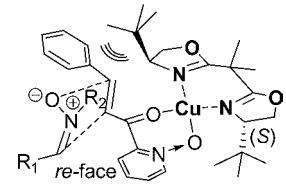


Figure 2. Proposed stereochemical model for the 1,3-dipolar cycloaddition between 2-alkenoyl pyridine *N*-oxides and nitrones.

In conclusion, we have shown that 2-alkenoyl pyridine *N*-oxides are efficient dipolarophiles for 1,3-dipolar cycloadditions of nitrones catalyzed by chiral Cu(II)−BOX complexes. This kind of substrates enlarges the range of electron-deficient alkenes that can be used in these cycloaddition reactions to favor formation of the *endo* adducts. Isoxazolidines bearing a pyridine-containing substituent are obtained with yields as well as diastereo- and enantioselectivities from good to excellent.

Acknowledgment. Financial support from the Ministerio de Ciencia e Innovación and FEDER (CTQ2006-14199 and CTQ2009-13083) and from Generalitat Valenciana (ACOMP/2009/338) is acknowledged. S.B. thanks the Universitat de Valencia for a predoctoral grant (V Segles program).

Supporting Information Available: Experimental procedures, characterization data and copies of NMR spectra, and chiral HPLC analysis for compounds **3**. X-ray structure plot and CIF file for compound **3fa**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102716E