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Synthesis of novel chiral ligands from amino acids by the Ugi reaction

Gerald Dyker,* Klaus Breitenstein and Gerald Henkel

Fachbereich 6, Institut für Synthesechemie, Gerhard-Mercator-Universität Duisburg, Lotharstraße 1, D-47048 Duisburg, Germany

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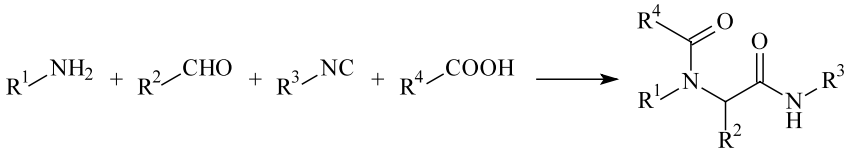
Abstract—The Ugi multi-component reaction is employed for the efficient synthesis of chiral ligands starting from amino acids and aryl aldehydes bearing a Lewis-base functionality. Tests on the products as ligands for enantioselective transition metal catalysis gave promising results in the palladium-catalyzed allylic substitution with e.e. values up to 81%.

1. Introduction

Since the beginning of the last decade combinatorial chemistry and the systematic screening of compound libraries have given major impetus to the search for new drugs.[1] Multi-component reactions (MCRs) are of particular importance for the generation of compound libraries, due to their exploratory power,[2] their atom economy and the convergent character of the reaction. Thus, a given lead structure is modified and optimized towards the desired activity. This procedure is essentially the same in the search for novel ligands for transition metal catalysis: Once a complex of a transition metal and a ligand is found to have a certain activity, structural optimization of the ligand's lead structure is carried out with the aim to drive the catalytic activity of the complex towards a maximum. Additionally, in stereoselective catalysis the stereoselectivity of the reaction is to be maximized. Combinatorial chemistry has been employed for this type of optimization.[3–5]

Among the MCRs known today, the Ugi four component reaction (U-4CR, Scheme 1), which combines an amine, an aldehyde or ketone, a carboxylic acid and an isocyanide to give an amino acid derivative, has gained considerable importance in drug discovery,[6] e.g. in the synthesis of lactams,[7–10] piperazines,[7,11–14] benzodiazepinediones,[12,13] other heterocycles of different ring sizes,[15–18] and bioconjugates.[19,20]

Most interestingly, the reaction of an amino acid with an aldehyde and an isocyanide in a nucleophilic solvent (e.g. methanol) results in a modification of the U-4CR, classified as the Ugi five-center four-component reaction (U-5C-4CR), which yields a 1,1′-iminodicarboxylic acid derivative[21] (Scheme 2). High yields and good diastereoselectivities are usually obtained, making the U-5C-4CR especially attractive for the synthesis of chiral multifunctionalized molecules which might be suitable for the complexation of transition metals.



Scheme 1. General scheme of the U-4CR.

* Corresponding author. Present address: Fakultät für Chemie, Ruhr-Universität Bochum, D-44780 Bochum, Germany. Tel.: +49-203-32-24551; fax: +49-203-32-14353; e-mail: gerald.dyker@ruhr-uni-bochum.de

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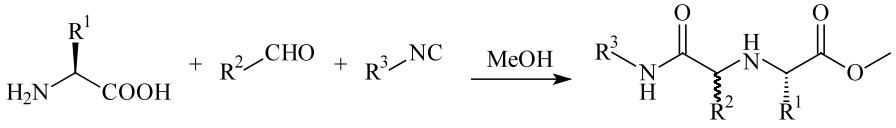
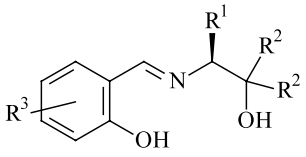


Scheme 2. The U-5C-4CR resulting in 1,1′-iminodicarboxylic acid derivatives.

Amino acids are an attractive source of stereochemical information and have therefore been commonly employed for the synthesis of chiral ligands,[22] e.g. in Aratani's Schiff base ligands **1**[23] and in the popular PHOX ligands **2** introduced by Pfaltz,[24] Helmchen[25,26] and Williams.[27]



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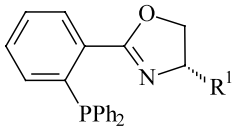

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However, these approaches for the synthesis of amino acid based ligands generally represent linear syntheses with respect to the amino acid and the inherent necessity to control racemization is a serious drawback of this concept, because detection of racemization can be troublesome. Due to its shortness and simplicity the U-5C-4CR represents a versatile tool for the synthesis of chiral compounds from amino acids. It was shown to proceed without racemization of the utilized amino acid.[21]

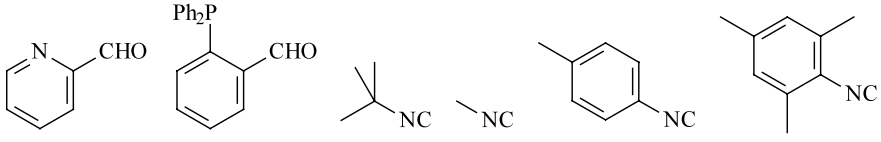
For these reasons we tested the U-5C-4CR for the synthesis of ligands to be used in enantioselective transition metal catalysis.

2. Ligand synthesis

Since the backbone of the iminodicarboxylic acid derivative typically contains a secondary amino group, we decided to introduce a phosphine and a pyridine functionality, respectively, as second donor functionality for novel *N*,*N*- and *P*,*N*-ligands. To obtain ligands capable of forming chelates with reasonable ring size, the second donor was to be introduced in the aldehyde component. For the first evaluation pyridine-2-aldehyde **3** and *o*-(diphenylphosphino)benzaldehyde **4**,[28] respectively, were condensed with L-valine ($R^1 = i$-propyl) and *tert*-butyl isocyanide **5a** in anhydrous methanol at room temperature (cf. Table 1, entries 1 and 3). Good to excellent yields and moderate to high diastereomeric excesses (de) were obtained. To study the effect of the reaction temperature, ligand **7a** was also synthesized at low (rising from −60 to 0°C, entry 2) and elevated temperature (100°C, entry 4). It was found that the best yield was achieved at room temperature (entry 3). The increased diastereoselectivity at lower temperature was only marginal and does not justify the prolonged reaction time and extra experimental requirements.

For comparison, the sterically demanding mesityl isocyanide **5d**, and two relatively unhindered aryl isocyanides (methyl-**5b**, *p*-tolyl-**5c**) were tested as model components (entries 5–7). In all cases the U-5C-4CR was indeed successful, confirming that the correspond-

Table 1. Results of ligand syntheses



3 **4** **5a** **5b** **5c** **5d**

Entry	Compound no.	Aldehyde R^2–CHO	Isocyanide R^3–NC	Time (h)	Temperature (°C)	Yield (%)	D.e.[a] (%)
1	**6**	**3**	**5a**	26	20	67	41
2	**7a**	**4**	**5a**	190	−60 to 0	70	84
3	**7a**	**4**	**5a**	45	20	90	81
4	**7a**	**4**	**5a**	18	100	77	78
5	**7b**	**4**	**5b**	50	20	73	82
6	**7c**	**4**	**5c**	74	20	39	76
7	**7d**	**4**	**5d**	74	20	60	76

[a] Determined by ^{1}H NMR spectroscopy

ing solid-phase synthesis of immobilized ligands should be possible, if an isocyanide-functionalized solid phase is employed.

The absolute configuration of the newly formed stereogenic center for the main diastereomer of ligand **7a** was analyzed by X-ray crystallography. Since most of the ligands synthesized are sticky oils or glassy solids it was necessary to oxidize **7a** to the corresponding phosphine oxide **8a** (H_2O_2 in acetone) in order to obtain suitable crystals. The newly formed stereogenic center proved to have the *R* configuration (Fig. 1),[29] which contradicts the results reported by Ugi,[21,22] but is in agreement with the findings of Kim;[15] therefore a general mechanistic interpretation of the stereochemical course of the reaction requires more experimental investigation.

3. Ligand testing in transition metal catalysis

The Ni-catalyzed Michael addition reaction is known to proceed stereoselectively in the presence of *N*,*N*-ligands.[30,31] However, no catalytic activity was observed with neither ligand **6** nor **7a**.

The Pd-catalyzed allylic substitution reaction of an allylic acetate functionality by a malonate[26,32] (Scheme 3) is known to proceed stereoselectively in the presence of chiral *P*,*N*-ligands (e.g. PHOX ligands), hence this reaction was employed for testing the chirality transfer properties of the ligands. 1,3-Diphenylpropenylacetate **9**[33] was utilized as the substrate.

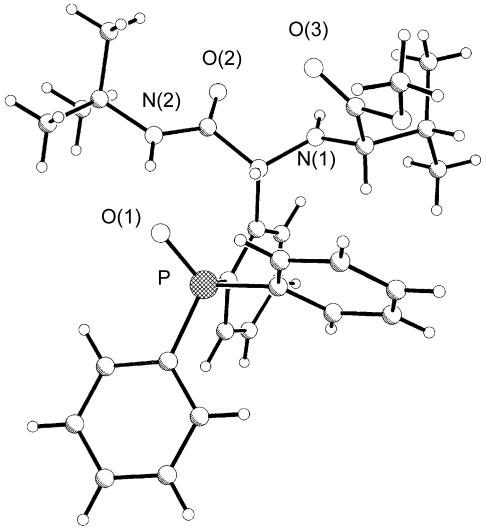
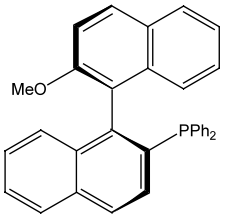


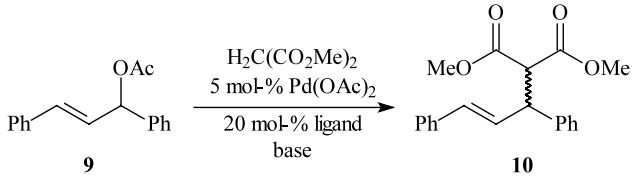
Figure 1. X-Ray crystal structure of **8a**.

The results obtained are shown in Table 2. Although *N*,*N*-ligands (e.g. aza-semicorrins introduced by Pfaltz[35] and the diaziridine introduced by Andersson and Tanner[36]) proved to be useful in the Pd-catalyzed allylic substitution reaction, the *N*,*N*-ligand **6** gave a virtually inactive catalyst with $Pd(OAc)_2$ (entry 1). In contrast, catalysts formed with the *P*,*N*-ligands **7** showed moderate to very good activities: from the yields obtained it can be concluded that ligands bearing alkyl substituents as R^3 (Table 2, entries 2 and 3) give more active catalysts than those with aromatic substituents (entries 4 and 5). Furthermore, considering the enantiomeric excess achieved, it becomes clear, that a bulky alkyl substituent results in significantly higher enantioselectivity (entry 2). Therefore, further optimization was carried out with the *tert*-butyl substituted ligand **7a**.



11

Fuji et al. reported on the significant influence of the base employed in the reaction with the BINOL based ligand MeO–MOP, **11**.[37] Hence, we investigated the effect of different bases on the selectivity of the model reaction (Table 3).



9 **10**

Scheme 3. Employed test reaction for ligand evaluation: Pd-catalyzed allylic substitution reaction.

Table 2. Results of the Pd-catalyzed allylic substitution reaction with a variety of ligands

Entry	Ligand (% d.e.)	Reaction time (h)	Yield **10** (%)	E.e. (configuration)[a] (%)
1	**6** (41)	66	10	Not determined
2	**7a** (81)	23	91	75 (*R*)
3	**7b** (82)	45	86	2 (*S*)
4	**7c** (76)	115	28	37 (*R*)
5	**7d** (76)	90	70	33 (*R*)

Reaction conditions: 5 mol% $Pd(OAc)_2$, 20 mol% ligand, *N*,*O*-bis(trimethylsilyl)acetamide (BSA)/KOAc as base, THF as solvent, room temperature.

[a] Determined by ^1H NMR spectroscopy with $Eu((+)\text{-hfc})_3$ and comparison of specific rotation value with literature data.[34]

Table 3. Results of the Pd-catalyzed allylic substitution reaction with ligand **7a** and different bases

Entry	Ligand (% d.e.)	Base	Yield **10** (%)	E.e. (configuration) (%)
1	**7a** (84)	NaH	99	64 (*R*)
2	**7a** (81)	BSA/KOAc	91	75 (*R*)
3	**7a** (84)	BSA/CsOAc	94	70 (*R*)

Reaction conditions as described for Table 2.

Our findings are in accord with the results reported by Fuji et al.: the utilization of *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) (entries 2 and 3) leads to higher e.e. than NaH (entry 1). However, the catalysts formed with the ligands presented here are influenced much less by the nature of the base.

Whereas ligands like PHOX **2** or MeO–MOP **11** contain only few polar functional groups and hence are rather non-polar, our ligands contain very polar groups that are capable of hydrogen bonding. Therefore, we were interested to elaborate on the influence of the solvent on the catalyst formed. Thus, three solvents were tested: THF (polar, complexing), dichloromethane (polar, not complexing), and toluene (unpolar, not complexing). The results are shown in Table 4.

In both polar solvents THF and DCM, the reactions proceed in high yields and with good enantioselectivities (entries 1 and 2). However, the time to complete the reaction is significantly prolonged in neat dichloromethane (entry 2). Surprisingly, a mixture of both polar solvents gives a quantitative yield in a shorter reaction time (entry 3), with similar enantioselectivity to the single solvent systems. Obviously, a certain amount of an additional complexing agent (here: solvent) enhances the reactivity of the complexes formed. Toluene is clearly unsuitable as a solvent in this case, with virtually no catalysis taking place (entry 4).

Since the enantioselectivity of the catalytic reaction is essentially unaffected by the solvent, the ligands show rigidity to varying reaction conditions, which may be advantageous.

As the U-5C-4CR usually yields a mixture of diastereomers, we aimed to gain knowledge on the way each diastereomer affects the catalytic reaction. Ligand **7a** (*R*,*S*-**7a**) was therefore employed with various diastereomeric excess; from a 2:1 mixture of diastereomers to almost pure (*R*,*S*)-isomer (the major isomer obtained from the U-5C-4CR). The results (Table 5) indicate, that with the major isomer a more selective catalyst is formed (entry 1): despite the prolonged reaction time the yield obtained with the 2:1 mixture of diastereomers (entry 3) is lower and decreased enantiomeric excess is observed.

4. Summary

In summary, we have shown that the Ugi reaction is suitable for the synthesis of chiral ligands for transition metal catalysis. Incorporating a phosphine functionality yielded novel *P*,*N*-ligands, which were successfully tested in the Pd-catalyzed allylic substitution reaction.

The major advantage of this approach is the immediate utilization of amino acids as a source of stereochemical information. Since the Ugi reaction is excellently suited to the synthesis of compound libraries by application of combinatorial principles, further optimization of the ligand structure could be driven forward in a systematic manner by screening of ligand libraries.

Table 4. Results of the Pd-catalyzed allylic substitution reaction with ligand **7a** in different solvents

Entry	Ligand (% d.e.)	Solvent	Reaction time (h)	Yield **10** (%)	E.e. (configuration) (%)
1	**7a** (81)	THF	23	91	75 (*R*)
2	**7a** (81)	CH_2Cl_2	42	92	73 (*R*)
3	**7a** (81)	CH_2Cl_2/THF 11:2*	17	100	76 (*R*)
4	**7a** (81)	Toluene	93	8	Not determined

Reaction conditions as described for Table 2.
* Volume proportions.

Table 5. Results of the Pd-catalyzed allylic substitution reaction with ligand **7a** at varying excesses of the (*R*,*S*)-diastereomer

Entry	Ligand (% d.e.)	Reaction time (h)	Yield **10** (%)	E.e. (configuration) (%)
D1	**7a** (>95)	24	92	81 (*R*)
D2	**7a** (81)	23	91	75 (*R*)
D3	**7a** (53)	42	82	69 (*R*)

Other conditions as described for Table 2.

5. Experimental

NMR spectra were recorded at 500.1 MHz proton resonance frequency in $CDCl_3$ unless otherwise stated. Melting points are uncorrected. Diastereomeric excesses were determined by ^{1}H NMR spectroscopy, enantiomeric excesses were determined by ^{1}H NMR spectroscopy with Eu((+)-hfc)$_3$ (25 mol%) and comparison of specific rotation values with the literature data.[33] Ligand syntheses and catalyses are carried out in dry solvents under argon. Methanol was dried by refluxing with magnesium turnings and distilled, dichloromethane was dried by refluxing with CaH_2 and subsequent distillation, toluene and THF were distilled from Na/benzophenone prior to use. Isocyanides were synthesized according to literature procedures.[38] The substrate **9** for the Pd-catalyzed allylic substitution reaction was synthesized according to Bosnich.[39]

5.1. General procedure for synthesis of ligands by U-5C-4CR

The aldehyde (2 mmol) and L-Valine (2 mmol) were suspended in dry methanol (15 ml) in a screw-cap vessel. A solution of the isocyanide **5** (2.1 mmol) in methanol (5 ml) was added and the reaction mixture was stirred for the time indicated in Table 1. The solvent was evaporated and the ligand is isolated from the residue by flash chromatography.

5.1.1. (2*S*,1′*RS*)-2-[1′-*N*-*tert*-Butylcarbamoyl-(pyridine-2-yl)-methyl]amino-3-methylbutanoic acid methyl ester, 6. R_f (MTBE/PE 1:1) = 0.21. Yield 433 mg (1.35 mmol, 67%), yellow oil, d.e. = 41%; $C_{17}H_{27}N_3O_3$ (321.42): calcd C, 63.53; H, 8.45; N, 13.01; found C, 63.50; H, 8.47; N, 13.07; IR (film): ν = 3333 cm^{-1} (m), 3057 (w), 2964 (s), 2875 (m), 1735 (s), 1675 (s), 1591 (s), 1569 (m), 1512 (s), 1467 (s), 1431 (s), 1390 (s), 1363 (s), 1270 (s), 1227 (s), 1199 (s), 1154 (s), 1096 (w), 1049 (m), 998 (m), 929 (w), 905 (w), 821 (w), 768 (m), 752 (s), 625 (m); UV–vis (acetonitrile): λ_{max} (log ε) = 208 nm (3.91, sh), 255 nm (3.51, sh), 261 (3.56), 268 (3.46); ^{1}H NMR: δ = 1.05 (d, J = 6.8 Hz, 3H, (CH_3)$_2$CH), 1.07 (d, J = 6.8 Hz, 3H, (CH_3)$_2$CH), 1.33 (s, 9H, (CH_3)$_3$C), 2.08 (m, 1H, (CH$_3$)$_2$CH), 3.04 (d, J = 5.6 Hz, 1H, CHCOOCH$_3$), 3.61 (s, 3H, COOCH_3), 3.64 (b, 1H, NH), 4.05 (s, 1H, CHCONH), 7.19 (m, 1H, 4-H), 7.55 (m, 1H, 2-H), 7.59 (b, 1H, CONH), 7.63 (m, 1H, 3-H), 8.55 (ddd, J = 4.9, 1.7, 0.9 Hz, 5-H); ^{13}C NMR: δ = 18.31 (q, (CH_3)$_2$CH), 20.03 (q, (CH_3)$_2$CH), 28.64 (q, (CH3)3C), 31.51 (d, (CH$_3$)$_2$CH), 50.59 (s, (CH$_3$)$_3$$C$), 51.58 (q, COO$CH_3$), 66.65 (d, CHCOOCH$_3$ or CHCONH), 66.73 (d, CHCOOCH$_3$ or CHCONH), 122.56 (d, C-2 or C-4), 122.63 (C-2 or C-4), 136.42 (d, C-3), 148.63 (d, C-5), 156.65 (s, C-1), 170.62 (s, CONH), 174.85 (s, COOCH$_3$); MS (70 eV, 60°C); m/z (%): 321 (1) [M+], 221 (100), 161 (46), 107 (66), 58 (59).

5.1.2. (2*S*,1′*RS*)-2-[*N*-(1′-*N*-*tert*-Butylcarbamoyl)-(*o*-diphenylphosphino)-benzyl)]amino-3-methylbutanoic acid methyl ester, 7a. R_f (MTBE/PE 1:4) = 0.25. Yield 908 mg (1.8 mmol, 90%), colorless crystals, mp 104–106°C, d.e. = 81%; $C_{30}H_{37}N_2O_3P$ (504.61): calcd C, 71.41; H, 7.39; N, 5.55; found C, 71.20; H, 7.33; N, 5.48; IR (film): ν = 3416 cm^{-1} (w), 3337 (w), 3054 (w), 2964 (s), 2873 (w), 1735 (s), 1678 (s), 1585 (w), 1510 (s), 1477 (m), 1451 (m), 1432 (s), 1390 (w), 1364 (m), 1303 (w), 1266 (m), 1224 (m), 1198 (s), 1153 (m), 1119 (w), 1092 (w), 1070 (w), 997 (w), 745 (s), 698 (s); UV–vis (acetonitrile): λ_{max} (log ε) = 192 nm (4.90), 194 (4.91), 196 (4.90), 265 (3.96); ^{1}H NMR: δ = 0.82 (d, J = 6.8 Hz, 3H, (CH_3)$_2$CH), 0.87 (d, J = 6.8 Hz, 3H, (CH_3)$_2$CH), 1.08 (s, 9H, (CH_3)$_3$C), 1.83 ('sext', 'J' = 6.8 Hz, 1H, (CH$_3$)$_2$CH), 2.69 (b, 1H, NH), 2.78 (d, J = 5.6 Hz, 1H, CHCOOCH$_3$), 3.62 (s, 3H, COOCH_3), 5.22 (d, $^4J_{H,P}$ = 9.8 Hz, 1H, CHCONH), 5.59 (bs, 1H, CONH), 7.00 (ddd, J = 7.2, 3.9, 1.2 Hz, 1H, Ar), 7.17–7.21 (m, 3H, Ar), 7.27–7.39 (m, 9H, Ar), 7.66 (ddd, J = 7.8, 4.4, 1.2 Hz, 1H, Ar); ^{13}C NMR: δ = 18.33 (q, (CH_3)$_2$CH), 19.18 (q, (CH_3)$_2$CH), 28.34 (q, (CH_3)$_3$C), 31.47 (d, (CH$_3$)$_2$CH), 50.88 (s, (CH$_3$)$_3$$C$), 51.46/51.48 (2 d, COO$CH_3$), 61.73 (dd, $^3J_{C,P}$ = 27.0 Hz, CHCONH), 64.10 (d, CHCOOCH$_3$), 127.95 (d, Ar), 128.16 (dd$_{C,P}$, $^3J_{C,P}$ = 5.0 Hz, Ar), 128.50 (dd$_{C,P}$, $^3J_{C,P}$ = 5.5 Hz, Ar), 128.50 (d, Ar), 128.82 (dd$_{C,P}$, $^3J_{C,P}$ = 7.5 Hz, Ar), 129.08 (d, Ar), 129.84 (d, Ar), 133.13 (dd$_{C,P}$, $^2J_{C,P}$ = 19.0 Hz, Ar), 134.02 (dd$_{C,P}$, $^2J_{C,P}$ = 19.9 Hz, Ar), 134.37 (dd, $J_{C,P}$ = 1.5 Hz, Ar), 135.85 (sd$_{C,P}$, $^2J_{C,P}$ = 9.5 Hz, Ar), 136.31 (sd$_{C,P}$, $^2J_{C,P}$ = 12.5 Hz, Ar), 136.87 (sd$_{C,P}$, $^3J_{C,P}$ = 10.5 Hz, Ar), 144.80 (sd$_{C,P}$, $^3J_{C,P}$ = 25.4 Hz, Ar), 170.66 (s, CONH), 175.09 (s, COOCH$_3$); ^{31}P NMR: δ = −19.46; MS (70 eV, 150°C); m/z (%): 504 (2) [M$^+$], 445 (3), 404 (100), 317 (29), 288 (20), 261 (20), 183 (29).

5.1.3. (2*S*,1′*RS*)-2-[*N*-(1′-*N*-Methylcarbamoyl)-(*o*-diphenylphosphino)-benzyl)]amino-3-methylbutanoic acid methyl ester, 7b. R_f (MTBE/PE 2:1) = 0.39. Yield 670 mg (1.45 mmol, 73%) colorless glassy solid, mp 40–42°C, d.e. = 82%; $C_{27}H_{31}N_2O_3P$ (462.53): calcd C, 70.11; H, 6.76; N, 6.06; found C, 69.62; H, 6.94; N, 6.02 (correction by 4.5 mol% CH_2Cl_2 (also detected be NMR and MS) C, 69.63; H, 6.72; N, 6.00, correct elemental analysis was obtained for the corresponding phosphine oxide; IR (film): ν = 3426 cm^{-1} (w), 3343 (w), 3053 (w), 2961 (m), 2873 (w), 1731 (s), 1676 (s), 1585 (w), 1518 (m), 1462 (m), 1432 (s), 1410 (w), 1386 (w), 1366 (w), 1307 (w), 1246 (m), 1200 (s), 1153 (m), 1092 (w), 1070 (w), 998 (w), 916 (w), 853 (w), 746 (s), 698 (s); UV–vis (acetonitrile): λ_{max} (log ε) = 192 nm (4.83), 194 (4.87), 197 (4.87), 226 (4.26, sh), 266 (3.81); ^{1}H NMR: δ = 0.83 (d, J = 6.8 Hz, 3H, (CH_3)$_2$CH), 0.88 (d, J = 6.8 Hz, 3H, (CH_3)$_2$CH), 1.86 ('sext', 'J' = 6.7 Hz, 1H, (CH$_3$)$_2$CH), 2.45 (d, J = 4.8 Hz, 3H, CONCH_3), 2.77 (b, 1H, NH), 2.80 (d, J = 5.7 Hz, 1H, CHCOOCH$_3$), 3.64 (s, 3H, COOCH_3), 5.22 (d, $^4J_{H,P}$ = 9.9 Hz, 1H, CHCONH), 5.45 (bs, 1H, CONH), 6.99 (ddd, J = 7.7, 4.0, 1.0 Hz, Ar), 7.19–7.24 (m, 2H, Ar), 7.30–7.39 (m, 9H, Ar), 7.66 (ddd, J = 7.8, 4.4, 1.2 Hz, 1H, Ar); ^{13}C NMR: δ = 18.43 (q, (CH_3)$_2$CH), 19.31 (q, (CH_3)$_2$CH), 26.14 (q, CONCH_3), 31.51 (d, (CH$_3$)$_2$CH), 51.64/51.65 (2 d, COOCH$_3$), 61.41 (dd, $^3J_{C,P}$ = 26.4 Hz, CHCONH), 64.17 (d, CHCOOCH$_3$), 128.17 (d, Ar), 128.46 (dd$_{C,P}$, $J_{C,P}$ = 5.0 Hz, Ar), 128.63 (dd$_{C,P}$, $J_{C,P}$ = 9.0 Hz, Ar), 128.65 (d, Ar), 128.84 (dd$_{C,P}$, $J_{C,P}$ = 7.5 Hz, Ar), 129.25 (d, Ar), 129.86 (d, Ar), 133.36 (dd$_{C,P}$, $J_{C,P}$ = 19.5 Hz, Ar), 134.15 (d, Ar), 134.37 (dd$_{C,P}$, $J_{C,P}$ =

20.4 Hz, Ar), 135.89 ($sd_{C,P}$, $^2J_{C,P}=9.5$ Hz, Ar), 136.49 ($sd_{C,P}$, $^2J_{C,P}=10.0$ Hz, Ar), 136.79 ($sd_{C,P}$, $^3J_{C,P}=13.5$ Hz, Ar), 144.06 ($sd_{C,P}$, $^3J_{C,P}=24.4$ Hz, Ar), 171.93 (s, *C*ONH), 175.19 (s, *C*OOCH$_3$); ^{31}P NMR: $\delta=-18.55$; MS (70 eV, 170°C); *m*/*z* (%): 462 (10) [M$^+$], 404 (100), 333 (22), 306 (37), 291 (27), 275 (25).

5.1.4. (2*S*,1′*RS*)-2-[*N*-(1′-*N*-*p*-Tolylcarbamoyl)(*o*-diphenylphosphino)benzyl)]amino-3-methylbutanoic acid methyl ester, 7c. R_f (MTBE/PE 1:4)=0.30. Yield 417 mg (0.77 mmol, 39%) yellow oil, d.e.=76%; $C_{33}H_{35}N_2O_3P$ (538.63): calcd C, 73.59; H, 6.55; N, 5.20; found C, 73.47; H, 6.63; N, 5.02; IR (film): $\nu=3395$ cm^{-1} (w), 3321 (w), 3053 (w), 2961 (m), 2873 (w), 1733 (s), 1690 (s), 1594 (m), 1520 (s), 1478 (m), 1459 (m), 1432 (s), 1403 (m), 1367 (w), 1312 (m), 1296 (m), 1242 (m), 1200 (m), 1182 (m), 1151 (m), 1122 (w), 1092 (w), 1027 (w), 997 (w), 910 (w), 815 (m), 745 (s), 697 (s), 647 (w); UV–vis (acetonitrile): λ_{max} (log ε)=194 nm (4.95), 197 (4.96), 199 (4.95), 201 (4.94), 252 (4.32); ^{1}H NMR: $\delta=0.84$ (d, $J=6.8$ Hz, 3H, (CH_3)$_2$CH), 0.86 (d, $J=6.8$ Hz, 3H, (CH_3)$_2$CH), 1.86 (sepd, $J=6.8$, 5.5 Hz, 1H, (CH$_3$)$_2$C*H*), 2.26 (s, 3H, tolyl-CH_3), 2.65 (b, 1H, N*H*), 2.90 (d, $J=5.5$ Hz, 1H, C*H*COOCH$_3$), 3.60 (s, 3H, COOCH_3), 5.34 (d, $^4J_{C,P}=9.1$ Hz, 1H, C*H*CONH), 6.98–7.04 (m, 3H, Ar), 7.13–7.18 (m, 2H, Ar), 7.19–7.27 (m, 3H, Ar), 7.28–7.40 (m, 9H, Ar), 7.66 (ddd, $J=7.8$, 4.3, 1.2 Hz, 1H, Ar), 8.10 (b, 1H, CON*H*); ^{13}C NMR: $\delta=18.35$ (q, (*C*H$_3$)$_2$CH), 19.20 (q, (*C*H$_3$)$_2$CH), 20.84 (q, tolyl-*C*H$_3$), 31.53 (d, (CH$_3$)$_2$*C*H), 51.71 (q, COO*C*H$_3$), 62.63 ($dd_{C,P}$, $J=24.9$ Hz, *C*HCON), 64.56 (d, *C*HCOOCH$_3$), 119.40 (d, Ar), 128.37 (d, Ar), 128.70 ($dd_{C,P}$, $^3J_{C,P}=6.5$ Hz, Ar), 128.84 (d, Ar), 128.97 ($dd_{C,P}$, $^3J_{C,P}=7.0$ Hz, Ar), 129.22 (d, Ar), 129.22 (d, Ar), 130.10 (d, Ar), 133.48 ($dd_{C,P}$, $^2J_{C,P}=19.0$ Hz, Ar), 133.47 (s, Ar), 134.04 ($dd_{C,P}$, $^2J_{C,P}=20.0$ Hz, Ar), 134.59 (d, Ar), 135.26 (s, Ar), 125.75 ($sd_{C,P}$, $^1J_{C,P}=9.0$ Hz, Ar), 136.20 ($sd_{C,P}$, $^1J_{C,P}=12.0$ Hz, Ar), 136.31 ($sd_{C,P}$, $^1J_{C,P}=9.5$ Hz, Ar), 144.26 ($sd_{C,P}$, $^1J_{C,P}=25.4$ Hz, Ar), 169.68 (s, *C*ONH), 174.92 (*C*OOCH$_3$); ^{31}P NMR: $\delta=-18.16$; MS (70 eV, 170°C); *m*/*z* (%): 538 (12) [M$^+$], 431 (14), 404 (100), 306 (30), 288 (23), 183 (25), 165 (18).

5.1.5. (2*S*,1′*RS*)-2-[*N*-(1′-*N*-2,4,6-Trimethylphenylcarbamoyl)-(*o*-diphenylphosphino)-benzyl)]amino-3-methylbutanoic acid methyl ester, 7d. R_f (MTBE/PE 1:4)=0.28. Yield 680 mg (1.20 mmol, 60%), yellow oil, d.e.=76%; $C_{35}H_{39}N_2O_3P$ (566.68): calcd C, 74.18; H, 6.94; N, 4.94; found C, 74.15; H, 6.98; N, 4.80; IR (film): $\nu=3385$ cm^{-1} (w), 3329 (w), 3053 (w), 2959 (m), 2872 (w), 1733 (w), 1691 (s), 1609 (w), 1585 (w), 1491 (s), 1433 (s), 1384 (w), 1366 (w), 1309 (w), 1236 (m), 1198 (m), 1155 (m), 1092 (w), 1027 (w), 998 (w), 851 (w), 745 (s), 698 (s); UV–vis (acetonitrile): λ_{max} (log ε)= 192 nm (5.02), 194 (5.06), 196 (5.07), 199 (5.05), 265 (3.99); ^{1}H NMR: $\delta=0.83$ (d, $J=6.8$ Hz, 3H, (CH_3)$_2$CH), 0.87 (d, $J=6.8$ Hz, 3H, (CH_3)$_2$CH), 1.88 (s, 7H, Ar-*o*-CH_3 and (CH$_3$)$_2$C*H*), 2.21 (s, 3H, Ar-*p*-CH_3), 2.82 (d, $J=5.4$ Hz, 1H, C*H*COOCH$_3$), 2.90 (b, 1H, N*H*), 3.61 (s, 3H, COOCH_3), 5.44 (d, $J=9.3$ Hz, 1H, C*H*CONH), 6.77 (s, 2H, Ar), 6.96 (b, 1H, CONH), 6.99 (ddd, $J=7.7$, 4.0, 1.3 Hz, 1H, Ar), 7.19–7.38 (m, 11H, Ar), 7.41 (td, $J=7.6$, 1.3 Hz, 1H, Ar), 7.78 (dd, $J=6.9$, 4.4 Hz, 1H, Ar); ^{13}C NMR: $\delta=18.07$ (q, Ar-*o*-*C*H$_3$), 18.30 (q, (*C*H$_3$)$_2$CH), 19.30 (q, (*C*H$_3$)$_2$CH), 20.88 (q, Ar-*p*-*C*H$_3$), 31.50 (d, (CH$_3$)$_2$*C*H), 51.61 (q, COO*C*H$_3$), 61.43 ($dd_{C,P}$, $^3J_{C,P}=25.4$ Hz, *C*HCON), 64.09 (d, *C*HCOOCH$_3$), 128.32 (d, Ar), 128.64 (d, Ar), 128.70 ($dd_{C,P}$, $^3J_{C,P}=6.5$ Hz, Ar), 128.84 (d, Ar), 128.89 ($dd_{C,P}$, $^3J_{C,P}=6.0$ Hz, Ar), 129.27 (d, Ar), 129.85 (d, Ar), 130.87 (s, Ar), 133.48 ($dd_{C,P}$, $^2J_{C,P}=18.9$ Hz, Ar), 134.16 (dd, $^2J_{C,P}=20.0$ Hz, Ar), 134.21 (d, Ar), 135.03 (s, Ar), 135.64 ($sd_{C,P}$, $^1J_{C,P}=9.0$ Hz, Ar), 136.30 ($sd_{C,P}$, $^1J_{C,P}=8.0$ Hz, Ar), 136.39 ($sd_{C,P}$, $^1J_{C,P}=11.0$ Hz, Ar), 136.52 (s, Ar), 144.46 ($sd_{C,P}$, $^1J_{C,P}=24.9$ Hz, Ar), 169.95 (s, *C*ONH), 174.99 (s, *C*OOCH$_3$); ^{31}P NMR: $\delta=-17.95$; ^{1}H NMR (DMSO-D$_6$): $\delta=0.70$ (d, $J=6.8$ Hz, 3H, (CH_3)$_2$CH), 0.76 (d, $J=6.8$ Hz, 3H, (CH_3)$_2$CH), 1.76 ('sext', 'J'=6.7 Hz, 1H, (CH$_3$)$_2$C*H*), 1.94 (s, 6H, Ar-*o*-CH_3), 2.19 (s, 3H, Ar-*p*-CH_3), 2.79 (dd, $J=9.4$, 5.2 Hz, 1H, C*H*COOCH$_3$), 2.87 (dd, $J=9.5$, 5.0 Hz, 1H, N*H*), 3.51 (s, 3H, COOCH_3), 5.44 (dd, $J=9.7$, 4.8 Hz, 1H, 6.82 (s, 2H, Ar), 6.99 (ddd, $J=7.8$, 3.8, 1.3 Hz, 1H, Ar), 7.15–7.48 (m, 12H, Ar), 7.72 (ddd, $J=7.8$, 4.4, 1.2 Hz, 1H, Ar), 8.66 (s, 1H, CONH); ^{13}C NMR (DMSO-D$_6$): $\delta=18.00$ (q, (*C*H$_3$)$_2$CH), 18.35 (q, (*C*H$_3$)$_2$CH), 19.03 (q, Ar-*o*-*C*H$_3$), 20.64 (q, Ar-*p*-*C*H$_3$), 31.16 (d, (CH$_3$)$_2$*C*H), 51.56 (q, COO*C*H$_3$), 62.04 ($dd_{C,P}$, $^3J_{C,P}=26.4$ Hz, *C*HCON), 64.07 (d, C*H*COOCH$_3$), 128.10 ($dd_{C,P}$, $^2J_{C,P}=5.5$ Hz, Ar), 128.22 (d, Ar), 128.35 (d, Ar), 128.70 ($dd_{C,P}$, $^3J_{C,P}=6.5$ Hz, Ar), 128.75 (d, Ar), 128.82 ($dd_{C,P}$, $^3J_{C,P}=6.0$ Hz, Ar), 128.84 (d, Ar), 129.78 (d, Ar), 132.23 (s, Ar), 133.12 ($dd_{C,P}$, $^2J_{C,P}=19.0$ Hz, Ar), 133.40 ($dd_{C,P}$, $^2J_{C,P}=19.0$ Hz, Ar), 134.70 (d, Ar), 135.17 (s, Ar), 135.67 (s, Ar), 136.39 ($sd_{C,P}$, $^1J_{C,P}=$ 13.5 Hz, Ar), 136.92 ($sd_{C,P}$, $^1J_{C,P}=11.0$ Hz, Ar), 137.15 ($sd_{C,P}$, $^1J_{C,P}=11.0$ Hz, Ar), 145.00 ($sd_{C,P}$, $^1J_{C,P}=26.4$ Hz, Ar), 169.92 (s, *C*ONH), 174.31 (s, *C*OOCH$_3$); ^{31}P NMR (DMSO-*D*$_6$): $\delta=-18.98$; MS (70 eV, 205°C); *m*/*z* (%): 567 (4) [M$^+$+1], 566 (9) [M$^+$], 435 (18), 404 (100), 306 (30), 292 (20), 291 (20), 183 (11), 165 (10).

5.2. General procedure for the Pd-catalyzed allylic substitution reaction

Catalyst solution: $Pd(OAc)_2$ (11.2 mg (49.9 μmol, 5 mol%) and the respective ligand (200 μmol, 4 equiv.) were dissolved in the solvent (3 ml) in a vessel fitted with a septum. After 10 min a solution of 1,3-diphenyl-prop-2-en-1-yl acetic acid ester **9** (253 mg, 1.0 mmol) in solvent (2 ml) was added. Dimethyl malonate (212 mg, 1.60 mmol, 1.6 equiv.) and the respective base (cf. Table 3) were stirred in solvent (4 ml). The catalyst solution was added after 25 min and the mixture was stirred for the time indicated in Tables 2–5. The mixture was then hydrolyzed with phosphate buffer (pH 7, 10 ml), the phases are separated, the organic phase dried with Na_2SO_4, evaporated and separated into its components by flash chromatography.

5.3. (2*S*,1′*RS*)-2-[*N*-(1′-*N*-*tert*-Butylcarbamoyl)-(*o*-diphenylphosphinoyl)-benzyl)]amino-3-methylbutanoic acid methyl ester, 8a

A solution of **7a** (252 mg, 0.5 mmol) in acetone (20 ml)

was stirred for 50 min with H_2O_2 (1 ml, 30%). After evaporation of the solvent the residue was dissolved in dichloromethane and dried with Na_2SO_4. Removal of the solvent and drying under high vacuum afforded **8a** as a colorless oil (259 mg, 0.5 mmol, 100%). Crystals of the major diastereomer (confirmed by ^{1}H NMR) suitable for X-ray crystal analysis are obtained by recrystallization from Et_2O/PE 1:3. R_f (MTBE) = 0.71, mp 136–138°C; $C_{30}H_{37}N_2O_4P$ (520.61): calcd C, 69.21; H, 7.16; N, 5.38; found C, 69.10; H, 7.22; N, 5.30; IR (film): ν = 3259 cm^{-1} (w), 3226 (m), 3063 (m), 2963 (s), 2873 (w), 1732 (s), 1678 (s), 1566 (m), 1437 (s), 1388 (w), 1363 (m), 1304 (m), 1259 (w), 1227 (m), 1173 (s), 1119 (s), 1071 (w), 998 (w), 749 (m), 723 (s), 696 (s), 669 (w).

UV–vis (acetonitrile): λ_{max} (log ε) = 194 nm (4.86), 196 (4.88), 198 (4.85), 201 (4.80), 224 (4.37, sh), 273 (3.35); ^{1}H NMR: δ = 0.65 (d, J = 6.8 Hz, 3H, (CH_3)$_2$CH), 0.69 (d, J = 6.8 Hz, 3H, (CH_3)$_2$CH), 1.27 (s, 9H, (CH_3)$_3$C), 1.61 ('b sext', 'J' = 6.3 Hz, (CH$_3$)$_2$CH), 2.08 (d, J = 5.0 Hz, 1H, CHCOOCH$_3$), 3.10 (b, 1H, NH), 3.49 (s, 3H, CHCOOCH_3), 4.87 (s, 1H, CHCONH), 6.89 (ddd, J = 14.3, 7.6, 1.2 Hz, 1H, Ar), 7.18 (tdd, J = 7.5, 2.5, 1.2 Hz, 1H, Ar), 7.45–7.65 (m, 11H, Ar), 7.91 (dd, J = 7.9, 4.1 Hz, Ar), 8.80 (s, 1H, CONH); ^{13}C NMR: δ = 18.09 (q, (CH_3)$_2$CH), 19.22 (q, (CH_3)$_2$CH), 28.55 (q, (CH_3)$_3$C), 31.29 (d, (CH$_3$)$_2$CH), 50.69 (s, (CH$_3$)$_3$C), 51.31 (q, COOCH_3), 61.34 (dd$_{C,P}$, $^3J_{C,P}$ = 5.0 Hz, CHCONH), 65.25 (d, CHCOOCH$_3$), 126.43 (dd$_{C,P}$, $^3J_{C,P}$ = 13.0 Hz, Ar), 128.88 (sd$_{C,P}$, $^1J_{C,P}$ = 101.2 Hz, Ar), 128.68 (dd$_{C,P}$, $^3J_{C,P}$ = 12.5 Hz, Ar), 128.84 (dd$_{C,P}$, $^3J_{C,P}$ = 12.0 Hz, Ar), 129.82 (dd$_{C,P}$, $^2J_{C,P}$ = 10.0 Hz, Ar), 131.91 (sd$_{C,P}$, $^1J_{C,P}$ = 107.2 Hz, Ar), 132.15 (sd$_{C,P}$, $^1J_{C,P}$ = 103.0 Hz, Ar), 131.80 (dd$_{C,P}$, $^2J_{C,P}$ = 10.5 Hz, Ar), 132.23 (dd$_{C,P}$, $^2J_{C,P}$ = 9.5 Hz, Ar), 132.25 (dd$_{C,P}$, $^4J_{C,P}$ = 3.0 Hz, Ar), 132.63 (dd$_{C,P}$, $^4J_{C,P}$ = 3.0 Hz, Ar), 132.64 (dd$_{C,P}$, $^4J_{C,P}$ = 3.00 Hz, Ar), 132.82 (dd$_{C,P}$, $^3J_{C,P}$ = 13.5 Hz, Ar), 148.07 (s, Ar), 170.45 (s, CONH), 174.70 (s, COOCH$_3$); ^{31}P NMR: δ = 35.04; MS (70 eV, 160°C); m/z (%): 521 (0.7) [M$^+$+1], 520 (0.7) [M$^+$−1], 420 (47), 362 (32), 306 (100), 292 (92), 213 (17), 165 (17).

5.4. (2*S*,1′*RS*)-2-[*N*-(1′-*N*-Methylcarbamoyl)-(*o*-diphenylphosphinoyl)-benzyl)]amino-3-methylbutanoic acid methyl ester, 8b

A solution of **7b** (231 mg, 0.5 mmol) in acetone (20 ml) was stirred for 45 min with H_2O_2 (30%, 1 ml). After workup as described for **8a** 237 mg (0.5 mmol, 100%) **8b** was isolated as a colorless oil that crystallized upon standing. R_f (MTBE) = 0.43, mp 182–184°C; $C_{27}H_{31}N_2O_4P$ (478.53): calcd C, 67.77; H, 6.53; N, 5.85; found C, 67.77; H, 6.54; N, 5.90; IR (film): ν = 3455 cm^{-1} (w), 3332 (w), 3249 (m), 3078 (m), 2958 (m), 2874 (w), 2334 (w), 1731 (s), 1677 (s), 1567 (m), 1482 (w), 1467 (m), 1436 (s), 1413 (w), 1380 (m), 1364 (w), 1338 (w), 1310 (m), 1254 (m), 1172 (s), 1119 (s), 1071 (w), 1028 (w), 998 (w), 911 (w), 801 (w), 750 (m), 723 (s), 696 (s), 658 (m), 627 (m); UV–vis (acetonitrile): λ_{max} (log ε) = 196 nm (4.80), 221 (4.37), 260 (3.21), 266 (3.30), 273 (3.32), 280 (3.09); ^{1}H NMR: δ = 0.64 (d, J = 6.7 Hz, 3H, (CH_3)$_2$CH), 0.70 (d, J = 6.9 Hz, 3H, (CH_3)$_2$CH), 1.60 ('sext', 'J' = 6.8 Hz, 1H, (CH$_3$)$_2$CH), 2.07 (d, J = 5.1 Hz, 1H, CHCOOCH$_3$), 2.74 (d, J = 4.7 Hz, 3H, CONCH_3), 3.10 (b, 1H, NH), 3.49 (s, 3H, COOCH_3), 4.87 (s, 1H, CHCONH), 6.91 (ddd, J = 14.3, 7.8, 1.1 Hz, 1H, Ar), 7.19 (tdd, J = 7.5, 2.5, 1.3 Hz, 1H, Ar), 7.45–7.65 (m, 11H, Ar), 7.96 (ddd, J = 7.9, 4.2, 1.0 Hz, 1H, Ar), 8.93 (d, J = 4.4 Hz, 1H, CONH); ^{13}C NMR: δ = 18.03 (q, (CH_3)$_2$CH), 19.77 (q, (CH_3)$_2$CH), 26.32 (q, CONCH_3), 31.21 (d, (CH$_3$)$_2$CH), 51.32 (q, COOCH_3), 60.95 (dd$_{C,P}$, $^3J_{C,P}$ = 5.5 Hz, CHCONH), 65.08 (d, CHCOOCH$_3$), 126.66 (dd$_{C,P}$, $^3J_{C,P}$ = 13.0 Hz, Ar), 128.70 (dd$_{C,P}$, $^3J_{C,P}$ = 12.5 Hz, Ar), 129.19 (sd$_{C,P}$, $^1J_{C,P}$ = 101.2 Hz, Ar), 129.00 (dd$_{C,P}$, $^3J_{C,P}$ = 12.5 Hz, Ar), 130.24 (dd$_{C,P}$, $^2J_{C,P}$ = 10.0 Hz, Ar), 131.53 (sd$_{C,P}$, $^1J_{C,P}$ = 107.2 Hz, Ar), 131.66 (dd$_{C,P}$, $^2J_{C,P}$ = 10.0 Hz, Ar), 131.69 (sd$_{C,P}$, $^1J_{C,P}$ = 102.7 Hz, Ar), 132.28 (dd$_{C,P}$, $^2J_{C,P}$ = 9.5 Hz, Ar), 132.31 (dd$_{C,P}$, $^4J_{C,P}$ = 3.00 Hz, Ar), 132.49 (dd$_{C,P}$, $^4J_{C,P}$ = 3.00 Hz, Ar), 132.86 (dd$_{C,P}$, $^3J_{C,P}$ = 13.5 Hz, Ar), 132.80 (overlapped, Ar), 147.46 (s, Ar), 172.03 (s, CONH), 174.57 (s, COOCH$_3$); ^{31}P NMR: δ = 34.87; MS (70 eV, 85°C); m/z (%): 478 (3) [M$^+$], 420 (100), 306 (45), 304 (40), 292 (33), 291 (39).

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