ORGANIC LETTERS

2013
Vol. 15, No. 6
1230–1233

Phase-Transfer-Catalyzed Asymmetric Conjugate Cyanation of Alkylidenemalonates with KCN in the Presence of a Brønsted Acid Additive

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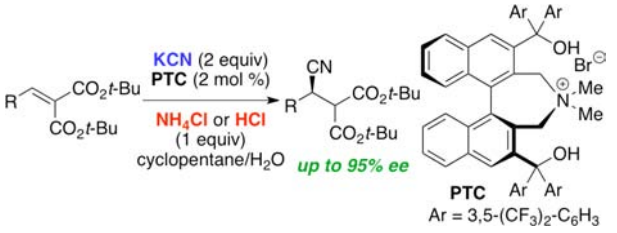
Received January 17, 2013

ABSTRACT



Highly enantioselective conjugate cyanation of alkylidenemalonates with KCN was achieved under mild phase-transfer conditions with a bifunctional phase-transfer catalyst. The effect of Brønsted acid additives was examined based on the hypothetical catalytic cycle, and the Brønsted acid additive was found to be essential to promote the conjugate cyanation efficiently.

Asymmetric conjugate cyanation of α,β-unsaturated carboxylic acid derivatives offers an efficient synthetic method for chiral β-substituted γ-aminobutyric acids (GABA),[1] which are an important class of pharmaceutical compounds. Hence, the development of efficient asymmetric conjugate cyanation of α,β-unsaturated carbonyl compounds is an important task for organic chemistry.[2] Although several catalytic asymmetric cyanations of α,β-unsaturated carbonyl compounds have recently been developed using HCN,[3] TMSCN,[4] ethyl cyanoformate,[5] and acetone cyanohydrin[6] as cyanide sources, further advances in practical methods for the asymmetric transformation are still highly desirable. In this context, we are interested in the development of the phase-transfer-catalyzed[7] asymmetric conjugate cyanation of alkylidenemalonates **1** with KCN[8] as one of the most economical and

(1) (a) Roberts, E. *Biochem. Pharmacol.* **1974**, *23*, 2637. (b) Sytinsky, I. A.; Soldatenkov, A. T.; Lajtha, A. *Prog. Neurobiol.* **1978**, *10*, 89. (c) Sivilotti, L.; Nistri, A. *Prog. Neurobiol.* **1991**, *36*, 35.

(2) For a review on stereoselective synthesis of γ-amino acids, see: Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3.

(3) Kurono, N.; Nii, N.; Sakaguchi, Y.; Uemura, M.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 5541.

(4) (a) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (b) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928. (c) Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 514. (d) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 5820. (e) Mazet, C.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1762. (f) Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 6072. (g) Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 8862. (h) Yang, J.; Wu, S.; Chen, F.-X. *Synlett* **2010**, 2725.

(5) Wang, J.; Li, W.; Liu, Y.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2010**, *12*, 1280.

(6) (a) Provencher, B. A.; Bartelson, K. J.; Liu, Y.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 10565. (b) Kawai, H.; Okusu, S.; Tokunaga, E.; Sato, H.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4959.

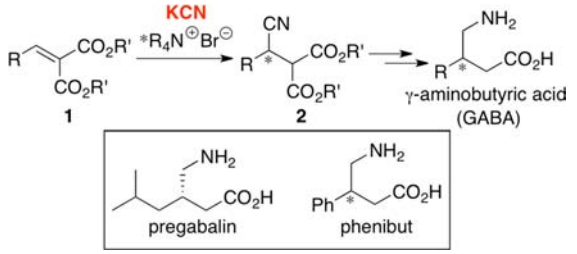
(7) For recent reviews on asymmetric phase-transfer catalysis, see: (a) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3. (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (d) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (e) Vachon, J.; Lacour, J. *Chimia* **2006**, *60*, 266. (f) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222. (g) Ooi, T.; Maruoka, K. *Aldrichimica Acta* **2007**, *40*, 77. (h) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. (i) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679. (j) Jew, S.-s.; Park, H.-g. *Chem. Commun.* **2009**, 7090. (k) Maruoka, K. *Chem. Rec.* **2010**, *10*, 254.

(8) (a) Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, V. S.; Franklin, L. C.; Granger, E. J.; Karrick, G. L. *Org. Process Res. Dev.* **1997**, *1*, 26. (b) Silverman, R. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 3500. (c) Martinez, C. A.; Hu, S.; Dumond, Y.; Tao, J.; Kelleher, P.; Tully, L. *Org. Process Res. Dev.* **2008**, *12*, 392. (d) Mukherjee, H.; Martinez, C. A. *ACS Catal.* **2011**, *1*, 1010.

10.1021/ol400143m
Published on Web 03/05/2013

practical cyanide sources (Scheme 1).[9] Here we report the first example of highly enantioselective conjugate cyanation with KCN under phase-transfer conditions.[10]

Scheme 1. Phase-Transfer-Catalyzed Conjugate Cyanation of Alkylidenemalonate for the Synthesis of GABA



In initial attempts of the phase-transfer-catalyzed conjugate cyanation in Scheme 1, we have observed a slow rate of reaction with a catalytic amount of chiral phase-transfer catalyst (~2 mol %).[11] This slow reaction rate is attributed to the slow regeneration step of ammonium cyanide ($R_4N^+CN^-$). That is to say, the ammonium salt of the adduct **2** (**2′·NR$_4^+$**) as a result of the conjugate cyanation with ammonium cyanide ($R_4N^+CN^-$) and alkylidenemalonate **1** is relatively stable under the reaction conditions, and the subsequent step of **2′·NR$_4^+$** with KCN seems to be relatively slow for the regeneration of the ammonium cyanide ($R_4N^+CN^-$) (Figure 1, right cycle). From this assumption, we expected that addition of a Brønsted acid (HX) as a proton source might be helpful for the acceleration of the slow reaction rate for this conjugate cyanation (Figure 1, left cycle).[12,13]

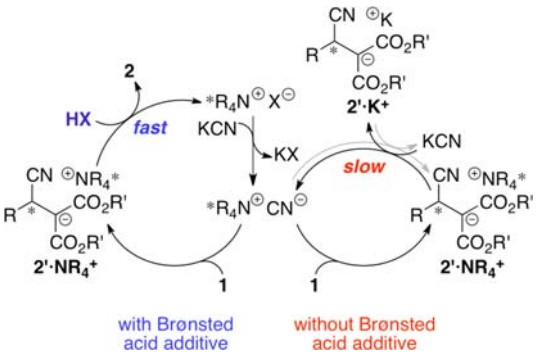


Figure 1. Hypothetical catalytic cycle of the phase-transfer-catalyzed conjugate cyanation in the presence and absence of a Brønsted acid additive.

Based on this hypothesis, we examined the effect of Brønsted acid additives[13] in the asymmetric conjugate cyanation of alkylidenemalonate **1a** with KCN under the influence of chiral bifunctional phase-transfer catalyst (*S*)-**3a** (2 mol %)[14,15] in cyclopentane−H_2O biphasic conditions[16] (Scheme 2). In the absence of a Brønsted acid additive, the reaction proceeded very sluggishly and only a trace amount of cyanation product **2a** was obtained. On the other hand, the reaction with an equimolar amount of a Brønsted acid additive, such as NH_4Cl, HCl, or AcOH, proceeded smoothly, and cyanation product **2a** was produced in good yields (80−86%) with high enantioselectivities (88−90% ee). Reduction of the amount of Brønsted acid additive (0.2 equiv) caused a decrease in yields (26−34% yields). It should be noted that the use of TMSCN, which generates HCN in the presence of H_2O, as a cyanide source instead of KCN completely shuts off the reaction. This result indicates that the use of KCN as a cyanide source is essential to promote the present phase-transfer-catalyzed conjugate cyanation.

(9) For catalytic asymmetric cyanation of aldehydes and imines with KCN, see: (a) Juliá, S.; Ginebreda, A. *Tetrahedron Lett*. **1979**, *20*, 2171. (b) Belokon, Y. N.; Carta, P.; Gutnov, A. V.; Maleev, V.; Moskalenko, M. A.; Yashkina, L. V.; Ikonnikov, N. S.; Voskoboev, N. V.; Khrustalev, V. N.; North, M. *Helv. Chim. Acta* **2002**, *85*, 3301. (c) Belokon, Y. N.; Gutnov, A. V.; Moskalenko, M. A.; Yashkina, L. V.; Lesovoy, D. E.; Ikonnikov, N. S.; Larichev, V. S.; North, M. *Chem. Commun*. **2002**, 244. (d) Belokon, Y. N.; Blacker, A. J.; Carta, P.; Clutterbuck, L. A.; North, M. *Tetrahedron* **2004**, *60*, 10433. (e) Huang, W.; Song, Y.; Wang, J.; Cao, G.; Zheng, Z. *Tetrahedron* **2004**, *60*, 10469. (f) Huang, W.; Song, Y.; Bai, C.; Cao, G.; Zheng, Z. *Tetrahedron Lett*. **2004**, *45*, 4763. (g) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc*. **2006**, *128*, 2548. (h) Khan, N.-u. H.; Agrawal, S.; Kureshy, R. I.; Abdi, S. H. R.; Mayani, V. J.; Jasra, R. V. *Eur. J. Org. Chem*. **2006**, 3175. (i) Belokon, Y. N.; Clegg, W.; Harrington, R. W.; Young, C.; North, M. *Tetrahedron* **2007**, *63*, 5287. (j) Ooi, T.; Uematsu, Y.; Fujimoto, J.; Fukumoto, K.; Maruoka, K. *Tetrahedron Lett*. **2007**, *48*, 1337. (k) Reingruber, R.; Baumann, T.; Dahmen, S.; Bräse, S. *Adv. Synth. Catal*. **2009**, *351*, 1019. (l) Khan, N.-u. H.; Sadhukhan, A.; Maity, N. C.; Kureshy, R. I.; Abdi, S. H. R.; Saravanan, S.; Bajaj, H. C. *Tetrahedron* **2011**, *67*, 7073. (m) Yan, H.; Oh, J. S.; Lee, J.-W.; Song, C. E. *Nat. Commun*. **2012**, *3*, DOI: 10.1038/ncomms2216.

(10) For phase-transfer-catalyzed asymmetric conjugate cyanation using KCN with modest enantioselectivities, see: Davies, B. S.; Guzman, M. M.; Martinez, C. A.; McDaid, P. O.; O'Neill, P. M.; Shanmugam, E. WO 2010070593, 2010.

(11) Various types of binaphthyl-modified chiral phase-transfer catalysts developed in our group (see ref 7), such as commercially available (*S*)-4,4-dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3*H*-dinaphtho-[2,1-*c*:1′,2′-*e*]azepinium bromide (Simplified Maruoka Catalyst), were examined in asymmetric conjugate cyanation in Scheme 2 without Brønsted acid additive. The reactions proceeded very sluggishly, and only a trace amount of cyanation product was obtained.

(12) For a study on the effect of Brønsted acid additives in organocatalyzed asymmetric conjugate addition, see: Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, *94*, 719.

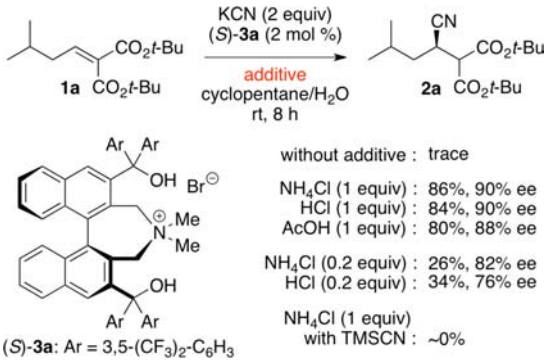
(13) For asymmetric phase-transfer reactions with Brønsted acid additives, see: (a) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc*. **2004**, *126*, 9685. (b) Lygo, B.; Beynon, C.; Lumley, C.; McLeod, M. C.; Wade, C. E. *Tetrahedron Lett*. **2009**, *50*, 3363.

(14) For examples of chiral bifunctional phase-transfer catalysts, see: (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc*. **1984**, *106*, 446. (b) Loupy, A.; Zaparucha, A. *Tetrahedron Lett*. **1993**, *34*, 473. (c) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc*. **2004**, *126*, 6844. (d) Liu, Y.; Provencher, B. A.; Bartelson, K. J.; Deng, L. *Chem. Sci*. **2011**, *2*, 1301. (e) Ohmatsu, K.; Kiyokawa, M.; Ooi, T. *J. Am. Chem. Soc*. **2011**, *133*, 1307. (f) Johnson, K. M.; Rattley, M. S.; Sladojevich, F.; Barber, D. M.; Nuñez, M. G.; Goldys, A. M.; Dixon, D. J. *Org. Lett*. **2012**, *14*, 2492.

(15) (a) He, R.; Shirakawa, S.; Maruoka, K. *J. Am. Chem. Soc*. **2009**, *131*, 16620. (b) Wang, X.; Lan, Q.; Shirakawa, S.; Maruoka, K. *Chem. Commun*. **2010**, *46*, 321. (c) Wang, L.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed*. **2011**, *50*, 5327. (d) Shirakawa, S.; Terao, S. J.; He, R.; Maruoka, K. *Chem. Commun*. **2011**, *47*, 10557. (e) Shirakawa, S.; Ota, K.; Terao, S. J.; Maruoka, K. *Org. Biomol. Chem*. **2012**, *10*, 5753.

(16) The reaction in cyclopentane−H_2O gave the best result in terms of enantioselectivity.

Scheme 2. Effect of Brønsted Acid Additives



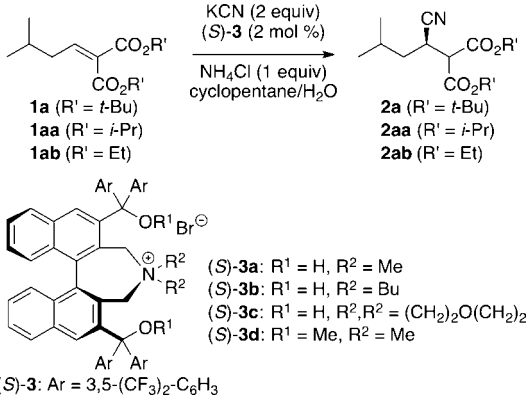
Based on these observations, we further optimized the reaction conditions (Table 1). A change of the alkyl group (R^2) on the nitrogen of the catalyst from (*S*)-**3a** (R^2 = Me) to (*S*)-**3b** and (*S*)-**3c**[15] caused a decrease in both reactivities and enantioselectivities (entries 2 and 3). Importantly, hydroxy-protected catalyst (*S*)-**3d** (R^1 = R^2 = Me) gave the product **2a** with low enantioselectivity (30% ee, entry 4). This result indicates that the bifunctional design of catalyst (*S*)-**3a** is essential to achieve high enantioselectivity in this reaction. The importance of the hydroxy group in catalyst (*S*)-**3a** was further supported by X-ray diffraction analysis of the related ammonium iodide (*S*)-**3e** (Figure 2).[17] The hydrogen-bonding interaction between the hydroxy group and counteranion (I^-) is clearly observed in the crystal structure of (*S*)-**3e**, and hence it is assumed that the position of the cyanide anion in ammonium cyanide derived from (*S*)-**3a** is fixed by the hydrogen bond.

Switching the alkyl group of the ester moiety in the alkylidenemalonate from *tert*-butyl to isopropyl and ethyl gave the products **2aa** (R′ = *i*-Pr) and **2ab** (R′ = Et) in good yields with slightly lower enantioselectivities (76−87% ee, entries 5 and 6). Lower reaction temperatures increased the enantioselectivities slightly (entries 7−9), and the highest enantioselectivity was attained at −10 °C (95% ee, entry 9). A decrease of the catalyst loading to 0.2 mol % still gave the product **2a** in acceptable yield (64%) with high enantioselectivity (91% ee, entry 10). The reaction with NaCN gave comparable results with the use of KCN (compare entries 11 and 7).

With optimal reaction conditions in hand, we studied the substrate generality of the asymmetric conjugate cyanation of alkylidenemalonates **1** with KCN and a Brønsted acid additive (NH_4Cl or HCl) in the presence of chiral bifunctional catalyst (*S*)-**3a** under the biphasic phase-transfer conditions (Table 2). Various types of alkylidenemalonates **1** were found to be employable for the reactions. The reactions of alkylidenemalonates **1** with simple alkyl chains gave the corresponding cyanation products **2a**−**d** in high

(17) The crystal structure of (*S*)-**3e** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 911649). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	R′	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	(*S*)-**3a**	*t*-Bu	rt	8	86	90
2	(*S*)-**3b**	*t*-Bu	rt	72	15	4
3	(*S*)-**3c**	*t*-Bu	rt	72	59	0
4	(*S*)-**3d**	*t*-Bu	rt	24	51	30
5	(*S*)-**3a**	*i*-Pr	rt	0.5	81	87
6	(*S*)-**3a**	Et	rt	0.5	82	76
7	(*S*)-**3a**	*t*-Bu	0	24	68	93
8[d]	(*S*)-**3a**	*t*-Bu	0	10	86	92
9	(*S*)-**3a**	*t*-Bu	−10	72	64	95
10	(*S*)-**3a**[e]	*t*-Bu	0	96	64	91
11[f]	(*S*)-**3a**	*t*-Bu	0	24	71	93

[a] Reaction conditions: **1a** (0.050 mmol), KCN (0.10 mmol), and NH_4Cl (0.050 mmol) in the presence of (*S*)-**3** (2 mol %) in cyclopentane (2 mL)/H_2O (0.1 mL). [b] Yield of isolated products. [c] Determined by chiral HPLC analysis. [d] HCl was used instead of NH_4Cl. [e] Reaction was performed with 0.2 mol % of (*S*)-**3a**. [f] NaCN was used instead of KCN.

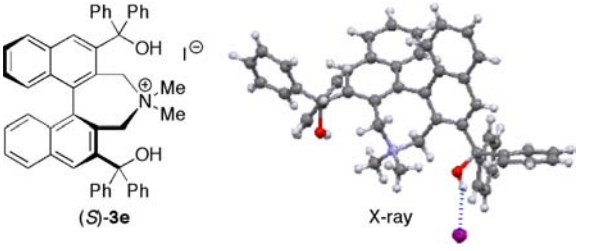
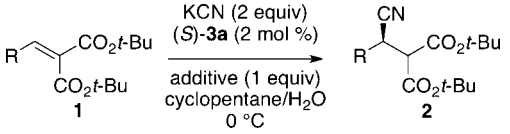


Figure 2. X-ray crystal structure of (*S*)-**3e**.

enantioselectivities (88−93% ee, entries 1−6). The alkylidenemalonates **1** possessing functional groups were also employable for the reaction to give the corresponding products **2e**−**g** in high enantioselectivities (88−91% ee, entries 7−11). The cyanation with phenyl-substituted alkylidenemalonate **1** (R = Ph) gave the product **2h** in moderate enantioselectivity (entry 12).

The synthetic utility of cyanation product **2f** with a chloride functional group was demonstrated in the intramolecular

Table 2. Asymmetric Conjugate Cyanation of Alkylidenemalonate **1** with KCN[a]

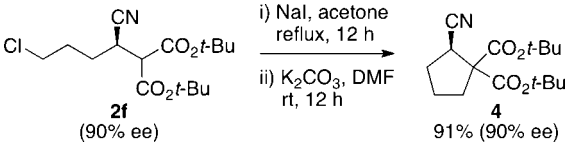


entry	R	additive	time (h)	yield (%)[b]	ee (%)[c]
1	$(CH_3)_2CHCH_2$	NH_4Cl	24	68 (**2a**)	93
2	$(CH_3)_2CHCH_2$	HCl	10	86 (**2a**)	92
3	Me	NH_4Cl	36	74 (**2b**)	92
4	Me	HCl	12	76 (**2b**)	92
5[d]	Et	HCl	24	76 (**2c**)	89
6[d]	$Ph(CH_2)_2CH_2$	HCl	24	70 (**2d**)	88
7	$CH_2{=}CHCH_2CH_2$	NH_4Cl	12	64 (**2e**)	90
8	$CH_2{=}CHCH_2CH_2$	HCl	12	75 (**2e**)	90
9	$Cl(CH_2)_2CH_2$	NH_4Cl	8	74 (**2f**)	90
10	$Cl(CH_2)_2CH_2$	HCl	8	72 (**2f**)	91
11	$TBSO(CH_2)_2CH_2$	HCl	12	84 (**2g**)	88
12	Ph	HCl	48	34 (**2h**)	50

[a] Reaction conditions: **1** (0.050 mmol), KCN (0.10 mmol), and NH_4Cl or HCl (0.050 mmol) in the presence of (*S*)-**3a** (2 mol %) in cyclopentane (2 mL)/H_2O (0.1 mL) at 0 °C. [b] Yield of isolated products. [c] Determined by chiral HPLC analysis. [d] Reaction was performed at −10 °C.

cyclization to give product **4** as a useful chiral building block (Scheme 3).

Scheme 3. Transformation of the Cyanation Product **2f**



In summary, we have successfully developed a highly enantioselective conjugate cyanation of alkylidenemalonates with KCN in the presence of a chiral bifunctional ammonium bromide under biphasic phase-transfer conditions. The effect of Brønsted acid additives such as NH_4Cl and HCl was examined based on the hypothetical catalytic cycle, and we found that such an additive is essential to promote the conjugate cyanation efficiently.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from JSPS and MEXT (Japan). We are grateful to Dr. Hiroyasu Sato (Rigaku Corporation) for X-ray crystallographic analysis.

Supporting Information Available. Experimental details, characterization data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.