

## Synthetic utilization of highly stereoselective conjugate addition reactions of phosphorus and sulfur stabilized allylic carbanions

Richard Freeman, Richard K. Haynes,\* Wendy A. Loughlin, Craig Mitchell, and John V. Stokes.

Department of Organic Chemistry, University of Sydney, N.S.W. 2006, Australia.

### Abstract

The completely stereoselective formation of a syn vinylic phosphine oxide from the conjugate addition of lithiated (*E*)-butenyldiphenylphosphine oxide to cyclopentenone has been extended to enantiomerically pure (*S*)-*tert*-butyl-(*E*)-but-2-enylphenylphosphine oxide to provide enantiomerically pure conjugate addition products with cyclic enones. A completely new preparation of the enantiomerically pure phosphine oxide, and exploitation of the conjugate addition reaction of the lithiated reagent with 2-methylcyclopent-2-enone in the synthesis of a vitamin D precursor is described. A novel NMR assay method for determining enantiomeric purity of the phosphine oxide is also described.

Lithiated reagents derived from butenyl sulfoxides and phosphine oxides as revealed by X-ray crystallographic and other studies of related reagents are best considered as structural analogues of ester or ketone enolates; that is, they are planar, or near planar at C1, and possess O-Li contacts (Fig. 1).<sup>1</sup>

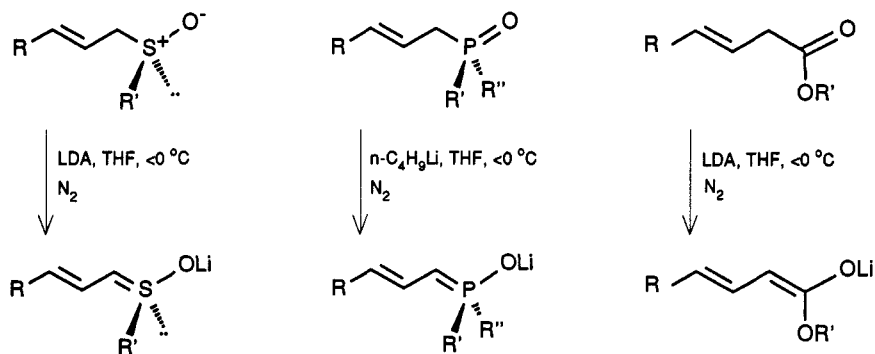


Fig 1. Lithiated reagents from allylic sulfoxides, phosphine oxides and esters.

Reactions of the first two classes of reagents with cyclic enones are rapid, high yielding, and completely stereoselective in providing vinylic sulfoxides and phosphine oxides arising from reaction through C3 of the lithiated system.<sup>2</sup> Examples of the reactions involving racemic (*E*)- and (*Z*)-lithiated allylic sulfoxides with a racemic enone are presented in Fig. 2. These particular examples are remarkable; the result implies a complete mutual kinetic enantioselection - each enantiomer reacts

with a single enantiomer of the enone.<sup>3</sup> This family of reactions have been thoroughly studied, and all known features are completely accounted for through assumption of a ten-membered transition state referred to as 'trans-decyl'-like, or 'trans-fused chair-chair'-like for the lithiated reagents derived from 3-alkylallylic sulfoxides and phosphine oxides (Fig 2).

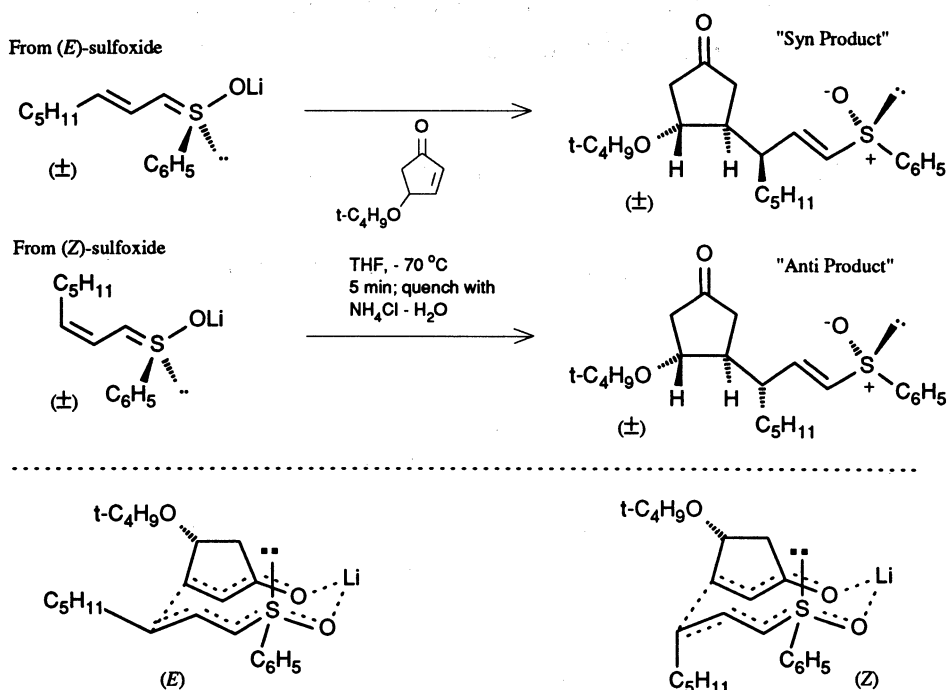


Fig. 2 Reactions of Lithiated (*E*)- and (*Z*)-Allylic Sulfoxides, and Transition State representations.

The planar lithiated reagent adopts an endo preference with respect to the enone, and chelation between Li<sup>+</sup>, the sulfoxide and carbonyl oxygens directs reaction through C3 of each reactant. HOMO-LUMO interactions between the lithiated reagent and the enone are likely to be important, and are invoked to explain the subtly different reactivity of lithiated sulfones vis-à-vis the lithiated sulfoxides.<sup>4</sup> Note also that the enone is constrained to react as an *s*-trans system. For conformationally mobile acyclic enones, other products corresponding to reactions via conventional six-membered transition states involving *s*-cis enones are obtained.<sup>5</sup>

The concise stereochemical control exerted by the polar heteroatom group clearly lends itself to exploitation in synthesis. One obvious application is in the preparation of CD-precursors of the clinically-important 1,25-dihydroxyvitamin D<sub>3</sub> and analogues. In a model study, we prepared a racemic hydrindenone precursor bearing a functional group at C7 from lithiated (*E*)-butenyldiphenylphosphine oxide and 2-methylcyclopentenone which nicely illustrates the value of the reactions.<sup>6</sup> We were now ready to select enantiomerically pure targets through commencing with an enantiomerically pure lithiated phosphine oxide. The overall strategy is illustrated in Fig. 3. Conjugate addition of the lithiated phosphine oxide will under the aprotic conditions generate a specific enolate amenable to trapping with a methyl vinyl ketone equivalent. Whilst use of methyl vinyl ketone under aprotic conditions is rarely successful, we have already developed highly effective reagents for this purpose;<sup>6,7</sup> one variant will be described further below.

The conjugate addition-enolate trapping will set up the correct stereochemistry at *three centers in one chemical operation*. The enantiomerically pure phosphine oxide must both possess exclusively the (*E*)-configuration, and bear non-allylic substituents R and R' which ensure that addition takes place exclusively at the desired, *si* face of the enone (Fig. 3). Any leakage into the *re* face mode

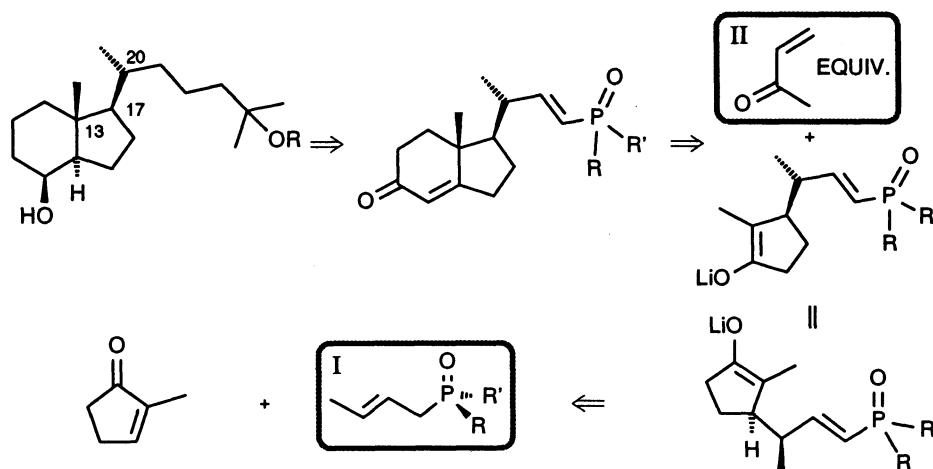


Fig. 3 Antithetic Analysis for Preparation of a CD-Precursor of Vitamin D

of addition will generate a diastereomer. Thus the lithiated phosphine oxide must possess an R group which becomes *pseudoequatorial*, and an R' group which becomes *pseudoaxial* in the extended TS. That is, R must be substantially larger than R'. Clearly, the ideal substrates in this regard are not phosphine oxides, but rather sulfoxides, which have a pseudoaxial lone pair (*cf.* Fig 2) in the TS. However, these substrates are considerably less satisfactory from an overall synthetic viewpoint, and in order to preclude facile epimerization of such substrates via [2,3]-sigmatropic rearrangement, an over-elaborate non-allylic substituent must be used.<sup>8</sup> However, the very first phosphine oxide we examined, racemic (*E*)-but-2-enyl-*tert*-butylphenylphosphine oxide, upon lithiation reacted cleanly with cyclopentenone to deliver the conjugate adduct as a single diastereoisomer. Consequently, we embarked upon a program to synthesize the requisite (*S*)(*E*)-but-2-enyl-*tert*-butylphenylphosphine oxide as dictated by the foregoing considerations and the representation in Fig. 4.

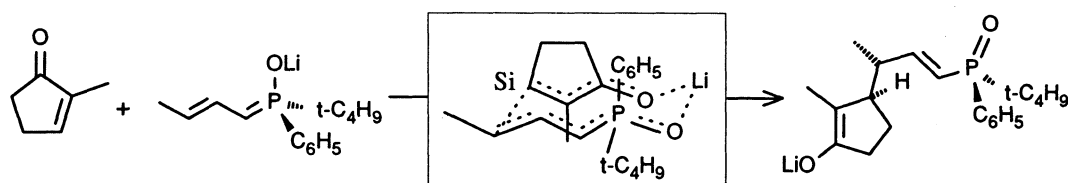


Fig. 4 TS for Lithiated (*S*)(*E*)-but-2-enyl-*tert*-butylphenylphosphine Oxide

We developed a relatively straightforward route based on the lithiation of the known (*S*)- and (*R*)-*tert*-butylmethylphenylphosphine oxide<sup>9</sup> and sequential treatment of the reagent with  $\text{BF}_3$  etherate and propylene oxide. The resulting diastereomeric mixture of alcohols was then dehydrated with camphorsulfonic acid in toluene to provide the requisite (*S*)-(+)- and (*R*)-(-)-phenyl-(*E*)-but-2-enyl-*tert*-butylphosphine oxide which was separated by chromatography from a small amount of the 3-butenyl isomer.<sup>10</sup> Whilst the preparations work reasonably well on a small scale, there is an



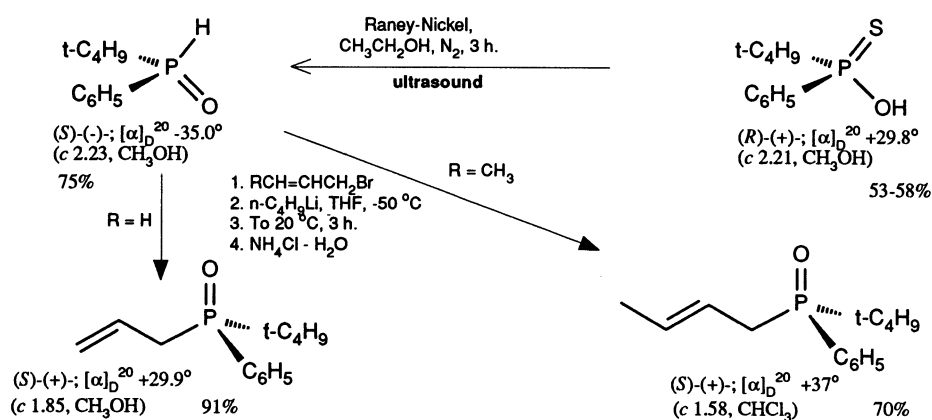
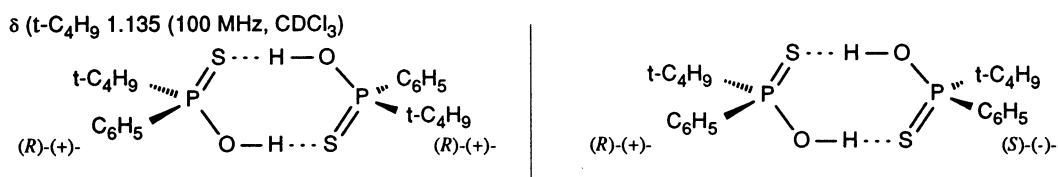


Fig. 6 Preparation of Allyl and Butenyl Phosphine Oxides

$(R)\text{-}(+)\text{-}\alpha\text{-methylbenzylamine}$  in the initial resolution step, access to the other enantiomers is assured. This work is underway in our laboratory at the present time.

The NMR assay method is based on the observation that whereas the optically pure  $(R)\text{-}(+)\text{-phosphinothioic acid}$  presents one signal for the *tert*-butyl group in its  $^1\text{H}$  NMR spectrum, admixture with the other enantiomer produces two signals up to the limiting case of a racemic mixture, which presents one signal.<sup>13</sup> The signal intensities directly reflect the enantiomer ratios. In a mixture enriched in the  $(R)$ -enantiomer, each of the  $(R)$ - and  $(S)$ -enantiomers will be preferentially 'solvated' by  $(R)$ -enantiomers, and thus net chemical shifts of protons in each enantiomer will differ (Fig. 7).



For mixture containing 80%  $(R)$ -enantiomer, minor  $[(S)\text{-}]$  enantiomer is more likely to be associated with  $(R)$ -enantiomer. Two signals, at  $\delta$  1.120, and at 1.080 are observed, with intensity ratio 80:20.<sup>13</sup>

Fig. 7 Determination of Enantiomeric Purity

Although association via hydrogen bonding is depicted in Fig 7, it must be emphasized that this is *not* a necessary condition for imprinting different net chemical shifts. It stands to reason that the chemical shift for say the *tert*-butyl group in the racemic mixture will be different to that of the pure enantiomer. Thus, at 600 MHz, it was possible to assay in very straightforward fashion the enantiomeric purity of the phosphinothioic acid. Further, after addition of an equivalent amount of the  $(R)$ -phosphinothioic acid to either the allyl or butenyl phosphine oxides of Fig. 6, enantiomeric purities were very easily assayed through inspection of the vinyl or *tert*-butyl signals. The individual enantiomers of the allyl and butenyl phosphine oxide, being 'solvated' by just the one enantiomer of the phosphinothioic acid, now display different proton chemical shifts. For racemic mixtures of the allyl phosphine oxide, the individual enantiomers at 600 MHz displayed clear baseline separation of the vinylic and *tert*-butyl signals. At the time of preparation of this manuscript (in Switzerland), diagrams and figures were not available from Australia, but have been given with the oral presentation of this paper at the ICHAC-3

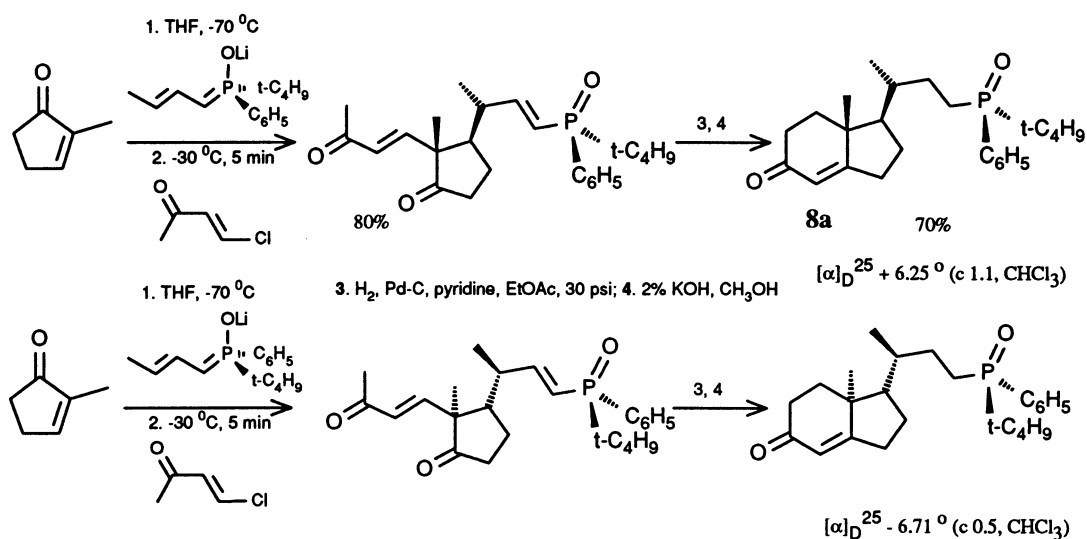


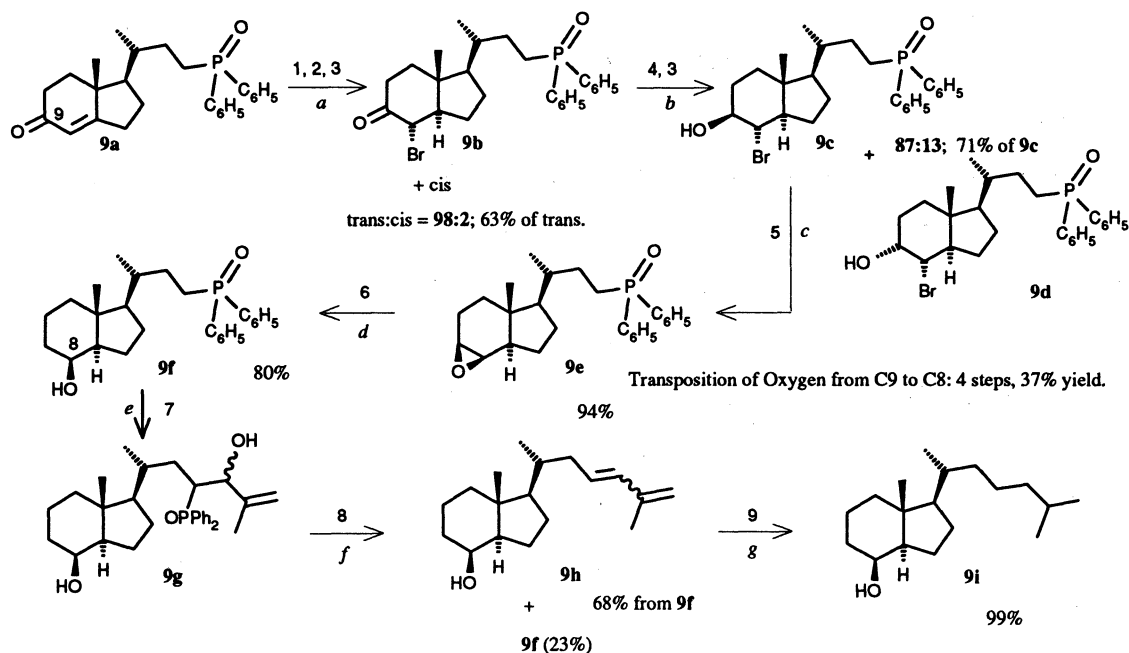
Fig. 8 Preparation of Optically Active Hydrindenones.

Conference. These are available on request from Sydney. This non-destructive enantiomer assay method is particularly attractive, especially as it employs the phosphinothioic acid intermediate required for the preparation of the target phosphine oxides. Its application to assay of chiral, non-racemic alcohols, ketones and carboxylic acids is obvious.

The synthesis of the hydrindenone and its enantiomer in Fig. 8 from the butenyl phosphine oxide enantiomers was completed as described recently,<sup>10</sup> and requires no further comment. The use of the  $\beta$ -chlorovinyl ketone as an enolate trapping agent in conjunction with an ensuing hydrogen step is noteworthy, and probably represents the most efficient operational equivalent of MVK yet developed.

In order to convert the hydrindenone **8a** of Fig. 8 into the CD precursor of Fig. 3, transposition of oxygen from C9 to C8 (steroid numbering), installation of the trans ring fusion, and chain extension according to Wittig-Horner technology are required. The exploratory nature of the sequence demanded initial use of the racemic hydrindenone **9a**. This was prepared in 8-10 g lots in yields greater than 80% via conjugate addition of lithiated (*E*)-but-2-enyldiphenylphosphine oxide to 2-methylcyclopentenone followed by enolate trapping with  $\beta$ -chlorovinyl methyl ketone. Subsequent transformations are as indicated in Fig. 9 overleaf. The conjugate reduction - enolate trapping (step *a*) is effected by means of a new soluble reagent combination based on DIBAL and an alkylcopper derived from Cu(I) cyanide. In previous cases, insoluble reagents derived from copper(I) iodide, which required the use of HMPA, were used. The oxygen transposition is an adaptation of known methodology, and provides the most concise means of effecting this difficult transformation.<sup>15</sup> The chain extension follows our previous method.<sup>6</sup> The strategic location of the phosphine oxide group for employment of the Horner-Wittig reaction is noteworthy. Nevertheless, the formation of relatively large amounts of dissociation product **9a** during the second stage of this reaction (step *f*) is problematical. It is anticipated that with the substrates derived from the *tert*-butylphenylphosphine oxides, this step should become less important in line with lower stability of the anionic phosphine oxide intermediate.

In summary, the sequences outlined herein represent one efficient utilization of a family of



1 ( $i\text{-C}_4\text{H}_9$ )<sub>2</sub>AlH - C<sub>4</sub>H<sub>9</sub>Li - CuCN (2:1:1), THF, -50 - -20 °C; 2 Br<sub>2</sub>; 3 NH<sub>4</sub>Cl - H<sub>2</sub>O; 4 LiAlH<sub>4</sub>, ether, -20 °C; 5 NaH - DMF, 20 °C  
5 ( $i\text{-C}_4\text{H}_9$ )<sub>2</sub>AlH, CH<sub>2</sub>Cl<sub>2</sub>, reflux; 7 a C<sub>4</sub>H<sub>9</sub>Li, THF, -20 °C, b methacrolein, -90 - -20 °C; 8 NaH - DMF, 70 °C; 9 H<sub>2</sub>, Pd - C, EtOAc

Fig. 9 Exploratory Preparation of a Model CD Precursor

disastereoselective aprotic conjugate addition reactions involving heteroatom-stabilized lithiated allylic anions. The challenge is render the sequences capable of providing enantiomerically pure products. The development of a relatively easy route to (*S*)- and (*R*)-*tert*-butylmethylphenylphosphine oxides now provides us with the wherewithal to answer the challenge.

#### Acknowledgements

We thank the Australian Research Grants Scheme for support of this work.

#### REFERENCES

1. Boche, G. *Angew. Chem. Internat. Ed. Engl.* **1989**, *28*, 277, and references therein; Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403.
2. Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 5411; Binns, M. R.; Hambley, T. W.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 5423.
3. For an excellent review of our reactions, see Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227.
4. Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Org. Chem.* **1989**, *54*, 1960.
5. Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Vonwiller, S. C. *Aust. J. Chem.* **1989**, *42*, 1671; Haynes, R. K.; Katsifis, A. G.; Vonwiller, S. C. *Aust. J. Chem.* **1989**, *42*, 1785.

6. Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1987**, 92; Haynes, R. K.; Vonwiller, S. C. *J. Org. Chem.* **1989**, 54, 5162.
7. Haynes, R. K.; King, L. M.; Stokes, J. P.; Vonwiller, S. C. *Aust. J. Chem.* **1988**, 41, 881.
8. Goodridge, R. J.; Hambley, T. W.; Haynes, R. K.; Ridley, D. D. *J. Org. Chem.* **1988**, 53, 2881.
9. Imamoto, T.; Sato, K.; Johnson, C. R. *Tetrahedron Lett.* **1985**, 26, 783.
10. Haynes, R. K.; Stokes, J. P.; Hambley, T. W. *J. Chem. Soc., Chem. Commun.* **1991**, 58.
11. Skrzypczynski, Z.; Michalski, J. *J. Org. Chem.* **1988**, 53, 4549.
12. Michalski, J.; Skrzypczynski, Z. *J. Organomet. Chem. C* **1975**, 97, C31.
13. Harger, M. J. P. *J. Chem. Soc., Perkin Trans. II*, **1978**, 326.
14. Tsuda, A.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, 51, 537.
15. Daniewski, A. R.; Kiegel, J. *Synth. Commun.* **1988**, 18, 115; Daniewski, A. R.; Kiegel, J. *J. Org. Chem.* **1988**, 53, 5534.