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TETRAHEDRON: *ASYMMETRY*

# Chiral pyridylmethyl- and quinolinyl-oxazolines as ligands for enantioselective palladium-catalyzed allylic alkylation

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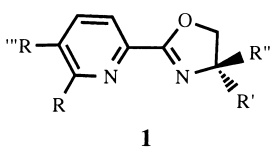
**Abstract**

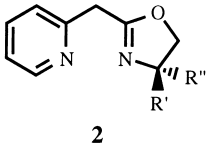
Chiral pyridylmethyl- and quinolinyl-oxazolines were prepared and assessed in the enantioselective palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. Enantioselectivities up to 77% were obtained. 

## 1. Introduction

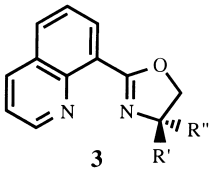
Palladium complexes using a variety of P–P-, P–N- and N–N-based ligands, with $C_1$ as well as $C_2$ symmetry, have been proven to induce impressive levels of enantioselectivity in the catalyzed asymmetric C–C bond forming reactions with allylic compounds.[1] Recently, we and others have introduced the use of chiral oxazolinylpyridines as ligands for enantioselective palladium-catalyzed allylic substitutions, obtaining nearly absolute enantiomeric excesses in the alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate.[2] More recently, by using this process, we have prepared and assessed a number of chiral oxazolinylpyridines **1** (Scheme 1) having different substituents (alkyl, aryl, electron-donating and withdrawing groups) on the pyridine and oxazoline rings and we have disclosed their cross effects on the catalytic activity and stereoselectivity of the process (steric control and electronic control).[3]




**1**




**2**




**3**

Scheme 1.

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*PII:* S0957-4166(99)00114-7

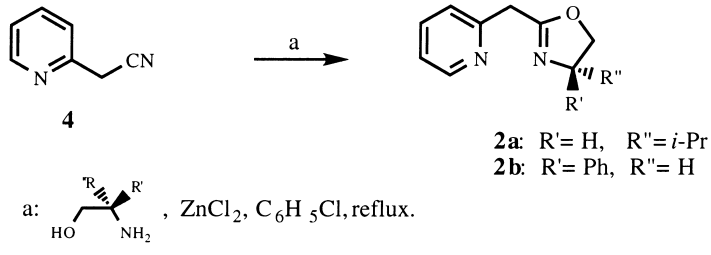
While pursuing our work in this field (in the search of a ring-size control in this reaction) we have been attracted by the possibility of modifying the structure of the pyridyloxazoline ligands by changing the chelate ring size of the Pd complex. In fact, the significance of this parameter on the design of chiral ligands for asymmetric catalysis has been pointed out previously.[4] Since the pyridyloxazolines form a five-membered chelate ring, we became interested in obtaining ligands bearing both a pyridine and an oxazoline moiety which, by coordination with the metal, form a six-membered chelate ring. Expansion to a six-membered chelate ring of the pyridyloxazoline ligands can be obtained in the most simple approach by interposing a one-carbon spacer between the two heterocyclic units. Insertion of a methylene unit would result in the conformationally mobile pyridylmethyloxazolines **2**,[5] while ligands of increased stiffness[6] could be obtained appending the oxazoline substituent onto the quinolyl scaffold, as in the case of derivative **3**.[7]

We report here on the synthesis of pyridylmethyl- and quinolinyl-oxazolines **2** and **3** and the results obtained with these ligands in the palladium-catalyzed alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate.

## 2. Results and discussion

### 2.1. Synthesis of ligands

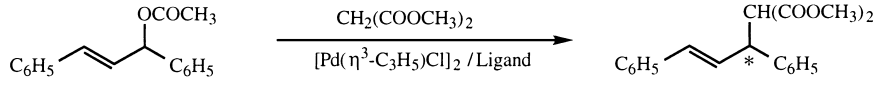
Pyridylmethyloxazolines **2** were easily prepared by heating a chlorobenzene solution of 2-cyanomethylpyridine **4** under reflux with the appropriate aminoalcohol in the presence of a catalytic amount of zinc chloride[8] (42–57% yield; Scheme 2). These ligands provided a disappointingly low asymmetric induction in the palladium-catalyzed alkylation of 1,3-diphenylprop-2-enyl acetate (Table 1).




Scheme 2.

We then devoted our attention to the preparation of the related quinolinyl-oxazoline **3**. Since our initial attempts to achieve direct condensation of 8-cyanoquinoline with (*S*)-valinol failed, a conventional protocol involving the sequence amide–mesylate–oxazoline was evaluated[9] (Scheme 3). Heating 8-quinolinecarboxylic acid methyl ester (**5**) under reflux with the appropriate aminoalcohol in the presence of a catalytic amount of potassium cyanide[10] gave the corresponding amides **6a**–**c** in an almost quantitative yield. The reaction of **6** with $MeSO_2Cl$ in $Et_3N/CH_2Cl_2$ did not give the relevant **7** but afforded a mixture of the oxazolines **3** and chlorides **8** (derived from nucleophilic attack of the chloride ion on the intermediate **7**) in about a 1:1 ratio. Since these chlorides were successfully cyclized into **3** by treatment with 5% KOH in refluxing methanol, in further preparations the crude mixtures obtained by cyclization of amides **6** were treated with KOH to provide the desired ligands **3a**–**c** in good overall yield (50–74%). Both ligands **2** and **3** are fairly unstable compounds and upon standing at room temperature for some weeks they undergo ring opening to the corresponding amides.

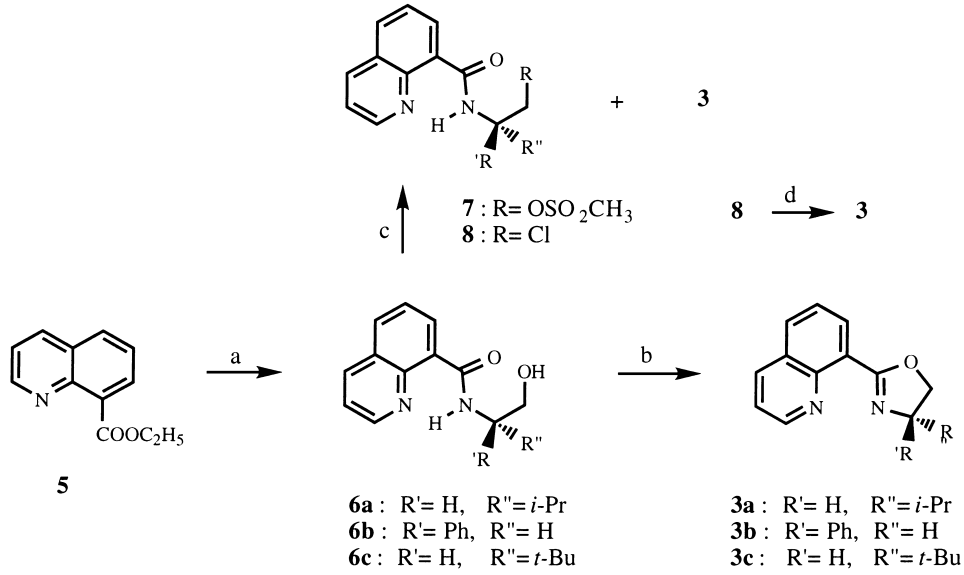
Table 1
Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[a]

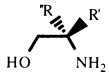



**9** **10**

| Entry | Ligand | React. time, h | Yield[b] | % Ee[c] | Conf.[d] |
|---|---|---|---|---|---|
| 1 | **1a** | 1 | 84 | 24 | S[e] |
| 2 | **2a** | 4 | 83 | 9 | S |
| 3 | **1b** | 2.5 | 86 | 55 | R[e] |
| 4 | **2b** | 75 | 67 | 16 | R |
| 5 | **3a** | 0.5 | 96 | 42 | S |
| 6 | **3b** | 1 | 88 | 59 | R |
| 7 | **3c** | 2 | 94 | 77 | S |

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




a: 

, cat. KCN, toluene, reflux; b: $CH_3SO_2Cl$, $Et_3N$, $CH_2Cl_2$, r.t. then 5 % KOH, $CH_3OH$, reflux 12 h; c: $CH_3SO_2Cl$, $Et_3N$, $CH_2Cl_2$, r.t.; d: 5 % KOH, $CH_3OH$, reflux 12 h

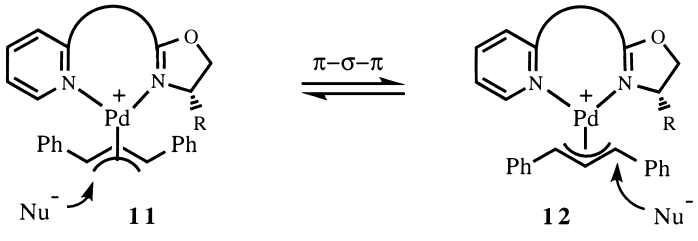
Scheme 3.

### 2.2. Palladium-catalyzed allylic alkylation

Allylic substitutions were carried out employing Trost's procedure which demands the use of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as procatalyst and a mixture of dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in methylene chloride at room temperature.[11]

The results obtained in a set of experiments with the new ligands are summarized in Table 1. Contrasting results were obtained with pyridylmethyloxazoline ligands **2a** and **2b**. Whereas the catalyst originating from **2a** led to total conversion of the starting material **9** in less than 4 h, affording the 1,3-diphenylprop-2-enylmalonate **10** in high yield, the palladium complex obtained from ligand **2b** required, for the complete conversion of **9**, a reasonably long reaction time (75 h). With both ligands **2a** and **2b**, catalytic activity and enantioselectivity were lower than those obtained with the related 2-[4,5-dihydro-4-(1-methylethyl)oxazol-2-yl]pyridine **1a** and 2-(4,5-dihydro-4-phenyloxazol-2-yl)pyridine **1b** (entries 2 versus 1 and 4 versus 3). These results appear to indicate that the five-membered chelate ring palladium–pyridyloxazoline catalysts are more enantioselective than the corresponding six-membered counterparts despite the fact that in the latter case the substituent at the stereocentre is closer to the allylic termini and is expected to exert a larger influence on the stereoselectivity of the reaction. We may speculate whether this result is related to the increased degree of conformational mobility attained by the ligand when the pyridine and the oxazoline rings are separated by the methylene spacer. This hypothesis seems corroborated by the results observed with the ligands **3**. The Pd catalysts formed by both **3a** and **3b** were more active and enantioselective than the ones obtained from the corresponding ligands **2** (entries 6 versus 2 and 7 versus 4). Interestingly, they were slightly better even than the relevant five-membered counterparts **1** (entries 5 versus 1 and 6 versus 3). The best enantioselectivity (77% ee) was obtained with ligand **3c** bearing the *tert*-butyl group on the oxazoline moiety.

The different behaviours of these ligands can be explained by considering the related π-allyl palladium complexes. The accepted mechanism for palladium-catalyzed allylic substitutions which proceed through a *meso* $\eta^3$-allyl intermediate, foresees that the nucleophile attacks the allylic termini of two alternative diastereomeric π-allyl palladium complexes which interconvert through a π–σ–π mechanism and which are present in the equilibrium in a different ratio (for instance **11** and **12** for ligands with the (*S*)-configuration: Scheme 4). Since the prevailing configuration obtained in the substitution product **10** is the one expected from the configuration of the oxazoline stereocentre, it is reasonable to assume that the reactive transition states are the same as those previously observed using pyridyloxazolines **1**. We may then draw the conclusion that also in this case the nucleophile predominantly attacks the allylic terminus *trans* to the oxazoline nitrogen in the more stable diastereomer **11**.[2,3]




Scheme 4.

## 3. Conclusions

Since it has usually been observed that the prevailing reaction product comes from a nucleophilic attack to the allylic terminus of the most abundant complex,[12] the ability of the ligand to stabilize one of the two diastereomeric complexes is a crucial point in determining the stereochemical outcome. Both ligands **1** and **3** provide rigid structures where the chelate rings, albeit of different sizes, are substantially planar. Therefore, in both cases stabilization of the diastereomeric transition state **11** should rely on similar arguments and the enantioselection is expected to improve as the chirogenic element of the ligand gets closer to the metal centre, as occurs in the case of the six-membered ring. The pyridylmethyloxazolines **2** coordinate to the metal in the same way as the ligands **3**, but the chelate ring is no more rigid in this case and can adopt different conformations. This should result in an increased number of diastereomeric transition states of different reactivities which can be responsible for the low enantiomeric excesses observed.

We are currently addressing our efforts to modify the structure of the pyridylmethyl- and quinolinyl-oxazolines in order to optimize their use in this and other asymmetric processes.

## 4. Experimental

### 4.1. General methods

Boiling points are uncorrected. Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. The $^1$H NMR (300 MHz) spectra were obtained with a Varian VXR-300 spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin–Elmer 240 B analyser. 2-Cyanomethylpyridine **4** was a commercial product (Aldrich A.G.) and 8-quinolinecarboxilic acid methyl ester **5**[13] was prepared following the literature procedure.

### 4.2. General procedure for the preparation of oxazolinylmethylpyridines *2*

In a 25 ml two-necked flask, zinc chloride (14 mg, 0.10 mmol) was melted under high vacuum and cooled under argon. After cooling to room temperature, chlorobenzene (12 ml) was added followed by nitrile (2 mmol) and the aminoalcohol (3.0 mmol). The resulting mixture was heated under reflux for the appropriate time (vide infra) and then the solvent was evaporated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (6 ml) and the resulting solution was washed with water (3×4 ml). The aqueous solution was extracted with $CH_2Cl_2$ (6 ml), the combined organic phases were dried over anhydrous $Na_2SO_4$ and the solvent was evaporated. The residue was purified by chromatography on a silica gel column (benzene:acetone, 8:2).

#### 4.2.1. (S)-2-{[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl]methyl}pyridine *2a*

Reaction time: 48 h; 0.230 g (57%); oil; $[\alpha]_D^{25}$ −62.1 (*c* 1.2, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ: 8.53 (d, 1H, J=4.5 Hz), 7.62 (dt, 1H, J=7.8, 1.8 Hz), 7.32 (d, 1H, J=7.8 Hz), 7.14 (dd, 1H, J=5.4, 6.9 Hz), 4.23 (m, 1H), 3.91 (m, 2H), 3.84 (s, 2H), 1.75 (m, 1H), 0.95 (d, 3H, J=6.9 Hz), 0.87 (d, 3H, J=6.9 Hz). Anal. calcd for $C_{12}H_{16}N_2O$: C, 70.54; H, 7.90; N, 13.72. Found: C, 70.22; H, 7.84; N, 13.43.

*4.2.2. (*R*)-2-[(4,5-Dihydro-4-phenyloxazol-2-yl)methyl]pyridine* ***2b***

Reaction time: 96 h; 0.200 g (42%); 72–74°C; $[\alpha]_D^{25}$ +10.3 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ: 8.58 (d, 1H, J=4.2 Hz), 7.62 (dt, 1H, J=7.5, 1.5 Hz), 7.40–7.17 (m, 7H), 5.21 (t, 1H, J=9.3 Hz), 4.63 (dd, 1H, J=8.4, 9.9 Hz), 4.11 (t, 1H, J=8.7 Hz), 3.95 (s, 2H). Anal. calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.93; N, 11.76. Found: C, 75.55; H, 5.98; N, 11.58.

*4.3. General procedure for the preparation of 8-quinolinecarboxamides* ***6***

A mixture of 8-quinolinecarboxylic acid methyl ester **5** (1 g, 5 mmol), the aminoalcohol (6.5 mmol) and KCN (65 mg, 1 mmol) in toluene (15 ml) was heated under reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on a silica gel column with the indicated eluent if not otherwise stated.

*4.3.1. (*S*)-*N*-[2-Hydroxy-1-(1-methylethyl)ethyl]-8-quinolinecarboxamides* ***6a***

Chromatographic eluent: benzene:acetone, 1:1; 1.23 g (95%); oil; $^1H$ NMR ($CDCl_3$) δ: 11.47 (d, 1H, J=7.2 Hz), 8.74 (dd, 1H, J=4.2, 1.6 Hz), 8.70 (dd, 1H, J=7.4, 1.6 Hz), 8.08 (dd, 1H, J=8.2, 1.6 Hz), 7.75 (dd, 1H, J=8.2, 1.6 Hz), 7.43 (t, 1H, J=7.8 Hz), 7.30 (dd, 1H, J=8.4, 5.0 Hz), 4.15 (broad, 1H), 4.05 (m, 1H), 3.75 (m, 2H), 2.05 (m, 1H), 0.99 (d, 3H, J=3.8 Hz), 0.95 (d, 3H, J=3.8 Hz). Anal. calcd for $C_{15}H_{18}N_2O_2$: C, 69.73; H, 7.03; N, 10.84. Found: C, 69.88; H, 7.12; N, 10.70.

*4.3.2. (*R*)-*N*-[2-Hydroxy-1-phenylethyl]-8-quinolinecarboxamides* ***6b***

In this case the residue was taken up with ethyl ether to give a white solid: 1.34 g (96%); mp 155–156°C. $^1H$ NMR ($CDCl_3$) δ: 12.12 (d, 1H, J=5.9 Hz), 8.89 (d, 1H, J=4.1 Hz), 8.82 (d, 1H, J=7.3 Hz), 8.30 (dd, 1H, J=8.3, 1.2 Hz), 7.98 (d, 1H, J=8.1 Hz), 7.46 (t, 1H, J=7.7 Hz), 7.55–7.12 (m, 6H), 5.49 (m, 1H), 4.04 (m, 2H), 3.58 (broad, 1H). Anal. calcd for $C_{18}H_{16}N_2O_2$: C, 73.94; H, 5.53; N, 9.58. Found: C, 73.93; H, 5.68; N, 9.77.

*4.3.3. (*S*)-*N*-[2-Hydroxy-1-(1,1-dimethylethyl)ethyl]-8-quinolinecarboxamides* ***6c***

Chromatographic eluent: benzene:acetone, 8:2; 1.17 g (87%); mp 138–140°C; $^1H$ NMR ($CDCl_3$) δ: 11.70 (d, 1H, J=5.5 Hz), 8.93 (dd, 1H, J=4.3, 1.8 Hz), 8.86 (dd, 1H, J=7.4, 1.6 Hz), 8.33 (dd, 1H, J=8.3, 1.8 Hz), 7.98 (dd, 1H, J=8.1, 1.6 Hz), 7.70 (t, 1H, J=7.8 Hz), 7.52 (dd, 1H, J=8.3, 4.3 Hz), 4.15 (dt, 1H, J=8.4, 1.8 Hz), 4.06 (dd, 1H, J=8.4, 1.4 Hz), 3.73 (m, 2H), 1.14 (s, 9H). Anal. calcd for $C_{16}H_{20}N_2O_2$: C, 70.55; H, 7.41; N, 10.29. Found: C, 70.63; H, 7.48; N, 10.27.

*4.4. General procedure for the preparation of oxazolinylquinolines* ***3***

Methanesulfonyl chloride (0.38 ml, 6.25 mmol) was added to a cold (0°C) solution of quinolinecarboxamides (5 mmol) and $Et_3N$ (1.39 ml, 10 mmol) in $CH_2Cl_2$ (20 ml). The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. The reaction mixture was then poured into a saturated aqueous ammonium chloride solution, the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic phases were dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was taken up with a 5% KOH methanolic solution (20 ml) and the resulting solution was heated under reflux for 3 h. The solvent was evaporated and the residue was poured into water and extracted with $CH_2Cl_2$. The organic phase was dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column with the indicated eluent.

*4.4.1. (S)-8-[4,5-Dihydro-4-(1-methylethyl)oxazol-2-yl]quinoline* ***3a***

Chromatographic eluent: benzene:acetone, 1:1; 0.94 g (78%); oil; $[\alpha]_D^{25}$ −57.6 (*c* 1.0, EtOH). $^1$H NMR ($CDCl_3$) δ: 9.05 (d, 1H, J=5.9 Hz), 8.17 (dd, 1H, J=8.3, 1.7 Hz), 8.12 (dd, 1H, J=7.3, 1.4 Hz), 7.90 (dd, 1H, J=8.4, 1.4 Hz), 7.56 (dd, 1H, J=8.1, 1.4 Hz), 7.43 (dd, 1H, J=8.1, 4.2 Hz), 4.56 (m, 1H), 4.28 (m, 2H), 2.02 (m, 1H), 1.12 (d, 3H, J=6.8 Hz), 1.03 (s, 3H, J=6.8 Hz). Anal. calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.63; H, 6.68; N, 11.67.

*4.4.2. (R)-8-(4,5-Dihydro-4-phenyloxazol-2-yl)quinoline* ***3b***

Chromatographic eluent: ethyl acetate; 0.81 g (62%); oil $[\alpha]_D^{25}$ +38.9 (*c* 1.0, EtOH). $^1$H NMR ($CDCl_3$) δ: 9.09 (dd, 1H, J=4.2, 1.8 Hz), 8.24 (dd, 1H, J=6.9, 1.5 Hz), 8.19 (dd, 1H, J=8.4, 1.8 Hz), 7.95 (dd, 1H, J=8.4, 1.5 Hz), 7.59 (t, 1H, J=7.2 Hz), 7.20–7.55 (m, 6H), 5.57 (dd, 1H, J=10.2, 8.1 Hz), 4.97 (dd, 1H, J=10.2, 1.7 Hz), 4.45 (t, 1H, J=8.3 Hz). Anal. calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.73; H, 5.18; N, 10.22.

*4.4.3. (S)-8-[4,5-Dihydro-4-(1,1-dimethylethyl)oxazol-2-yl]quinoline* ***3c***

Chromatographic eluent: benzene:acetone, 1:1; 0.79 g (58%); mp 137–139°C; $[\alpha]_D^{25}$ −73.5 (*c* 1.1, EtOH). $^1$H NMR ($CDCl_3$) δ: 9.03 (dd, 1H, J=4.2, 1.8 Hz), 8.16 (dd, 1H, J=8.3, 1.8 Hz), 8.08 (dd, 1H, J=7.1, 1.5 Hz), 7.90 (dd, 1H, J=8.2, 1.5 Hz), 7.56 (dd, 1H, J=8.2, 7.2 Hz), 7.42 (dd, 1H, J=8.3, 4.2 Hz), 4.57 (dd, 1H, J=10.1, 8.6 Hz), 4.39 (t, 1H, J=8.0 Hz), 4.20 (dd, 1H, J=10.1, 8.0 Hz), 1.05 (d, 9H, J=3.4 Hz). Anal. calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.63; H, 7.15; N, 11.07.

*4.5. Allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate: general procedure*

A solution of ligand (0.04 mmol, 10 mol%) and $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (4 mg, 2.5 mol%) in dry $CH_2Cl_2$ (2 ml) was stirred at room temperature for 15 min. This solution was treated successively with a solution of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (0.4 mmol) in $CH_2Cl_2$ (1 ml), dimethyl malonate (1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (1.2 mmol) and anhydrous potassium acetate (3.5 mol%). The reaction mixture was stirred for the appropriate time (see Table 1) until conversion was complete as shown by TLC analysis (light petroleum:ether, 3:1). The reaction mixture was diluted with ether (25 ml) and washed with ice-cold saturated aqueous ammonium chloride. The organic phase was dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (light petroleum:ether, 3:1) to afford dimethyl 1,3-diphenylprop-2-enylmalonate. The enantiomeric excess was determined from the $^1$H NMR spectrum in the presence of enantiomerically pure shift reagent Eu(hfc)$_3$; splitting of the signals for one of the two methoxy groups was observed.

## Acknowledgements

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