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Enantioselective Allylic Substitution using a Novel (Phosphino-1,3-Oxazine)Palladium Catalyst

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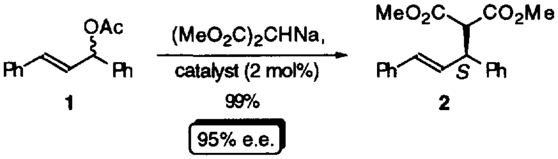
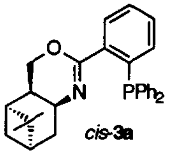
Abstract: *Treatment of 1,3-diphenyl-2-propenyl acetate **1** with the sodium salt of dimethyl malonate and the palladium complex of the phosphino-1,3-oxazine ligand* cis-***3a*** *gave the allylic substitution product **2** in 99% yield and 95% enantiomeric excess.* Copyright © 1996 Elsevier Science Ltd

Recent developments in the area of asymmetric catalysis have clearly demonstrated its potential for the enantioselective formation of new covalent bonds.[1] This has made the search for new asymmetric ligands an increasingly popular area of investigation. The ability to prepare new ligands permits subtle refinements that facilitate the fine-tuning of a particular catalytic system to achieve the optimal reaction conditions. Although the steric requirements for asymmetric induction are well understood, the ability to control turn-over rates remains somewhat elusive. Several groups have made significant contributions to the area of palladium catalyzed allylic alkylation.[2-4] The asymmetric ligands are generally derived from chiral pool substrates, making them very attractive starting materials for *de novo* synthesis. In a program directed at developing new ligands for asymmetric catalysis, we have prepared a series of amino alcohols from (-)-β-pinene.[5] In this paper, we report a new phosphino-1,3-oxazine ligand **3a** that shows remarkable acceleration in addition to excellent enantiomeric excess in asymmetric allylic alkylation (**Scheme 1**).

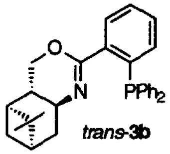
Scheme 1



A key feature of the amino alcohol derived ligand systems is that they generally incorporate 1,3-oxazolines.[2,4] We decided to investigate the complementary 1,3-oxazines as potential ligands. This would also provide additional information on the role of conformation in ligand design, and might lead to further insight into the origin of asymmetric induction. The less planar conformation of the six-membered ring provides an additional variable for the transition state which may facilitate the optimization of a particular transformation. The phosphino-1,3-oxazine ligands **3a/b**, readily available from (-)-β-pinene, were designed to incorporate the key topological features that have proven reliable in related systems for achieving asymmetric induction. (-)-β-pinene is readily available in either enantiomer, and it was anticipated that this would serve as a versatile carbocyclic template for conversion into an array of structurally and stereochemically related ligand systems.



cis-**3a**



trans-**3b**

Our initial efforts were focused on providing a direct comparison of the *cis*- and *trans*-1,3-oxazine ligands **3a/b** with the 1,3-oxazolines and related ligand systems.[2-4] **Table 1** summarizes our efforts with 1,3-diphenyl-2-propenyl acetate **1** which has become the prototypical system in which to assay this type of reaction. Treatment of 1,3-diphenyl-2-propenyl acetate **1** with dimethyl malonate sodium salt and 5 mol% of the palladium complex of the *cis*-phosphino(1,3-oxazine) **3a** furnished the allylic substitution product **2** in 94% yield and in 95% enantiomeric excess (Table 1, Entry 1). However, the *trans*-phosphino(1,3-oxazine) **3b** under analogous reaction conditions gave only modest enantiomeric induction (Entry 2).

Efforts were then concentrated on optimizing the reaction with the *cis*-phosphino(1,3-oxazine) **3a**. Initial experiments were directed at examining the effect of temperature using a reduced amount of the catalyst (Entries 3, 4 and 5). Although, the optimum enantiomeric excess was obtained at –20 °C (Entry 5), the reaction failed to go to completion. However, when the amount of catalyst was increased to 5 mol% the reaction was again complete within 5 minutes with a comparable enantiomeric excess (Entry 1 *vs* 6). In order to conserve the amount of catalyst necessary to effect the reaction, the transformation was optimized using 2 mol% of the catalyst and the effect of solvent examined in which dichloromethane proved optimum in terms of the turn-over rate (Entries 7 and 8). Previous studies had demonstrated the nature of the counter ion to be important to the enantioselectivity (Li > Na > K). However, treatment of the allylic acetate **1** with the lithium salt of dimethyl malonate at 0 °C gave the allylic substitution product **2** in an analogous enantiomeric excess (Entry 9). Therefore, it appears that the catalyst affords the product in high yield and enantiomeric excess under a wide range of reaction conditions.

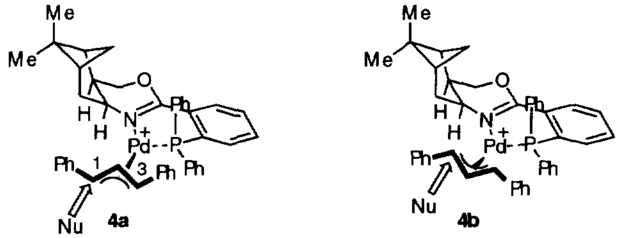
The turn-over rate for both catalysts is particularly noteworthy. A comparison of the 1,3-oxazine ligands with the corresponding 1,3-oxazolines, under analogous conditions, indicates the former to have superior turnover rate which may be a significant practical advantage.[4e] The palladium complex of both *cis*-**3a** and *trans*-**3b** gave products of *S*-absolute configuration, in accordance with the model proposed by Helmchen and others[7] for the 1,3-oxazoline ligands. This model proposes that trapping of the π-allyl species occurs opposite to the phosphine, as its superior π-accepting properties makes C-1 of the allylic acetate electron deficient (**Fig. 1**). Therefore, based on this analysis, **4a** rather than **4b** would be the transition state responsible for the product.

Table 1: Allylic Alkylation of 1,3-Diphenyl-2-Propenyl Acetate **1** with Dimethyl Malonate Alkali Metal Salt

Entry	Ligand[a]	Mol % Cat.[b]	Alkali Metal	Solvent	Temp.	Time	Yield (%)[c]	% e.e.[d,e]
1	**3a**	5	Na	THF	0 °C	5 min.	94	95
2	**3b**	5	"	"	"	5 min.	97	64
3	**3a**	2	"	"	RT	30 min.	96	91
4	"	2	"	"	0 °C	5 hrs 20 min.	94	91
5	"	2	"	"	−20 °C	4 hrs 30 min.	52	95
6	"	5	"	"	"	5 min.	96	95
7	"	2	"	MeCN	0 °C to RT	3 hrs	89	95
8	***3a***	***2***	***Na***	CH_2Cl_2	***0 °C***	***40 min.***	***99***	***95***[6]
9	"	3	Li	THF	0 °C	2 hrs 30 min.	95	95

[a] Reactions were all carried out on a 0.5 mmol reaction scale with 2 equivalents of the dimethyl malonate alkali metal. [b] Catalyst was preformed from $[Pd(\eta^3\text{-}C_3H_5)Cl_2]_2$ and the ligand (Ratio: 1 : 2). [c] Isolated yields. [d] Enantiomeric excess was determined by 400 MHz ^1H NMR ($CDCl_3$) using the shift reagent (+)-Eu(hfc)$_3$. [e] The (*S*)-enantiomer was obtained in each reaction.

Figure 1



4a *Favored TS*

4b *Disfavored TS*

In conclusion, we have developed a new ligand for asymmetric allylic substitution. The ability to modify the 1,3-oxazine and the phosphino moiety should facilitate the fine-tuning necessary in more demanding systems. We are actively continuing our efforts with further synthetic applications of these novel ligands to a variety of transition metal catalyzed reactions.

Acknowledgments

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6. *Representative Experimental Procedure*: Dimethyl malonate (0.145 g, 1.1 mmol, 2.1 eq.) was dissolved in anhydrous dichloromethane (2 ml) and cooled with stirring to 0 °C. Sodium hydride (0.042 g, 1.06 mmol, 2 eq) was then added portionwise and the anion was allowed to form over *ca.* 30 minutes. The catalyst was preformed by dissolving $[Pd(\eta^3\text{-}C_3H_5)Cl_2]_2$ (2.1 mg, 5.7 μmol, 1 mol%) and the *cis*-phosphino-1,3-oxazine **3a** (9.9 mg, 22.5 μmol, 4 mol%) in dichloromethane (1 mL) and the mixture stirred at room temperature for *ca.* 40 minutes. The allylic acetate **1** (0.133 g, 0.53 mmol) in dichloromethane (0.5 ml and 2 x 0.25 ml rinse) was then added dropwise *via* Teflon® cannula to the sodium salt of dimethyl malonate, followed by a solution of the catalyst and the bright yellow solution stirred at 0 °C for *ca.* 40 minutes (TLC control). The brownish yellow reaction mixture was then poured into 1N aqueous NaOH and extracted with dichloromethane. The combined organic phases was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 7-20% gradient of ethyl acetate/hexane) gave the allylic alkylation product **2** (0.169 g, 99%) as a colorless oil.
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