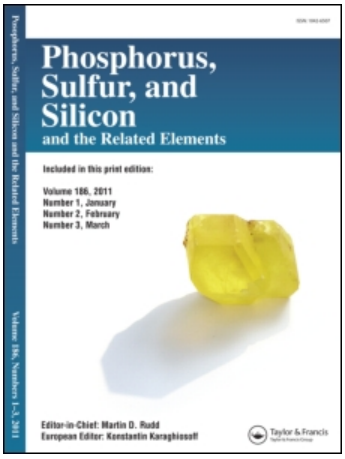

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P(RNCH 2 CH 2) 3 N as Very Strong Non-Ionic Bases and Catalysts: Recent Advances and Applications

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$P(RNCH_2CH_2)_3N$ AS VERY STRONG NON-IONIC BASES AND CATALYSTS: RECENT ADVANCES AND APPLICATIONS

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A rationale for the unusually strong Lewis basicity and catalytic activity of the title pro-azaphosphatranes is presented. Four stoichiometric and four catalytic uses of such pro-azaphosphatranes are described, as well as some unexpected reactions in which these bases take part. Mechanistic pathways are put forth for several of the transformations outlined.

Keywords: Bases; carbon-fluorine activation; catalysts; pro-azaphosphatranes; transannulation

INTRODUCTION

The basicity of the pro-azaphosphatranes **A** arises from the ease with which these compounds form stable transannulated conjugate acids **B** that possess trigonal bipyramidal molecular structures.[1,2] The axial N—P bond is sufficiently short (*ca* 200 pm) to allow considerable electron density to be transferred from the nitrogen to the phosphorus, thereby forming robust P—H bonds that confer pK_a values on **B** of about 33 in acetonitrile.[3] Gas phase UPS studies reveal that the phosphorus IE of **1a** is among the lowest reported for phosphorus compounds (5.6 eV), that of its gas phase transannulated bond stretch isomer, which features a transannulated bond, is even lower (4.6 eV).[4]

The versatility of compounds of type **A** as catalysts for useful organic transformations is associated with the flexibility of the transannular bridgehead–bridgehead interaction. The distance between the two bridgehead atoms progresses gradually from about 330 to 200 pm, depending on the nature of the axial substituent.[2] This distance varies

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A **B**

FIGURE 1

monotonically with the NPN angle at the phosphorus bridgehead, which gradually opens from about 104° in untransannulated proazaphosphatrane structures to 120° in fully transannulated trigonal bipyramidal phosphatranes. Compounds that exhibit structural metrics between these extremes are referred to as quasi-phosphatranes.[1]

It is interesting to note that the bridgehead nitrogen in proazaphosphatranes and some quasi-phosphatranes possesses a very nearly planar geometry. This stems from van der Waals interactions among the hydrogens on the methylene carbons adjacent to the bridgehead nitrogen and not from any detectable electronic interaction between the bridgehead atoms.[1]

In this talk, recent developments in three areas will be briefly discussed: syntheses utilizing our non-ionic bases stoichiometrically, syntheses utilizing our non-ionic bases catalytically, and some interesting and surprising results with these non-ionic bases.

Syntheses Utilizing Our Non-Ionic Bases Stoichiometrically

In most instances, the stoichiometric use of our bases involves deprotonation as a key step. Advantageous properties of our non-ionic bases include their relatively non-nucleophilic character and their bulky nature. Their neutrality and bulk allows them to behave as reactive naked species that are poorly solvated and lack counterions with which to form

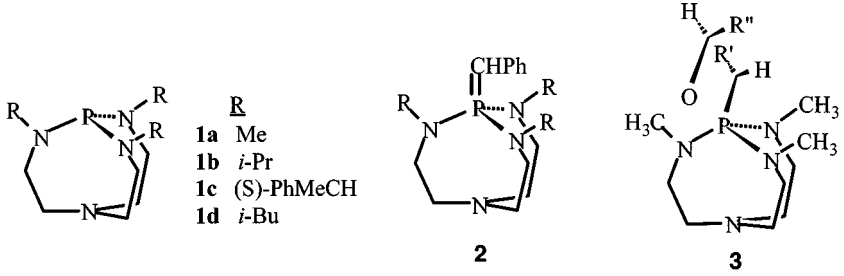


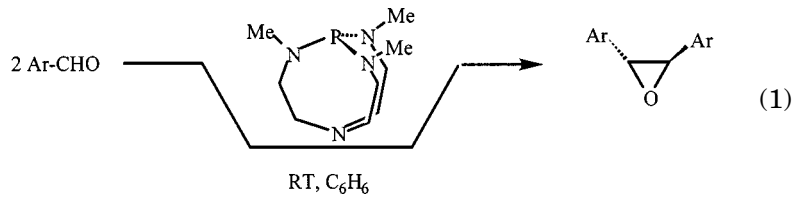
FIGURE 2

ion pairs. Although we have developed more than a dozen syntheses in which bases of type **A** are used stoichiometrically, time permits us to consider only four.

The first such synthesis features the use of ylide **2** in Wittig reactions that are highly stereoselective for the *E* configuration.[5,6] The olefination of aldehydes with phosphorus ylides is governed primarily by the nature of the ylide and the reaction conditions. Stabilized and nonstabilized ylides bearing an α-alkyl group tend to give *Z* alkenes, whereas stabilized ylides, which typically bear a *pi* acceptor group on the α-carbon, generally react with high selectivity for the *E* olefinic configuration. Semi-stabilized ylides, such as benzyl and allyl ylides, yield mixtures of *Z* and *E* isomers. Unexpectedly, we found that the semi-stabilized ylide **2**, synthesized from **1a** and benzyl bromide,[5] gave exclusively *E* olefins in high yield with aldehyde substrates, regardless of changes in the metal ion of the ionic base used to deprotonate the benzyl phosphonium precursor cation to **2**. Also somewhat unexpectedly, temperature and solvent polarity had no significant influence. The high *E* selectivity with **2** contrasts results with the acyclic semi-stabilized ylide PhCH=P(NMe$_2$)$_3$, which gave an *E/Z* mixture.[6]

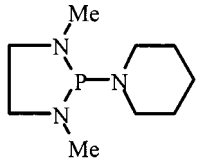
The stereoselectivity of **2** in the Wittig reaction can be rationalized in terms of the Vedjs model[7] and the X-ray molecular structure of **2**.[6] Thus, in contrast to flexible acyclic ylides, ylide **2** possesses a bicyclic phosphine whose compact and relatively rigid cage moiety dramatically reduces the 1,3-interaction between a CH_3 group and a substituent on the carbonyl substrate in the process of forming an oxaphosphetane intermediate as depicted in structure **3**. Consequently, 1,2-interactions between the R′ and R″ can then dominate, favoring formation of a four-centered *trans*-oxaphosphetane transition state that leads to *E*-alkene.

The second synthesis we consider is that of epoxides. Thus, the reaction depicted in Figure 3 transpires rapidly and cleanly in a highly stereoselective manner to form the *trans* product.[8] This contrasts our finding that P(NMe$_2$)$_3$ and the cyclic triaminophosphine **4** afford diastereomeric mixtures. We speculate that mechanistic considerations analogous to those put forth for the aforementioned Wittig synthesis



(1)

FIGURE 3



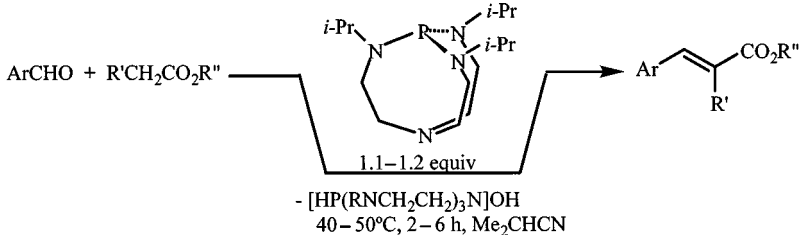
4

FIGURE 4

also apply in the present case. In support of this hypothesis is our observation that the more sterically hindered non-ionic base **1b** is not effective in the synthesis of trans-epoxides.

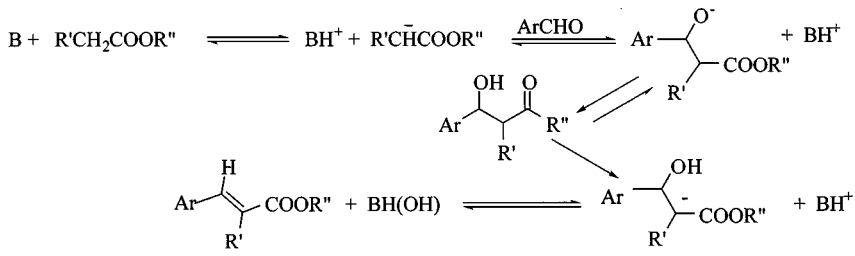
The third synthesis we consider is that of *E*-α,β-unsaturated esters.[9] The most common routes to these compounds are Horner and Wadsworth-Emmons reactions. Both methods, however, suffer from the drawback that they require the pre-preparation of intermediates. Organometallic catalysts have also been utilized for the synthesis of *E*-α,β-unsaturated esters, but such catalysts entail environmental concerns and they rarely produce only one isomer. Peterson olefination reactions require elevated temperatures yet afford only modest yields.

In the reaction depicted in Figure 5, it is seen that ethyl acetate reacts with aldehydes in the presence of **1b** to form exclusively *E*-isomers, though the higher homologue methyl propionate gives rise to a mixture of *E* and *Z* isomers (with the former as the major product). However, when methyl propionate is used as the solvent for the reaction, the corresponding *E*-α,β-unsaturated ester is formed exclusively. The proposed pathway of our reaction (shown in Scheme 1) is initiated by a pre-equilibrium that lies far to the left. Interesting is the observation that **1b** is more effective in reaction 2 than **1a**. We attribute this to the greater basicity of **1b**.[3] We suggest that the high diastereoselectivity of reaction 2 is because the reaction is thermodynamically rather than kinetically controlled.



(2)

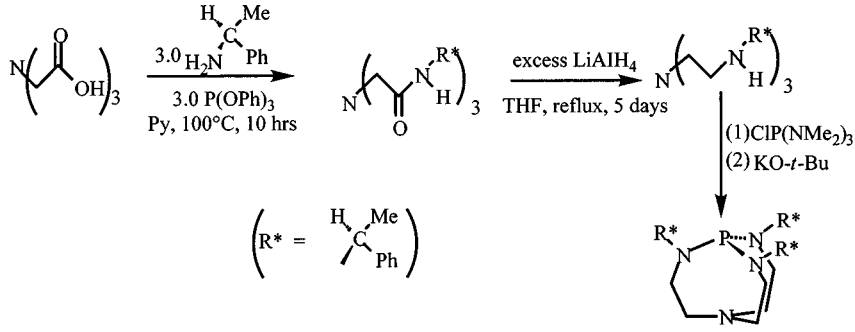
FIGURE 5



SCHEME 1

The fourth synthesis is that for iminophosphoranes of chiral **1c**. The products were made for the purpose of determining the *e.e.* values of the precursor organic azides.[10] Chiral azides are useful as ligands, auxiliaries and pharmaceutical intermediates, and also for the synthesis of natural products. Because of the attractive NMR properties of phosphorus, this nucleus has in the past been incorporated into various chiral reagents for the determination of *e.e.* values of alcohols, amines, and thiols, though not for azides.

The chiral tren precursor to reagent **1c** is easily made from nitrilotriactic acid and (S)-α-phenethylamine, both of which are commercially available (Scheme 2).[10] Base **1c** reacts with a wide variety of chiral azides at 50°C in an NMR tube to generate the corresponding chiral iminophosphoranes quantitatively. The ^{31}P NMR signals of the two product diastereomers are very well separated (*ca* 1 ppm), and their integration gives *e.e.* values that corresponded very closely to those for known mixtures and those determined from ^{1}H NMR integration of the peaks on the diastereomeric protons on the imino carbon.



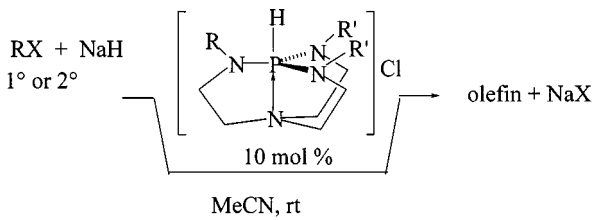
SCHEME 2

Syntheses Utilizing Our Non-Ionic Bases Catalytically

Of the more than twenty reactions we have found to be catalyzed by bases of type **A**, we will restrict ourselves to describing four of them, of which the first is dehydrohalogenation.[11] We have shown that **1a** functions as a better stoichiometric base than DBU for the dehydrohalogenation of primary and secondary halides in acetonitrile.[12] It was further shown in that report that with CD_3CN as the solvent, **1a** preferentially deprotonates the acetonitrile, and the resulting solvent anion dehydrohalogenates the organic halide.

More recently, we converted this dehydrohalogenation process to a catalytic version as shown in reaction 3 (see Figure 6). In this reaction, the procatalyst **1a** H^+ ($R = R' = R''$) can be used, or alternatively **1d** H^+ can be chemically bound via a nitrogen to the benzyl group of a Merrifield resin ($R =$ resin, $R' = R' = H$ in reaction 3).[12] Sodium hydride serves as a stoichiometric reagent that deprotonates the phosphatrane, forming hydrogen and NaCl and thus liberating the pro-azaphosphatrane catalyst. This catalyst deprotonates the acetonitrile, and the resulting solvent anion dehydrohalogenates the organic halide. The further action of sodium hydride on the procatalyst begins the cycle again. The advantage of the polymer procatalyst is that all but the organic halide starting material and the olefin product are quite insoluble in acetonitrile, thus providing for easy product isolation by simple filtration. The filtered material can also be recycled, with the addition of sodium hydride, in further dehydrohalogenations.

The second catalytic reaction to be described is the synthesis of diaryl ethers. Diaryl ether units are found in vancomycin antibiotics, the antitumor agent bouvardin, herbicides, and anti-inflammatories. They are also intermediates in the synthesis of xanthones and *p*-dibenzofurans. Although diaryl ethers can be made via the classical Ullman approach, this method requires elevated temperatures, and it is often accompanied by competitive reductive dehalogenation and homocoupling of aryl halides. Although recent improvements in the synthesis of diaryl ethers



(3)

FIGURE 6

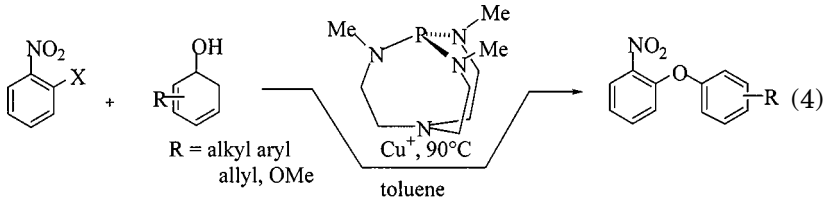


FIGURE 7

have been developed, our approach is competitive.[13] As shown in reaction 4 (depicted in Figure 7), we use two equivalents of **1a**. While this amount hardly seems a catalytic one, this pro-azaphosphatrane functions not only as a ligand for the copper(I) catalyst, but it also serves as the required base for the reaction. The reaction fails if copper(I) is absent and ^{31}P NMR studies confirm that **1a** coordinates to copper(I). Our approach gives moderate to good yields of product even with sterically hindered phenols. Advantages of our method include relatively mild conditions (90–100°) and the avoidance of prior preparation of a phenoxide.

The third reaction is the 1,2-addition of activated allyls to aromatic aldehydes.[14] As shown in reaction 5 (depicted in Figure 8), allyl esters give rise to α-addition products exclusively. In the case of allyl cyanide, however, allylic transposition occurs to give a Baylis-Hillman product in high yield with an *E*/*Z* ratio of 78/22 (reaction 6).

To our knowledge, there has been only one report in which allylic cyanides and esters of the type used here have been utilized in 1,2-addition to aldehydes.[15] The authors of that report achieved this reaction in the presence of (toxic) cadmium chloride and obtained a mixture

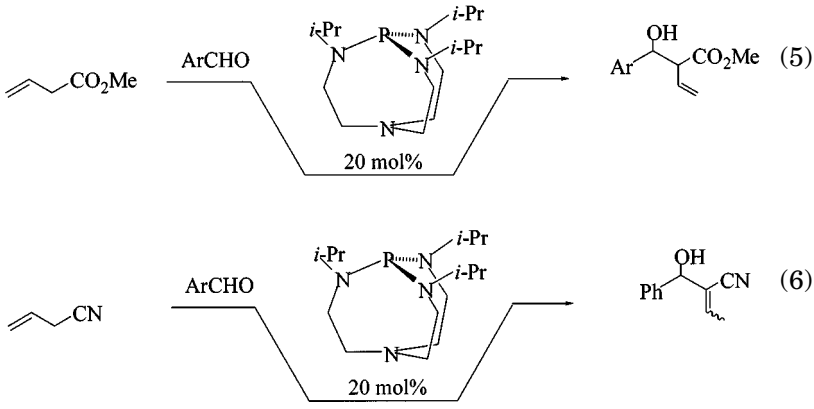
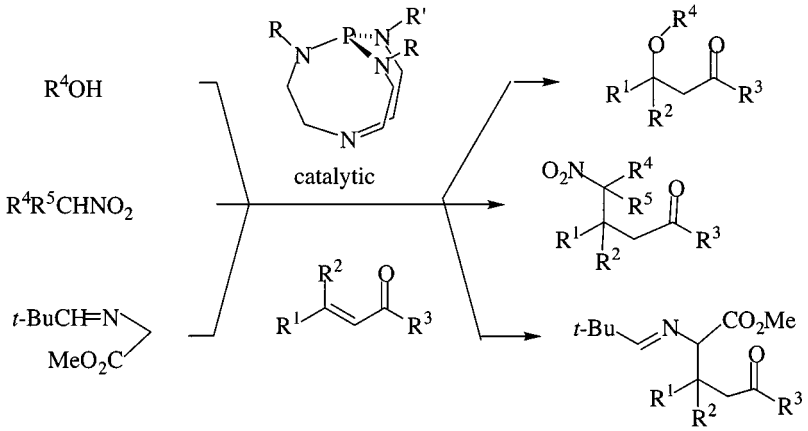


FIGURE 8

of α and γ-addition products, which contrasts out results in which exclusive α-addition is encountered. Moreover, Bayless-Hillman reactions are generally carried out at elevated pressures in the presence of an amine over long periods of time, giving unreliable results with aryl aldehydes. It is interesting to note that proazaphosphatrane **1b** is most advantageous for our reactions since **1a** and the more sterically hindered **1d** lead to low conversion.

The fourth reaction catalyzed reaction we discuss is 1,4-addition to α,β-unsaturated substrates (Scheme 3).[16] 1,4-Michael addition is one of the most effective methods for carbon–carbon bond formation. The reactions in Scheme 3 take place under mild conditions (−63 to 70°C) with bases **1a**, **1b**, or **1d** in isobutyronitrile. Our hydro alkoxylation reaction is rather unique in that no general reaction for the synthesis of beta-alkoxy ketones via Michael addition has been reported. Also, our Michael addition of nitroalkanes is superior to literature preparations using DBU or TMG.



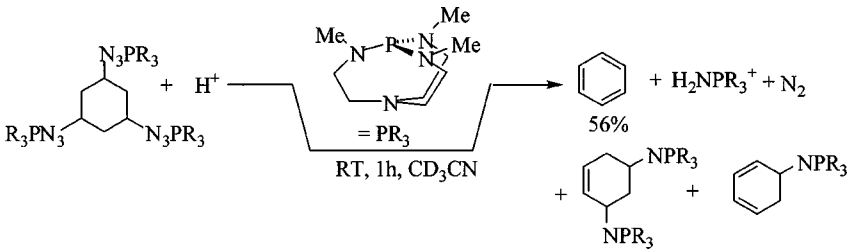
SCHEME 3

Michael additions of imines of α-amino esters have long been known as a method for functionalizing α-amino esters at the α position, although cycloaddition is a competing reaction. The ratio of Michael addition to cycloaddition product has been found to depend upon the metal ion employed to chelate the enolate produced upon deprotonation. Although the use of DBU in this reaction has been observed to give an α-functionalized α-amino ester as the exclusive product, a stoichiometric amount of LiBr is required to provide sufficient metal cation concentration for chelation.[17,18] It is worth noting that a weaker base such as triethylamine produces only the cycloadduct even in the presence of

LiBr.[19] Our imino ester addition reaction requires no metal ion, and it proceeds very cleanly.

Some Miscellaneous But Interesting and Surprising Results

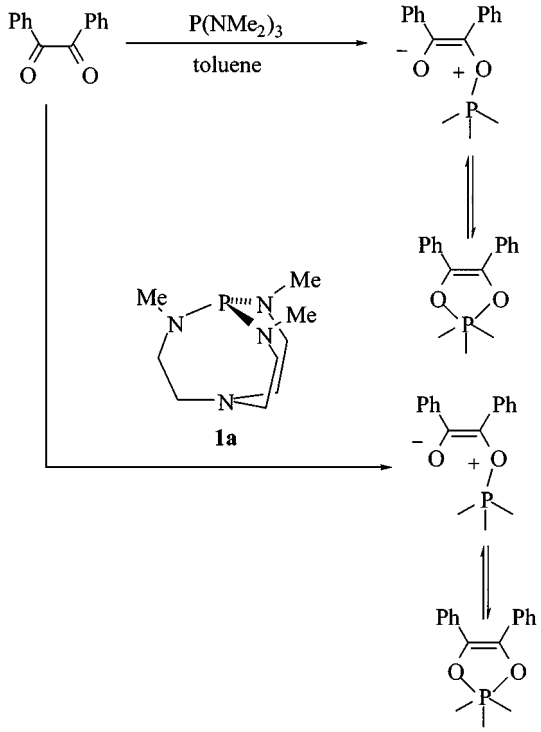
One such result is the facile formation of benzene from the cyclohexane derivative shown in Scheme 4.[20] Although this scheme represents a very expensive and inconvenient synthesis of benzene, it does contain several curious features. First, historical methods for converting cyclohexane derivatives to benzenes require harsh conditions (*ca* 400°C in the presence of zeolites and up to 900°C using precious metal catalysts). Our reaction occurs at room temperature and below. Secondly, the triazido starting material is exceedingly stable, withstanding detectable decomposition in refluxing toluene or after heating at 100°C in vacuum for hours. Thirdly, low temperature ^{31}P NMR experiments show that the bicyclic PR_3 moriety in the starting material transannulates upon protonation.



SCHEME 4

These and other observations strongly suggest the following. The starting material is prevented from undergoing the expected thermal decomposition to the corresponding tri-imido derivative (with the evolution of nitrogen), owing to steric protection afforded by the cyclohexane moiety and the electron rich character of the bicyclic proazaphosphatrane. Protonation of the starting material leads to a transannulated azaphosphatrane moiety that functions as an excellent leaving group, taking with it a proton from the cyclohexane ring to form $H_2NPR_3^+$ with concomitant evolution of dinitrogen. If at this point one of the two azidophosphorane substituents remaining on the ring is not protonated before thermal decomposition to an iminophosphorane substituent occurs, the cyclohexene and the cyclohexadiene molecules shown become possible products that can be formed sequentially.

A second interesting result concerns the observation we made while comparing the reactions of **1a** and of $P(NMe_2)_3$ with benzophenone.[20] It has long been known that the solution equilibrium involving $P(NMe_2)_3$ shown in Scheme 5 occurs. Not surprisingly, we could detect the solution equilibrium shown for **1a** in this scheme by ^{31}P NMR spectroscopy. Crystals obtained from our solution were the zwitterion, i.e., form, which was confirmed by X-ray means. Whereas the pentacoordinate species containing the $P(NMe_2)_3$ moiety can easily form a trigonal bipyramid in the solid state (as shown by X-ray crystallography), **1a** is apparently too sterically congested and too rigid to do so, and thus it prefers to stabilize a four-coordinate phosphorus by forming a zwitterion.



SCHEME 5

Last but not least is our observation that **1a** and **1b** are the first phosphines reported to be capable of cleaving carbon-fluorine bonds.[22] The results of this investigation are described in a poster being presented at this meeting (see *Poster Abstracts* in this journal).

ACKNOWLEDGMENTS

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REFERENCES

[1] J. G. Verkade, *Acc. Chem. Res*., **26,** 483 (1993).
[2] J. G. Verkade, *Coord. Chem. Rev*., **137,** 233 (1994).
[3] P. Kisanga, J. G. Verkade, and R. Schwesinger, *J. Org. Chem*., **65,** 5431 (2000).
[4] L. Nyulászi, T. Veszpremi, B. A. D'Sa, and J. G. Verkade, *Inorg. Chem*., **35,** 6102 (1996).
[5] Z. Wang and J. G. Verkade, *Tetrahedron Lett*., **39,** 9331 (1998).
[6] Z. Wang and J. G. Verkade, *J. Org. Chem*., **66,** 3521 (2001).
[7] E. Vedejs, C. F. Marth, and R. J. Ruggeri, *J. Am. Chem. Soc*., **110,** 39 (1988).
[8] X. Liu and J. G. Verkade, *J. Org. Chem*., **65,** 4560 (2000).
[9] P. B. Kisanga, B. D'Sa, X. Fei, and J. G. Verkade, *Tetrahedron*, in press.
[10] X. Liu, P. Ilankumaran, I. Guzei, and J. G. Verkade, *J. Org. Chem*., **65,** 701 (2000).
[11] X. Liu, Z. Yu, and J. G. Verkade, *J. Org. Chem*., **64,** 4840 (1999).
[12] S. Arumugam and J. G. Verkade, *J. Org. Chem.*, **62,** 4827 (1997).
[13] M. Nagarajan and J. G. Verkade, submitted.
[14] P. Kisanga and J. G. Verakde, ms in progress.
[15] L. Bo and A. G. Fallis, *Tetrahedron Lett*., **27,** 5193 (1986).
[16] P. Kisanga, P. Ilankumaran, and J. G. Verkade, submitted.
[17] H. Yamamoto, S. Kanemasa, and E. Wada, *Bull. Chem. Soc. Jpn*., **64,** 2739 (1991).
[18] S. Kanemasa, O. Uchida, and E. Wada, *J. Org. Chem*., **55,** 4411 (1990).
[19] O. Tsuge, S. Kanemasa, and M. Yoshioba, *J. Org. Chem*., **53,** 1384 (1988).
[20] X. Liu, G. Zhang, and J. G. Verkade, *Tetrahedron Lett*., **42,** 4449 (2001).
[21] J. Yang and J. G. Verkade, ms in progress.
[22] X. Liu, J. M. Hernandez, I. Guzei, P. McLaughlin, and J. G. Verkade, ms in progress.