Enantiotopic Discrimination in Palladium-Mediated Nucleophilic Substitutions on Achiral Substrates: Chiral Ligand versus Chiral Nucleophile

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Dedicated to Prof. Oleg Kulinkovich on the occasion of his retirement

Abstract: The Tsuji–Trost reaction performed on an achiral allylic ester using a chiral ligand–achiral nucleophile couple or a achiral ligand–chiral nucleophile couple, afforded optically enriched β-vinylcyclohexenyl amines. Thus, the hypothesis of a differentiation between two diastereotopic allylic sites of a π-allyl palladium complex by a nucleophile, confirm previous observations.

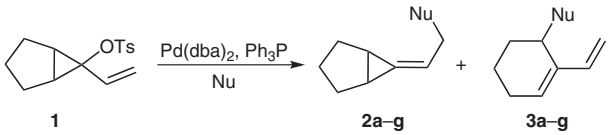
Key words: nucleophilic substitutions, π-allyl palladium complexes, cyclopropylidenes, cyclohexenes, amines

Recently,[1] we showed that the regioselectivity of palladium(0)-mediated nucleophilic substitution on bicyclo[3.1.0]hexanol allylic sulfonic ester **1** was highly dependent on the nature of the nucleophile (Table 1). Thus, depending on the nucleophilic species, cyclopropylidenes **2a–g** or vinylcyclohexenes **3a–g** could be obtained as unique regioisomeric products (entries a and b) or as a mixture of regioisomers (entry c). Interestingly, *N*-tosyl benzylamine (entry d) only afforded the cyclopropylidene, but as a mixture of diastereomers that were inseparable by silica gel chromatography.

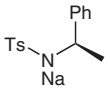
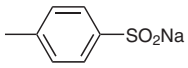
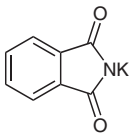
Here we show, with some additional supporting examples, that the conversion, regio- and diastereoselectivities of the palladium-catalyzed nucleophilic substitution are also closely linked to the nature of the solvent and the temperature of the reaction. In a complementary fashion, we examine the behavior of an achiral substrate in the same reaction in order to study both diastereo- and enantioselectivities.

Thus, a dramatic effect of the solvent was observed when the reaction was performed with sodium *p*-tolylsulfinate (entry e), giving low conversion in tetrahydrofuran and an inverse diastereomeric ratio in dimethyl sulfoxide. As for *N*-tosyl benzylamine, the lithium diphenylphosphine borane (entry f) only gave the cyclopropylidene derivative, while potassium phthalimide (entry g) furnished a mixture of the two possible products. Unexpectedly, when the reaction was carried out with the (*R*)-2-methylbenzylamine as basic nucleophile in dimethyl sulfoxide at 80 °C, no trace of the possible diastereomeric cyclopropylidenes

Table 1 Palladium(0)-Mediated Nucleophilic Substitution on **1**

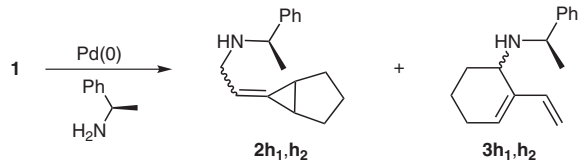


1 **2a–g** **3a–g**

Entry	Nu	Solvent	Temp (°C)	Yield (%)	Ratio **2/3**	
a	HCOONa	THF	20	83	0	100
b	NaN_3	THF	20	80	0	100
c	$(CO_2Et)_2CHNa$	THF	20	82	32	68
d		THF	20	73	100	0
e		THF	20	44[a]	61	39
		DMSO	20	84	35	65
f	$LiP(BH_3)Ph_2$	THF	20	85	100	0
g		DMSO	80	79	80	20

[a] 50% conversion.

2h$_1$ or **2h$_2$** (formed in THF at 20 °C) was detected in NMR analysis. Under these conditions, only the cyclohexene derivatives were isolated as a separable mixture of diastereomers **3h$_1$** and **3h$_2$** (Scheme 1).



2h$_1$,h$_2$ **3h$_1$,h$_2$**

solvent	temp (°C)	yield (%) (ratio)	
THF	20	25 (62:38)	55 (60:40)
DMSO	80	0	81 (54:46)

Scheme 1

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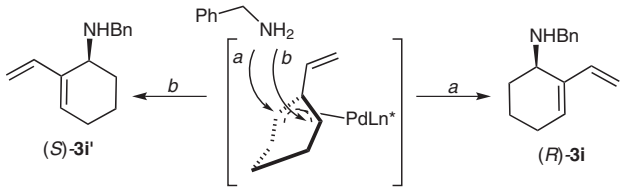
The advantage of forming separable isomers, on the one hand, allowed access to enantiomerically pure vinylcyclohexenamines **2** and, on the other hand, provided a tool with which to explore an inverse approach using our substrate with benzylamine in the presence of a chiral ligand of palladium(0).

The mechanistic implications of the asymmetric induction in the palladium-catalyzed coupling reaction between both achiral allylic esters and nucleophiles have previously been reported using a chiral phosphine ligand.[2] In our example, the achiral nucleophile is able to distinguish between two diastereotopic allylic sites of the palladium π-allyl complex (Scheme 2, route *a* or *b*), to afford the enantiomeric amines **3i** or **3i′**. This substitution thus probes a competitive route, furnishing optically enriched amines.



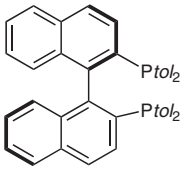
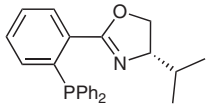
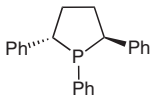
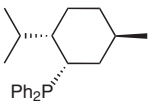
Scheme 2

When the reaction was carried out using triphenylphosphine as ligand, total conversion occurred in dimethyl sulfoxide when gentle heating was applied. As expected, total chemoselectivity was observed and the racemic amine **3i/3i′** was isolated with acceptable yields (67%; Table 2, entry 1).

Performing the reaction with (*R*)-*tol*BINAP (entry 2), under the conditions described above (DMSO, 80 °C), gave a good yield with a moderate enantioselectivity (determined by chiral HPLC). Curiously, using a phenyloxazoline derivative as chiral ligand (entry 3), an inverse enantioselectivity was found with moderate yield, while the (2*S*,5*S*)-1-phenyl-2,5-diphenylphospholane (entry 4) gave the same isomer as with (*R*)-*tol*BINAP and a comparable enantiomeric excess. Lastly, the reaction failed in the presence of neomenthyldiphenylphosphine as chiral ligand (entry 5).

In conclusion, firstly we undertook a study of the regioselectivity of the palladium-promoted nucleophilic substitution on bicyclo[3.1.0]hexane allylic sulfonates. The regioselectivity of the reaction was highly dependent on the nature of the nucleophile, the solvent and the temperature of the reaction. Secondly, the experimental conditions were optimized, allowing the vinylcyclohexylamine moieties to be obtained exclusively using an achiral substrate and a chiral nucleophile. We then pursued a comparative study on the enantioselectivity when the nucleophilic substitutions were performed using an achiral substrate and chiral ligands of palladium. The positive results reported here are promising and the extension of this pathway could constitute a novel approach to the enantioselective synthesis of biologically active natural products.

Table 2 Effect of Ligand on the Palladium(0)-Mediated Nucleophilic Substitution[a]

Entry	Ligand L*	Yield (%)	er[b]
1	PPh_3	67	–
2		83	60:40
3		42	40:60
4		27	60:40
5		0	50:50

[a] Reaction performed in DMSO at 80 °C.
[b] Enantiomeric ratio determined by chiral HPLC.

Preparative column chromatography was performed on SDS flash silica gel (35–70 mesh). Polarimetric measurements were performed on a Perkin–Elmer 241 polarimeter. Infrared (IR) spectra were recorded as thin films on a FT-IR Perkin–Elmer spectrophotometer (Spectrum One). ^{1}H NMR (250 and 360 MHz), ^{13}C (63 and 90 MHz) and ^{31}P NMR (101 MHz) spectra were recorded in $CDCl_3$ on Bruker AM 250 and AM 360 spectrometers and the data are reported in δ (ppm) units from $CDCl_3$ (^{1}H, δ = 7.27 ppm; ^{13}C, δ = 77 ppm), or from H_3PO_4 (^{31}P, δ = 0.0 ppm). Mass spectra (electronic impact or chemical ionization) were measured with a Nermag R-10 coupled with a OK1 DP 125 gas chromatographer and a Agilent 5973 Network coupled with a 6890N gas chromatograph; relative percentages are shown in brackets. High resolution mass spectra (electron impact or electrospray) were recorded with a Finnigan MAT 95S instrument. Elemental analyses were carried out on a Carlo Erba 1106 analyzer.

Palladium-Catalyzed Nucleophilic Substitution; General Procedure

In a Schlenk tube, a solution of $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 2 mol%) and ligand (0.025 mmol, 5 mol%) in solvent (1 mL) was stirred for 15 min at r.t. under argon. This solution was added to a solution of allylic sulfonic ester **1** (139 mg, 0.5 mmol) in solvent (1 mL). This mixture was then transferred under argon through a cannula to a solution of nucleophile (0.6 mmol, 1.2 equiv) in solvent (2 mL) and brought to the desired temperature. After about 12 h, the disappearance of the tosylate was observed on TLC and the cooled solution was hydrolyzed by addition of a solution of sat. NH_4Cl (1 mL). The aqueous phase was then extracted with Et_2O (2 × 5 mL) and the combined organic phases were dried on $MgSO_4$, concentrated and purified by flash column chromatography.

2-Bicyclo[3.1.0]hex-6-ylideneethyl 4-Methylphenyl Sulfone (2e) and 1-Methyl-4-[(2-vinylcyclohex-2-en-1-yl)sulfonyl]benzene (3e)

The reaction using sodium *p*-toluene sulfinate as nucleophile and performed in DMSO at 20 °C for 12 h gave, after flash chromatog-

raphy (silica gel; hexanes–EtOAc, 9:1), a 35:65 inseparable mixture of **2e** and **3e**.

Yield: 84%; pale-yellow oil.

IR (neat): 2964, 2867, 1920, 1803, 1598 cm^{-1}.

2e

^1H NMR (250 MHz, $CDCl_3$): δ = 1.37–1.47 (m, 2 H), 2.02–2.07 (m, 2 H), 2.16–2.22 (m, 2 H), 2.37 (m, 2 H), 2.45 (s, 3 H), 3.87 (dd, *J* = 7.0, 5.7 Hz, 2 H), 5.73 (t, *J* = 7.0 Hz, 1 H), 7.32 (m, 2 H), 7.72 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 20.4, 21.1, 21.6, 22.4, 59.7, 106.5, 128.5, 129.5, 136.5, 138.2, 143.0.

HRMS (EI): *m*/*z* calc for $C_{15}H_{18}O_2S$: 262.1027; found: 262.1013.

3e

^1H NMR (250 MHz, $CDCl_3$): δ = 1.56–1.81 (m, 6 H), 2.46 (s, 3 H), 4.04 (d, *J* = 4.8 Hz, 1 H), 4.89 (d, *J* = 10.9 Hz, 1 H), 5.10 (d, *J* = 17.5 Hz, 1 H), 6.17 (t, *J* = 3.9 Hz, 1 H), 6.24 (dd, *J* = 17.5, 10.9 Hz, 1 H), 7.32 (m, 2 H), 7.75 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.8, 23.6, 24.7, 27.4, 61.2, 112.3, 124.2, 128.9, 129.1, 135.6, 137.6, 142.6, 144.4.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{18}O_2S$: 262.1027; found: 262.1008.

{2-Bicyclo[3.1.0]hex-6-ylidenethyl(diphenyl)phosphonio}(trihydrido)borate (2f)

The nucleophile was prepared at –78 °C by addition of *n*-BuLi (1.6 M in hexane, 0.32 mL) to a solution of diphenylphosphine borane (100 mg, 0.5 mmol) in THF (2 mL) then allowed to warm to r.t. before addition of the π-allyl complex. After flash chromatography (silica gel; hexanes–EtOAc, 9:1), the cyclopropylidene **2f** was obtained as the unique product.

Yield: 130 mg (85%); pale-yellow oil.

IR (neat): 3369, 2953, 2862, 2381 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.21–1.75 (m, 11 H), 3.14 (m, 2 H), 5.74 (q, *J* = 7.6 Hz, 1 H), 7.46 (m, 6 H), 7.67 (m, 4 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 20.5, 21.2, 29.6, 30.5, 109.5, 128.6, 128.7, 131.1, 131.2, 132.1, 132.2, 132.3, 137.0.

^{31}P NMR (101 MHz, $CDCl_3$): δ = 16.0 (d, *J* = 69 Hz).

HRMS (ES): *m*/*z* calcd for $C_{20}H_{24}BPNa$: 329.1606; found: 329.1601.

2-(2-Bicyclo[3.1.0]hex-6-ylideneethyl)-1*H*-isoindole-1,3(2*H*)-dione (2g) and 2-(2-Vinylcyclohex-2-en-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (3g)

The reaction using potassium phthalimide as nucleophile, performed in DMSO at 80 °C for 12 h gave, after flash chromatography (silica gel; hexanes—EtOAc, 9:1), an 80:20 inseparable mixture of **2g** and **3g**.

Yield: 79%; pale-yellow oil.

IR (neat): 2977, 2863, 1772, 1713 cm^{-1}.

2g

^1H NMR (250 MHz, $CDCl_3$): δ = 1.04–1.50 (m, 4 H), 2.05 (m, 2 H), 2.10–2.20 (m, 2 H), 4.39 (d, *J* = 5.4 Hz, 2 H), 5.84 (t, *J* = 5.4 Hz, 1 H), 7.71–7.88 (m, 4 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 20.0, 20.5, 21.2, 29.4, 38.8, 113.2, 123.2, 132.3, 133.7, 133.8, 168.1.

MS (EI): *m*/*z* (%) = 253 (4) [M^+], 160 (61), 148 (83), 130 (36), 106 (100), 91 (71).

HRMS (ES): *m*/*z* calcd for $C_{16}H_{15}NO_3$: 253.1103; found: 253.1101.

3g

^1H NMR (250 MHz, $CDCl_3$): δ = 1.60–1.85 (m, 6 H), 4.80 (d, *J* = 11.7 Hz, 1 H), 5.12 (m, 1 H), 5.12 (d, *J* = 17.4 Hz, 1 H), 6.15 (t, *J* = 4.8 Hz, 1 H), 6.25 (dd, *J* = 17.4, 11.7 Hz, 1 H), 7.71–7.88 (m, 4 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 20.1, 25.5, 29.4, 45.6, 110.9, 123.2, 131.9, 132.5, 133.0, 137.2, 138.5, 168.5.

MS (EI): *m*/*z* (%) = 253 (1) [M^+], 148 (100), 130 (34), 106 (95), 91 (71).

HRMS (ES): *m*/*z* calcd for $C_{16}H_{15}NO_3$: 253.1103; found: 253.1098.

(1*R*)-*N*-2-Bicyclo[3.1.0]hex-6-ylethyl-1-phenylethenamine $2h_1$/$2h_2$ and [(1*R*)-1-Phenylethyl](2-vinylcyclohex-2-en-1-yl)amine $3h_1$ and $3h_2$

The reaction using sodium (1*R*)-1-phenylethylamine as nucleophile in THF at 20 °C for 12 h gave, after flash chromatography (silica gel; hexanes–EtOAc, 9.5:0.5), a 31:69 mixture of inseparable diastereomers $\mathbf{2h_1}$ and $\mathbf{2h_2}$ (ratio 68:32) and separable diastereomers $\mathbf{3h_1}$ and $\mathbf{3h_2}$ (ratio 40:60) in 80% overall yield. The ratio of the inseparable diastereomers $\mathbf{2h_1}$ and $\mathbf{2h_2}$ was determined by HPLC [Regis (*S*,*S*)-Whelk® 01] after amidation to the benzoyl derivatives. When the reaction was carried out in DMSO at 80 °C for 12 h, only the separable diastereomers $\mathbf{3h_1}$ and $\mathbf{3h_2}$ (ratio 46:54) were obtained.

Diastereomers $2h_1$ and $2h_2$

Yield: 25% (THF, 20 °C); 0% (DMSO, 80 °C); colorless oil; R_f = 0.1 (EtOAc).

^1H NMR (360 MHz, $CDCl_3$): δ = 1.11–1.35 (m, 2 H), 1.39 (d, *J* = 6.8 Hz, 6 H), 1.52–1.56 (m, 2 H), 1.70–1.90 (m, 12 H), 2.03–2.28 (m, 2 H), 3.22–3.24 (m, 4 H), 3.86 (q, *J* = 6.8 Hz, 2 H), 5.82 (t, *J* = 6.5 Hz, 2 H), 7.24–7.37 (m, 10 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 20.3, 20.5, 21.3, 24.1, 24.4, 29.5, 29.6, 48.6, 48.7, 57.3, 118.1, 118.3, 126.6, 126.8, 128.4, 131.8, 132.0, 145.7.

MS (EI): *m*/*z* (%) = 227 (2) [M^+], 122 (16), 120 (16), 106 (22), 105 (100), 79 (22).

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_{22}N$: 228.1747; found: 228.1752.

Diastereomer $3h_1$

Yield: 22% (THF, 20 °C); 37% (DMSO, 80 °C); pale-yellow oil; R_f = 0.8 (EtOAc); $[\alpha]_D^{20}$ +50 (*c* 1.18, $CHCl_3$).

IR (neat): 3435, 2959, 2863, 1641 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.20–2.20 [m, 7 H including 1.36 (d, *J* = 6.9 Hz, 3 H)], 3.53 (m, 1 H), 3.92 (q, *J* = 6.9 Hz, 1 H), 5.00 (d, *J* = 11.0 Hz, 1 H), 5.31 (d, *J* = 17.5 Hz, 1 H), 5.81 (t, *J* = 4.0 Hz, 1 H), 6.29 (dd, *J* = 17.5, 11.0 Hz, 1 H), 7.20–7.43 (m, 5 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 16.5, 24.4, 25.9, 27.1, 50.2, 58.0, 110.1, 126.6, 126.7, 128.2, 131.8, 138.3, 138.9, 147.4.

MS (EI): *m*/*z* (%) = 227 (15) [M^+], 120 (24), 106 (52), 105 (100), 79 (30), 77 (19).

Anal. Calcd for $C_{16}H_{21}N$ (227.34): C, 84.53; H, 9.31. Found: C, 84.29; H, 9.28.

Diastereomer $3h_2$

Yield: 33% (THF, 20 °C); 44% (DMSO, 80 °C); pale-yellow oil; R_f = 0.7 (EtOAc); $[\alpha]_D^{20}$ +24 (*c* 1.31, $CHCl_3$).

IR (neat): 3430, 2934, 2864, 1643 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 0.85–2.30 [m, 7 H including 1.38 (d, *J* = 6.5 Hz, 3 H)], 3.18 (m, 1 H), 3.91 (q, *J* = 6.5 Hz, 1 H), 4.72 (d, *J* = 17.6 Hz, 1 H), 4.76 (d, *J* = 10.8 Hz, 1 H), 5.78 (t, *J* = 4.0 Hz, 1 H), 6.14 (dd, *J* = 17.6, 10.8 Hz, 1 H), 7.20–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5, 24.4, 25.2, 25.7, 46.7, 54.8, 110.5, 125.3, 127.0, 127.9, 128.7, 134.7, 143.2, 144.8.

MS (EI): *m*/*z* (%) = 227 (17) [M^+], 120 (18), 106 (51), 105 (100), 95 (18), 94 (17), 91 (17), 79 (28), 77 (19).

Anal. Calcd for $C_{16}H_{21}N$ (227.34): C, 84.53; H, 9.31. Found: C, 84.18; H, 9.25.

***N*-Benzyl-2-vinylcyclohex-2-en-1-amine 3i and 3i′**

After flash chromatography (silica gel; hexanes–EtOAc, 9:1), the enantiomeric excess was determined by HPLC (Chiralpak AD; hexane–*i*-PrOH, 98:2; 0.5 mL/min; λ = 254 nm; temp = 20 °C; t_R = 7.75 and 9.52 min).

Yield: 0–83%; pale-yellow oil.

IR (neat): 3430, 2932, 2865, 1645 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42–1.50 (m, 1 H), 1.52–1.60 (m, 1 H), 1.80–1.89 (m, 1 H), 1.98–2.05 (m, 1 H), 2.16 (m, 2 H), 3.53 (m, 1 H), 3.92 (q, *J* = 6.9 Hz, 1 H), 5.00 (d, *J* = 11.0 Hz, 1 H), 5.31 (d, *J* = 17.5 Hz, 1 H), 5.81 (t, *J* = 4.0 Hz, 1 H), 6.29 (dd, *J* = 17.5, 11.0 Hz, 1 H), 7.20–7.43 (m, 5 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.0, 26.0, 26.2, 49.8, 52.1, 110.1, 126.9, 128.3, 128.4, 132.2, 137.7, 138.6, 140.7.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{19}N$: 213.1517; found: 213.1511.

Anal. Calcd for $C_{15}H_{19}N$ (213.32): C, 84.46; H, 8.98. Found: C, 84.17; H, 8.91.

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