Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 4301–4305

TETRAHEDRON: *ASYMMETRY*

The application of Pd-complexes of *trans*-2,5-dialkylpyrrolidinyl-benzyldiphenylphosphines to enantioselective allylic alkylation

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Received 7 October 1998; accepted 20 October 1998

Abstract

The preparation of cationic palladium (η^3-C_3H_5) complexes **6** and **7**, possessing an enantiopure *trans*-2,5-dialkylpyrrolidinyl unit, is described. These complexes were applied to the enantioselective alkylation of the test substrate, 1,3-diphenylpropenyl acetate **8**, with dimethyl malonate in good to high conversions with enantioselectivities of up to 90% ee for the 2,5-diethylpyrrolidinyl substituted complex **7**. Attempts to optimise reaction conditions included variation of solvent and temperature and the source of the malonate nucleophile. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

The enantioselective substitution of allylic acetates is the most studied of the range of asymmetric carbon–carbon bond forming processes catalysed by transition metal complexes of palladium.[1] It is an important transformation and has proved to be a useful testing ground for the design of new ligands and for gaining mechanistic insights into organopalladium chemistry. To date, successful results have been observed using C_2-symmetric homobidentate ligands, such as diphosphines and diamines.[2,3] In these cases the asymmetric induction arises primarily from steric interactions between the ligand and the η^3-bound substituted allyl. Numerous examples of heterobidentate ligands, such as mixed phosphorous–nitrogen (phosphinamines)[4] and sulfur–nitrogen systems,[5] have been prepared and tested with success in allylic substitution. In contrast to their homobidentate analogues, these ligands induce asymmetry through a combination of steric and electronic interactions. The diphenylphosphinooxazolines **1**, one of the most successful examples of phosphinamine ligands, afforded excellent enantioselectivities in the standard test allylic substitution (99% ee using ligand **1** (R=*i*-Pr).[4a] The axially chiral phosphinamine Quinap **2**, reported by Brown, gave an ee of 98%.[4e] The diphenylphosphino-pyrrolidines of type **3** developed by Koga gave poor enantioselectivities of 11–20%.[4d] We have recently reported the preparation

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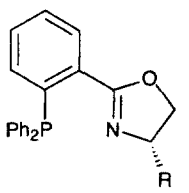
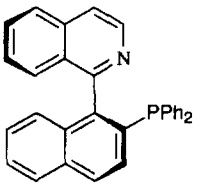
0957-4166/98/$ - see front matter
PII: S0957-4166(98)00425-X

of phosphinamine ligands, **4** and **5**, bearing an enantiopure *trans*-2,5-disubstituted pyrrolidine unit[6] and their application in Ir-catalysed enantioselective imine reduction[7] and Pd-catalysed asymmetric Heck reaction.[8] These were designed so that: (i) the chelate ring size would be six; (ii) the backbone would be more rigid than in **3**; and (iii) the stereogenic centres would be close to the nitrogen donor atom as reaction of the nucleophile is known to occur *trans* to the phosphorous donor atom.[9] We now report the application of their palladium complexes to enantioselective allylic substitution.



1

R = Bn, *i*-Pr, *t*-Bu, etc.



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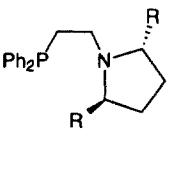
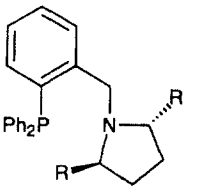


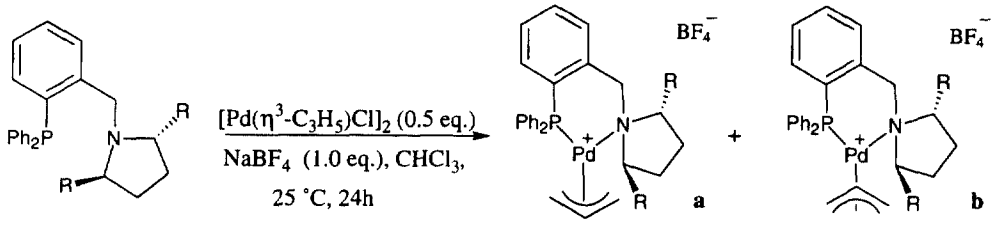
3

R = Me, Et, Bn.



4: R = Me.; **5**: R = Et.

In carrying out an allylic substitution it is possible to use, as the catalyst, either a pre-formed palladium (η^3-allyl) complex of the ligand or to assume such a complex is formed when a slight excess of ligand is added to an η^3-allyl palladium chloride dimer. We have chosen the former possibility and hence we have prepared the air-stable η^3-allyl palladium tetrafluoroborate salts **6** and **7**, in 96 and 87% yield, respectively (Scheme 1).



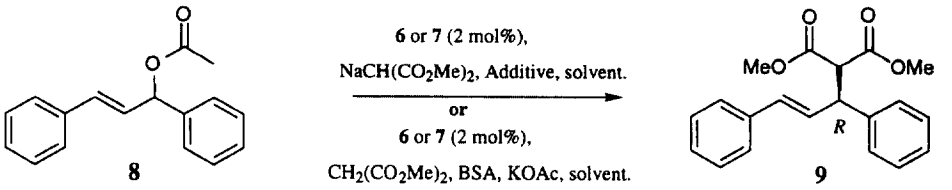
6: R = Me (96%) (**a** :**b** =4 : 5).

7: R = Et (87%) (**a** : **b** =2 : 3).

Scheme 1.

{[(2′*R*,5′*R*)-Dimethylpyrrolidin-1-yl-methyl]-1-(diphenylphosphino)benzene}-[π-allyl]palladium] tetrafluoroborate **6** was obtained as a mixture of the two possible diastereomers, with the *endo*-diastereomer **6b** favoured over the *exo*-diastereomer **6a** in a ratio of 5:4. This ratio was deduced from the ^{31}P NMR spectrum, with the key peaks appearing at 20.5 and 20.9 ppm, respectively.[10] Similarly, the diethyl analogue **7** appeared as two diastereomers with **7b** favoured over **7a** in a slightly higher ratio of 3:2 (^{31}P NMR peaks at 20.3 and 20.5 ppm, respectively). Once prepared, we wished to test their asymmetry-inducing ability in what has become one of the standard test reactions in allylic substitution, namely that between the soft nucleophile derived from dimethyl malonate and 1,3-diphenylpropenyl acetate **8**, Scheme 2. The results of our preliminary investigations are given in Table 1.

The malonate nucleophile can be pre-formed as its sodium salt (NaMal) or prepared in situ by Trost's procedure using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and catalytic quantities of potassium acetate.[11] A further variant was 15-crown-5, an additive which helps to solvate the sodium malonate salt.[4e] Dichloromethane as solvent using either the NaMal or BSA method gave good yields but poor ees of 25–27% (entries 1–2). The chemical yields were lower when acetonitrile was used as solvent, although the ees were improved to 44–47% (entries 3–5). Dimethylformamide was found to be the solvent which



Scheme 2.

Table 1
Application of Pd-complexes **6** and **7** to the asymmetric allylic alkylation of acetate **8**[a]

Entry	Method	Catalyst	Solvent	Additive	Temp. °C	% Conversion[b]	% ee[c] (config.[d])
1	NaMal	**6**	CH_2Cl_2	15-C-5	25	89	25 (*R*)
2	BSA	**6**	CH_2Cl_2		25	73	27 (*R*)
3	NaMal	**6**	CH_3CN	15-C-5	25	70	44 (*R*)
4	NaMal	**6**	CH_3CN	15-C-5	0	53	47 (*R*)
5	BSA	**6**	CH_3CN		0	34	45 (*R*)
6	NaMal	**6**	DMF	15-C-5	25	65	50 (*R*)
7	NaMal	**6**	DMF	15-C-5	0	62	55 (*R*)
8	NaMal	**6**	DMF		0	57	54 (*R*)
9	BSA	**6**	DMF		25	61	50 (*R*)
10	BSA	**6**	DMF		0	32	53 (*R*)
11	NaMal	**7**	CH_2Cl_2	15-C-5	25	68	74 (*R*)
12	NaMal	**7**	DMF	15-C-5	25	45	84 (*R*)
13	NaMal	**7**	DMF	15-C-5	0	60	88 (*R*)
14	NaMal	**7**	CH_3CN	15-C-5	25	89	90 (*R*)
15	NaMal	**7**	CH_3CN	15-C-5	0	58	86 (*R*)

[a] The reaction was carried out over 24h in the presence of 2 mol% of the pre-formed catalyst using either NaMal or BSA method.
[b] Isolated yield after silica gel chromatography. [c] Enantiomeric excesses were determined by ^{1}H NMR using Eu(hfc)$_3$ as the chiral shift reagent. [d] Assignment is based on the sign of the optical rotation and comparison with lit.[3a].

afforded the highest ees for complex **6** and there was not a significant difference in ee between the NaMal or BSA method (compare entries 6–8 with 9–10). For this reason, further reactions utilised only the NaMal method. The diethyl complex **7** was then investigated using the optimal conditions found for complex **6**, and enhanced ees of 84–88% were obtained in dimethylformamide at both room temperature and at 0°C although in moderate yield (entries 12–13). For completeness, reactions in dichloromethane and acetonitrile were also performed, and again, considerably higher ees were obtained compared to complex **6**. In dichloromethane, an ee of 84% was obtained (compare entries 1–2 with 11), whilst in acetonitrile the highest chemical yield (89%) and highest ee (90%) were observed. The reaction time of 24 h is longer than for related phosphinamine palladium complexes although it was noted experimentally that similar, but never quantitative, yields were obtained in shorter reaction times of 3 h which suggests some loss of catalytic activity. Despite this, it is worth noting that palladium complexes of our ligand system gave an ee of 90% compared to the aforementioned poorer ees of 11–20% obtained by Koga with the related diphenylphosphinopyrrolidines **3**. The groups at the pyrrolidine stereocentres are similar in size, which suggests that rigidifying the backbone and increasing the chelate ring size were the crucial elements of our ligand design.

In conclusion, we have prepared new palladium complexes of diphenylphosphinopyrrolidine ligands **4** and **5** and applied them with good to high enantioselectivities in a test allylic alkylation. Further work will be disclosed on the preparation of related pyrrolidine-containing ligands and on our mechanistic studies in this area.

Acknowledgements

We thank Forbairt for a Basic Research Award (SC/94/565) to support this work and a Forbairt Research Scholarship (BR/94/158) to JPC. The loan of Pd salts from Johnson Matthey is also gratefully acknowledged.

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s, 2H, H-3_b′, H-4_a′), 2.18 (br s, 2H, H-3_b′, H-4_a′), 2.92 (br s, 1H, H-2′), 3.19 (br s, 1H, H-5′), 3.39 (br s, 1H, allyl H_1), 3.55 (dd, 1H, J=13.2, 4.4, allyl H_4), 4.08 (dd, 1H, J=14.2, 9.3, allyl H_3), 4.78 (app. t, 1H, J=6.8, allyl H_2), 5.95 (br s, 1H, allyl H_5), 6.95–7.74 (m, 28H, Ar-H); δ_C (67.5 MHz, $CDCl_3$) 15.57 (Me-2′), 16.06 (Me-5′), 29.11 (C-3′), 29.41 (C-4′), 39.57 (C-2′), 43.12 (C-5′), 55.52 (benzylic-C), 61.38 (central allyl-C), 68.10 (allyl-C *trans* N), 84.86 (d, J=26.9, allyl-C *trans* P), 122.05 (C-3), 128.70, 128.76, 128.86, 129.41, 129.58, 129.88, 130.09, 130.18, 131.58, 131.80, 132.24, 132.27, 132.70, 133.19, 133.67, 133.79, 134.03, 134.23, 139.61; δ_P (109.3 MHz, $CDCl_3$) 20.5 and 20.9; m/z (ESI/pos in CH_3OH) 520=M–BF_4.

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