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Synthesis of a novel spiro-phosphino-oxazine ligand and its application to Pd-catalyzed asymmetric allylic alkylation

Susan M. Lait, Masood Parvez and Brian A. Keay*

Department of Chemistry, University of Calgary, Calgary, Alta, Canada T2N 1N4

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Abstract—Spiro-phosphino-oxazine (+)-**8** is prepared from the amino alcohol (+)-**5** in two steps with an isolated yield of 90%. When used as a ligand in the Pd-catalyzed alkylation of 1,3-diphenylallyl acetate with dimethyl malonate, products having enantiomeric excesses up to 91% were obtained.

1. Introduction

A wide range of chiral phosphino-oxazoline ligands have been synthesized from 1,2-amino alcohols, many of which are readily derived from amino acids. These ligands have demonstrated their efficiency at chiral induction in many transition-metal catalyzed reactions[1] including Pd-catalyzed allylic alkylations,[2] allylic aminations,[2j,3] Heck reactions[2i,4] and Diels–Alder reactions,[5] Pt-catalyzed allylic alkylations,[6] Cu-catalyzed conjugate additions[7] and Diels–Alder reactions,[8] Rh-catalyzed hydrosilylations[9] and Ni-catalyzed Grignard cross-coupling reactions.[10]

Whereas phosphino-oxazolines are derived from 1,2-amino alcohols, phosphino-oxazines are derived from 1,3-amino alcohols, which are far less common. As such, only a few examples of phosphino-oxazines have been reported to date (Scheme 1). Of these, **1**,[11] **2a**,[12] **2b**,[12] **4a**[13] and **4b**[13] have been used in Pd-catalyzed allylic alkylations of 1,3-diphenylallyl acetate with dimethyl malonate, giving enantiomeric excesses of up to 99%, 95%, 64%, 84% and 95%, respectively. The only example that was not an allylic substitution was the use of **3b** in a Pd-catalyzed Heck reaction between phenyl triflate and 2,3-dihydrofuran, giving a product with 91% ee.[14]

As such, phosphino-oxazines have demonstrated themselves to be an effective class of ligands. Evans and Brandt[12a] also noted that **2a** and **2b** gave better turnover rates than the corresponding phosphino-oxazolines under the same reaction conditions. The main factor limiting the study of phosphino-oxazines as ligands for transition metal-catalyzed reactions appears to be a lack of variety in 1,3-amino alcohol precursors.

We recently reported the synthesis of spiro-amino alcohol **5**, which can easily be resolved to give both enantiomers in >99% ee.[15] Herein we report the synthesis of spiro-phosphino-oxazine **8**, which is the first phosphino-oxazine to contain a fused spiro system. We also report the application of this ligand to the Pd-catalyzed alkylation of 1,3-diphenylallyl acetate with dimethyl malonate.

2. Results and discussion

Phosphino-oxazine (+)-**8** was prepared in two steps from (+)-**5** and **6** (Scheme 2).[16] In an adaptation of Pfaltz's method[17] for the synthesis of phosphino-oxazolines, (+)-**5** and **6** were coupled by refluxing in chlorobenzene with $ZnCl_2$ to give (+)-**7**. Treating this adduct with 2,2′-dipyridyl removes the complexed $ZnCl_2$ giving phosphino-oxazine (+)-**8** in an isolated yield of 90%. Compound **8** proved to be not conformationally mobile at room temperature as only one set of sharp peaks was observed in the ^1H NMR spectrum. To confirm that the oxazine (+)-**7** had indeed formed, an X-ray crystal structure of (+)-**7** was obtained (Fig. 1).[18]

To begin studying the effectiveness of (+)-**8** as a chiral ligand in transition metal-catalyzed reactions, we chose to use it in the well-defined Pd-catalyzed alkylation of

* Corresponding author. E-mail: keay@ucalgary.ca

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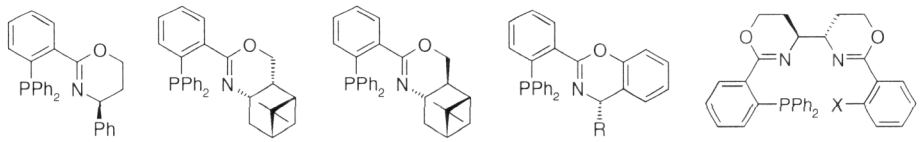
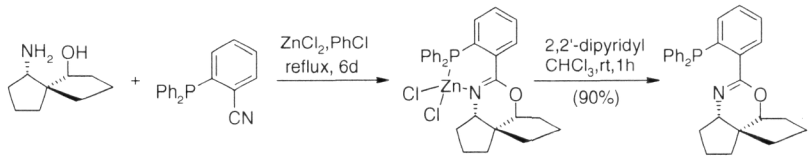


1 **2a** **2b** **3a** R=iPr **3b** R=tBu **4a** X=F **4b** X=PPh_2

Scheme 1.



(+)-5 **6** **(+)-7** **(+)-8**

Scheme 2.

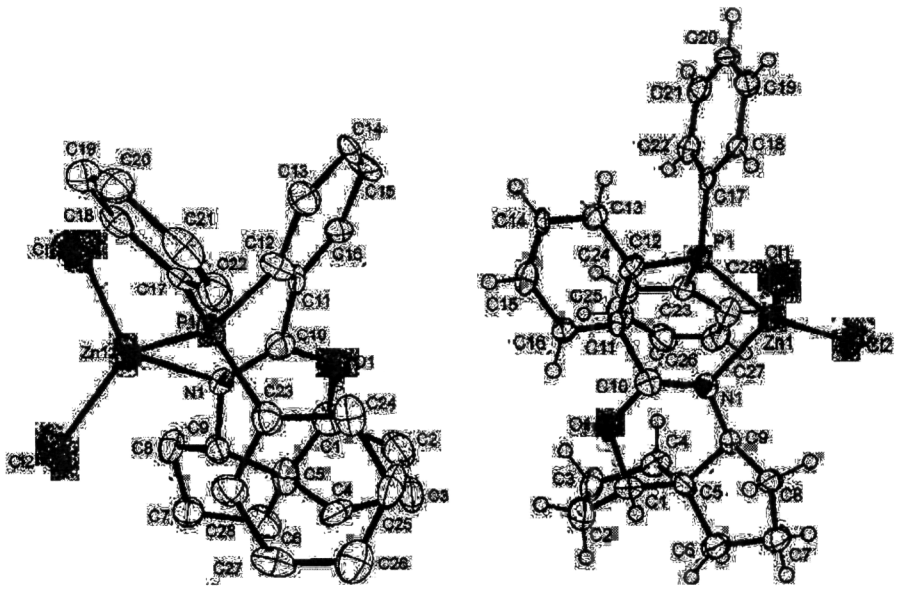
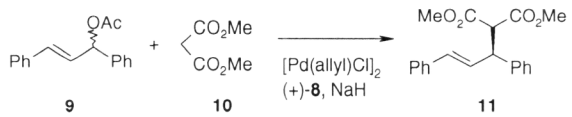


Figure 1.

1,3-diphenylallyl acetate **9** with dimethyl malonate **10** (Table 1). The results proved promising; the use of NaH as the base gave 89%ee (99% yield) and 91%ee (75% yield) in THF and DME, respectively. Several trends in reactivity and chiral induction were observed. A slight counter ion effect was observed; under otherwise identical conditions, NaH gave higher %ee and a faster reaction than KH, which in turn was better than Cs_2CO_3 (CsH was unavailable for a direct comparison; amine bases gave no reaction). It would thus be expected that the LiH would be the ideal base; however, the reactivity was significantly reduced presumably due to the incomplete formation of the malonate anion. Even after preheating the malonate and LiH together, a significant amount of bubbling was observed when eventually quenching the reaction, indicating the presence of unreacted LiH. A slight solvent effect was also observed when all other reaction conditions remained the same with the more polar solvents giving a product with a higher %ee. Unfortunately, due to a decrease in reactivity of the system in the most polar solvents (in DMF, the acetate was simply cleaved from **9**), DME proved to be the most polar solvent in which the reaction would still occur at 0 °C and thus the best solvent in terms of %ee of product.

In summary, we have synthesized the first spiro-phosphino-oxazine from spiro-1,3-amino alcohol (+)-**5**. Its application in the Pd-catalyzed allylic alkylation reaction has shown that it is capable of chiral induction,

Table 1. Pd-catalyzed allylic alkylation reactions of **9** and **10** using (+)-**8** as a chiral ligand[a]



9 **10** **11**

Base	Solvent	Temperature[b] (°C)	Duration	Yield[c] (%)	%ee[d]
LiH[e]	THF	25	48 h	62	81 (*S*)
LiH[e]	DME	25	48 h	61	85 (*S*)
NaH	CH_2Cl_2	0	4 h	96	87 (*S*)
NaH	**THF**	**0**	**30 min**	**99**	**89 (*S*)**
NaH	**DME**	**0**	**90 min**	**75**	**91 (*S*)**
NaH	1,4-Dioxane	25	1 h	78	81 (*S*)
NaH	CH_3CN	25	24 h	68	87 (*S*)
KH	CH_2Cl_2	25	48 h	86	80 (*S*)
KH	THF	0	1 h	91	87 (*S*)
KH	DME	0	90 min	62	86 (*S*)
KH	1,4-Dioxane	25	1 h	63	80 (*S*)
Cs_2CO_3	THF	25	48 h	77	81 (*S*)

[a] All reactions were performed using 2 mol% $[Pd(allyl)Cl]_2$, 4 mol% (+)-**8**, 2 equiv base, 2 equiv **10** and 1 equiv **9** in dry solvent under N_2.
[b] Reactions performed at 25 °C gave no observable reaction at 0 °C (except for reactions in 1,4-dioxane, which freezes at 11 °C).
[c] Isolated yield.
[d] %ee ±2[19] of **11** was determined by ^1H NMR (200 MHz, $CDCl_3$) with 0.3 equiv $Eu(hfc)_3$.
[e] After addition of **10** to LiH, the suspension was refluxed for 2 h then cooled to reaction temperature prior to adding **11** and the Pd–ligand complex. If this was not done, no alkylation occurred. Also, no reaction occurred if Li_2CO_3 was used instead of LiH.

giving a product with up to 91% ee. Further asymmetric applications with oxazine (+)-**8** are currently underway and will be disclosed in due course.

3. Experimental procedures

3.1. Synthesis of phosphino-oxazine (+)-8

2-Diphenylphosphinobenzonitrile **6** (535 mg, 1.86 mmol), (+)-**5** (402 mg, 2.59 mmol) and $ZnCl_2$ (504 mg, 3.70 mmol) were refluxed in chlorobenzene (8 mL) for 6 d. After cooling to rt, the resulting solution was filtered through silica (5 cm) rinsed with EtOAc (6 column volumes). Concentration in vacuo gave (+)-**7** as a beige solid, which was used without further purification.

2,2′-Dipyridyl (299 mg, 1.91 mmol) and (+)-**7** were dissolved in 15 mL dry $CHCl_3$ and stirred at rt for 1 h. The resulting solution was filtered through silica (5 cm), and rinsed with $CHCl_3$ (100 mL). Concentration in vacuo gave (+)-**8** (746 mg, 1.75 mmol, 89.5%) as a fluffy sticky white solid: mp 146–148 °C; $[\alpha]_D^{21}$ +68.6 (*c* 1.25, $CHCl_3$); IR (film) ν_{max} 3066, 3051, 2952, 2930, 2865, 2209, 1663, 1650, 1582, 1555, 1461, 1432, 1345, 1314, 1273, 1254, 1198, 1177, 1142, 1096, 1070, 1026, 908, 777, 742, 692, 667, 545, 501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, $J = 7.1$, 3.6 Hz, 1H), 7.40–7.20 (m, 12H), 6.85 (dd, $J = 7.5$, 4.3 Hz, 1H), 3.79 (d, $J = 4.4$ Hz, 1H), 3.46 (t, $J = 8.2$ Hz, 1H), 2.23–2.12 (m, 1H), 1.89–1.76 (m, 1H), 1.73–1.18 (m, 9H), 0.91–0.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5 (C), 139.3 (C, d, $J = 20.7$ Hz), 138.9 (C, d, $J = 21.7$ Hz), 138.8 (C, d, $J = 20.9$ Hz), 137.2 (C, d, $J = 20.9$ Hz), 134.0 (CH, d, $J = 19.7$ Hz), 133.8 (CH, d, $J = 20.4$ Hz), 130–128 (CH, m), 80.2 (CH), 60.3 (CH), 47.8 (C), 36.2 (CH_2), 35.4 (CH_2), 35.1 (CH_2), 30.5 (CH_2), 21.7 (CH_2), 20.7 (CH_2); ^{31}P NMR (160 MHz, $CDCl_3$) −6.3; MS (VG7070): *m/z* 425 (2, M^+), 261 (26), 225 (28), 208 (34), 183 (73), 153 (23), 152 (22), 127 (21), 125 (22), 113 (26), 111 (31), 107 (24), 99 (32), 97 (38), 95 (35), 79 (47), 71 (68), 69 (40), 67 (34), 58 (100), 56 (45), 45 (52), 43 (78); HRMS calcd for $C_{28}H_{28}NOP$ 425.19085, found 425.18906.

(+)-**7**: mp 222—224 °C; $[\alpha]_D^{21}$ +60.4 (*c* 1.05, $CHCl_3$); IR (film) ν_{max} 3055, 2955, 2928, 2868, 2235, 1622, 1478, 1469, 1434, 1365, 1263, 1154, 1131, 1102, 1072, 909, 746, 729, 696, 542, 509, 493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, $J = 7.2$, 4.8 Hz, 1H), 7.40–7.20 (m, 11H), 7.36–7.23 (m, 1H), 6.92 (t, $J = 8.4$ Hz, 1H), 4.17 (d, $J = 4.4$ Hz, 1H), 3.96 (t, $J = 8.8$ Hz, 1H), 2.72–2.62 (m, 1H), 2.03–1.07 (m, 9H), 0.92–0.68 (m, 1H), 0.34 (dt, $J = 12.7$, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1 (C, d, $J = 3.7$ Hz), 134.7 (CH, d, $J = 14.8$ Hz), 134.4 (CH, d, $J = 14.1$ Hz), 133.8 (C, d, $J = 10.9$ Hz), 133.2 (CH, d, $J = 2.6$ Hz), 132.3 (CH, d, $J = 5.7$ Hz), 132.0 (CH, d, $J = 5.4$ Hz), 131.9 (CH, d, $J = 2.1$ Hz), 131.8 (CH, d, $J = 2.1$ Hz), 131.1 (CH), 129.6 (CH, d, $J = 10.3$ Hz), 129.5 (CH, d, $J = 10.4$ Hz), 128.8 (C, d, $J = 34.6$ Hz), 126.8 (C, d, $J = 35.7$ Hz), 125.1 (C, d, $J = 33.3$ Hz), 82.8 (CH), 60.1 (CH), 46.9 (C), 35.9 (CH_2), 34.6 (CH_2), 32.4 (CH_2), 30.5 (CH_2), 20.7 (CH_2), 20.2 (CH_2); ^{31}P NMR (160 MHz, $CDCl_3$) −18.6; MS (VG7070): *m/z* 425 (8, $[M-ZnCl_2]^+$), 304 (32), 302 (48), 288 (22), 287.4 (48), 287.2 (100), 286 (99), 261 (22), 259 (27), 257 (27), 241 (32), 239 (20), 228 (35), 227 (25), 226

(55), 225.2 (23), 225.1 (59), 210 (30), 209 (54), 208.2 (44), 208.0 (96), 184 (37), 183.2 (30), 183.0 (95), 182 (50), 181 (43), 178 (29), 165 (22), 153 (46), 152 (46), 151 (37), 143 (46), 132 (27), 121 (21), 117 (25), 107 (64), 91 (64), 79 (26), 77 (28); HRMS calcd for $C_{28}H_{28}Cl_2NOPZn$ 559.05770, found 559.05715.

4. General procedure for Pd-catalyzed allylic alkylation reactions

Base (1.0 mmol) was suspended in dry solvent (2.0 mL) and cooled to 0 °C. Dimethyl malonate (**10**, 0.12 mL, 1.05 mmol) was added. After stirring for 1 h, **9** (0.50 mmol) was added in a dry solvent (1.0 mL). A premixed solution of allylpalladium chloride dimer (4 mg, 0.01 mmol) and (+)-**8** (9 mg, 0.02 mmol) in dry solvent (1.0 mL; precooled to 0 °C) was then added, and the reaction stirred until monitoring by TLC showed that all of **9** had been consumed. Quenching with $NaOH_{(aq)}$ (4%, 5 mL), extraction with Et_2O (3 × 5 mL), drying over Na_2SO_4, concentration in vacuo and flash column chromatography (silica, 9:1 hexanes/EtOAc) gave **11** as a white waxy solid: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43–7.17 (m, 10H, H4–H11), 6.55–6.26 (m, 2H, H2–H3), 4.28 (dd, J = 10.8, 5.5 Hz, 1H, H1), 3.96 (d, J = 10.8 Hz, 1H, H12), 3.71 (s, 3H, H14), 3.53 (s, 3H, H14). Enantiomeric excess of **11** was determined by ^{1}H NMR (200 MHz, $CDCl_3$) with 0.3 equiv $Eu(hfc)_3$.

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18. X-ray crystallographic analysis of (+)-**7** was performed by Dr. M. Parvez at the University of Calgary. CCDC 218863 contains the crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html. Compound (+)-**7**: monoclinic $P2_1$; a = 8.555(4) Å, b = 18.608(13) Å, c = 8.972(6) Å, β = 113.69(4)°, V = 1307.9(14) Å^3; Z = 2; R = 0.056; R_w = 0.142.
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