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Use of 5,5-(Dimethyl)-*i*-Pr-PHOX as a Practical Equivalent to *t*-Bu-PHOX in Asymmetric Catalysis

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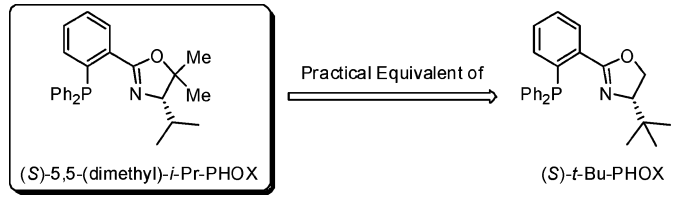
ABSTRACT



The use of 5,5-(dimethyl)-*i*-Pr-PHOX as a practical equivalent of *t*-Bu-PHOX in asymmetric catalysis is reported. This new member of the phosphinooxazoline (PHOX) ligand family behaves similarly in terms of stereoinduction to *t*-Bu-PHOX with the key advantage of being readily accessible as both enantiomers starting from either (*S*)- or (*R*)-valine.

The phosphinooxazoline ligands (PHOX ligands) developed by Pfaltz, Helmchen, and Williams are a versatile class of P,N-chiral ligands (Figure 1).[1] The only difference between the well-known members of this class of ligands is the substituent at C-4 (i.e., **1**−**4**, Figure 1). Within this group, the one bearing a *t*-butyl group at C-4 (i.e., **1**) is often the one affording the highest enantioselectivities, and therefore it is extensively used in asymmetric catalysis[1−3] and in natural product synthesis.[4] The (*S*)-enantiomer of this ligand is now commercially available.[5] Alternatively, it can be synthesized in four steps from (*S*)-*tert*-leucine ((*S*)-**6**),[6] a rather expensive non-natural amino acid (Figure 1).[7,8] However, the other enantiomer of *tert*-leucine, (*R*)-*tert*-leucine ((*R*)-**6**), is prohibitively expensive, thus (*R*)-*t*-Bu-

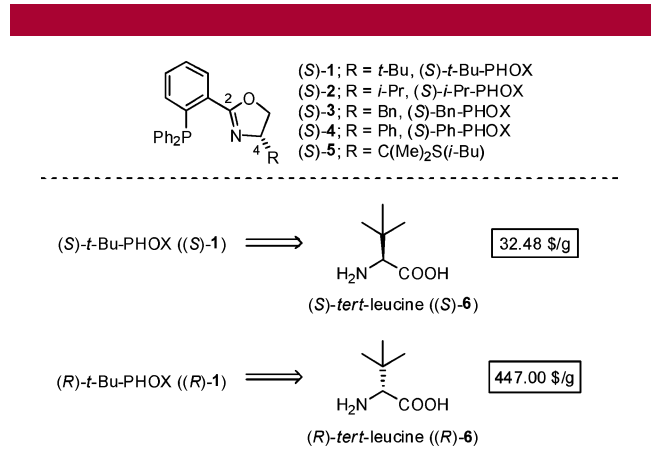


Figure 1. Some members of the PHOX ligand family and synthetic precursor for the preparation of *t*-Bu-PHOX (**1**).

(1) (a) Williams, J. M. J. *Synlett* **1996**, 705–710. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.

(2) For selected examples of the use of (*S*)-*t*-Bu-PHOX in asymmetric catalysis, see: (a) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200–202. (b) Langer, T.; Helmchen, G. *Tetrahedron Lett.* **1996**, *37*, 1381–1384. (c) Hiroi, K.; Watanabe, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1841–1843. (d) Hayashi, T.; Suzuka, T.; Okada, A.; Kawatsura, M. *Tetrahedron: Asymmetry* **2004**, *15*, 545–548. (e) Cook, M. J.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 9302–9303. (f) Schulz, S. R.; Blechert, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3966–3970. (g) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039–1042. (h) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873–6876. (i) Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162–16163.

(3) For our own work using (*S*)-*t*-Bu-PHOX, see: (a) Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034–1035. (b) Bélanger, É.; Houzé, C.; Guimond, N.; Cantin, K.; Paquin, J.-F. *Chem. Commun.* **2008**, 3251–3253.

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PHOX is virtually not accessible.[9] This drawback has serious consequence in asymmetric catalysis since it limits access to one enantiomeric series for any given reaction using the *t*-Bu-PHOX ligand. In this context, a readily accessible substitute for *t*-Bu-PHOX that would be available in both enantiomeric series at reasonable cost would be highly valuable.[10]

It has been shown by Davies[11] that the incorporation of a *gem*-dimethyl group at C-5 of a 4-*iso*-propyloxazolidinone (Evans' auxiliary) resulted in a chiral auxiliary that behaved similarly to a 4-*tert*-butyl-propyloxazolidinone in terms of stereoinduction in a wide range of transformations. It was also demonstrated that steric interaction between the *gem*-dimethyl group at C-5 and the *iso*-propyl group at C-4 resulted in a conformation of the *i*-Pr where the two methyl groups pointed toward the reaction center (i.e., enolate fragment) such that the *i*-Pr mimicked a *tert*-butyl group.[11a]

On the basis of these results, we envisioned that the incorporation of a *gem*-dimethyl group at C-4 of *i*-Pr-PHOX (**2**) could result in a practical replacement for *t*-Bu-PHOX (**1**). These new ligands would not only have a major economic advantage over *t*-Bu-PHOX since the cost of the starting amino acids, (*S*)- or (*R*)-valine (**8**), is much lower than the corresponding *tert*-leucines (**6**) but also allow easy access to both enantiomers.

Herein, we describe a new and readily available member of the PHOX family,[12] 5,5-(dimethyl)-*i*-Pr-PHOX (**7**) (Figure 2), which has a parallel reactivity to (*S*)-*t*-Bu-PHOX with the key advantage of being easily accessible as both enantiomers. The synthesis of these ligands and their application in two enantioselective Pd-catalyzed transformations will also be demonstrated.

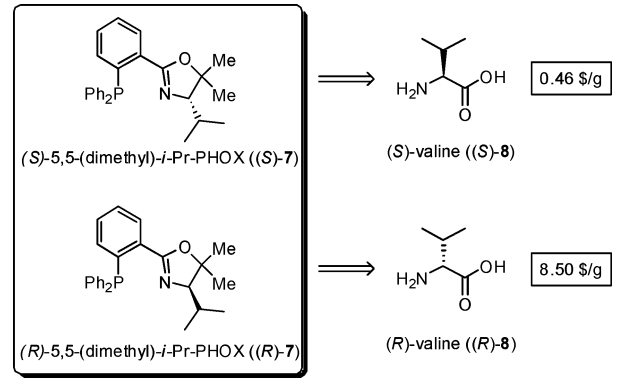


Figure 2. New ligands 5,5-(dimethyl)-*i*-Pr-PHOX and their synthetic precursor.

The desired ligand can be accessed by two different routes from a common intermediate (*S*)-**9**[13] (Scheme 1). The synthesis of the latter starts from (*S*)-valine ((*S*)-**8**) that was first transformed into (*S*)-valine methyl ester hydrochloride salt using a known procedure.[14,15] The ester was then converted into the previously reported amino alcohol (*S*)-**9** in a three-step process involving protection of the amine, methyl Grignard addition followed by deprotection of the Boc group under acidic conditions.[13] From (*S*)-**9**, the route parallels the original sequence to access (*S*)-*t*-Bu-PHOX.[6] In this case, amide formation with 2-fluorobenzoyl chloride followed by cyclization under acidic conditions[16] gave (*S*)-**10**. The latter was converted to the desired ligand (*S*)-**7** via a S_NAr reaction using $KPPh_2$. Although this sequence provided easy access to (*S*)-**7**, the intrinsic limitation of the last step, the anionic displacement, where either electron-rich phosphine anions or electron-rich aryl fluorides cannot be used, puts unwanted boundaries on the eventual fine-tuning of the electronic properties of the ligand for specific reactions. To circumvent this potential limitation, a second route was investigated taking profit of a recently published

(4) For recent examples of the use of (*S*)-*t*-Bu-PHOX in total synthesis, see: (a) Coe, J. W. *Org. Lett.* **2000**, *2*, 4205–4208. (b) Bian, J.; Van Wingarden, M.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 7428–7429. (c) Behenna, D. C.; Stockdill, J. L.; Stoltz, B. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 4077–4080. (d) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (e) Dounay, A. M.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377.

(5) Available from Sigma-Aldrich Co.

(6) Peer, M.; de Jong, J. C.; Jiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547–7583.

(7) The price per gram (in American dollars) was calculated using the largest amount available from Sigma-Aldrich Co. (March 2009).

(8) Bommarius, A. S.; Schwarm, M.; Stingl, K.; Kottenhahn, M.; Huthmacher, K.; Drauz, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2851–2888.

(9) According to a recent SciFinder Scholar search (March 2009), only 5 examples of the use of (*R*)-*t*-Bu-PHOX had been reported. See: (a) Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293–2297. (b) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844–4849. (c) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039–1042. (d) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289–292. (e) Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293–295.

(10) These issues have been partly addressed before and resulted in the design of (*S*)-**5** (Figure 1).[6] However, to date, the use of this ligand in asymmetric catalysis remains scarce. See: (a) Langer, T.; Joerg, J.; Helmchen, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1599–1602. (b) Wiese, B.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 5727–5730.

(11) (a) Bull, S. D.; Davies, S. G.; Key, M.-S.; Nicholson, R. L.; Savory, E. D. *Chem. Commun.* **2000**, 1721–1722. (b) Bull, S. D.; Davies, S. G.; Garner, A. C.; Kruchinin, D.; Key, M.-S.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2006**, *4*, 2945–2964.

(12) Pfaltz has recently reported a few related 5,5-(disubstituted)-*i*-Pr-PHOX (not including (*S*)- or (*R*)-**7**) that were used in a different context, i.e., [3 + 2] cycloadditions of azomethine ylides with moderate to excellent results). See: Stohler, R.; Wahl, F.; Pfatlz, A. *Synthesis* **2005**, 1431–1436.

(13) Gibson, S. E.; Mainolfi, N.; Kalindjian, S. B.; Wright, P. T.; White, A. J. P. *Chem.—Eur. J.* **2005**, 69–80.

(14) Bowman, N. J.; Hay, M. P.; Love, S. G.; Easton, C. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 259–264.

(15) (*S*)- and (*R*)-valine methyl ester hydrochloride are also commercially available.

(16) (a) Denmark, S. E.; Stavenger, R. A.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375–3389. (b) Ginotra, S. K.; Singh, V. K. *Tetrahedron* **2006**, *62*, 3573–3581.

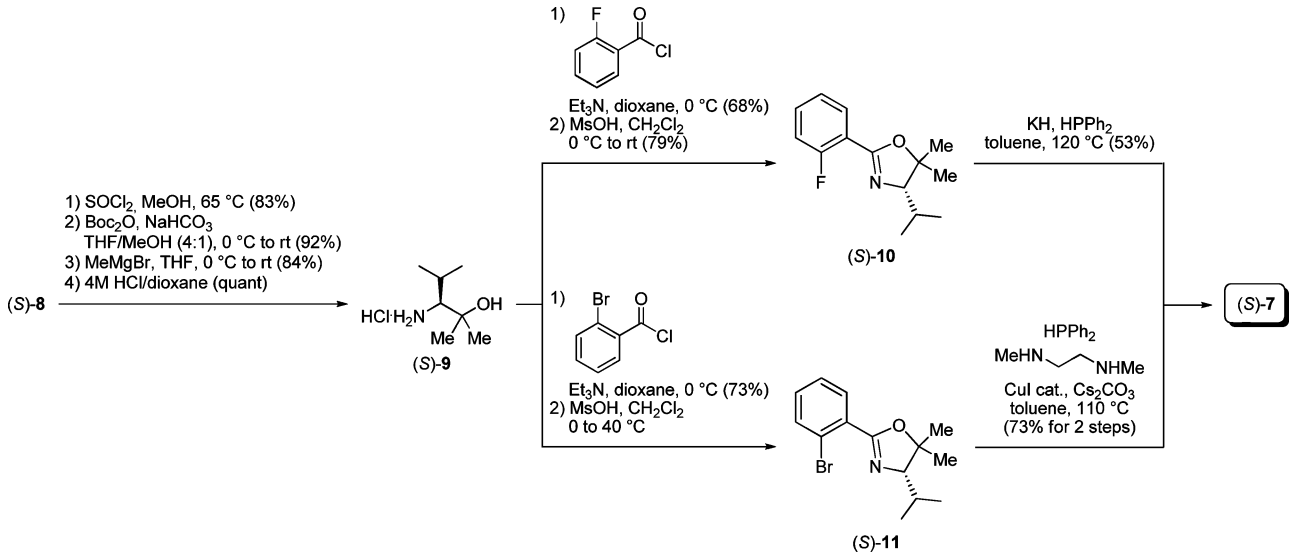
(17) (a) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531. (b) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.

(18) Gelman, D.; Jiang, L.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2315–2318.

(19) For reviews on the asymmetric allylic alkylation reaction, see: (a) Paquin, J.-F.; Lautens, M. In *Comprehensive Asymmetric Catalysis, supplement #2*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 2004; pp 73—95, and references therein. (b) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 833—884, and references therein.

(20) Ligand (*R*)-**7** was prepared using "Stoltz's approach" in Scheme 1. See the Supporting Information for details.

Scheme 1. Synthetic Approaches to (*S*)-**7**

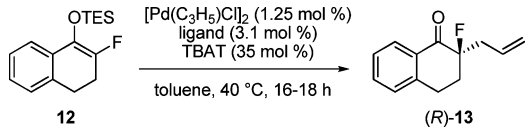


approach to PHOX ligands by Stoltz.[17] In this case, the key C−P bond is made through an Ullmann-type coupling developed by Buchwald[18] allowing synthesis of ligand (*S*)-**7** from (*S*)-**11** in good yield.

The new ligands were first examined in the enantioselective allylation reaction[19] using fluorinated silyl enol ether precursors (**12**), a transformation developed recently by our research group (Table 1).[3a] This reaction provides an efficient access to allylated tertiary α-fluoroketones (**13**) and was developed initially with (*S*)-*t*-Bu-PHOX as the chiral ligand which gave (*R*)-**13** in excellent yield and 92% ee (entry 1). Using our new ligand (*S*)-**7**, the α-fluoroketone was obtained in nearly identical results (93% yield, 90% ee). The use of the enantiomer of the ligand, (*R*)-**7**,[20] provided the other enantiomer of the ketone, (*S*)-**13**, with identical results (entry 3). Finally, it is interesting to note that (*S*)-*i*-Pr-PHOX, which lacks the *gem*-dimethyl at C-5 compared to (*S*)-**7**, provided (*R*)-**13** with excellent yield but with lower ee (80% ee), thus demonstrating the beneficial effect of the substituents at C-5.

The ligands were then tested in the enantioselective Heck reaction[21] between 2,3-dihydrofuran (**14**) and phenyl triflate (**15**) where the use of the PHOX ligand, in particular (*S*)-*t*-Bu-PHOX, was first reported by Pfaltz.[2a] The reactions were conducted under microwave irradiation which has been shown to greatly reduce the reaction time (18 h @ 100 °C vs 4 days @ 70 °C).[22] Using (*S*)-*t*-Bu-PHOX, the desired 2,5-dihydrofuran (*R*)-**16** was isolated in good yield and 96% ee (Table 2, entry 1). Using (*S*)-**7**, the product was obtained in good yield with slightly reduced enantioselectivity (73% yield, 91% ee). The use of (*R*)-**7** provided (*S*)-**16** with nearly identical results (76% yield, 92% ee). Here again, the use of (*S*)-*i*-Pr-PHOX provided the desired product with lower ee (86% ee).

Table 1. Enantioselective Pd-Catalyzed Allylation Reaction of Fluorinated Silyl Enol Ether[a]

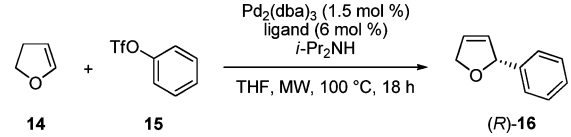


12 (*R*)-**13**

entry	ligand	yield (%)[b]	ee (%)[c]
1	(*S*)-*t*-Bu-PHOX	91	92
2	(*S*)-**7**	93	90
3	(*R*)-**7**	93	−90
4	(*S*)-*i*-Pr-PHOX	93	80

[a] See the Supporting Information and ref 3a for details concerning the reaction conditions. [b] Isolated yield. [c] Determined by chiral HPLC.

Table 2. Microwave-Assisted Enantioselective Heck Reaction of 2,3-Dihydrofuran[a]



14 **15** (*R*)-**16**

entry	ligand	yield (%)[b]	ee (%)[c]
1	(*S*)-*t*-Bu-PHOX	81	96
2	(*S*)-**7**	73	91
3	(*R*)-**7**	76	−92
4	(*S*)-*i*-Pr-PHOX	45	86

[a] See the Supporting Information and ref 22 for details concerning the reaction conditions. [b] Isolated yield. [c] Determined by chiral HPLC.

(21) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533–1552, and references therein.

(22) Nilsson, P.; Gold, H.; Larhed, M.; Hallberg, A. *Synthesis* **2002**, 1611–1614.

(23) See the Supporting Information for more details.

(24) Hydrogen atoms and solvent molecules have been omitted for clarity.

Palladium complexes of ligand (*S*)-**7** and (*S*)-*t*-Bu-PHOX were prepared by the reaction of $PdCl_2$ in CH_2Cl_2 at 40 °C for 48 h.[23] The resulting crystals were analyzed by X-ray diffraction, and the crystal structures are shown in Figure 3.[23,24] In $PdCl_2$[(*S*)-**7**], the distances from the palladium to the methyl groups of the *i*-Pr group are 3.615 and 4.376 Å, respectively. Correspondingly, in $PdCl_2$[(*S*)-*t*-Bu-PHOX], the same distances are 3.298 and 3.4357 Å suggesting a similar environment around the Pd atom from the stereoinducting groups. Thus, the *i*-Pr flanked by a *gem*-dimethyl group mimics a *tert*-butyl group. However, in $PdCl_2$[(*S*)-**7**], the presence of the *gem*-dimethyl group causes a slight distortion as indicated by a torsion angle between Cl2−Pd1−N1−C4 of 38.7° as opposed to 47.3° in $PdCl_2$[(*S*)-*t*-Bu-PHOX]. This subtle difference as well as the presence of the *gem*-dimethyl group at C-5 may explain why in certain reactions (e.g., Heck reaction) slight differences in the enantioselectivities are observed, whereas in others (e.g., allylic alkylation reaction) both ligands behave equally well.

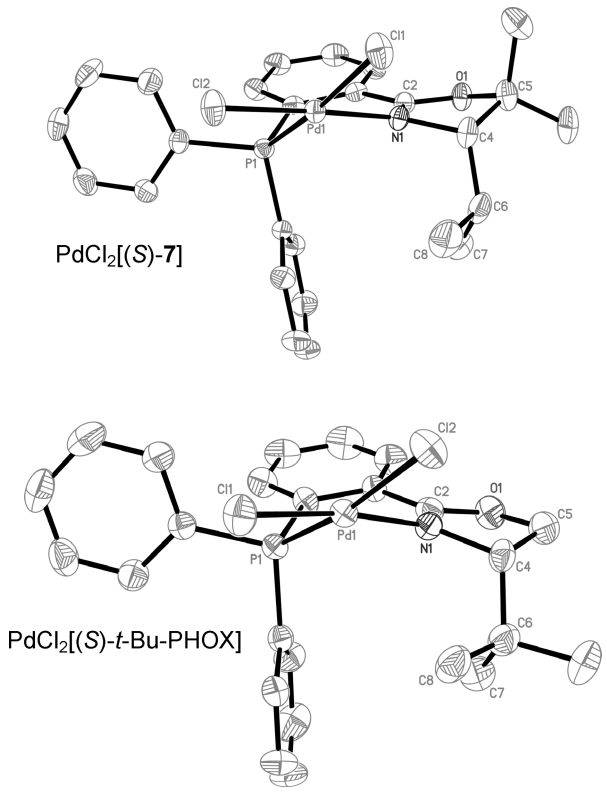


Figure 3. Crystal structure of $PdCl_2$[(*S*)-**7**] and $PdCl_2$[(*S*)-*t*-Bu-PHOX].

In conclusion, we have described a new and readily available member of the PHOX family, 5,5-(dimethyl)-*i*-Pr-PHOX (**7**), which in terms of stereoinduction behaves similarly to (*S*)-*t*-Bu-PHOX but is easily accessible as both enantiomers. The simple access of this family of ligands from readily available starting materials opens the way to the fine-tuning of the electronic/steric nature of the ligand for specific reactions. We believe that this practical equivalent to *t*-Bu-PHOX will find a wide use in asymmetric catalysis.

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Supporting Information Available: General experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for the new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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