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Enantiodivergence in alkylation of 1-(6-methoxynaphth-2-yl)ethyl acetate by potassium dimethyl malonate catalyzed by chiral palladium-DUPHOS complex

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

Alkylation of racemic 1-(6-methoxynaphth-2-yl)ethyl acetate by potassium dimethyl malonate catalyzed by a chiral palladium-DUPHOS complex afforded the substitution product with 87% ee, along with 6-methoxy-2-vinylnaphthalene that arose from an elimination process, in a 43/57 substitution/elimination ratio. The reaction performed on a mixture of quasi-enantiomeric substrates provided insight into the stereochemical course of the reaction, establishing that—for a given enantiomer of the catalyst, one enantiomer of the substrate afforded mainly the substitution product whereas the other enantiomer underwent elimination.

1. Introduction

Production of optically active organic compounds can be achieved from optically active substrates (through stereoselective reactions or transfer of chirality) from achiral substrates (asymmetric synthesis) or from chiral racemic substrates. In this latter case, kinetic resolution may give access to the enantiomerically enriched substrate, and may lead to an optically active product. The total conversion of a racemic substrate into an optically active product may be achieved through dynamic kinetic resolution or parallel kinetic resolution. Interesting cases are known where—under the influence of an external chiral agent (either reagent or catalyst)—each enantiomer of the substrate affords regioisomers or different products, one of them being enantioenriched (enantiodivergent reactions). The chirality of the optically active reagent or catalyst can then control the selectivities of such reactions.

For enantiodivergent chemical transformations of a racemic mixture under the influence of external chirality (chiral reagent, chiral catalyst) into two products, it was shown that (i) the chirality (configuration) of the reagent or the catalyst may control the distribution of the products; (ii) a quantitative relationship may be established between ees and relative quantities of the products; (iii) the analysis of the product distribution allows the prediction of the distribution of products when using an enantiomerically pure substrate.[1]

An example of such an enantiodivergent reaction has been described for the Pd-catalyzed alkylation of racemic bicyclic allylic carbonates **1**.[2] Both the product of nucleophilic substitution **2** and the 1,3-diene **3** as the elimination product were obtained in moderate enantiomeric excesses. The substitution product arose mainly from one enantiomer of the substrate while the elimination product came from the other enantiomer (Scheme 1).

Herein we report a novel example of the analysis of the control of the distribution and enantiomeric purity of the products formed in a Pd-catalyzed benzylic alkylation reaction of a racemic substrate by a chiral Pd-catalyst.

2. Results and discussion

2.1. The enantioselective Pd-catalyzed benzylic alkylation

In 1992, we disclosed the palladium-catalyzed benzylic alkylation of 1-naphthylethyl acetates and carbonates with malonates.[3] This benzylic substitution by nucleophiles and organometals was further developed by Kuwano.[4] We investigated the stereochemistry of this reaction and the asymmetric synthesis of alkylated products[5] and showed the reaction to be regio- and stereoselective proceeding with overall retention of configuration at the benzylic carbon center. We suggested that the reaction would take place through the formation of π-benzylic palladium complexes with inversion of configuration, followed by a regioselective attack of the π-benzylic ligand also with inversion of configuration.

Optically active alkylation products **5** could be obtained at full conversion of the racemic substrate **4** under Pd/(*S,S*)-BDPP (2,4-bis diphenyldiphosphinopentane) catalysis, albeit in low (30%) ee (Scheme 2). Since neither the substrate nor the product racemized under the reaction conditions, we assumed that the asymmetric

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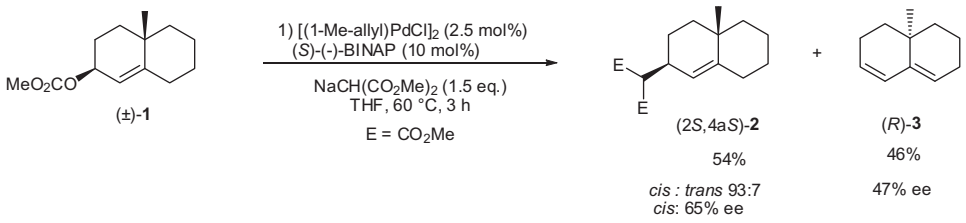
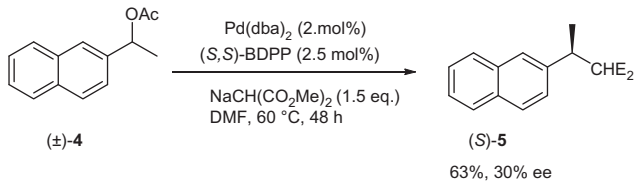
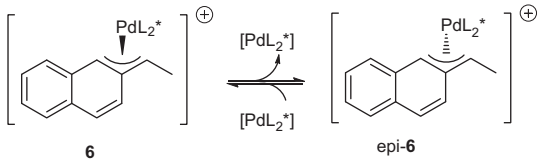


Scheme 1. Enantiodivergent Pd-catalyzed alkylation of bicyclic allylic acetates.[2]



Scheme 2. Enantioselective Pd-catalyzed benzylic alkylation.

induction arose from an equilibration of the diastereomeric π-benzyl intermediate palladium complexes **6**, through a S_N2 mechanism (Scheme 3). Such an isomerization process has been documented for equilibration (interconversion, epimerization) of π-allylic Pd-complexes.[6]



Scheme 3. Equilibration of π-benzylic Pd-complexes through S_N2 displacement.

Later on, in order to improve the enantioselectivity, we investigated the role of various chiral ligands.[7] The study was conducted on the reaction of racemic 6-methoxy-1-(2-naphthylethyl) acetate **7** with potassium dimethyl malonate in DMSO in the presence of $Pd(dba)_2$ as the palladium source and a diphosphine as the chiral ligand. We found that *i*-Pr-DUPHOS ligand was the best compromise in terms of distribution of products (substitution vs elimination) and enantioselectivity for the substitution product (Scheme 4).

The substitution product **8** was obtained along with some decarbomethoxylated compound **9** and the vinyl naphthalene **10** as the elimination product. The decarbomethoxylation of **8** into **9** was shown to proceed without loss of stereochemistry. The combined isolated yield of substitution products of **8** and **9** was 31% versus 42% for the elimination product.

The stereochemical course of the reaction might be the result of several processes, according to the mechanistic scheme depicted in Scheme 5.

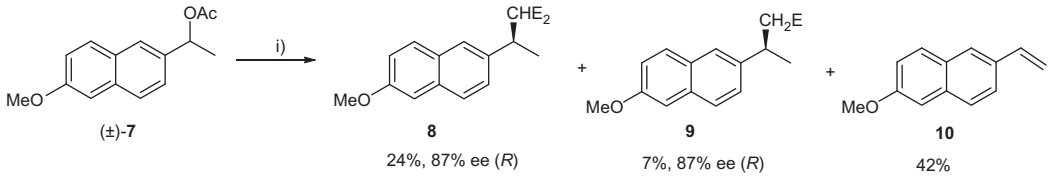
The chiral catalyst may discriminate ($k_S \neq k_R$) between the two enantiomers in the oxidative addition step (ionization) to produce two postulated diastereomeric π-benzylic palladium complexes. These complexes **11** and *epi*-**11** may interconvert (k, k_{-1}) through an S_N2 displacement of the palladium catalyst, resulting in epimerisation by inversion of the stereochemistry. The Pd-complexes may react at different rates with the malonate anion to give (*R*)-**8** and (*S*)-**8**, the alkylation products ($k'_S \neq k'_R$), or elimination product **10** ($k''_S \neq k''_R$). The data obtained (substitution/elimination ratio, enantiomeric purity of the substitution product) did not allow rationalization of the stereochemical course of the reaction, since, for example, the origin of the elimination product could not be determined.

2.2. The use of a quasi-enantiomer mixture as substrate

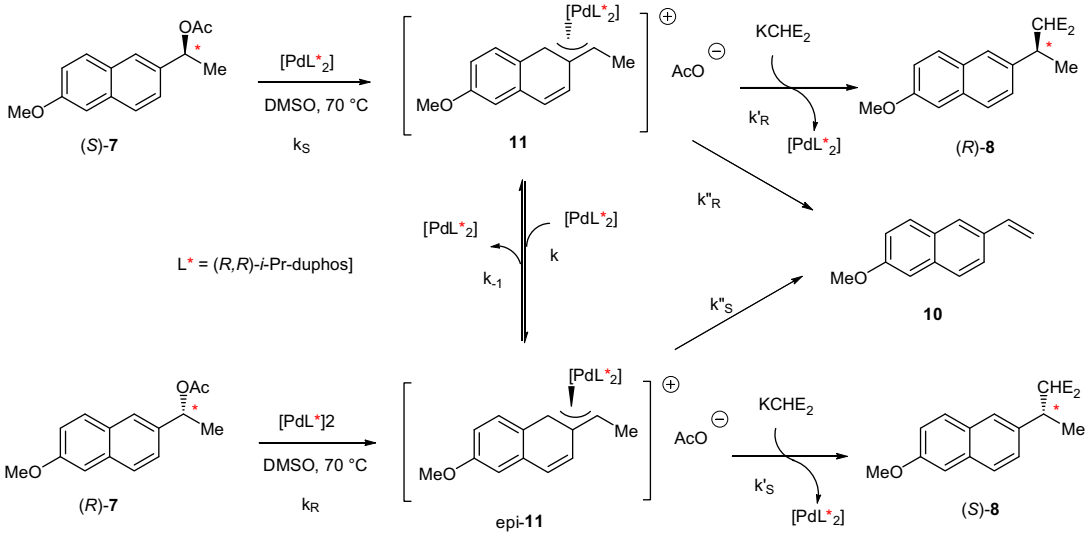
In order to get a deeper insight into the implication of each process for the control of the distribution of substitution/elimination products and the enantioselectivity of the process, we undertook a study of the reaction performed on quasi-enantiomeric[8] substrates (*R*)-**7**[d_3] and (*S*)-**7**. This would allow us to determine the origin of the elimination product **10**. Six compounds (*S*)- and (*R*)-**8**, (*S*)- and (*R*)-**8**-[d_3], **10**, and **10**-[d_3] would then be produced (products arising from decarbomethoxylation were neglected, since they were in small amounts and with the same ee as the malonate they come from) (Scheme 6). For the mechanism it was considered that (i) the π-benzylpalladium complexes have a *syn* stereochemistry; (ii) the discrimination of enantiomers is not so relevant for the enantioselectivity, since a rough estimate of the ratio of rate constants showed a small value for $k_R/k_S \sim 2$; (iii) there is no primary kinetic isotope effect since the deuterium labels are located far from the reactive center (this point was confirmed experimentally), the relative amounts *c*–*h* of these six products may be calculated on the basis of two hypotheses.

The synthesis of (*R*)-**7**[d_3] was achieved by methylation, reduction of 6-hydroxy-2-acetyl-naphthalene, followed by lipase-catalyzed resolution (Scheme 7). This latter compound was obtained from the commercially available 6-bromo-2-naphthol.

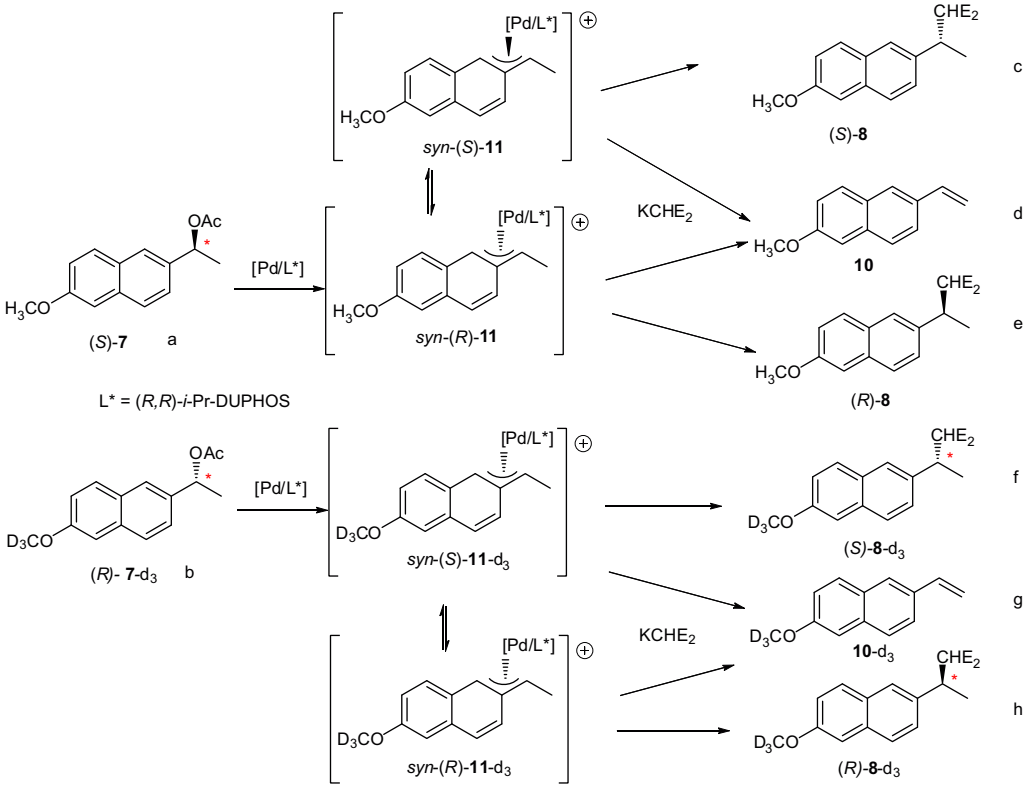
Identification of products (*S*)-**8** and (*R*)-**8**-d_3 will be the indication of the equilibration of Pd-complexes operating by a S_N2 process. Ratios for elimination of deuterated compounds versus elimination of non-deuterated compounds (E_D/E_{ND}), and substitution of deuterated compounds versus/non-deuterated compounds (S_D/S_{ND}) will be indicative of diastereoselection in the elimination process.



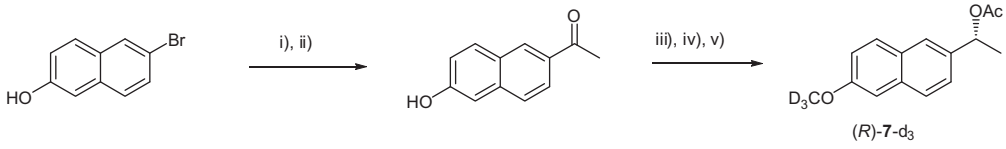
Scheme 4. Alkylation of (±)-**7** with potassium dimethyl malonate under Pd-(*R*,*R*)-*i*-Pr-DUPHOS catalysis. Reagents and conditions: (i) $KCH(CO_2Me)_2$ (2 equiv), $Pd(dba)_2$ (2 mol%), (*R*,*R*)-*i*-Pr-DUPHOS (2 mol%), DMSO, 70 °C, 48 h.



Scheme 5. Processes likely to be involved for the control of product distribution and asymmetric induction.



Scheme 6. Palladium-catalyzed alkylation of quasi-enantiomeric substrates. The 6 compounds produced and their relative molar amounts *c*–*h*.



Scheme 7. Synthesis of (*R*)-**7**-d_3. Reagents and conditions: (i) Et_3N, TMSCl, toluene, 99%; (ii) TlOAc (1.1 equiv), *n*-Bu–O–CH=CH_2 (5 equiv), DMF, 80 °C, 24 h, 87%; (iii) NaH, CD_3I, THF, 55 °C, 12 h, 70%; (iv) $NaBH_4$, MeOH, 3 h, quant; (v) isopropenyl acetate, RGLipase, 43%; (iv) Ac_2O, DMAP, CH_2Cl_2, 68%.

Six independent relationships are needed to estimate the relative amounts *c*–*h* of the 6 products.

Denoting *a* and *b* as the molar fractions of non-deuterated and deuterated substrates, and *c*–*h* the molar fractions of the 6 products, the following data could be obtained:

- $E_D/E_{ND} = g/d$ ratio will be obtained by GC–MS.
- $S_D/S_{ND} = (f+h)/(c+e)$ will also be obtained by GC–MS.
- The 'quasi-enantiomeric excess' denoted as $[(c+f)-(e+h)]/(c+e+f+h)$ can be measured by chiral stationary-phase HPLC. This is positive when the (*S*)-substitution product is the major.
- The ee of the deuterated substitution product $ee_D = (f-h)/(f+h)$ will be determined by ^{2}H NMR in poly-γ-benzyl-L-glutamate (PBLG) anisotropic phase,[9] being positive when (*S*)-**8**-d_3 is the major enantiomer.
- The material balance for the deuterated and non-deuterated products affords the two last needed equations: $a = c + d + e$ and $b = f + g + h$.

The resolution of this system of equations would deliver the relative amounts of products *c*–*h*.

2.3. Two hypotheses depicting the stereochemical course of the reaction

One may anticipate the distribution of the six products obtained in the reaction of a 1:1 mixture of the quasi-enantiomeric substrates with potassium dimethyl malonate under Pd/*i*-Pr-DUPHOS catalysis. For the reaction that afforded substitution and elimination products **8** and **10** in a 43:57 ratio and 87% ee for the substitution product the two following hypotheses can be made.

2.3.1. First hypothesis

There is no equilibration of the diastereomeric intermediate palladium complexes (Scheme 8). This implies that:

- The asymmetric induction arises only from a diastereoselective elimination.
- (*R*)-**8** and (*S*)-**8**-d_3 are the sole substitution products obtained from the corresponding acetates with overall retention of the configuration at the benzylic carbon atom and thus $c = h = 0$.
- The elimination products **10** and **10**-d_3 come from two separate routes.

Under this hypothesis, and with $a = b = 0.5$, one may establish that $E_D/E_{ND} = g/d = [2b - s(1+ee)]/[2a - s(1-ee)]$ and $S_D/S_{ND} = f/e = (1+ee)]/(1-ee)$ where $s = e + f$ and $ee = (f-e)/(e+f)$.

The reaction with (*R,R*)-*i*-Pr-DUPHOS afforded (*R*)-**8** with 87% ee (ee = −0.87) and a selectivity for substitution/elimination 43/57 ($s = 0.43$). Using the above equations, the relative molar portions of the 4 products should be $d = 0.10$ for **10**, $e = 0.40$ for (*R*)-**8**, and $f = 0.03$ for (*S*)-**8**-d_3, $g = 0.47$ for **10**-d_3.

One would measure by GC–MS spectrometry $E_D/E_{ND} = g/d = 4.7$ and $S_{ND}/S_D = e/f = 13$.

A selectivity substitution/elimination factor, which is characteristic of the enantiopure ligand used in the transformation, can then be determined for each enantiomer of the substrate: A_R and A_S. In this case $A_R = k_R$ sub/k_R elim = f/g and $A_S = k_S$ sub/k_S elim = e/d. Using molar ratios obtained for hypothesis 1, one calculates $A_R < 0.1$ and $A_S = 4$.

2.3.2. Second hypothesis

The elimination is not diastereoselective. The rate constants for substitution and for elimination are the same whatever the configuration of the complexes (Scheme 9).

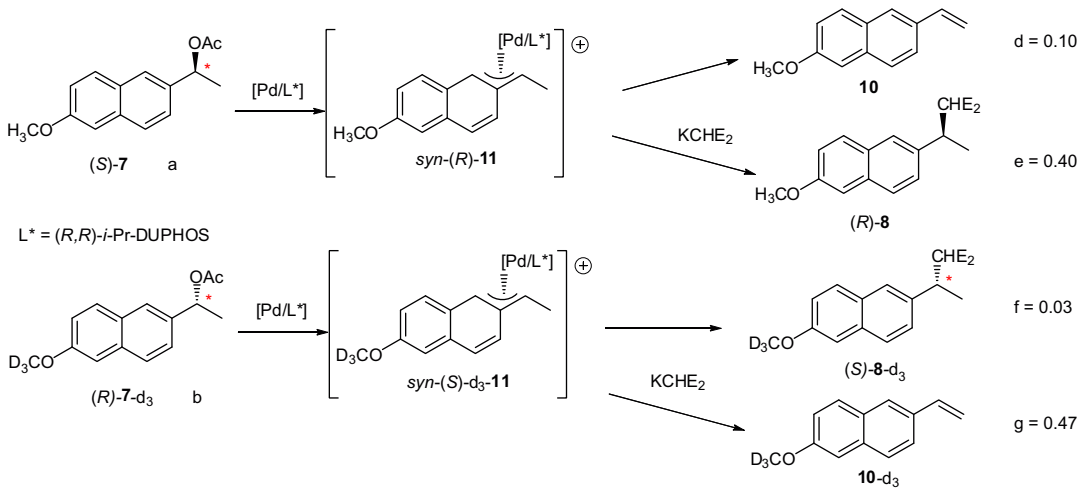
Under this hypothesis, the origin of the asymmetric induction would arise solely from a fast isomerization of intermediate Pd-complexes (*S*)-**11**/(*R*)-**11** and complexes (*S*)-**11**-d_3/(*R*)-**11**-d_3, which interconvert—with the same efficiency—more rapidly than they react with the nucleophile.

One may calculate the molar ratio for each product, when $a = b = 0.5$, $c = f = 0.015$ for (*S*)-**8**-d_3 and (*S*)-**8**, $e = h = 0.20$ for (*R*)-**8**-d_3 and (*R*)-**8**, $d = g = 0.285$ for **10** and **10**-d_3. The deuterated and non-deuterated pathways would afford the same data when the reaction is performed from the racemic substrate. Hence, mass spectrometry will afford $E_D/E_{ND} = g/d = 1$ and $S_D/S_{ND} = f/e = 1$. In fact these values should be corrected for the real values of *a* and *b*, if different from 0.5.

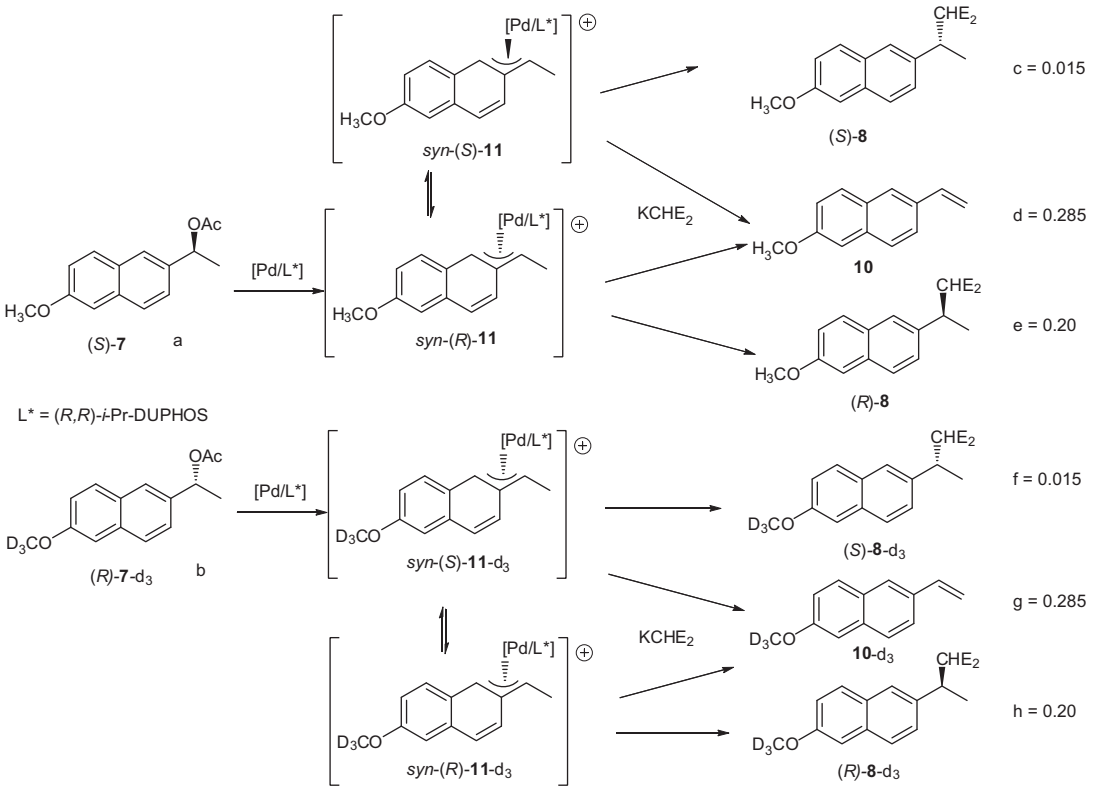
If the intermediate Pd-complexes interconvert more rapidly than they react with the nucleophile (Curtin–Hammett conditions), one may calculate the equilibrium constant between the complexes to be $K = [(S)\text{-}\mathbf{11}]/[(R)\text{-}\mathbf{11}] = 0.1$, while $A_R = A_S = k_{sub}/k_{elim} = 0.8$.

2.4. Results of the Pd-catalyzed alkylation of quasi-enantiomeric substrates

The reaction was actually performed on a *a*/*b* = 53/47 mixture of quasi-enantiomers (*S*)-**7** and (*R*)-**7**-d_3. Under these conditions, a 36/64 selectivity in favor of elimination products was obtained.

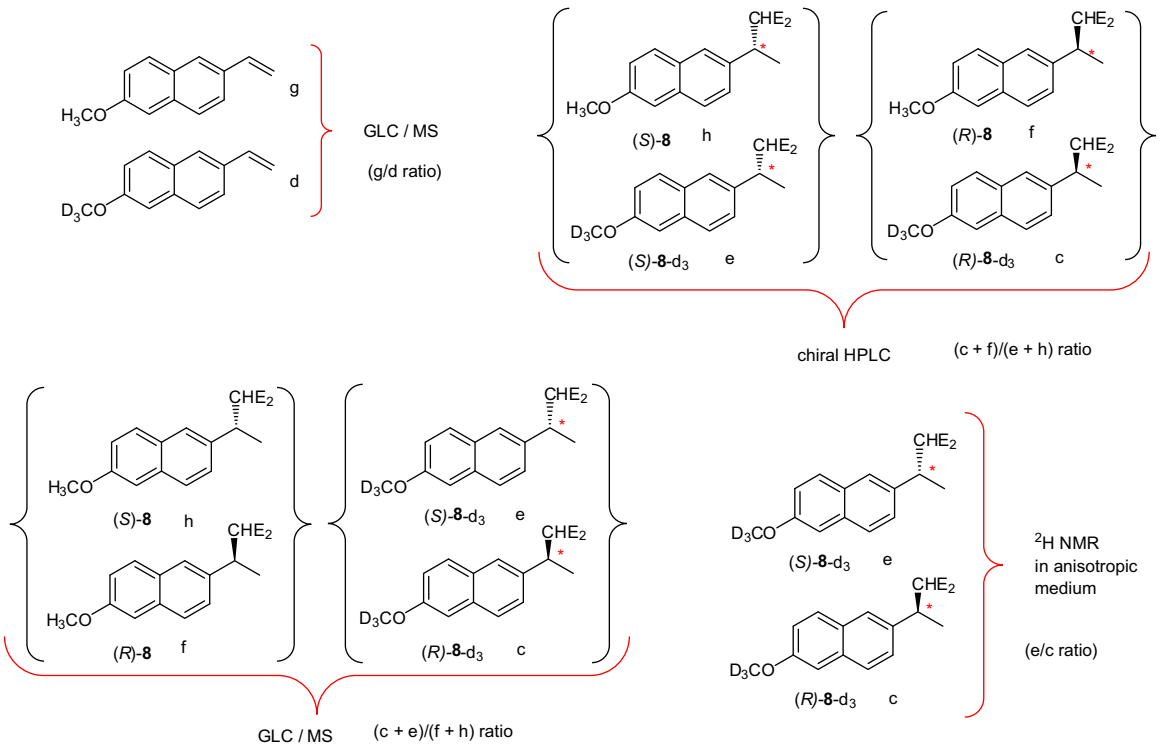


Scheme 8. Hypothesis 1: predicted distribution of products upon the hypothesis that no equilibration of the π-benzylic palladium complexes takes place.



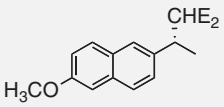
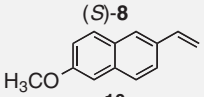
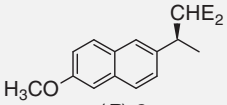
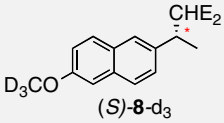
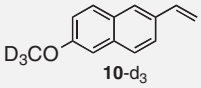
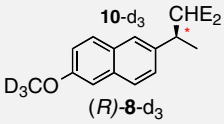
Scheme 9. Second hypothesis: predicted distribution of products upon the hypothesis that for each isomer of palladium complex there is no stereoselection for the substitution/elimination process. The asymmetric induction then arises from the equilibration of the diastereomeric π-benzyl intermediate palladium complexes.

Chiral HPLC analysis gave a 'quasi-enantiomeric excess' of 86% (ee = −0.86). The relative amount of each product was measured through a combination of GC–MS, chiral HPLC, and chirally oriented ^{2}H NMR analyses (Scheme 10). This latter was performed in PBLG/chloroform/THF liquid crystal on the diacids obtained after hydrolysis of substitution products **8** and **8**-d_3.



Scheme 10. Analyses of sets of quasi-enantiomers and isotopomers.

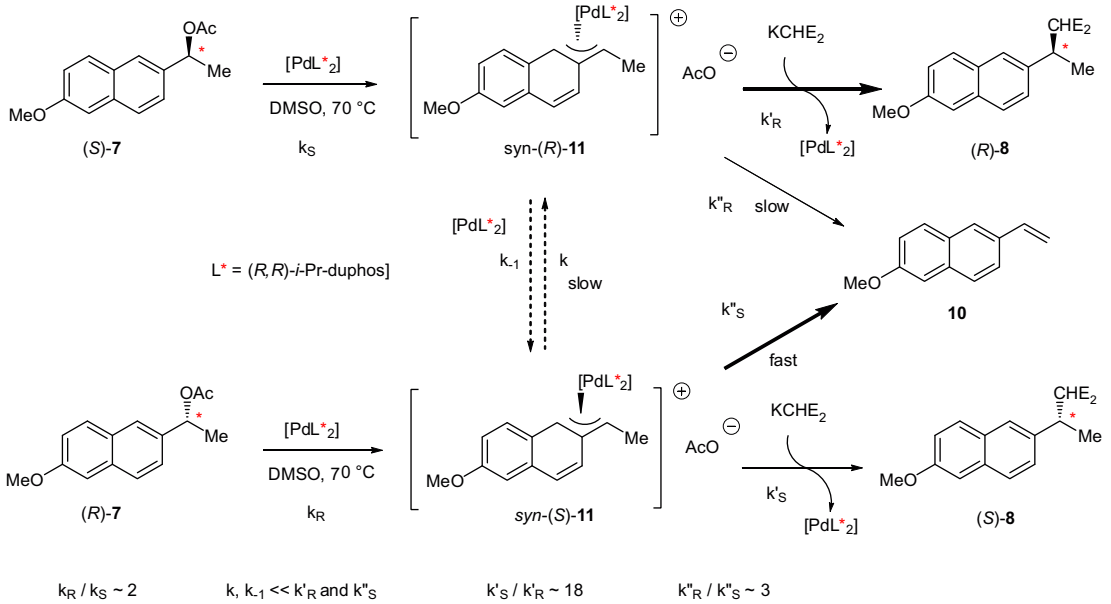
Table 1
Comparison between predicted and experimental data for the Pd/(*R,R*)-*i*-Pr-DUPHOS-catalyzed alkylation of the quasi-racemate with potassium dimethyl malonate

Product	1st Hypothesis		2nd Hypothesis		Experimental results[c]
	a	b	a	b	
 (*S*)-**8**	0	**0**	0.015	**0.013**	**0.02**
 **10**	0.10	**0.195**	0.285	**0.339**	**0.17**
 (*R*)-**8**	0.40	**0.335**	0.200	**0.177**	**0.34**
 (*S*)-**8**-d_3	0.03	**0.025**	0.015	**0.012**	**<0.01**
 **10**-d_3	0.47	**0.445**	0.285	**0.301**	**0.47**
10-d_3  (*R*)-**8**-d_3	0	**0**	0.200	**0.157**	**0.01**
E_D/E_{ND}	4.7	**2.3**	1	**0.9**	**2.8**
S_D/S_{ND}	0.07	**0.07**	1	**0.9**	**<0.1**

[a] Calculated values with a quasi-enantiomeric substrate ($a = b = 0.5$) afforded a 43/57 substitution/elimination ratio (**8**/**10**) and ee = 87% (ee = −0.87).
[b] Calculated values with a mixture of quasi enantiomers showing $a = 0.53$ and $b = 0.47$ afforded a 36/64 substitution/elimination ratio (**8**/**10**) and ee = 86% (ee = −0.86).
[c] Measured values with a mixture of quasi enantiomers showing $a = 0.53$ and $b = 0.47$ afforded a 36/64 substitution/elimination ratio (**8**/**10**) and ee = 86% (ee = −0.86).

Table 1 collects the data of predicted and experimental values for the amounts of the 6 products. It is found that the set of experimental values is closer to the set expected for the first hypothesis (no equilibration of the Pd-intermediate complexes) than to the second one (equilibration of the Pd-intermediate complexes).

The observation of small amounts of (*S*)-**8** and (*R*)-**8**-d_3 is indicative of the existence of an equilibrium involving the Pd-complexes. This is however a slow and poorly effective process, since the substitution products show an overall retention of configuration. The elimination process taking place from (*R*)-**7** via *syn*-(*S*)-



Scheme 11. Asymmetric induction scheme: estimated rate constant ratio values.

11 is highly favored over nucleophilic substitution (by a factor of ~20) since $g/(f+h)$ = [0.46/0.02] = 23. Conversely, for the enantiomer (*S*)-**7** via *syn*-(*R*)-**11**, substitution is favored over elimination by a factor 2 since $(c+e)/d$ = (0.34 + 0.02)/0.17. The measured 2.7 ratio for E_D/E_{ND} means that complex *syn*-(*S*)-**11** undergoes faster elimination than *syn*-(*R*)-**11**. This experimental ratio is closer to the calculated value for hypothesis 1 (no equilibrium between the palladium complexes and a diastereoselective elimination process).

On the basis of these data, an asymmetric induction scheme can now be depicted (Scheme 11). The complex arising from the (*R*)-substrate undergoes elimination around three times faster than the one formed from the (*S*)-substrate. The complex arising from the (*S*)-substrate reacts with the nucleophile 18 times faster than the one formed from the (*R*)-substrate.

One may conclude that the (*S*)-**7** substrate and the (*R,R*)-*i*-Pr-DUPHOS ligand are matched for the production of the substitution product (*R*)-**8**. Indeed, to produce high yields of (*R*)-**8** one has to react enantiomerically pure (*S*)-**7** with dimethylmalonate using Pd/(*R,R*)-*i*-Pr-DUPHOS as the catalyst. Conversely, reaction of enantiomerically enriched (>95% ee) (*R*)-**7** with sodium dimethylmalonate under Pd/(*S,S*)-*i*-Pr-DUPHOS catalysis will afford (*S*)-**8** with reduced amounts of elimination product.

3. Conclusion

In conclusion, the use of quasi-enantiomeric substrates produced a deep insight into the course of the enantiodistinctive Pd-catalyzed alkylation reaction of naphthylethyl acetates with the dimethyl malonate anion. For a given configuration of the catalyst, one enantiomer of the substrate affords mainly the substitution product whereas the other enantiomer is converted mainly into the elimination product.

This informs the choice of the proper matched pair chiral substrate/chiral catalyst in order to minimize the unwanted elimination reaction and optimize the yield and ee of the alkylation product.

4. Experimental

4.1. General

HPLC analyses were performed on a Thermo Separation Product Pump P100 with an UV detector and chiral stationary-phase columns (Chiralcel OD-H, Chiralpak IA).

^{1}H and ^{13}C NMR spectra were recorded on Bruker AM 360, AM 300, and AM 250 spectrometers, operating at 360, 300, and 250 MHz for ^{1}H and at 90.6, 75, and 62.5 MHz for ^{13}C in $CDCl_3$. Chemical shifts for ^{1}H and ^{13}C spectra were referenced internally according to the residual solvent resonances and reported in ppm relative to $CDCl_3$ (7.27 ppm for ^{1}H and 77 ppm for ^{13}C). High resolution mass spectra were measured on a Finnigan MAT 95 S spectrometer or at 70 eV (EI) with a Trace DSQ Thermo Electron spectrometer.

The Rabbit Gastric Lipase (RGL) is a crude lipase extracted from rabbit stomach and was obtained from Sipsy-Jouveinal Company. It is a lyophilized powder showing 20 U/mg (tributyrin as substrate).[10]

4.2. Liquid crystalline NMR sample preparation

PBLG (100 mg, Mol. Wt. 70.000–150.000 purchased from Sigma–Aldrich) and 10 mg of the chiral deuterated solute were weighted into a 5-mm od NMR tube. 380 μl of chloroform and 12 μl of THF were added. After complete dissolution of the polymer, the NMR tube was repeatedly centrifuged (20 times) on a low speed (600 rpm) bench top centrifuge, turning the tube upside-down between each centrifugation, in order to homogenize the viscous mixture.

4.3. Deuterium NMR measurements in PBLG liquid crystal

^{2}H–{^{1}H} NMR spectra were recorded at 61.4 MHz on a Bruker DRX-400 spectrometer equipped with a selective deuterium probe. The temperature was held at 300 K using a BVT3000 variable temperature unit. Proton broad-band decoupling was achieved using the WALTZ-16 composite pulse sequence.

4.4. Preparation of substrates

4.4.1. (6-Bromonaphth-2-yloxy)trimethylsilane

A two-necked round-bottomed flask with condenser was charged with 6-bromo-2-naphthol (2.0 g, 9 mmol), triethylamine (2.53 mL, 18 mmol), and dry toluene (15 mL). Trimethylsilyl chloride (1.4 mL, 11 mmol) was added dropwise and the reaction mixture was stirred for 2 h at reflux. After cooling to room temperature, the mixture was filtered and the organic solvents were removed in vacuo to give (6-bromonaphth-2-yloxy)trimethylsilane (2.63 g, 99%) as a crude product, mp 129 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.31 (s, 9H, $3CH_3Si$), 7.08 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.4 Hz, Ar), 7.15 (br s, 1H, Ar), 7.46 (dd, 1H, ^3J = 8.5 Hz, ^4J = 1.8 Hz, Ar), 7.55 (d, 1H, ^3J = 8.5 Hz, Ar), 7.62 (d, 1H, ^3J = 8.5 Hz, Ar), 7.90 (1H, Ar). ^{13}C NMR ($CDCl_3$, 62.9 MHz): 0.38, 115.0, 117.5, 123.1, 128.4, 128.7, 129.5, 129.7, 130.4, 133.1, 153.3. MS *m/z* (%): 295.9 (100.0), 293.9 (97.1), 280.8 (45.1), 278.8 (43.5), 199.9 (56.4).

4.4.2. 6-Hydroxy-2-acetonaphthone

A DMF solution (9 mL) of $Pd(OAc)_2$ (34 mg, 9.15 mmol), dppp (69 mg, 0.165 mmol), (6-bromonaphth-2-yloxy)trimethylsilane (888 mg, 3 mmol), and TlOAc (868 mg, 3.3 mmol) was stirred at room temperature under argon for 0.25 h. Then, *n*-butyl vinyl ether (4.85 mL, 15 mmol) in DMF (6 mL) was added. The resulting reaction mixture was stirred at 60 °C for 24 h. After cooling to room temperature, 20 mL of 3 M aqueous HCl was added and the hydrolysis was monitored by tlc. The mixture was then neutralized with 1 M aqueous NaOH and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silicagel, heptane/ethyl acetate: 85/15), to give 6-hydroxy-2-acetonaphthone, mp 161 °C (95% yield). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.70 (s, 3H, CH_3–C(O)), 7.19–7.24 (m, 2H, Ar), 7.69 (d, 1H, ^3J = 8.8 Hz, Ar), 7.85 (d, ^3J = 9.3 Hz, Ar), 7.97 (d, 1H, ^3J = 8.8 Hz, Ar), 8.04 (br s, 1H, Ar).

HRMS: calcd for $C_{12}H_{10}O_2$ 186.0675; found: 186.0675.

4.4.3. 6-Methoxy-d_3-2-acetonaphthone

An oven-dried Schlenk tube was charged with NaH (290 mg, 12.1 mmol), 6-hydroxy-2-acetonaphthone (2.045 g, 11 mmol), and purged with argon before adding THF (24 mL). To the cooled mixture (ice-bath) was added dropwise methyl-d_3 iodide (820 μL, 13.2 mmol) and the resulting solution was stirred overnight at 55 °C. After cooling to room temperature, the solution was concentrated and 20 mL of aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with aqueous saturated NaCl solution, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silicagel, heptane, ethyl acetate: 80/20) to give 6-methoxy-d_3-2-acetonaphthone (1.56 g, 70%), mp 110 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.69 (s, 3H, CH_3–C(O)), 7.13–7.22 (m, 2H, Ar), 7.76 (d, 1H, ^3J = 8.5 Hz, Ar), 7.84 (d, 1H, ^3J = 8.5 Hz, Ar), 8.00 (dd, 1H, ^3J = 8.5 Hz and ^4J = 1.8 Hz, Ar),

8.39 (br s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 62.9 MHz): 26.6, 54.7 (h, J = 21.8 Hz, OCD_3), 105.8, 123.1, 119.8, 124.7, 127.2, 127.9, 130.1, 131.2, 132.7, 137.4, 159.8, 197.9.

4.4.4. 1-(6-Methoxy-d_3-naphth-2-yl)ethyl acetate

(*R*)-**7**-[d_3] was prepared by RGL-catalyzed kinetic resolution of the racemic corresponding alcohol obtained by $NaBH_4$ reduction of 6-methoxy-d_3-2-acetonaphthone. The procedure is as follows: to a diethyl ether solution (25 mL) of racemic 1-(6-methoxy-d_3-naphth-2-yl)ethanol (1.025 g, 5 mmol) and isopropenyl acetate (1.5 g, 15 mmol), RGL (200 mg) was added. After 24 h stirring at room temperature, the reaction mixture was filtered over Celite and the organic solution was concentrated in vacuum. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate: 80/20) to give (*R*)-**7**-[d_3] (531 mg, 43%) enantiomerically pure and remaining alcohol (369 mg, 35%) with an enantiomeric excess of 37% for the (*S*)-configuration.

A second RGL-catalyzed kinetic resolution of remaining alcohol (ee = 37%) provided (*R*)-**7**-[d_3] (123 mg) and (*S*)-1-(6-methoxy-d_3-naphth-2-yl)ethanol which could be obtained enantiomerically pure after recrystallization with EtOAc/hexane.

Enantiomers of 1-(6-methoxy-d_3-naphth-2-yl)ethanol and of **7**-[d_3] were resolved by HPLC analysis with a chiral stationary-phase column Chiracel OD-H [hexane/isopropanol: 90/10, 0.5 mL min^{-1}, t = 17 min ((*S*)-enantiomer), t = 23 min ((*R*)-enantiomer)] and t = 10 min ((*S*)-enantiomer), t = 11 min ((*R*)-enantiomer)], respectively.

4.5. Procedure for asymmetric palladium-catalyzed benzylic alkylation

Acetate **7** (244 mg, 1 mmol) in 1 mL of DMSO was added under argon to a mixture of $Pd(dba)_2$ (11.5 mg, 0.02 mmol) and (*R*,*R*)-*i*Pr-DUPHOS (12.6 mg, 0.03 mmol) in 1 mL of DMSO. After 0.25 h stirring, this solution was added to a suspension of potassium dimethyl malonate obtained from *t*-BuOK (224 mg, 2 mmol) and dimethyl malonate (230 mL, 2 mmol) in 2 mL of DMSO. The reaction mixture was stirred at 70 °C for 48 h. After cooling to room temperature, it was diluted with ethyl acetate (20 mL) and the organic layer was washed with 2 × 10 mL of water. The aqueous layers were extracted with ethyl acetate (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by flash chromatography (silica gel, heptane/ethyl acetate in various ratios as eluent's gradient) to give successively **10** (78 mg, 42%), **9** (17 mg, 7%), and **8** (75 mg, 24%, 87% ee).

4.6. Products

4.6.1. 6-Methoxy-d_3-2-vinylnaphthalene 10-d_3

^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.27 (d, 1H, ^3J = 10.9 Hz, CH_2=CH), 5.81 (d, 1H, ^3J = 17.5 Hz, CH_2=CH), 6.84 (dd, 1H, , ^3J = 17.5 Hz and ^3J = 10.9 Hz, CH_2=CH), 7.09 (br s, 1H, Ar), 7.12 (dd, 1H, ^3J = 8.8 Hz and ^4J = 2.5 Hz, Ar), 7.66–7.71 (m, 3H, Ar). MS (EI) *m/z* (%): 188.1 (12.5), 187.1 (100.0), 168.9 (23.5), 140.9 (52.9), 138.9 (10.6), 114.9 (21.9).

4.6.2. Dimethyl 2-[6-methoxy-d_3-naphth-2-yl)ethyl]malonate 8-d_3

Isolated as a colorless oil; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.39 (d, 3H, ^3J = 6.3 Hz, CH_3–CH), 3.42 (s, 3H, OCH_3), 3.56–3.76 (m, 2H, 2C*H*), 3.78 (s, 3H, OCH_3), 7.09 (s, 1H, Ar), 7.12 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.5 Hz, Ar), 7.33 (dd, 1H, ^3J = 8.3 Hz, ^4J = 1.5 Hz, Ar), 7.59 (br s, 1H, Ar), 7.66–7.70 (m, 2H, Ar).

MS (EI) *m/z* (%): 319.1 (14.5), 189.1 (13.9), 188.0 (100.0).

Enantiomers of **8**-d_3 were analytically resolved by HPLC with a chiral stationary-phase column Chiralcel OD-H [hexane/isopropanol: 99/1, 0.5 mL min^{-1}, t_R = 30.5 min [(*R*)-enantiomer] and t_S = 33.9 min [(*S*)-enantiomer].

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