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Enantioselective palladium catalyzed allylic substitution with 2,2′-bipyridine ligands

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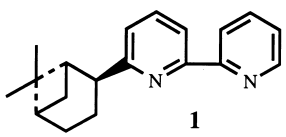
Abstract

A number of chiral C_1-symmetric 2,2′-bypyridines were prepared and assessed in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate. Enantioselectivity up to 89% was obtained. © 1998 Elsevier Science Ltd. All rights reserved.

Enantioselective reactions based on palladium catalyzed allylic substitutions are currently an actively pursued research area.[1] In this context a number of nitrogen ligands are now reaching high levels of stereocontrol.[1,2]

Recently, continuing our interest in the synthesis and application of chiral pyridine derivatives as ligands for metal complexes in enantioselective catalysis,[3] we have evaluated the potential utility of a number of chiral ligands with sp^2-nitrogen donors as chiral controllers for enantioselective palladium catalyzed allylic substitutions.[4] This preliminary investigation indicated that C_1-symmetric 2,2′-bipyridines were able to provide active palladium catalysts and that the use of the related bipyridines with C_2-symmetry was detrimental for both the catalytic activity and stereoselectivity of the reaction. The best enantioselectivity (32% ee) was obtained with the ligand **1**, while with **2** the process was not enantioselective.



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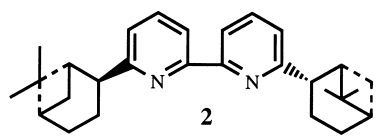

2

These promising results prompted us to prepare and assess in this catalytic process C_1-symmetric bipyridines in which the substituents on the stereocentre bonded to the heterocyclic ring are arranged in a rigid backbone in such a way as to provide a more rigid array of the ligand around the metal centre.

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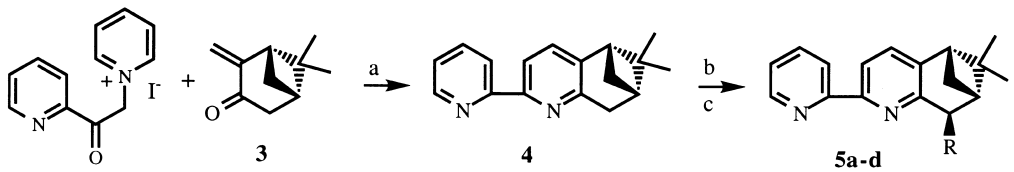
In this paper we report the application of a number of chiral 2,2′-bipyridines derived from 6,6-dimethyl-5,7-methano-2-(2-pyridinyl)-5,6,7,8-tetrahydroquinoline **4**[5] in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate.

The ligands **5–7** were prepared from the bipyridine **4**,[6] readily accessible by reaction of (+)-pinocarvone **3**[6] with 1-phenacylpyridinium iodide[5] (Scheme 1). The red solution of lithiated **4**, obtained by treatment with lithium diisopropylamine (LDA) at −40°C for 3 h and then 1 h at 0°C, was quenched with the proper alkyl halide to give ligands **5a–c**.[7,8] To obtain the ligands **6** and **7** lithiated **4** was quenched with acetone and then the obtained carbinol **5d**[6] was converted into the corresponding methyl ether **6**[7] and trimethylsilyl ether **7**[7] with sodium hydride/methyl iodide and imidazole/trimethylsilyl chloride, respectively



R= **a** CH_3, **b**: CH_2-C_6H_5, **c**: $CH(CH_3)_2$, **d**: $C(CH_3)_2OH$

a: AcOH, $AcONH_4$, 120°C, 4h; b: LDA, THF, 1h at -40 °C then 1h at 0 °C; c: -78 °C, CH_3I or $C_6H_5CH_2Br$ or *i*-C_3H_7I or $(CH_3)_2CO$; d: NaH, THF, then CH_3I; e: imidazole, DMF, $ClSi(CH_3)_3$.

Scheme 1.

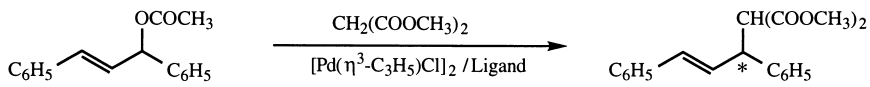
To test the ability of these new ligands to provide asymmetric induction in the palladium-catalysed allylic substitutions we examined the alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. Allylic substitutions were carried out employing Trost's procedure which used $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as procatalyst and a mixture of dimethyl malonate, N,O-bis(trimethylsilyl)acetamide (BSA) and potassium acetate.[9] The reactions were carried out in methylene chloride at room or at reflux temperature. The results of the catalytic reaction are reported in Table 1.

2,2′-Bipyridines **4–7** were able to provide effective palladium catalysts. Total conversion of the starting material was achieved with these ligands in less than 48 h at room temperature to give high yields of dimethyl 1,3-diphenylprop-2-enylmalonate **9**. Only the reaction employing **7** proceeded much slower than those with the other ligands and was complete in 12 days.

The effect of the introduction of alkyl groups at the 8-position of the tetrahydroquinoline ring of **4** was dramatic for the stereoselectivity and reaction rate of the process. The best stereoselectivity (89% ee) was obtained with the 8-benzyl substituted ligand **5b**. Unexpectedly, the bipyridine **6** bearing the crowded $C(CH_3)_2OCH_3$ group gave a stereoselectivity and reaction rate similar to that of unsubstituted bipyridine **4**. With the bipyridine **7**, bearing the very sterically demanding $C(CH_3)_2OSi(CH_3)_3$ group, a dramatic drop of the catalytic activity was observed and the stereochemical outcome was inverted. Indeed, while in all cases the absolute configuration of the substitution product **9** was controlled by the absolute configuration at the stereogenic centre at the 8-position of tetrahydroquinoline ring, resulting in the preferred formation of (R)-**9**, in this case **9** was obtained with (S)-configuration. This stereochemical result is probably due to this ligand being too sterically crowded to enable effective coordination to palladium. Therefore, in this case the reactive transition states could be different from those of the others ligands.

Finally, it should be noted that the 8-unsubstituted bipyridine **4** gave a much lower enantiomeric excess

Table 1
Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[a]



8 **9**

Entry	Ligand	Temperature	React. time, h[b]	Yield[c]	% Ee[d]	Conf.[e]
1	**4**	r.t.	3	93	11	R
2	**5a**	r.t.	12	95	74	R
3	**5b**	r.t.	48	94	89	R
4	**5b**	reflux	20	83	78	R
5	**5c**	r.t.	12	91	79	R
6	**6**	r.t.	3	77	16	R
7	**7**	r.t.	288	68	26	S

[a]Reaction of the ligand (10 mol %) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) with 1,3-diphenylprop-2-enyl acetate (0.4 mmol), $CH_2(COOMe)_2$ (1.2 mmol), N,O-bis(trimethylsilyl)acetamide (BSA) (1.2 mmol) and KOAc (3.5 % mol) in CH_2Cl_2 (2 ml) at room or reflux temperature. [b]Determined by TLC analysis (SiO_2; light petroleum:ether:3/1; R_f **8** = 0.42; R_f **9** = 0.30. [c]Isolated yields. [d]Determined by ^{1}H-NMR using Eu(hfc)$_3$ as chiral shift reagent. [e]The assignement is based on the sign of the specific rotation: Leutenegger, U.; Umbricht, G.; Fahrni, C.; Matt, P.V.; Pfaltz, A. *Tetrahedron*, **1992**, *48*, 2143.

than the 8-substituted bipyridine **5** but the same sense of enantioselection. This stereochemical result reasonably indicates that in bipyridine **5** the stereocentre at the 8-position and those at the 5,7-positions are not in a mismatching relation.

Very good results in palladium catalysed allylic substitutions have been achieved using a C_2-symmetric as well as C_1-symmetric nitrogen-containing ligands.[1] The origin of the selectivity, however may be different with the two types of ligands. Considering palladium catalysed allylic substitutions, which proceed through a meso η^3-allyl intermediate, the accepted mechanism foresees that the nucleophile attacks at the allylic termini of two alternative diastereomeric π-allyl palladium complexes. The regioselectivity and stereoselectivity of the nucleophilic attack is determined by steric and electronic properties of the ligand. While steric factors may be controlled with C_2-symmetric ligands, electronic factors may be more easily controlled with C_1-symmetric ligands in which two different donor atoms (such as in phosphinooxazolines,[10] thiophenooxazolines[11] and phosphinoamines[12]) or two identical atoms insert in different surroundings (such as the nitrogen atoms in aminopyridines,[13] pyridyloxazolines[14]) may be chosen.

We have now found that C_1-symmetric 2,2′-bipyridines, ligands which don't possess such a requirement (the electronic properties of the nitrogen atoms of the two pyridine rings are nearly identical) are able to give very good enantioselectivity in palladium catalysed allylic substitutions. Therefore these results contribute to the understanding of which factors are important for the palladium catalysed allylic alkylation.

References

1. Trost, B. M.; Van Vranken, D. L. *Chem. Rev.*, **1996**, 96, 395. Reiser, O. *Angew. Chem.*, **1993**, *105*, 576; *Angew. Chem. Int. Ed. Engl.*, **1993,** *32*, 547. Hayashi, T. In *Catalytic Asymmetric Synthesis*, Ed. Ojima, VCH, Weinheim, 1993. Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry*, **1992**, 3, 1089. Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron: Asymmetry*, **1995**, 2535, and references therein.
2. Togni, A.; Venanzi, L. M. *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 497.
3. Chelucci, G.; Marchetti, M.; Sechi, B. *J. Mol. Catal.*, **1997**, *122*, 111. Chelucci, G.; Berta, D.; Saba, A. *Tetrahedron*, **1997**, *53*, 3843. Chelucci, G. *Tetrahedron: Asymmetry*, **1997**, *8*, 2667 and references therein.
4. Chelucci, G.; Caria, V.; Saba, A. *J. Mol. Catal.*, **1997**, in press.
5. Havoz, P.; von Zelewsky, A. *Tetrahedron Lett.*, **1992**, *33*, 5165.
6. Compound **4**: mp 80–81°C; $[\alpha]^{25}_{D}$ +97.46 (*c* 2.6, $CHCl_3$). We prepared compound **3** by MnO_2 oxidation of (−)-*trans*-pinocarveol (Fluka A. G.).
7. All compounds showed satisfactory spectroscopic and analytical data. Compounds **5a–c**: Chen et al.[8] Compound **5d** was isolated in 89% yield after chromatographic purification on Al_2O_3 (petroleum ether:ethyl ether=1:1): mp 122–3°C; $[\alpha]^{25}_{D}$ −26.2 (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.65 (d, 1H), 8.20 (d, 1H), 8.07 (s, 1H), 7.78 (t, 1H), 7.42 (d, 1H), 7.28 (m, 1H), 3.28 (s, 1H), 2.81 (t, 1H), 2.62 (m, 1H), 2.38 (d, 1H), 1.86 (s, 1H), 1.45 (s, 3H), 1.42 (d, 1H), 1.36 (s, 3H), 1.12 (s, 3H), 0.71 (s, 3H). Compound **6** was isolated in 83% yield after flash chromatography (petroleum ether:ethyl acetate): oil, $[\alpha]^{25}_{D}$ +48.0 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.64 (d, 1H), 8.38 (d, 1H), 8.13 (d, 1H), 7.79 (t, 1H), 7.32 (d 1H), 7.24 (m, 1H), 3.65 (s, 1H), 3.23 (s, 3H), 2.75 (m, 1H), 2.61 (m, 1H), 1.85 (s, 3H), 1.60 (d, 1H), 1.45 (s, 3H), 1.36 (d, 1H), 1.23 (s, 3H), 0.62 (s, 3H). Compound **7**: was isolated in 95% yield after chromatographic purification on Al_2O_3 (petroleum ether:ethyl acetate=7:3): mp 121–122; $[\alpha]^{25}_{D}$ −44.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.62 (d, 1H), 8.36 (d, 1H), 8.12 (d, 1H), 7.75 (t, 1H), 7.26 (d, 1H), 7.22 (m, 1H), 3.07 (s, 1H), 2.70 (m, 1H), 2.66 (m, 1H), 2.49 (m, 1H), 1.79 (d, 1H), 1.71 (s, 3H), 1.53 (s, 3H), 1.42 (s, 3H), 0.58 (s, 3H), 0.08 (s, 9H).
8. Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.*, **1995**, *60*, 5386.
9. Trost, B. M.; Murphy, D. J. *Organometallics*, **1985**, *4*, 1143.
10. von Matt, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.*, **1993,** *32*, 556. Sprinz, J.; Helmchen, G. *Tetrahedron Lett.*, **1993**, *34*, 1767. Dawson, G. J.; Frost, C.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.*, **1993**, *34*, 3149.
11. Allen, V. J.; Bower, J. F.; Williams, J. M. J. *Tetrahedron: Asymmetry*, **1994**, 5, 1895.
12. Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 2386. Trost, B. M.; Van Vranken, D. L. *Angew. Chem. Int. Ed. Engl.*, **1992**, *31*, 228.
13. Chelucci, G.; Pinna, G. A.; Saba, A. *Tetrahedron: Asymmetry*, **1997**, *8*, 2571.
14. Nordström, K.; Macedo, E.; Moberg, C. *J. Org. Chem.*, **1997**, *62*, 1604. Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry*, **1997**, *8*, 3183.