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Enantioselective Preparation of *P*-Chiral Phosphine Oxides

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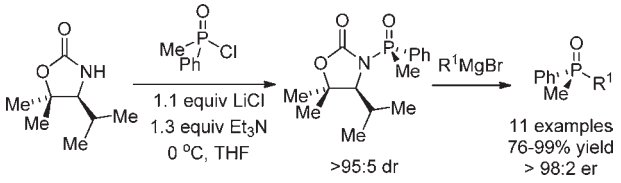
ABSTRACT



A highly efficient chiral auxiliary-based strategy for the asymmetric synthesis of *P*-chiral phosphine oxides in >98:2 er has been developed. The methodology involves the highly stereoselective formation of *P*-chiral oxazolidinones that then undergo displacement with a variety of Grignard reagents to prepare the desired phosphine oxides.

Nonsymmetrically substituted phosphorus compounds are commonplace in asymmetric synthesis, both as chiral ligands[1] and more recently as organocatalysts.[2] Despite their frequent use, the synthesis of such species still remains a challenge. Commonly employed methods often involve the formation and separation of diastereomeric mixtures of menthyl phosphinates and cyclic phosphoramidates, strategies originally developed by Mislow,[3] and Jugé and Genet,[4] respectively. More recently, such a methodology has facilitated the synthesis of *P*-chiral phosphine boranes and phosphine sulfides.[5] Further strategies toward introduction of *P*-chirality have been reviewed,[6] with representative methods including enantioselective deprotonation of phosphine-boranes and sulfides,[7] enzymatic resolution,[8] organometallic mediated transformations,[9] and most recently through an asymmetric oxidation of racemic phosphines under Appel conditions.[10]

As part of the need to synthesize a series of chiral phosphine oxides, the compatibility of Mislow's menthyl phosphinate with a range of Grignard reagents was

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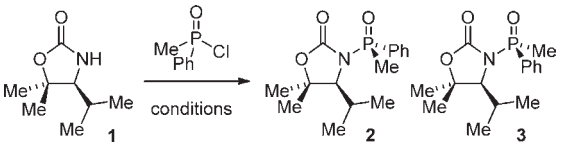
examined. Application of the reported conditions gave essentially no diastereoselectivity in the addition of methyl phenyl phosphinoyl chloride to menthol, followed by time-consuming and low-yielding separation of these isomers by iterative fractional crystallization. Subsequent nucleophilic displacement with an organometallic reagent required long reaction times at elevated temperatures and led to poor overall yields of the desired target (< 10% over two steps). Application of a similar strategy noted by Hii and co-workers using 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose (DCG)[11] gave an improvement in the diastereoselectivity (93:7 dr) in reasonable yield (84% of a single isolated diastereoisomer), but essentially no reactivity with organometallic reagents other than vinyl magnesium bromide as reported in their work.

Recent studies from our laboratories exploring the chemistry of *N*-phosphoryl oxazolidinones highlighted the reaction of an oxazolidinone with racemic ethyl(methyl)-chloro phosphate, albeit with poor diastereoselectivity, and the subsequent displacement with a magnesium alkoxide.[12] Although no chemistry has been reported on the reactions of oxazolidinones with phosphinoyl chlorides or their subsequent reaction with organometallic reagents, we investigated this as a possible route to access the desired *P*-chiral phosphine oxides.

Deprotonation of the oxazolidinone **1** with *n*-BuLi at −78 °C followed by addition of methylphenylphosphinoyl chloride gave limited conversion to a diastereomeric mixture of the desired *N*-phosphinoyl oxazolidinones **2** and **3**, with the major product identified as *n*-butylmethylphenyl phosphine oxide, derived from attack of unreacted *n*-BuLi with the phosphinic chloride (Table 1, entry 1). Warming the reaction to 0 °C still gave low conversion; however, changing the base to the less nucleophilic LiHMDS resulted in complete conversion of the oxazolidinone **1**, providing products **2** and **3** in a diastereomeric ratio of 83:17 in favor of **2** (Table 1, entry 3). The use of MeMgBr increased the diastereoselectivity further but with a significant drop in the conversion to product (Table 1, entry 4). However, use of lithium chloride and triethylamine originally reported by Ho and Mathre[13] gave complete conversion to the *N*-phosphinoyl oxazolidinone in excellent diastereoselectivity and good yield after isolation of the major diastereoisomer by column chromatography (Table 1, entry 5). This process can be been conducted on a 2 g scale with no significant loss in yield or selectivity. No formation of the *N*-phosphinoyl oxazolidinones was observed using either LiCl or Et_3N in isolation, confirming the synergistic nature of these reagents. The absolute configuration of the major diastereoisomer **2** was established by X-ray crystallography.

The isolation of the major diastereoisomer in greater than 50% yield rules out the reaction proceeding by kinetic resolution, analogous to recent reports of the synthesis of chiral sulfoxides using an Evans derived auxiliary.[14] The possibility of the reaction proceeding by dynamic kinetic resolution of the phosphinoyl chloride was also ruled out, as no change in selectivity was observed when the stoichiometry of the phosphinoyl chloride and auxiliary were altered. Thus it is highly likely that the reaction proceeds by apical attack of the oxazolidinone opposite the electronegative chlorine atom to generate two diastereomeric trigonal pyramidal intermediates (Scheme 1).[15] These intermediates undergo pseudorotation in order to avoid the steric interaction of the phenyl group with the stereodirecting group of the auxiliary. This converts the higher energy diastereoisomer into the more favored trigonal pyramidal intermediate that delivers the observed product. Experimental and computational studies to substantiate this proposal are currently in progress.

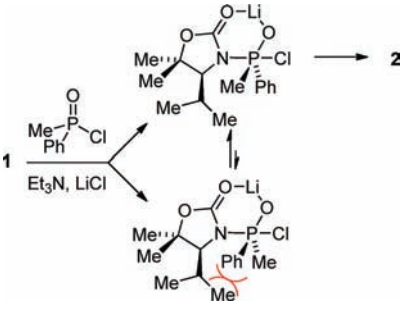
Table 1. Optimisation of the Diastereoselectivity for the Formation of *N*-Phosphinoyl Oxazolidinones **2** and **3**



entry	conditions[a]	conv (%)[b]	ratio **2**:**3**[b]	yield (%)[c]
1	1.1 equiv *n*-BuLi, −78 °C to rt	<10	ND	
2	1.1 equiv *n*-BuLi, 0 °C	<10	ND	
3	1.1 equiv LiHMDS, 0 °C	100	83:17	54
4	1.1 equiv MeMgBr, 0 °C	64	89:11	62
5	1.1 equiv LiCl, 1.3 equiv NEt_3, 0 °C	100	>95:5	74

[a] All reactions performed on a 1 mmol scale in THF (5 mL) and stirred for 18 h. [b] Determined by integration of appropriate signals in the ^1H NMR spectrum of the crude reaction material. [c] Refers to isolated diastereoisomer **2**.

Scheme 1. Proposed Model for the Diastereoselective Formation of Oxazolidinone **2**



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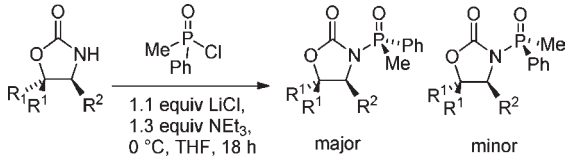
(12) Jones, S.; Selitsianos, D. *Tetrahedron: Asymmetry* **2005**, *16*, 3128–3138.
(13) Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271–2273.
(14) Liu, L.-J.; Chen, L.-J.; Li, P.; Li, X.-B.; Liu, J.-T. *J. Org. Chem.* **2011**, *76*, 4675–4681.
(15) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279–1332.

To probe the effect of the substituents upon the diastereoselectivity of the reaction, a series of 4- and 5-substituted oxazolidinones was prepared[16] and screened under the optimized conditions (Table 2). The optimum reaction time was found to be 18 h, with lower conversion being observed when left for shorter reaction times. The diastereoselectivity was good to excellent, but none surpassed that obtained with the original valine derived auxiliary.

Table 2. Effect of Varying the Oxazolidinone Substituents on the Diastereoselectivity of the *N*-Phosphinoyl Oxazolidinone Formed

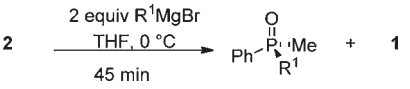


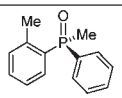
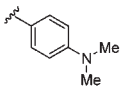
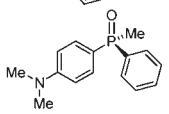
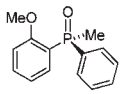
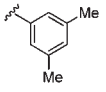
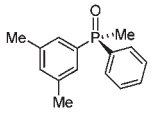
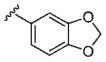
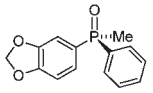
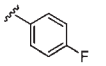
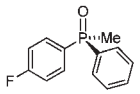
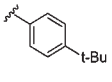
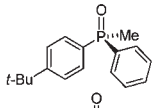
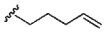
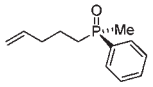
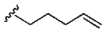
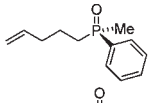
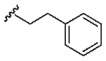
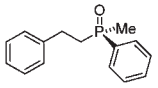
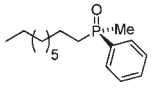
entry	R^1	R^2	conv (%)[a]	dr[b]
1	H	i-Pr	100	88:12
2	Me	Me	100	90:10
3	H	Me	100	81:19
4	Me	Bn	100	82:18
5	H	Bn	100	81:19

[a] All reactions performed on a 1 mmol scale in THF (5 mL) and stirred for 18 h. [b] Determined by integration of appropriate signals in the ^{1}H NMR spectrum of the crude reaction product.

Functionalized oxazolidinones are known to undergo nucleophilic attack and subsequent cleavage of the *N*-acyl bond with a multitude of oxygen,[17] sulfur,[18] nitrogen,[19] and hydride derived nucleophiles[17] but never appear to have been evaluated in reactions with carbon-based nucleophiles. Treatment of *N*-phosphinoyl oxazolidinone **2** with 2 equiv of *o*-tolyl magnesium bromide at 0 °C resulted in complete formation of the phosphine oxide after 45 min, which was then isolated in 83% yield. Use of fewer equivalents of Grignard reagent led to significantly lower yields. Analysis of the enantioselectivity of the phosphine oxide showed an er of 98:2 in favor of the (*S*)-enantiomer, with the identity being confirmed by comparison with the literature.[20] The apparent leakage in enantioselectivity was established to be due to trace quantities of minor diastereoisomer **3** by HPLC analysis in the starting material and confirms that the reaction proceeds by S_N2 (P) attack at the stereogenic phosphorus center with inversion of stereochemistry. Oxazolidinone **1** could easily be recovered from the reaction because of the significant polarity difference between it and the phosphine oxide. This represents the most efficient stereoselective method reported to date for this type of displacement. Screening of a range of aryl Grignard reagents showed that both *ortho*- and *para*-substituted aromatics were well-tolerated by the reaction, and the resulting phosphine oxides were isolated in good yield and an er of over 98:2 in favor of the major isomer (Table 3, entries 2−7). Attempts at expanding the

Table 3. Scope of the Reaction of *N*-Phosphinoyl Oxazolidinone **2** with Grignard Reagents[a]



entry	R^1	product	yield (%)[b]	er[c]
1			83	98:2
2			81	98:2
3			86	98:2
4			81	98:2
5			76	99:1
6			95	98:2
7			93	99:1
8			99	75:25
9[d]			99	99:1
10[d]			99	99:1
11[d]			65	99:1
12[d]			76	99:1

[a] All reactions performed on a 1 mmol scale in THF (5 mL) and stirred for 45 min. [b] Refers to isolated product. [c] Determined by chiral phase HPLC analysis. [d] Reaction performed by dropwise addition of a solution of *N*-phosphinoyl oxazolidinone **2** to Grignard reagent.

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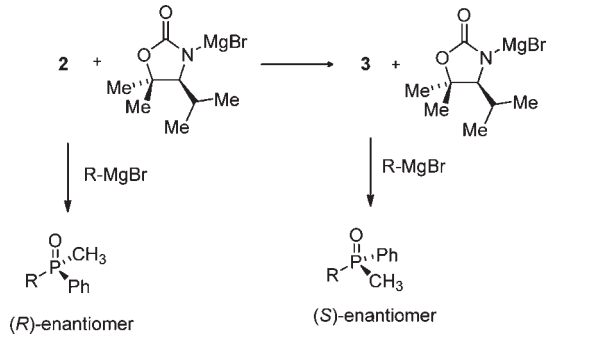
(20) Chodkiewicz, W.; Jore, D.; Pierrat, A.; Wodzki, W. *J. Organomet. Chem.* **1979**, *174*, C21–C23.

methodology toward aliphatic Grignard reagents initially proved troublesome with a noticeable decrease in er, for example, in the addition of pent-4-enylmagnesium bromide (Table 3, entry 8). With aliphatic Grignard reagents, it was envisaged that the *N*-phosphinoyl oxazolidinone **2** may undergo nucleophilic substitution by the metalated oxazolidinone byproduct, resulting in inversion of stereochemistry at the phosphorus center, analogous to that proposed by Liu.[14] Subsequent nucleophilic attack of the Grignard reagent would result in formation of the opposite enantiomer of phosphine oxide (Scheme 2).

Scheme 2. Proposed Racemisation Pathway for Reaction with Alkyl Grignard Reagents



A control experiment involving reaction of a 5,5 di-*n*-butyl oxazolidinone with *N*-phosphinoyl oxazolidinone **2** in the presence of methylmagnesium bromide gave the expected crossover products by LC−MS, confirming this reaction pathway. This unwanted process could be minimized by introduction of the *N*-phosphinoyl oxazolidinone **2** dropwise to a solution of excess Grignard reagent (Table 3, entry 9). Gratifyingly, under these conditions no racemisation was observed, and the resulting phosphine oxide was obtained with an excellent er.

In conclusion, a range of diaryl-methyl and alkyl-methylphenyl chiral phosphine oxides have been synthesized quickly under mild conditions in good yield and excellent enantioselectivity using the *N*-phosphinoyl oxazolidinone derived from L-valine and methylphenyl phosphinic chloride. Further studies into the origin of the stereoselectivity, expanding the methodology to encompass the synthesis of phosphine sulfides and boranes and diversifying the scope of both the Grignard reagent and phosphinic chloride used are in progress and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data and spectra for all new compounds, and X-ray data for compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.