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Synthesis of amino acid derivatives *via* enantio- and diastereoselective Pd-catalyzed allylic substitutions with a non-stabilized enolate as nucleophile†

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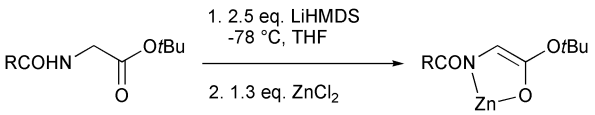
Diastereomer ratios of up to 95 : 5 and enantiomeric excesses of up to 95% were achieved in Pd-catalyzed asymmetric allylic substitutions with zinc enolates of glycine esters as nucleophiles; a remarkable effect of the ligand on the diastereoselectivity of the substitution was found.

Pd-catalyzed asymmetric allylic substitution is a valuable synthetic method.[1] Most *C*-nucleophiles in use are conjugated carbanions prepared from *CH*-acidic compounds with pK_a < *ca.* 20, *i.e.* malonates and β-keto esters. With symmetric nucleophiles, giving rise to only one stereogenic center in the coupling step, good yields and high enantioselectivities can now be consistently obtained. With unsymmetrical *C*-nucleophiles, *e.g.* β-keto esters or imines of amino acid esters, mixtures of diastereomers are usually generated because of configurational lability of the products. An exception was recently reported by Trost *et al.* who used substituted azlactones as nucleophiles which gave rise to α-alkylated γ,δ-unsaturated amino acids with a high degree of stereoselectivity.[2]

The epimerization problem does not exist for products generated with more basic carbanions such as enolates of esters and ketones; however, these were found to be problematic because of side reactions, in particular elimination and cyclopropane formation.[3] To overcome this problem, considerable effort has been expended on varying the counter ion of these enolates. Some success was obtained with tin and boron enolates.[4] In our laboratory, successful alkylations were achieved with the Zn enolates **2** and **4** (Scheme 1),[5] which gave excellent degrees of diastereoselectivity and b made valuable, γ,δ-unsaturated amino acids available (Scheme 2).



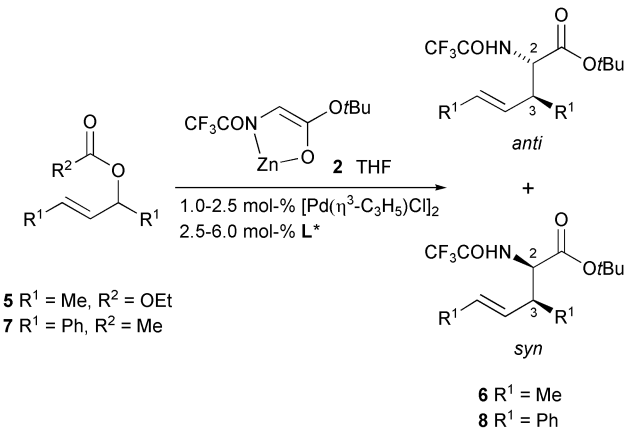
1 R = CF_3
3 R = *t*BuO

2 R = CF_3
4 R = *t*BuO

Scheme 1

With our group's background on asymmetric allylic substitutions,[6] we of course initiated an investigation on an enantioselective version of this reaction.[7] Related work was recently reported by Braun *et al.* who found examples of highly enantio- and diastereoselective reactions of ketone enolates with 1,3-diphenylallyl acetate[8] and Trost *et al.* who obtained excellent results for allylic substitutions with enolates of α-tetralones.[9]

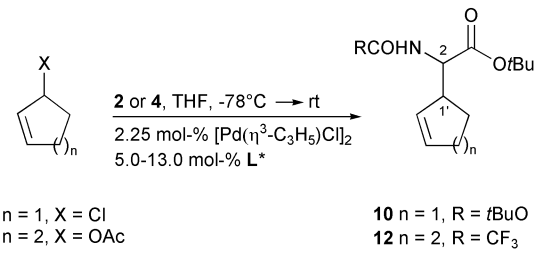
In order to assess the scope of the reactions with nucleophiles **2** and **4**, we not only used the particularly benevolent 1,3-diphenylallyl acetate (**7**) but selected a representative set of substrates including a large and a small acyclic (Scheme 2) and two cyclic allylic derivatives (Scheme 3). As chiral ligands[10] we used phosphinooxazolines **L2** and **L3**, which are particularly suited for acyclic substrates as well as the cymantrene derivative **L4** and the phosphinomyrtanic acid **L5** which are better suited for cyclic compounds (Fig. 1).



5 R^1 = Me, R^2 = OEt
7 R^1 = Ph, R^2 = Me

6 R^1 = Me
8 R^1 = Ph

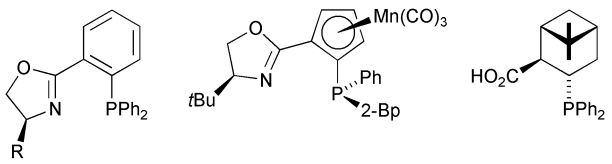
Scheme 2



9 n = 1, X = Cl
11 n = 2, X = OAc

10 n = 1, R = *t*BuO
12 n = 2, R = CF_3

Scheme 3



L1 R = H
L2 R = *i*Pr
L3 R = *t*Bu

L4

L5

Fig. 1 Chiral ligands.

Each of the reactions yields four stereoisomers. These isomers were base-line separable by GLC on the Chiralsil-L-Val phase. Individual isomers are characterized by their GLC retention times as given in Table 1.[11] Absolute and relative configurations were assigned for the full set of compounds **6**, **10**

† This work is dedicated to Professor Walter Siebert on the occasion of his 65th birthday.

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Table 1 Results of allylic alkylation

Entry	Substrate	Nucleophile	Ligand	Yield (%)	dr[a] *anti*:*syn*	ee (%)[a] *anti*	ee (%)[a] *syn*
1[b]	**5**	**2**	**L1**	75	82:18		
2[b]	**5**	**2**	**L2**	85	71:29	53 **6c**	19 **6b**
3[b]	**5**	**2**	**L3**	54	89:11	66 **6c**	7 **6b**
4[b]	**5**	**2**	**L5**	78	51:49	6 **6a**	74 **6b**
5[c]	**7**	**2**	**L1**	80	89:11		
6[c]	**7**	**2**	**L2**	62	95:5	94 **8d**	91 **8a**[d]
7[c]	**7**	**2**	**L3**	71	87:13	87 **8d**	61 **8a**[d]
8[e]	**9**	**4**	**L1**	29	65:35		
9[e]	**9**	**4**	**L4**	72	30:70	80 **10a**	95 **10d**
10[e]	**9**	**4**	**L5**	50	29:71	84 **10b**	58 **10c**
11[f]	**11**	**2**	**L1**	65	58:42		
12[f]	**11**	**2**	**L4**	80	51:49	75 **12a**	81 **12d**
13[f,g]	**11**	**2**	**1.4**	51	48:52	89 **12a**	77 **12d**
14[f]	**11**	**2**	dppp	81	82:18		
15[f]	**11**	**2**	**L5**	66	20:80	93 **12b**	53 **12c**

[a] The designations **a**, **b**, **c**, **d** are defined by the GLC retention times as follows: Chrompack Chirasil-L-Val; He; **6**: 80 °C, t_R = 17.0 min ((2*R*,3*R*)-**6a**), 17.9 min ((2*R*,3*S*)-**6b**), 22.9 min ((2*S*,3*S*)-**6c**), 24.5 min ((2*S*,3*R*)-**6d**). **8**: 165 °C, t_R = 49.2 min ((2*R*,3*R*)-**8a**), 52.3 min ((2*S*,3*S*)-**8b**), 56.2 min ((2*R*,3*S*)-**8c**), 64.5 min ((2*S*,3*R*)-**8d**); **10**: 95 °C, t_R = 12.8 min ((2*R*,1'*R*)-**10a**), 14.7 min ((2*S*,1'*S*)-**10b**), 15.4 min ((2*R*,1'*S*)-**10c**), 19.7 min ((2*S*,1'*R*)-**10d**). **12**: 95 °C, t_R = 25.0 min ((2*R*,1'*R*)-**12a**), 28.5 min ((2*S*,1'*S*)-**12b**), 30.1 min ((2*R*,1'*S*)-**12c**), 36.9 min ((2*S*,1'*R*)-**12d**). [b] 3.0 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$. [c] 1.2 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$. [d] The absolute configuration is assigned on the basis of analogy. [e] 0.5 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$. [f] 2.25 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$. [g] $Al(OiPr)_3$ was used instead of $ZnCl_2$.

and **12** by saponification, subsequent iodolactonization and X-ray crystal structure analysis. For **8** the absolute configuration of the *anti*-diasteromer was assigned *via* bromolactonization, while the absolute configuration of *syn*-**8** is tentative.

The reaction of substrate **5** with enolate **2** was previously carried out with PPh_3 as ligand which gave rise to a diastereomer ratio (dr) of 92:8 in favor of the *anti* diastereomer.[5] With the achiral phosphinooxazoline **L1** a dr of 82:18 was obtained (Table 1, entry 1). The chiral ligands **L2** and **L3** gave similar dr and ee of up to 66% for the *anti* product (*S*,*S*)-**6** (entries 2, 3). Chiral ligand **L5** gave only dr = 1:1 but 74% ee for the *syn* product (*R*,*S*)-**6** (entry 4). The steric course and the degree of enantioselectivity with respect to C(3) is very similar to that of the corresponding reactions of malonate enolates.[12] Thus, in accordance with our previous findings, the reactions of the non-stabilized enolate **2** closely resemble those of stabilized enolates. The dependence of the dr on the ligand is remarkable and indicates that both enantio- and diastereoselectivities of the substitutions can be controlled externally, *i.e.* by the ligand.

As anticipated, higher levels of selectivity were achieved with 1,3-diphenylallyl acetate (**7**) as substrate. With the achiral ligand **L1** a dr of 89:11 (80 % yield) (entry 5), with the chiral ligands **L2** and **L3** diastereoselectivity of up to 95:5 and ee of up to 94% could be obtained (entries 6, 7). Recrystallization of the crude product from diethyl ether–*n*-hexane gave diastereo- and enantiomerically pure major isomer (2*S*,3*R*)-**8**.

Allylic alkylations of cyclopent- and hex-2-enyl acetate (**9** and **11**) (Scheme 3) lead to cyclopent- and cyclohexenylglycines **10** and **12**, respectively, which display antibacterial activity and, therefore, are of particular interest.[13] For cyclopentenyl chloride (**9**) as substrate and nucleophile **4** the achiral ligand **L1** induced an *anti*–*syn* ratio of 65:35 (entry 8). The chiral ligands **L4** and **L5** gave rise to a reversal in the *anti*–*syn* ratio and enantioselectivity of up to 84% for *anti* and 95% ee for *syn* product **10** (entries 9,10). For the homologous cyclohex-2-enyl system the phosphinooxazoline ligands induced *ca.* 1:1 *anti*–*syn* ratios (entries 11–13) with ee of up to 89% for *anti* and 77% for *syn* isomers, respectively (**L4**) (entry 13). Again, a remarkably strong influence of the ligand on the *anti*–*syn* ratio was found: with the *P*,*P*-ligand dppp (1,3-bis(diphenylphosphanyl)propane), *anti*–*syn* ratio of 82:18 resulted (entry 14), whilst ligand **L5** gave rise to an *anti*–*syn* ratio of 20:80 and ee of 93% (*anti*) and 53% (*syn*) (entry 15). The reversed steric course with ligands **L4** and **L5** is also found for reactions with stabilized enolates.

In conclusion, we have shown that Pd-catalyzed allylic substitutions with glycine ester enolate derivatives **2** and **4** can yield derivatives of γ,δ-unsaturated amino acids with moderate to high levels of diastereo- and enantioselectivity. Generally, the steric course of the reactions of these non-stabilized enolates at the allylic carbon corresponds to that found with stabilized enolates. The diastereoselectivity of the substitution is strongly dependent on the ligand employed and can be controlled *via* ligand screening. This is an advantage but presently precludes proposal of a simple predictive model.

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