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(-)-α-Isosparteine as a Chiral Ligand in Asymmetric Allylic Alkylation

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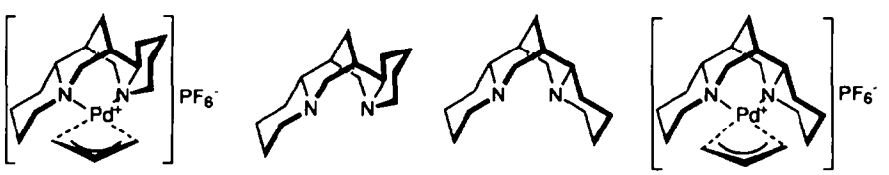
Abstract: The cationic complex [Pd(π-Allyl)(Isosparteine)]$^+$ PF_6^- was found to be a suitable catalyst for asymmetric alkylation of allylic acetates. Asymmetric allylic alkylation with $NaCH(CO_2Me)_2$ was carried out in the presence of a 5 mol % of the catalyst to give chiral alkylation products with high enantiomeric excesses.

Asymmetric allylic alkylation reactions catalyzed by π-allylpalladium complex are useful synthetic methods for asymmetric C-C bond formation by allowing the Pd-catalyzed substitution of a nucleophile for a suitable leaving group in an allylic position.[1,2] For this kind of chemical transformation, the chiral ligands for the dominant Pd(0) species in the catalytic cycle have been restricted to phosphines and phosphites which are able to stabilize low oxidation states by their π-acidic nature.[3] Recently, however, chiral nitrogen ligands such as bisoxazoline[4] and semicorrin[5] were prepared and found to render high enantioselectivity in the allylic alkylation of 1,3-diphenyl-2-propen-1-yl acetate.

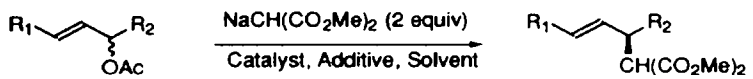
In the meantime, similar ligands have been prepared and used as effective chirality transmitters in several types of transition metal catalyzed reactions.[6] Also, Togni has described a Pd-catalyzed asymmetric alkylation with [Pd(π-Allyl)(sparteine)]$^+$ PF_6^- **1** as a chiral catalyst, which is readily prepared from the commercially available and naturally occurring alkaloid, (-)-sparteine **2**.[7]



1 **2** **3** **4**

We have been examining the utility of C_2 symmetric[8] (-)-α-isosparteine **3** in asymmetric synthesis, which can be synthesized from (-)-sparteine **2** in 2 steps by a known procedure.[9] The reasons for employing

(-)-α-isosparteine **3** in the asymmetric alkylations were as follows: It may be possible to bring the reactants together into a diastereomerically favored state. Another reason was that the related results with sparteine reported by Togni were not general and erratic.[7] Consequently, a new Pd complex **4** was synthesized from (-)-α-isosparteine, $[Pd(\pi\text{-}C_3H_5)Cl]_2$, and $AgPF_6$ in CH_2Cl_2. The catalytic activity of the complex [Pd(π-Allyl)(isosparteine)]$^+$ PF_6^- **4** in the alkylation of various allylic acetates by $NaCH(CO_2Me)_2$ in several solvents was examined. In parallel reactions, Pd-sparteine complex **1** was also studied for its catalytic activity, the results of which are summarized in Tables 1 - 4. Contrary to the previous report,[7] the reaction was best carried out in a solvent at reflux, which ensured rapid reaction to completion and also good enantiomeric purity and THF was the solvent of choice for universal use (*vide infra*).



5 **6**

Racemic 1,3-diphenyl-2-propen-1-yl acetate [**5** ($R_1 = R_2 = Ph$)] underwent smooth reaction, affording good chemical and optical yields of malonates of *R* configuration. In this case, sparteine was a slightly better chirality transmitter, and both DMF and THF were the solvents of choice (Table 1).

Table 1. Reaction of (*rac*)-1,3-Diphenyl-2-propen-1-yl Acetate [5 ($R_1 = R_2 = Ph$)].

Substrate Concn (M)	Catalyst (equiv)	Additive (equiv)	Solvent	Rxn Temp	Rxn Time	Yield[a] (%)	ee (%)
0.02	**4** (0.10)	3 (0.2)	THF	67 °C	12.0 h	92	70
0.02	**4** (0.10)	3 (0.2)	MeCN	82 °C	1.0 h	86	59
0.02	**4** (0.10)	3 (0.2)	toluene	110 °C	0.7 h	91	70
0.02	**4** (0.10)	3 (0.2)	DMF	153 °C	0.3 h	87	82
0.02	**4** (0.05)	3 (0.1)	THF	67 °C	24.0 h	81	67
0.02	**4** (0.05)	3 (0.1)	MeCN	82 °C	1.0 h	81	61
0.02	**4** (0.05)	3 (0.1)	toluene	110 °C	1.5 h	89	67
0.02	**4** (0.05)	3 (0.1)	DMF	153 °C	0.3 h	86	88[b]
0.02	**1** (0.10)	2 (0.2)	THF	67 °C	10.0 h	90	92
0.02	**1** (0.10)	2 (0.2)	MeCN	82 °C	0.4 h	91	89
0.02	**1** (0.10)	2 (0.2)	toluene	110 °C	1.3 h	89	90
0.02	**1** (0.10)	2 (0.2)	DMF	153 °C	0.5 h	85	84
0.02	**1** (0.05)	2 (0.1)	THF	67 °C	18.0 h	75	89
0.02	**1** (0.05)	2 (0.1)	MeCN	82 °C	1.0 h	75	89
0.02	**1** (0.05)	2 (0.1)	toluene	110 °C	1.5 h	81	65
0.02	**1** (0.05)	2 (0.1)	DMF	153 °C	0.5 h	81	95
0.10[c]	**1** (0.05)	2 (0.1)	THF	23 °C	72 h	77	75

[a]Isolated yields. [b]$[\alpha]_D^{22}$ +11.98 (*c* 0.69, EtOH). [c]Results reported by ref. 7.

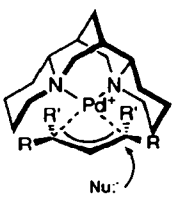
In the case of racemic 3-penten-2-yl acetate [**5** ($R_1 = R_2 = Me$)], sparteine gave low yield and erratic ee's of the corresponding product, which is in good contrast to the results with isosparteine reactions especially in THF. In this case the product had consistently *R* configuration (Table 2).

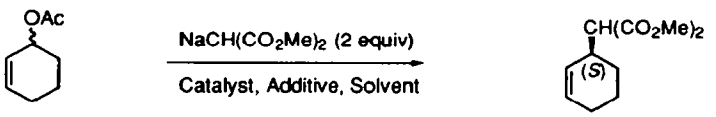
Table 2. Reaction of (*rac*)-3-Penten-2-yl Acetate [5 (R_1 = R_2 = Me)].

Substrate Concn (M)	Catalyst (equiv)	Additive (equiv)	Solvent	Rxn Temp	Rxn Time	Yield[a] (%)	ee (%)
0.02	**4** (0.05)	**3** (0.1)	THF	67 °C	16.0 h	83	69[b]
0.02	**4** (0.05)	**3** (0.1)	MeCN	82 °C	5.0 h	17	49
0.02	**4** (0.05)	**3** (0.1)	toluene	110 °C	7.0 h	27	13
0.02	**4** (0.05)	**3** (0.1)	DMF	153 °C	1.0 h	17	56
0.02	**1** (0.05)	**2** (0.1)	THF	67 °C	29.0 h	13	5
0.02	**1** (0.05)	**2** (0.1)	MeCN	82 °C	6.0 h	10	-11
0.02	**1** (0.05)	**2** (0.1)	toluene	110 °C	5.0 h	25	3
0.02	**1** (0.05)	**2** (0.1)	DMF	153 °C	1.0 h	15	-15
0.10[c]	**1** (0.05)	**2** (0.1)	THF	23 °C	72 h	trace	

[a]Isolated yields. [b]$[\alpha]_D^{22}$ +15.43 (*c* 0.92, $CHCl_3$). [c]Results reported by ref. 7.

The same trend as in Table 2 can be seen in the reactions with racemic 2-cyclohexen-1-yl acetate **7** with isosparteine (Table 3). Although we were unable to specify with certainty the absolute configuration of the major enantiomer **8** ($[\alpha]_D^{22}$ -8.69 (*c* 1.36, CH_2Cl_2)) formed in this reaction, it was tentatively assigned as *S* configuration according to general mode of reaction as the following.





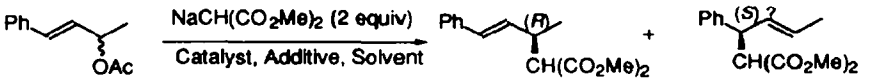
7 **8**

Table 3. Reaction of (*rac*)-2-Cyclohexen-1-yl Acetate 7.

Substrate Concn (M)	Catalyst (equiv)	Additive (equiv)	Solvent	Rxn Temp	Rxn Time	Yield[a] (%)	ee (%)
0.02	**4** (0.05)	**3** (0.1)	THF	67 °C	2.0 h	63	62[b]
0.02	**4** (0.05)	**3** (0.1)	MeCN	82 °C	24.0 h	21	25
0.02	**4** (0.05)	**3** (0.1)	toluene	110 °C	1.5 h	65	19
0.02	**4** (0.05)	**3** (0.1)	DMF	153 °C	48.0 h	trace	- 5
0.02	**1** (0.05)	**2** (0.1)	THF	67 °C	46.0 h	20	34
0.02	**1** (0.05)	**2** (0.1)	MeCN	82 °C	38.0 h	7	9
0.02	**1** (0.05)	**2** (0.1)	toluene	110 °C	1.0 h	63	32
0.02	**1** (0.05)	**2** (0.1)	DMF	153 °C	48.0 h	trace	9
0.10[c]	**1** (0.05)	**2** (0.1)	THF	23 °C	72 h	82	50

[a]Isolated yields. [b]$[\alpha]_D^{22}$ -8.69 (*c* 1.36, CH_2Cl_2). [c]Results reported by ref. 7.

Reaction of racemic 4-phenyl-3-buten-2-yl acetate [**5** (R_1 = Ph, R_2 = Me)] gave two products as expected with the major product being the conjugated product **9**. However, the reaction with sparteine in THF at room temperature could not be reproduced as reported.[7] Refluxing in the same solvent was required to get reasonable yield and ee's (Table 4).



5 (R_1 = Ph, R_2 = Me) **9** **10**

Table 4. Reaction of (*rac*)-4-Phenyl-3-buten-2-yl Acetate [5 (R_1 = Ph, R_2 = Me)].

Substrate Concn (M)	Catalyst (equiv)	Additive (equiv)	Solvent	Rxn Temp	Rxn Time	Yield[a] (%)	Ratio **9**:**10**	ee (**9**) (%)
0.02	**4** (0.05)	**3** (0.1)	THF	67 °C	40.0 h	79	3.2:1	39
0.02	**4** (0.05)	**3** (0.1)	THF	18 °C	7 d	trace	2.0:1	53
0.02	**4** (0.05)	**3** (0.1)	DMF	153 °C	0.3 h	86	4.0:1	20
0.02	**1** (0.05)	**2** (0.1)	THF	67 °C	40.0 h	79	4.0:1	32
0.02	**1** (0.05)	**2** (0.1)	THF	18 °C	7 d	trace	3.3:1	37
0.02	**1** (0.05)	**2** (0.1)	DMF	153 °C	0.5 h	84	21.7:1	-9
0.10[b]	**1** (0.05)	**2** (0.1)	THF	23 °C	72 h	75	4.8:1	21

[a]Isolated yields. [b]Results reported by ref. 7.

The results show that both sparteine and isosparteine can indeed behave as a chiral bidentate ligand, between which isosparteine is preferred overall, presumably because its pocket depth is deeper than that of sparteine. This fact is reflected in the stability of the allyl Pd complex and shorter reaction time. But there are more points to this: When 1,3-diarylallylic acetates were reacted with $NaCH(CO_2Me)_2$, Pd-sparteine system shows slightly higher enantiomeric excesses than Pd-isosparteine system (See Table 1.). Also, the 1,3-diarylallylic acetate gave significantly higher yields and enantiomeric excesses than the cyclic allylic acetate and 1,3-dialkylallylic acetate. However, with 1,3-dialkyl and cyclic allylic acetates satisfactory results were obtained from Pd-isosparteine complex (see Tables 2 - 4). Unsymmetrical 4-phenyl-3-buten-2-yl acetate illustrates the regioselectivity in the allylic alkylation. As it is found for most Pd-catalyzed substitution reactions,[10] the Pd-isosparteine catalyst preferentially directs the nucleophilic attack at the less hindered terminus of the allyl fragment: The observed product ratios of **9** to **10** with reasonable ee's were 2.0:1 to 4.0:1 in isosparteine reactions (see Table 4). Therefore, (-)-α-isosparteine, which can be readily synthesized from (-)-sparteine, was proven to be an effective chiral ligand for enantioselective control in Pd-catalyzed allylations.

EXPERIMENTAL

General: All reactions involving air- or moisture sensitive materials were carried out under an inert atmosphere of N_2. THF and diethyl ether were freshly distilled from sodium/benzophenone, DMF, CH_3CN and CH_2Cl_2 from powdered CaH_2, and MeOH from NaOMe. Melting points were determined on a Thomas-

Hoover capillary melting point apparatus and uncorrected. ^{1}H NMR spectra were obtained on a Varian Gemini 200 (200 MHz) or a Gemini 300 (300 MHz) spectrometer. Elemental analyses were performed by Carlo Erba EA 1108 elemental analyzer. Optical rotations were obtained on a Rudolph Autopol III digital polarimeter. Enantiomeric excess(%) of products were determined either by chiral HPLC or GC; methyl 2-carbomethoxy-3,5-diphenylpent-4-enoate [**6** ($R_1 = R_2$ = Ph): HPLC; a Daicel Chiral OP(+) column], methyl 2-carbomethoxy-3-methylhex-4-enoate [**6** ($R_1 = R_2$ = Me): GC; a Chiraldex GTA capillary column (30 m x 0.25mm)], dimethyl 2-cyclohexen-1-ylmalonate [**8**: GC; a Chiraldex BPH capillary column (30 m x 0.25mm)], and methyl 2-carbomethoxy-3-methyl-5-phenylpent-4-enoate [**9**: HPLC; a Daicel OJ column].

[Pd(π-allyl)(isosparteine)]PF_6 (**4**): Isosparteine (1.0 g, 4.25 mmol) was added to a solution of 707 mg (1.93 mmol) of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ in 30 mL CH_2Cl_2, which was followed by addition of a solution of 977 mg (3.86 mmol) $AgPF_6$ in 10 mL MeOH. And the mixture was stirred in the dark for 2 h. The precipitate of AgCl was filtered off on Celite. Et_2O (50 mL) was slowly added to the filtrate. And the resulting precipitate was collected by filtration, washed with Et_2O and pentane, and dried *in vacuo*. Yield: 1.7 g (85%). mp 174 - 7 °C (dec.). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.45 (m, 22 H), 2.96 (d, J = 11.7 Hz, 1 H), 3.20 - 3.45 (m, 4 H), 3.54 (dd, J = 2.3 and 6.8 Hz, 1 H), 3.75 (d, J = 12.8 Hz, 1 H), 4.15 (d, J = 6.8 Hz, 1 H), 5.76 - 5.91 (m, 1 H). Anal. calcd. for $C_{18}H_{31}F_6N_2PPd$: C 41.03, H 5.93, N 5.32; found: C 41.02, H 5.94, N 5.47.

Methyl (*R*)-2-carbomethoxy-3,5-diphenylpent-4-enoate [**6** ($R_1 = R_2$ = Ph)]: A solution of 0.40 mmol $NaCH(CO_2Me)_2$, generated from 52.4 mg (0.40 mmol) of dimethyl malonate and 9.5 mg (0.40 mmol) of NaH in 5 mL of DMF, were added dropwise to a solution of 5.2 mg (0.01 mmol) of [Pd(π-Allyl)(Isosparteine)]PF_6 (**4**), 50 mg (0.20 mmol) of 1,3-diphenyl-2-propen-1-yl acetate [**5** ($R_1 = R_2$ = Ph)], and 4.7 mg (0.02 mmol) of isosparteine (**3**) in 4.9 mL DMF. The reaction mixture was stirred under reflux. After 0.3 h, 5 mL of 1 N HCl was added and the reaction mixture was poured into water (20 mL) and extracted with ether. The resulting extracts were washed with brine, dried over $MgSO_4$, and filtered. The solution was evaporated under reduced pressure. The residue was purified by column chromatography (20% ethyl acetate in hexane) to afford the product (55 mg, 86%). 88% ee. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.52 (s, 3 H), 3.71 (s, 3 H), 3.96 (d, J = 11.1 Hz, 1 H), 4.27 (dd, J = 8.4 and 11.1 Hz, 1 H), 6.33 (dd, J = 8.4 and 15.9 Hz, 1 H), 6.49 (d, J = 15.9 Hz, 1 H), 7.20 - 7.35 (m, 10 H).

Methyl (*R*)-2-carbomethoxy-3-methylhex-4-enoate [**6** ($R_1 = R_2$ = Me)]: This compound was prepared from the corresponding allylic acetate [**5** ($R_1 = R_2$ = Me)] in THF following the same procedure as that given above for the preparation of methyl (*R*)-2-carbomethoxy-3,5-diphenylpent-4-enoate. The same isolation procedure gave a 83% yield of the product with 69% ee. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.06 (d, J = 6.8 Hz, 3 H), 1.64 (d, J = 6.2 Hz, 3 H), 2.80 - 2.98 (m, 1 H), 3.27 (d, J = 9.1 Hz, 1 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 5.28 - 5.58 (m, 2 H).

Dimethyl (*S*)-2-cyclohexen-1-ylmalonate (**8**): 63% yield. 62% ee. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32 - 1.43 (m, 1 H), 1.51 - 1.63 (m, 1 H), 1.70 - 1.83 (m, 2 H), 1.96 - 2.03 (m, 2 H), 2.87 - 2.95 (m, 1 H), 3.30 (d, J = 9.6 Hz, 1 H), 3.75 (s, 6 H), 5.51 - 5.55 (m, 1 H), 5.75 - 5.82 (m, 1 H).

Methyl (*R*)-2-carbomethoxy-3-methyl-5-phenylpent-4-enoate (9): 60% yield. 39% ee. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.20 (d, *J* = 6.7 Hz, 3 H), 3.03 - 3.21 (m, 1 H), 3.40 (d, *J* = 8.9 Hz, 1 H), 3.67 (s, 3 H), 3.74 (s, 3 H), 6.12 (dd, *J* = 8.4 and 15.8 Hz, 1 H), 6.46 (d, *J* = 15.8 Hz, 1 H), 7.18 - 7.36 (m, 5 H).

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REFERENCES

1. a) Hayashi, T.; Kumada, M. In *Asymmetric Synthesis*; Morrison, J. D., Ed.: Academic Press; Orlando, FL, 1985, Vol. 5, Chap. 5.
   b) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175.
   c) Bosnich, B.; Fryzuk, M. D. *ibid.* **1981**, *12*, 119.
   d) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901.
2. a) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G. et al., Eds.; Pergamon Press; Oxford, 1982, Vol. 8, p799.
   b) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361.
   c) Consiglio, G; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.
3. Trost, B. M.; Scanlan, T. S. *Tetrahedron Lett.* **1986**, *27*, 4141.
4. Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232.
5. Leutenegger, U.; Umbricht, G.; Fahrni, C.; Matt, P. V.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.
6. a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005.
   b) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.
   c) Corey, E. J.; Imai, N.; Zhang, H. Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.
7. Togni, A. *Tetrahedron: Asym.* **1991**, *2*, 683.
8. a) For a review on chemical application of C_2 symmetry, see Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
   b) Kubota, H.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 8135.
9. a) Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1316.
   b) Leonard, N. J.; Thomas, P. D.; Gash, V. W. *J. Am. Chem. Soc.* **1955**, *77*, 1552.
   c) Leonard, N. J.; Morrow, D. F. *J. Am. Chem. Soc.* **1958**, *80*, 371.
10. a) Trost, B. M.; Hung, M. H. *J. Am. Chem. Soc.* **1984**, *106*, 6837.
   b) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033.
   c) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723.

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