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# Chiral ligand-controlled diastereoselectivity and regioselectivity in palladium(0)-catalysed allylations

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**Abstract**

Diastereoselective allylations can be achieved on an epimeric mixture of optically active allylic benzoates having a fixed stereogenic centre allylic to the π-system using chiral ligands. The regiochemistry of these reactions is controlled by the chiral ligand and is different for the different diastereomeric complexes.
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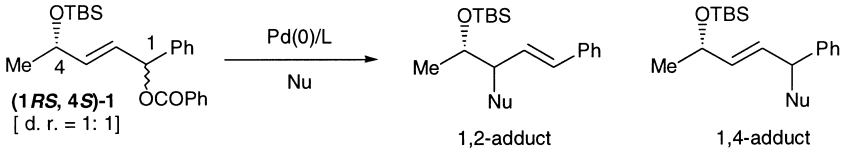
*Keywords:* chiral ligand; catalysis; palladium; regiochemistry; diastereoselection; allylation; allylic amine; malonate.

The control of remote stereocentres by asymmetric induction is an on-going challenge in organic synthesis. We are interested in developing methods for preparing 1,4-difunctionalised acyclic molecules[1] in a diastereoselective manner using palladium(0)-catalysed allylic alkylation chemistry. We report here our efforts to affect diastereoselective and regioselective 1,4-allylations on an epimeric mixture (d.r. = 1:1) of the optically active allylic benzoates (1*RS*,4*S*)- **1** having a fixed stereogenic centre allylic to the π-system (Eq. (1)).




(1)

Excellent methods have been developed for palladium(0)/chiral ligand-catalysed asymmetric allylation reactions that proceed via 1,3-symmetrically substituted allyl palladium cationic complexes (e.g. $\eta^3$-[RCHCHCHR]Pd(II)L*$_n$).[2] In contrast, the development of related asymmetric reactions that proceed via non-symmetrical intermediates is a challenge not only in controlling enantiofacial selectivity, with respect to the palladium–allyl complex, but also in the regioselectivity of nucleophilic addition.[3] These types of reactions could be further complicated by the presence of stereogenic centres on the substrate, as for example in compound **1**.[4] Interestingly, we have

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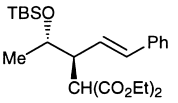
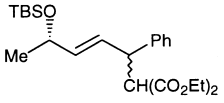
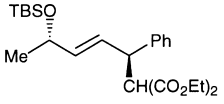
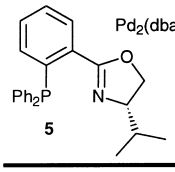
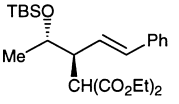
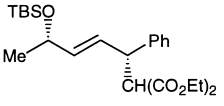
discovered that the two diastereoisomers of **1** give different regio-isomeric products, often with high diastereoselectivities, in the presence of a chiral ligand for the palladium.

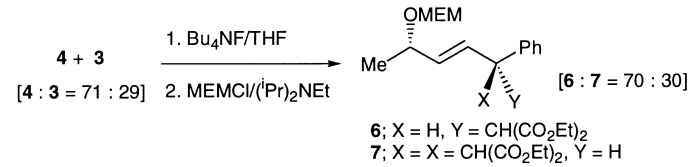
When sodium diethyl malonate was employed as a nucleophile and 5 mol% $Pd(Ph_3P)_4$ as the catalyst then, not unexpectedly, a 1:1 mixture of 1,4-adducts was obtained in quantitative yield (Table 1).[5] In contrast, when chiral ligands were employed the regioselectivity changed as did the diastereoselectivity. When the chiral ligand (*R*)-BINAP was used then 18% of the regioisomeric 1,2-adduct **2** was obtained, essentially as a single diastereomer, while the 1,4-adduct was obtained as a 1:1 diastereomeric mixture (Table 1). The use of (*S*)-BINAP gave mainly 1,4-adducts favouring the diastereomer **3**. The chiral phosphinoaryl oxazoline **5** gave similar results to that found for (*R*)-BINAP;[6] however, the 1,4-adduct was obtained in higher diastereoselectivity in favour of the diastereomer **4**. The stereochemistry of the 1,2-adduct **2** was determined by single-crystal X-ray structural analysis,[7] while that of **3** and **4** was determined by conversion to their *O*-MEM derivatives **7** and **6**, respectively. The $^1H$ NMR spectra of **6** and **7** correlated well with those reported for the known dimethyl esters of **6** and **7**, respectively.[8]

Table 1
Palladium(0)-catalysed reactions of **1** with sodium diethyl malonate[a]

| Ligand | Palladium | Time | Combined yield | 1,2 : 1,4 | Products | |
|---|---|---|---|---|---|---|
| | $Pd(PPh_3)_4$ | 18 h | 100% | 0 : 100 | 1,4 [d. r. = 1 : 1] | |
| (*R*)-BINAP | $Pd_2(dba)_3$ | 24 h | 83% | 18 : 82 |  **2** [d. r. = 99 : 1] |  [d. r. = 1 : 1] |
| (*S*)-BINAP | $Pd_2(dba)_3$ | 24 h | 72% | 0 : 100 | — |  **3** [d. r. = 38 : 62] |
|  **5** | $Pd_2(dba)_3$ | 24 h | 91% | 30 : 70 |  **2** [d. r. = 99 : 1] **X-ray** |  **4** [d. r. = 71 : 29] **Chemical correlation** |

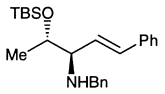
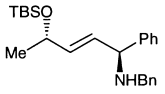
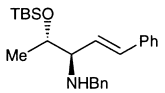
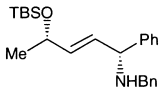
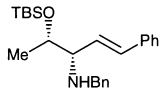
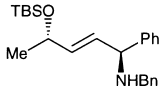
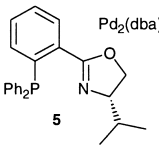
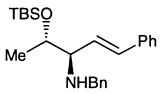
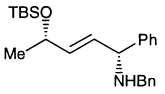
[a] 2.5 mol% $Pd_2(dba)_3$ and 5 mol% chiral ligand and sodium diethyl malonate (2 equiv.) were used with THF as solvent at RT

In contrast, the palladium(0)-catalysed benzylamination of **1**, in the absence of chiral ligand, gave 1,2- and 1,4-adducts, **8** and **9** respectively, with modest diastereoselectivity (Table 2).[5]

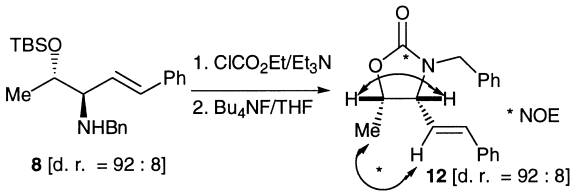



(2)

Table 2
Palladium(0)-catalysed reactions of **1** with benzylamine[a]

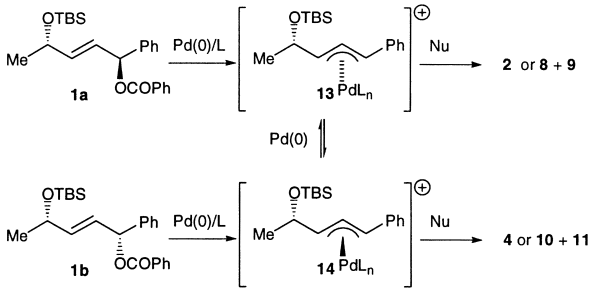
| Ligand | Palladium | Time | Combined yield | 1,2 : 1,4 | Products | |
|---|---|---|---|---|---|---|
| | $Pd(PPh_3)_4$ | 2.5 h | 95% | 7 : 93 |  **8** [d. r. = 61 : 39] |  **9** [d. r. = 76 : 24] |
| (*R*)-BINAP | $Pd_2(dba)_3$ | 48h | 68% | 44 : 56 |  **8** [d. r = 92 : 8] |  **10** [d. r = 93 :7] |
| (*S*)-BINAP | $Pd_2(dba)_3$ | 48h | 84% | 48 : 52 |  **11** [d. r = 98 : 2] |  **9** [d. r = 94 :6] |
|  **5** | $Pd_2(dba)_3$ | 168h | 74% | 18 : 82 |  **8** [d. r = 79 : 21] |  **10** [d. r = 92 :8] |

[a] 2.5 mol% $Pd_2(dba)_3$ and 5 mol% chiral ligand and benzylamine (1.5 equiv.)/triethylamine (1.5 equiv.) were used with THF as solvent at 50 °C



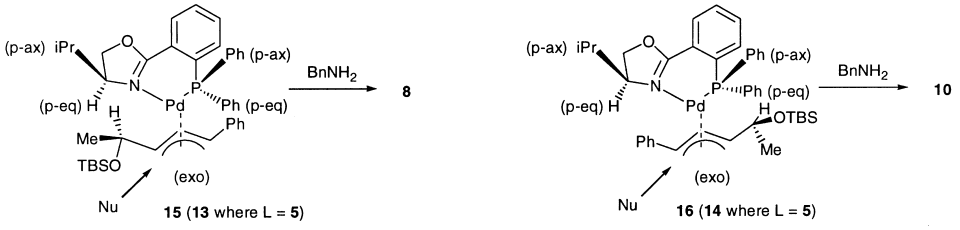

(3)

Unlike the reactions of **1** with malonate ion, the reactions of **1** with benzylamine required heating to 50°C and long reaction times. Furthermore, these reactions were highly diastereoselective in the presence of chiral ligands. Reactions involving (*R*)- and (*S*)-BINAP gave essentially a 1:1 mixture of 1,2- and 1,4-adducts in high diastereomeric purities. The chiral ligand **5** gave mainly the 1,4-adduct **10** with high diastereoselectivity (d.r. = 92:8). The stereochemistry of **8** was determined from NOE studies on its cyclic derivative **12** prepared according to Eq. (3). Thus, the 1,2-adducts from **1** and malonate or benzylamine with (*R*)-BINAP or **5** arise from attack of the nucleophile on the same diastereomeric palladium–allyl complex (i.e. **13** in Scheme 1). In light of this, and by analogy with the stereochemistry of **4**, we assign the stereochemistry to the 1,4-adduct **10** as that shown in Table 2. Interestingly, the regioisomeric pairs of products **2**, **4**, **8**, **9**, **10,** and **11** have arisen from different diastereomeric palladium complexes. For example, in the presence of (*R*)-BINAP or **5** the 1,2-adduct **8** arises from attack on the complex **13**, while the 1,4-adduct **10** from the diastereomeric complex **14** (Scheme 1). In the case of ligand **5** these results suggest that **13** and **14** are interconverting, most likely via the Pd(0) exchange mechanism[9]




Scheme 1.

(Scheme 1). Clearly, the rate of attack at the terminal carbons of the allyl moieties in **13** and **14** are different and this gives rise to the different diastereoselectivities for the 1,2- and 1,4-adducts. The stereochemical outcomes of the reactions employing chiral ligand **5** can be rationalised as arising from attack on the *exo–syn–syn* complexes[10] **15** and **16** with nucleophilic attack favoured on the terminal allylic carbon atom *trans* to the phosphorus donor.[2b–d,10] Thus, the regiochemistry in these reactions is controlled by the chiral ligand and different diastereomeric Pd complexes (e.g. **15** and **16**) give rise to different regiochemical outcomes (1,2- versus 1,4-) and different diastereoselectivities. Hence, we have demonstrated that chiral ligands not only control diastereoselectivity but also the regioselectivity of palladium(0)-catalysed allylation reactions on a chiral substrate. This affect is more pronounced with the less nucleophilic benzylamine.[11] In related studies, Pfaltz has demonstrated that the palladium(0) catalysed alkylations of (*S*)-PhCH=CHCH(OAc)Tol with (*R*)- and (*S*)-**5** occur with opposite regiochemistries.[12] Under these relatively milder conditions (23°C compared with our 50°C) no evidence for interconversion of intermediate diastereomeric palladium complexes was found. We are not, however, aware of other studies that demonstrate the dependence on regiochemistry on the chirality of (*R*)- and (*S*)-BINAP.




## Acknowledgements

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5. Significant $^1$H NMR data ($\delta$, 300 MHz, $CDCl_3$). Compound **2**: 6.43 (1H, d, $J=16.0$), 6.15 (1H, dd, $J=16.0$, 10.4), 4.21 (2H, q, $J=7.2$), 4.04 (4H, m), 3.72 (1H, d, $J=11.2$), 2.88 (1H, dt, $J=10.4$, 2.0), 1.28 (3H, t, $J=7.2$), 1.12 (3H, d, $J=6.0$), 1.10 (3H, t, $J=7.2$); compound **3**: 5.72 (1H, dd, $J=7.4$, 1.2), 0.84 (9H, s); compound **4**: 5.77 (1H, dd, $J=7.4$, 2.0), 0.86 (9H, s); compound **8**: 6.48 (1H, d, $J=16.2$), 6.10 (1H, dd, $J=16.2$, 8.4), 3.94 (1H, m), 3.92 (1H, d, $J=13.8$), 3.65 (1H, d, $J=13.8$), 3.18 (1H, dd, $J=9.0$, 3.6), 2.89 (1H, m), 1.16 (3H, d, $J=6.3$); compound **9**: 5.67 (2H, m), 4.31 (1H, m), 4.21 (1H, m), 3.72 (2H, d, $J=4.2$), 1.21 (3H, d, $J=6.3$); compound **10**: 5.68 (2H, m), 4.29 (1H, m), 4.20 (1H, m), 3.73 (2H, m), 1.19 (3H, d, $J=6.7$); compound **11**: 6.51 (1H, d, $J=16.5$), 6.03 (1H, dd, $J=16.5$, 8.7), 3.89 (1H, d, $J=13.2$), 3.80 (1H, m), 3.65 (1H, d, $J=13.2$), 3.07 (1H, dd, $J=8.1$, 8.1), 1.16 (3H, d, $J=6.3$).
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