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Regio- and stereoselectivity control in palladium-catalyzed allylic alkylation of 1-cycloalkenylmethyl acetates

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ABSTRACT

Enantiomerically pure allylic acetates **1a** and **1b** were obtained by lipase-catalyzed acylation through kinetic resolution processes of the racemates. Palladium-catalyzed alkylation of **1a** with dimethyl malonate was both regio- and stereoselective, showing that no isomerization of the acetate **1a** or the intermediate π-allylic palladium complex took place under the conditions used. Alkylation of **1b** was stereoselective but not regioselective. The regioselectivity could be partially controlled by the proper choice of a chiral ligand. Conditions were set up to perform both the alkylation of **1b** and the decarbomethoxylation of the resulting product to afford 3-(cyclohex-1-enyl) butanoate in a one-pot, one-step process.

1. Introduction

The palladium-catalyzed allylation of stabilized carbo- and heteronucleophiles by allylic alcohol derivatives is recognized as a useful method for the synthesis of enantiomerically enriched organic molecules.[1]

However, the control of regio- and stereoselectivity (including enantioselectivity) is necessary to ensure the synthetic usefulness of such a reaction.[2]

Different situations are met according to the structure of the intermediate π-allylpalladium complex: monosubstituted, symmetrically or dissymmetrically 1,3-disubstituted and trisubstituted allylic complex. A great deal of work has been published on reaction of symmetrically substituted allylic substrates under chiral Pd-complexes catalysis. In this case the asymmetric induction arises from the selection of diastereotopic sites of a chiral *meso* allylpalladium complex.

The control of regioselectivity is, however, crucial for the monosubstituted allylic derivatives, since only the branched isomer of the substitution product is chiral. The asymmetric induction may be regarded as the selection by an achiral nucleophile of two diastereomeric palladium complexes, which may interconvert via a π–σ–π isomerization process (Scheme 1).

To be synthetically useful, the substitution reaction from unsymmetrical 1,3-disubstituted (i.e., with different substituents) allylic substrate should be regio- and stereocontrolled.

Unsymmetrical allylical 1,3-disubstituted substrates are chiral compounds. Since it is accepted that the palladium-catalyzed substitution of the allylic leaving group by stabilized carbonucleophiles takes place with overall retention of configuration, the chiral information from an enantioenriched substrate should in principle be totally transferred to the product.

However, some examples are known where a loss of stereochemistry is observed. Hayashi early reported a loss of enantiomeric purity in alkylation of an enantiomerically enriched allylic acetate in the presence of an achiral Pd-catalyst, especially when high amounts of palladium are used. A likely explanation was given, which involves epimerization of the chiral intermediate π-allylpalladium complex, via a displacement of the palladium by a palladium(0) complex (a S_N2-type displacement) (Scheme 2). This process has been documented.[3] Another explanation has been put forward for the scrambling of stereochemistry: isomerization of the allylic substrate (namely an acetate) through attack of the acetate ion to the palladium atom of the π-allypalladium intermediate complex, followed by reductive elimination.[4]

Therefore, the palladium-catalyzed alkylation of a chiral, enantiomerically enriched allylic 1,3-disubstituted substrate may result in a perfect chirality transfer to give a single product provided: (i) the regioselectivity is controlled; (ii) the π-allylpalladium intermediate complex is stereochemically stable, i.e., the above described a S_N2-type displacement process is not operating.

Since optically active allylic alcohols are easily available from the racemic compounds either via kinetic resolution by enzymatic acylation or Sharpless epoxidation, we estimate that the problems of the control of regioselectivity and inhibition of the potential π-allylpalladium epimerization process would be important to investigate.

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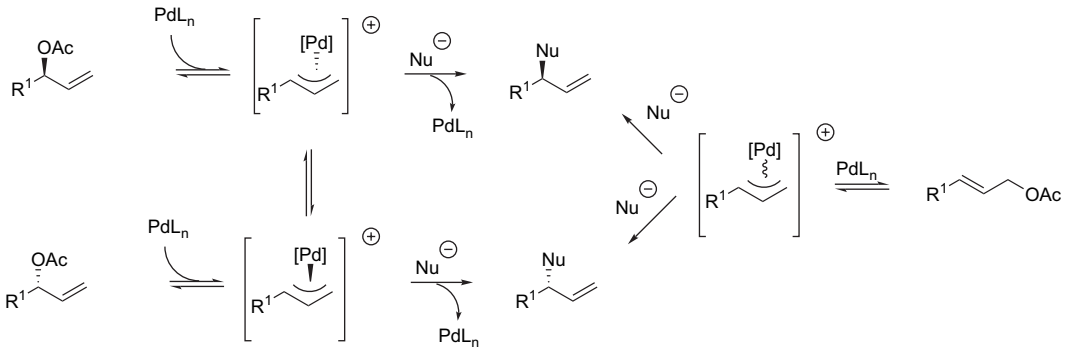
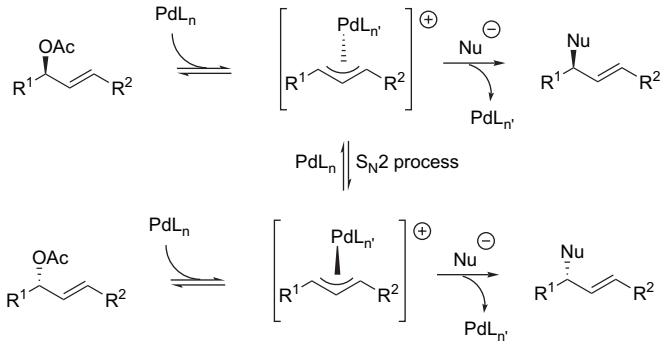
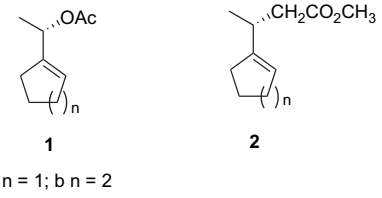


Scheme 1. Asymmetric induction processes in regioselective palladium-catalyzed substitution of monosubstituted allylic acetates.



Scheme 2. Asymmetric induction processes in regioselective palladium-catalyzed substitution of 1,3-disubstituted allylic acetates.

We aimed at looking at these considerations for the synthesis of enantiomerically enriched methyl 3-cyclopent-1-enyl and 3-cyclohex-1-enyl butanoates **2a** and **2b** from enantiomerically pure allylic acetates **1a** and **1b**.



a n = 1; b n = 2

A related problem has been addressed by Trost in his pioneering work on enantioselective catalysis dealing with palladium-catalyzed alkylation of racemic substrates **1a** and **1b** (Scheme 3). He reported that the reaction of sodium dimethyl malonate with racemic allylic acetate **1a**, upon catalysis by a chiral palladium catalyst afforded regioselectively optically active product **3a**.[5]

Examination of both the yields of alkylated product **3a** and decarbomethoxylated product **2a** (98% and 60%, respectively) together with the ee (37%) of product **2a** when DIOP was used as chiral ligand suggests that either an epimerization of the intermediate π-allyl palladium complex or a palladium-catalyzed acetate ion induced racemization of **1a** should have occurred.

These processes could alter the efficiency of asymmetry transfer of chirality from optically active substrates **1** to the alkylation product. We thus intended to look at the palladium-catalyzed alkylation of enantioenriched **1a** and **1b**, since we anticipated that through the evaluation of the chirality transfer level, the investigation of the occurrence and efficiency of the possible S_N2 process would be easier to perform.

The present paper thus describes the preparation of enantiomerically enriched allylic substrates **1a** and **1b**, the study of the palladium-catalyzed alkylation of these substrates with dimethyl malonate, and the search for experimental conditions to set up some control of regiochemistry and ensure a total asymmetry transfer. We report that conditions can be found for alkylation of the substrates and concomitant decarbomethoxylation of the resulting products. Moreover, we show that the chirality of the catalyst can control to some extent the regioselectivity for substitution of **1b**.

2. Results and discussion

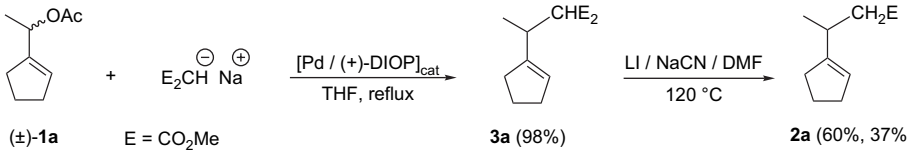
Enantiomerically enriched alcohol **4a** (89% ee) has been obtained by Ti-catalyzed enantioselective alkylation of the corresponding aldehyde by dimethylzinc.[6] Kinetic resolution of racemic alcohol **4b** has been performed through Ti-catalyzed Sharpless epoxidation[7a] and chiral phosphine-catalyzed acylation with isobutyric anhydride,[7b] to give enantiomerically enriched alcohol **4b** in 88% and >96% ee, respectively. Enantioselective Ru-catalyzed hydrogenation of the corresponding ketone (100% ee) afforded 99% of enantiomerically pure **4b**.[7c]

In this work, racemic alcohols **4a** and **4b** were resolved by lipase-catalyzed acylation, either with isopropenyl acetate (Scheme 4), or succinic anhydride (Scheme 5) as acylating agent.

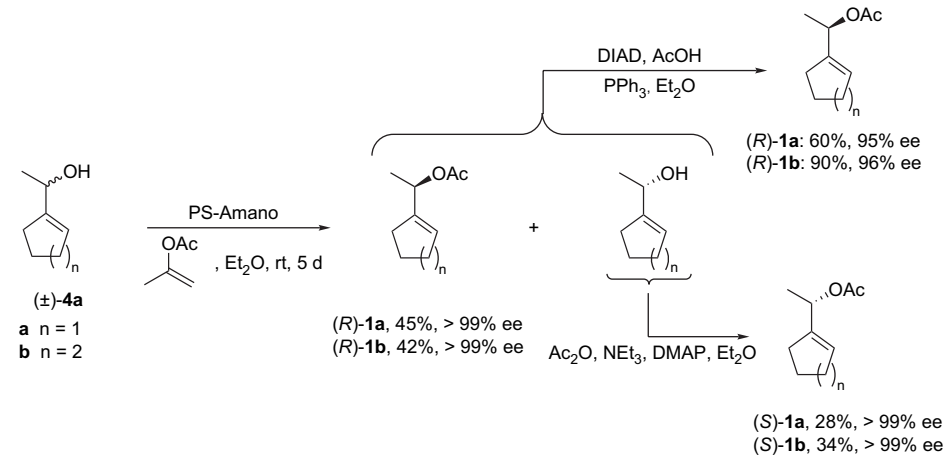
The first procedure required a separation of the acetate produced (*R*)-**1** from the unreacted substrate **4** (Scheme 4). This latter was converted into the enantiomeric acetate (*S*)-**1**. Both acetates obtained in this way showed >99%ee, as shown by chiral GLC analysis.

In a second procedure, the mixture of products resulting from acylation was subjected to Mitsunobu reaction conditions to afford (*R*)-**1a** in >95% ee (Scheme 4).[8] This one-pot acylation/inversion procedure did not require a chromatographic separation but furnished only one enantiomer of **1**.

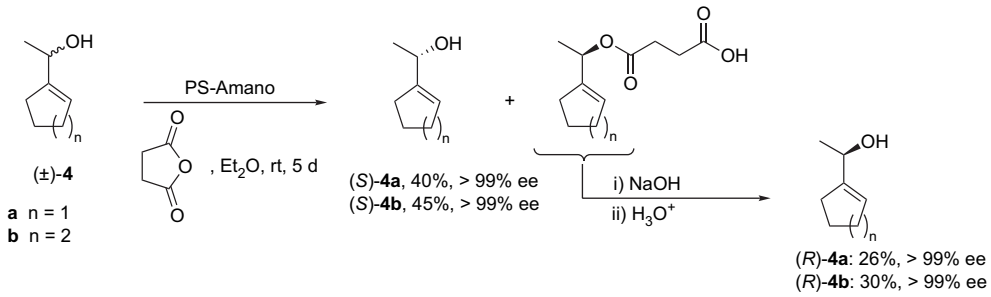
A third procedure allowed to get both enantiomers without chromatographic separation. The use of succinic anhydride as



Scheme 3. Palladium-catalyzed alkylation of (±)-**1a**.[5]



Scheme 4. Lipase-catalyzed resolution of **4a** and **4b** through acylation with isopropenyl acetate.



Scheme 5. Lipase-catalyzed resolution of **4a** and **4b** through acylation with succinic anhydride.

acylating agent afforded a hemisuccinate easily separated from the unreacted alcohol (Scheme 5).[9] Subsequent saponification of hemisuccinate gave the enantiomeric alcohol. In that way, both enantiomers of alcohols were obtained in >99% ee.

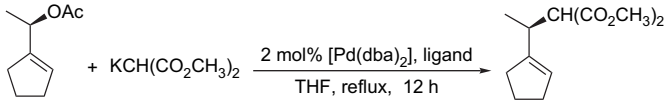
Enantiomerically enriched or racemic acetate **1a** was subjected to palladium-catalyzed alkylation with potassium dimethylmalonate, in the presence of various achiral or chiral catalysts. Results are collected in Table 1. The substitution of (*R*)-**1a** was indeed regioselective affording (*S*)-**3a** as the product, with >95%ee, as determined by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift reagent.

This means that under these conditions, neither the intermediate π-allyl palladium complex epimerizes nor the substrate **1a** undergoes racemization. Indeed under the same conditions alkylation of racemic substrate **1a** with a chiral catalyst afforded racemic **3a** at full conversion. Kinetic resolution of the racemic substrate **1a** took place when using 0.7 equiv of nucleophile and Pd/(*R*)-Tol-BINAP as catalyst. At 69% conversion, unreacted (*R*)-**1a** was recovered in 50% yield and 35% ee, corresponding to an enantioselectivity factor of approximately 2.[10]

Whereas the palladium-catalyzed substitution of **1a** by potassium dimethyl malonate was highly regioselective (>95:5), the regioselectivity of substitution of **1b** under analogous conditions was poorly controlled (**3b**/**5b**=60:40), as noticed by Trost.[4b] Moreover the reaction was slower. In order to improve the reaction rate, the substitution was carried out in DMSO. After 12 h at 120 °C, the substrate was fully converted into a 24:76 mixture of non-decarboxylated **3b**/**5b** and decarboxylated products **2b**/**6b**. Each product showed the same regioisomeric composition (**3b**/**5b** and **2b**/**6b** of 59:41 ratio each). Complete conversion and decarboxylation proceeded when the reaction was performed at 120 °C for 24 h, with the same ratio of regioisomeric decarbomethoxylated products **2b**/**6b** (59:41). Decarbomethoxylation of **3b** and **5b** thus took place with identical rates.

The efficiency of the decarbomethoxylation process was dependent upon the nature of the counter cation of the dimethyl malonate ion. The decarboxylation was more or less efficient according to the base used for the production of this anion (Table 2).

Table 1
Palladium-catalyzed alkylation of **1a** with potassium dimethylmalonate[a]

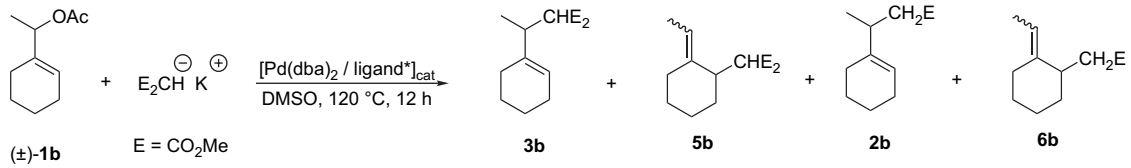


(*R*)-**1a** (*S*)-**3a**

Entry	Substrate	Ligand	Product	
			Yield[b] (%)	% ee[c] (Config.)[g]
1	(*R*)-**1a**	dppe[d]	84	>95 (*S*)
2	(*R*)-**1a**	(*R*)-BINAP[e]	79	>95 (*S*)
3	(*R*)-**1a**	(−)-(*R*,*R*)-DIOP[f]	81	>95 (*S*)
4	(*R*)-**1a**	(+)-(*S*,*S*)-DIOP[f]	83	>95 (*S*)
5	*rac*-**1a**	dppe	86	
6	*rac*-**1a**	(*R*)-BINAP[e]	70	<5
7	*rac*-**1a**	(+)-(*S*,*S*)-DIOP[f]	74	<5

[a] All reactions were carried out with **1a** (1 mmol), dimethyl malonate (2 equiv), Pd(dba)$_2$ (2 mol %), ligand (2 mol %), *t*-BuOK (2 equiv), in THF (4 mL) at reflux for 12 h.
[b] Yield of isolated product.
[c] Determined by ^{1}H NMR in the presence of Eu(hfc)$_3$.
[d] 1,2-Bis-diphenylphosphinoethane.
[e] (*R*)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene.
[f] DIOP is 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane.
[g] Assigned on the basis of the stereochemistry of substitution (overall retention).

Table 2
Alkylation of **1b** followed by decarbomethoxylation of substituted malonates **3b**–**5b**[a]



Base	Ligand	(**3b**+**5b**)/(**2b**+**6b**)[b]	**3b**/**5b**[b]	**2b**/**6b**[b]
LiH	dppe	89:11	58:42	59:41
NaH	dppe	74:26	59:41	59:41
t-BuOK	dppe	24:76	59:41	59:41
Cs_2CO_3	dppe	8:92	60:40	60:40
NaH+Me_4NBr	dppe	41:59	61:39	61:39
t-BuOK	(*R*)-Tol-BINAP	18:82	86:14	85:15
t-BuOK	(*R*,*R*)-*i*-PrDuphos[c]	58:42	78:22	78:22
t-BuOK	(*S*)-*i*-PrPOX	27:73	62:38	62:38

[a] Compound (±)-**1b** (1 mmol), dimethyl malonate (2 equiv), $Pd(dba)_2$ (2 mol %), ligand (2 mol %), base (2 equiv), DMSO, 120 °C, 12 h, 100% conversion.
[b] Conversion and product ratio were determined by GLC.
[c] 85% Conversion.

The best efficiency was obtained when the malonate anion was produced by deprotonation with cesium carbonate.

Attack of the nucleophile occurred onto the π-allylic palladium intermediate complex obtained from **1a** at the exocyclic carbon atom whatever the ligand was. This presumably indicates that the reaction pathway is over steric approach control: the nucleophile attacks the less hindered carbon atom.

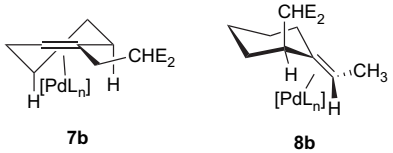
Results obtained from **1b** would be better rationalized by taking into account the relative stability of the initially formed π-olefinic palladium complexes **7b** and **8b** resulting from attacks of the nucleophile at the *exo*- or *endo*-cyclic allylic carbon atom of the π-allylic palladium intermediate complex. One might infer repulsive interactions of palladium/ligand with the axial hydrogen atoms of the ring in complex **7b**, that would be more effective than those of the corresponding five-membered ring, thus allowing some formation of **8b** (Scheme 6).

These trends are similar to those invoked by Trost for the rationalization of the stereochemical control occurring in the molybdenum-catalyzed allylation of carbon nucleophiles.[11]

Chiral ligands were then investigated to estimate their ability to control the regioselectivity of substitution of **1b**. The three ligands tested show a different behavior toward the yield of substitution and also the regioselectivity. Noteworthy is the same ratio of non-decarboxylated and decarboxylated regioisomers, indicative of similar rates of decarboxylation for both regioisomers.

The last point investigated was to know whether the use of enantiomeric complexes could induce some control of the regioselectivity. Since both enantiomers of the substrate were available (vide supra), they were subjected to alkylation by the malonate ion with (*R*)-Tol-BINAP- and (*S*)-*i*-Pr-POX-palladium catalytic system. The use of the former catalytic system allowed to produce two regioisomers from (*R*)-**1b** and a single regioisomer from (*S*)-**1b**, whereas with the latter a reversal of the regiochemistry was recorded from (*R*)-**1b** (Table 3).

Acetate (*S*)-**1b** as substrate and (*R*)-Tol-BINAP as ligand are matched to produce regioselectively enantiomerically enriched (*R*)-**2b** (>98% ee, by ^{1}H NMR in the presence of Eu(hfc)$_3$). Indeed, (*R*)-**2b** was obtained as a single isomeric product (80% yield in isolated compound) when the decarboxylation reaction was conducted to completion (120 °C, 24 h). It is then anticipated that enantiomerically enriched (>98%) (*S*)-**2b** should be produced through the use of the other matched pair acetate, i.e., (*R*)-**1b** as the substrate and (*S*)-Tol-binap as the ligand.



Scheme 6. Initially formed π-olefinic complexes of palladium-catalyzed substitution of **1b** by dimethyl malonate anion (noted E_2CH^-).

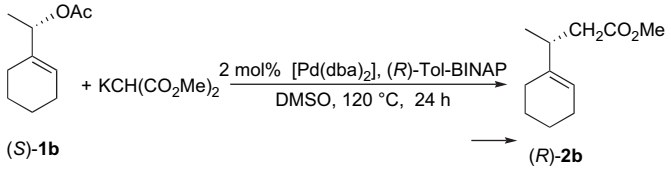


Table 3
Regioselectivity control by a chiral ligand in alkylation of **1b** followed by decarbomethoxylation of substituted malonates **3b**–**5b**[a]

Ligand	Substrate	Conversion (%)	(**3b**+**5b**)/(**2b**+**6b**)[b]	**3b**/**5b**[b]	**2b**/**6b**[b]
dppe	(*R*)-**1b**	100	24:76	59:41	59:41
(*R*)-Tol-BINAP	(*R*)-**1b**	100	34:66	76:24	76:24
	(*S*)-**1b**	100	14:86	100:0	100:0
(*S*)-*i*PrPOX	(*R*)-**1b**	100	34:66	34:66	34:66
	(*S*)-**1b**	100	23:77	89:11	87:13

[a] Compound **1b** (1 mmol), dimethyl malonate (2 equiv), *t*-BuOK (2 equiv), $Pd(dba)_2$ (2 mol %), chiral ligand (2 mol %), DMSO (3 mL), 120 °C, 12 h.
[b] Conversion and product ratios were determined by GLC.

^{1}H NMR of **5b** reveals one doublet (δ 1.50 ppm) for the methyl group on the double bond and one doublet (δ 3.78 ppm) for the –C*H*$(CO_2Me)_2$, indicative of a single stereoisomer. Moreover, no NOE effect could be detected between this methyl group and the proton of the –C*H*$(CO_2Me)_2$ group. Both achiral and chiral GLC analysis show a single peak for **5b** and **6b**. On basis of these data, together with the known stereochemistry of palladium-catalyzed allylic substitution (overall retention), an (*E*)-(*R*) stereochemistry can be assigned to **5b** and **6b**.

Enantiomerically enriched (*E*)-(*S*)-**6b** would be obtained as the major regioisomer (1:2 regioisomeric ratio for **2b**/**6b**) when using the combination (*S*)-**1b** as substrate and (*R*)-*i*-PrPOX as ligand.

3. Conclusion

As a conclusion, experimental conditions have been set up to regioselectively produce enantiomerically enriched alkylated compounds by asymmetry transfer from enantiomerically enriched allylic substrates **1a** and **1b** without loss of enantiomeric purity. The process involved an alkylation/decarbomethoxylation sequence. The alkylation of cyclopentenyl substrate **1a** was regioselective and stereoselective. The regioselectivity of alkylation of acetate **1b** could be controlled by the nature and the chirality of the catalyst. One regioisomer **6b** could be produced in high enantiomeric purity (>98% ee) by a proper choice of the matched stereochemistries of the enantiopure substrate and the catalyst.

4. Experimental

4.1. General

1-Acetyl-1-cyclopentene, 1-acetyl-1-cyclohexene, (*R*)-(+)-2-[2-(diphenylphosphino)phenyl]-4-isopropyl-2oxazoline, BINAP, Tol-BINAP, DIOP, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium (III) were purchased from Aldrich. Reactions were performed under an argon atmosphere using Schlenk tube technique and were monitored by TLC analysis. Bruker AM 250 spectrometer, operating at 250 MHz for ^{1}H, and at 62.5 MHz for ^{13}C, was used for the recording of NMR spectra, which are referenced to the solvent as internal standard. HRMS were obtained on a Thermo-Finnigan-Mat 95 spectrometer. Infrared spectra were recorded in $CHCl_3$ solution using CaF_2 cells on a Perkin–Elmer 1000 FT-IR spectrometer. Optical rotations were obtained from a Perkin–Elmer 241 polarimeter at room temperature using a cell of 1 dm length and λ=589 nm. Data are reported as follows: $[\alpha]_D^{20}$ (concentration in g/100 mL, solvent). Enantiomeric excesses of acetates **1a** and **1b** were determined by gas chromatograph (GC) analysis on Fisons 9000 apparatus equipped with Chiraldex-β-PM column (50 m×0.25 mm) and hydrogen as carrier gas (1.0 mL/min). Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} backed precoated plates.

4.2. Syntheses of (±)-1-(1′-cyclopentenyl)ethanol 4a and (±)-(±)-1-(1′-cyclohexenyl)-1-ethanol 4b

Dry cerium chloride (484 mg, 2 mmol) was dissolved in 2 mL of methanol followed by addition of 1 mmol of enone [1-acetyl-1-cyclopentene and 1-acetyl-1-cyclohexene]. After 5 min of stirring at room temperature, 49.5 mg (1.3 mmol) of sodium borohydride is added by portions. After 15 min of stirring at room temperature there is no substrate remaining. Water was then added until obtention of a homogeneous mixture. The solution was saturated with sodium chloride and diethylether was added. The aqueous layer is extracted with diethylether, the organic layers were dried over magnesium sulfate and the solvents were removed. Allylic alcohols were obtained as colorless oils. For spectral data, see below.

4.3. Acylation of allylic alcohols 4a and 4b: syntheses of 1-(1′-cyclopentenyl)ethanol

Allylic alcohol (1 mmol) was diluted in 4 mL of diethylether and 12 mg (0.1 mmol) of dimethylaminopyridine was added. When the mixture became homogeneous 195 μl (1.2 mmol) of triethylamine and 145 μl (1.5 mmol) of acetic anhydride were successively added. After stirring for 12 h at room temperature, the mixture was successively treated by 2×3 mL of a 1 N hydrochloric acid solution, 2×5 mL of a saturated solution of sodium hydrogenocarbonate, and 2×5 mL of a saturated solution of sodium chloride. The aqueous layers were extracted with 2×20 mL of diethylether, the organic layers were dried over magnesium sulfate and the solvents were removed. Allylic acetates were obtained as colorless oils after flash chromatography over silica gel (eluent: heptane/ethyl acetate 90:10). For spectral data, see below.

4.4. Kinetic resolution of 4a and 4b through lipase-catalyzed acylation

4.4.1. Acylation by isopropenyl acetate

To the allylic alcohol (1 mmol) dissolved in diethyl ether (4 mL) were successively added isopropenyl acetate (330 μL, 3 mmol) and PS-Amano lipase (40 mg). The heterogeneous mixture was stirred for 4 days at room temperature. After filtration of the enzyme, the solvent was removed. The unreacted allylic alcohol **4** and the acetate produced **1** were separated by silica gel flash chromatography (heptane/ethyl acetate 90:10).

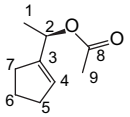
4.4.2. Acylation by succinic anhydride

To the allylic alcohol (1 mmol) dissolved in diethyl ether (4 mL) were successively added succinic anhydride (300 mg, 3 mmol) and PS-Amano lipase (40 mg). The heterogeneous mixture was stirred for 4 days at room temperature. The enzyme was removed by filtration and the filtrate treated with a saturated aqueous solution of sodium hydrogenocarbonate (2×5 mL). The organic layer was separated and the aqueous phase extracted with diethyl ether (5 mL). The combined organic layers were washed (water) and dried (magnesium sulfate). Removal of the solvent left the unreacted alcohol. Potassium carbonate (690 mg, 5 mmol) was added to the aqueous layer and the resulting solution stirred for 12 h at 100 °C, then cooled down and extracted with diethyl ether (3×5 mL).

4.4.3. Acylation/Mitsunobu reaction procedure

To the allylic alcohol (1 mmol) dissolved in diethyl ether (4 mL) were successively added isopropenyl acetate (330 μL, 3 mmol) and PS-Amano lipase (40 mg). The heterogeneous mixture was stirred for four days at room temperature. After dilution with dry diethyl ether (2.5 mL), triphenylphosphine (312 mg, 1.2 mmol), acetic acid (60 μL, 1.2 mmol), and diisopropylazidodicarboxylate (200 μL, 1.2 mmol) were added. The resulting mixture was stirred for 12 h at room temperature. Filtration, then removal of the solvent left the crude allylic acetate, which was purified by silica gel flash chromatography (heptane/ethyl acetate 90:10).

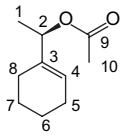
4.5. (*R*)-1-Cyclopent-1-enylethyl acetate 1a



Obtained as a colorless oil, with 45% yield, >99% ee (isopropenyl acetate) and 60% yield, 95% ee (isopropenyl acetate/Mitsunobu), respectively.

^{1}H NMR (250 MHz, $CDCl_3$): δ=1.33 (d, J=6 Hz, $3H_1$), 1.88 (q, J=7 Hz, $2H_6$), 2.05 (s, $3H_9$), 2.33 (m, $4H_{5\text{ and }7}$), 5.48 (q, J=7 Hz, $1H_2$), 5.62 (s, $1H_4$). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=19.5 (C_1), 21.5 (C_9), 23.9 (C_6), 31.2 (C_7), 31.6 (C_5), 69.2 (C_2), 126.2 (C_4), 144.0 (C_3), 172.1 (C_8). IR: 1733 cm^{-1}. GLC: the enantiomers are separable over a Chiraldex-β-PM column, isotherm program at 90 °C, t_1=33.1 min (*R*), t_2=37.9 min (*S*). $[\alpha]_D^{20}$ +85.3 (*c* 1.25, $CHCl_3$) (>99% ee, by chiral GLC analysis).

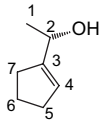
4.6. (*R*)-1-Cyclohex-1-enylethyl acetate 1b



It was obtained as a colorless oil, with 42% yield, >99% ee (isopropenyl acetate) and 90% yield, 96% ee (isopropenyl acetate/Mitsunobu), respectively.

^{1}H NMR (250 MHz, $CDCl_3$): δ=1.30 (d, J=6.6 Hz, $3H_1$), 1.65 (m, $4H_{6\text{ and }7}$), 1.99–2.05 (m, $4H_{5\text{ and }8}$), 2.06 (s, $3H_{10}$), 5.24 (q, J=6.6 Hz, $1H_2$), 5.71 (s, $1H_4$). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=18.8 (C_1), 21.3 (C_{10}), 22.3 (C_7), 22.4 (C_8), 24.1 (C_6), 24.2 (C_5), 74.1 (C_2), 123.6 (C_4), 137.1 (C_3), 170.4 (C_9). IR: 1738 cm^{-1}. HRMS (EI): 168.0149, calculated: 168.0150. GLC: the enantiomers are separable over a Chiraldex-β-PM column, column temp: 100 °C, t_1=45.2 min (*S*) (<0.5%), t_2=49.1 min (*R*) (>99.5%). $[\alpha]_D^{20}$ +61.3 (*c* 1, $CHCl_3$) (>99% ee, by chiral GLC analysis).

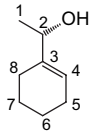
4.7. (*S*)-1-Cyclopent-1-enyl-ethanol 4a



Obtained as a colorless oil (40%), through succinic anhydride acylation procedure.

^{1}H NMR (250 MHz, $CDCl_3$): δ=1.30 (d, J=6 Hz, $3H_1$), 1.57 (s, $1H_{OH}$), 1.89 (q, J=7 Hz, $2H_6$), 2.33 (t, J=7 Hz, $4H_{5\text{ and }7}$), 4.42 (q, J=6 Hz, $1H_2$), 5.58 (s, $1H_4$). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=22.2 (C_1), 23.5 (C_6), 31.5 (C_7), 32.3 (C_5), 67.3 (C_2), 124.1 (C_4), 148.2 (C_5). IR: 3350 cm^{-1}. HRMS calcd for $C_7H_{12}0$: 112.0891, found: 112.0888. GLC: the enantiomers are separable over a Chiraldex-β-PM column, column temp: 90 °C, t_1=30.2 min (*R*), t_2=32.0 min (*S*). $[\alpha]_D^{20}$ −13.2 (*c* 1.0, $CHCl_3$) (>99% ee, by chiral GLC analysis). Lit:[6] $[\alpha]_D^{25}$ −16.3 (*c* 4.0, $CHCl_3$).

4.8. (*S*)-1-Cyclohex-1-enyl-ethanol 4b



Obtained as a colorless oil (45%), through succinic anhydride acylation procedure.

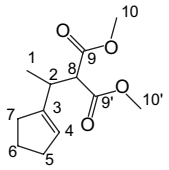
^{1}H NMR (250 MHz, $CDCl_3$): δ=1.26 (d, J=6.5 Hz, $3H_1$), 1.57–1.67 (m, $5H_{6,\ 7\text{ and }OH}$), 2.03 (m, $4H_{5\text{ and }8}$), 4.19 (q, J=6.5 Hz, $1H_2$), 5.69 (s, $1H_4$). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=21.5 (C_1), 22.6 (C_7), 22.7 (C_8), 23.7 (C_6), 24.9 (C_5), 72.2 (C_2), 121.5 (C_4), 141.3 (C_3). IR: 3350 cm^{-1}. HRMS calcd for $C_8H_{14}O$: 126.1045, found: 126.1047. $[\alpha]_D^{20}$ −5.5 (*c* 1.0, $CHCl_3$) (>99% ee, by chiral GLC analysis).

Lit:[12] $[\alpha]_D^{20}$ −7.4 (*c* 2.6, $CHCl_3$). Chiral GLC.[7b,13]

4.9. Procedure for palladium-catalyzed allylic alkylation without decarboxylation

*4.9.1. Synthesis of dimethyl 2-(1-cyclopent-1-enylethyl)-malonate **3a***

In a Schlenk tube, $Pd(dba)_2$ (11.5 mg, 0.02 mmol) and bis-diphenylphosphinoethane (12 mg, 0.03 mmol) were dissolved in dry DMSO (2 mL) and stirred for 15 min. Allylic acetate **1a** (154 mg, 1 mmol) dissolved in dry DMSO (2 mL) was added and the resulting solution was transferred via cannula into a Schlenk tube containing dimethyl malonate (230 mg, 2 mmol) and sodium hydride (48 mg, 2 mmol) in dry DMSO (1 mL). The mixture was stirred for 15 h at 60 °C. After cooling to room temperature, water (5 mL) and diethyl ether (5 mL) were added. The aqueous layer was separated and extracted with diethyl ether (2×5 mL). The combined organic layers were washed (saturated sodium chloride aqueous solution) and dried over magnesium sulfate. Removal of the solvent left the product, which was purified by silica gel flash chromatography (heptane/ethyl acetate 90:10).

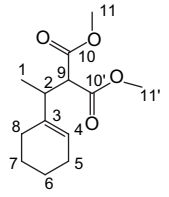


Obtained as an oil (181 mg, 80% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.05 (d, J=7 Hz, $3H_1$), 1.80 (m, $2H_6$), 2.22 (t, J=7 Hz, $4H_{5\text{ and }7}$), 3.05 (dq, J=7 and 11 Hz, $1H_2$), 3.44 (d, J=11 Hz, $1H_8$), 3.64 (s, $3H_{10}$), 3.70 (s, $3H_{10'}$), 5.39 (s, $1H_4$). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=17.3 (C_1), 23.3 (C_6), 32.1 (C_7), 32.2 (C_5), 35.9 (C2), 52.2 (C_{10}), 52.3 ($C_{10'}$), 56.8 (C_8), 125.3 (C_4), 145.4 (C_3), 168.9 ($C_{9\text{ and }9'}$). EIMS *m*/*z* (rel int.): 226 (M^+, 13.2), 194 (7.1), 167 (63.1), 166 (71.2), 134 (97.4), 107 (60.5), 95 (72.8), 79 (100), 67 (50.6).

*4.9.2. Synthesis of dimethyl 2-(1-cyclohex-1-enylethyl)malonate **3b***

Unseparable regioisomers **3b**/**5b** were obtained as an oil (171 mg, 71% yield) in a 60:40 mixture.

*4.9.2.1. Dimethyl 2-(1-cyclohex-1-enylethyl)malonate **3b**.*

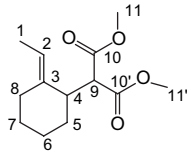


^{1}H NMR (250 MHz, $CDCl_3$): δ=1.00 (d, J=7 Hz, $3H_1$), 1.60 (m, $4H_{6\text{ and }7}$), 2.00 (m, $4H_{5\text{ and }8}$), 2.90 (dq, J=7 AND 11 Hz, $1H_2$), 3.45 (d, J=11 Hz, $1H_9$), 3.68 (s, $3H_{11}$), 3.77 (s, $3H_{11'}$), 5.50 (s, $1H_4$). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=17.2 (C_1); 22.1 (C_7), 22.5 (C_6); 25.0 (C_5), 27.4 (C_8), 42.2 (C_2), 45.0 (C_{11}), 52.1 ($C_{11'}$), 53.6 (C_9), 123.2 (C_4), 138.1 (C_3), 168.5 ($C_{10\text{ and }10'}$). IR ($CHCl_3$): 1763, 1740 cm^{-1}.

EIMS *m*/*z* (rel int.): 240 (M^+, 6.1), 222 (12.7), 208 (12.2), 181 (29.7), 176 (38.1), 148 (61.9), 108 (100), 93 (52.2), 79 (65.7).

HRMS calcd for $C_{13}H_{20}O_4$: 240.1362, found: 240.1371.

*4.9.2.2. Dimethyl 2-(2-ethylidenecyclohexyl)malonate **5b**.*



^{1}H NMR (250 MHz, $CDCl_3$): δ=1.30 (m, 2H), 1.50 (d, J=7 Hz, $3H_1$), 1.60 (m, 4H), 2.30 (m, 2H), 2.90 (m, $1H_4$), 3.60 (s, $3H_{11}$), 3.66 (s, $3H_{11'}$), 3.78 (d, J=11 Hz, $1H_9$), 5.24 (q, J=7 Hz, $1H_2$). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=12.6 (C_1), 22.3 (C_6), 22.4 (C_7), 24.9 (C_5), 29.7 (C_8), 30.5 (C_4), 52.2 ($C_{11\text{ and }11'}$), 56.8 (C_9), 118.0 (C_2), 138.2 (C_3), 168.6 ($C_{10\text{ and }10'}$). EIMS *m*/*z* (rel int.): 240 (M, 1.5), 222 (2.1), 177 (14.5), 165

(32.8), 148 (19.4), 133 (74.3), 108 (100), 93 (33.5), 79 (47.0). HRMS calcd for $C_{13}H_{20}O_4$: 240.1362, found: 240.1371.

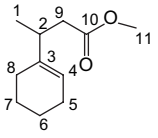
4.10. General procedure for palladium-catalyzed allylic alkylation followed by decarboxylation

*4.10.1. Synthesis of dimethyl 3-(cyclohex-1-enyl)butanoate **2b** and methyl 2-(2-ethylidenecyclohexyl) acetate **6b***

In a Schlenk tube, $Pd(dba)_2$ (11.5 mg, 0.02 mmol) and bis-diphenylphosphinoethane (12 mg, 0.03 mmol) were dissolved in dry DMSO (2 mL) and stirred for 15 min. Allylic acetate **1b** (168 mg, 1 mmol) dissolved in dry DMSO (2 mL) was added and the resulting solution was transferred via cannula into a Schlenk tube containing dimethyl malonate (230 μL, 2 mmol) and sodium hydride (48 mg, 2 mmol) in dry DMSO (1 mL). The mixture was stirred at 120 °C for 12 h. After cooling to room temperature, water (5 mL) and diethyl ether (5 mL) were added. The aqueous layer was extracted with diethyl ether (2×5 mL). The combined organic layers were washed (saturated sodium chloride solution), dried (magnesium sulfate). Removal of the solvent left the product, which was purified by silica gel flash chromatography (heptane/ethyl acetate 90:10).

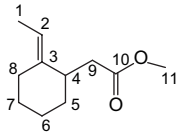
The two regioisomers (109 mg, 60% yield, **2b**/**6b** in a 60:40 ratio) were obtained as a yellow oil and could not be separated by silica gel chromatography. Full conversion of **1b** into the decarbomethoxylated product **6b** (TLC) could be reached on heating at 120 °C for 24 h.

*4.10.1.1. Methyl 3-(cyclohex-1-enyl)butanoate **2b**.*



^{1}H NMR (250 MHz, $CDCl_3$): δ=1.05 (d, J=7 Hz, $3H_1$), 1.52–1.64 (m, $4H_{6\text{ and }7}$), 1.90–2.05 (m, $4H_{5\text{ and }8}$), 2.20–2.27 (dd, J=5 and 13 Hz, $2H_9$), 2.4 (m, $1H_2$), 3.67 (s, $3H_{11}$), 5.45 (s, $1H_4$). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=19.2 (C_1); 23.0 (C_7), 25.2 (C_6), 25.5 (C_5), 25.8 (C8), 37.8 (C_2), 40.4 (C_9), 51.4 (C_{11}), 120.7 (C_4), 140.5 (C_3), 173.5 (C_{10}). HRMS calcd for $C_{11}H_{18}0_2$: 182.1307, found: 182.1311.

*4.10.1.2. Methyl 2-(2-ethylidenecyclohexyl) acetate **6b**.*



^{1}H NMR (250 MHz, $CDCl_3$): δ=1.52–1.64 (m, $4H_{5\text{ and }6}$ and d, J=4.7 Hz, $3H_1$); 1.90–2.05 (m, $2H_7$); 2.31 (m, $3H_{8\text{ and }9}$); 2.56 (m, $2H_{4\text{ and }9}$); 3.68 (s, $3H_{11}$); 5.10 (q, J=4.7 Hz, $1H_2$).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ=12.7 (C_1), 22.6 (C_6), 24.5 (C_7), 26.9 (C_8), 27.6 (C_5), 33.8 (C_9), 38.1 (C_4), 51.3 (C_{11}), 114.2 (C_2), 141.3 (C_3), 173.7 (C_{10}). EIMS m/z (rel int.): 182 (M^+, 22.9), 150 (23.0), 122 (30.0), 108 (100), 93 (34.7), 79 (46.4). HRMS calcd for $C_{11}H_{18}0_2$: 182.1307, found: 182.1311. IR ($CHCl_3$): 1734 cm^{-1}. The enantiomers are separable over a Chiraldex-β-PM column, isotherm program at 140 °C, t_1=39.9 min, t_2=40.5 min.

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