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Catalyst Controlled Diastereoselective *N*-Alkylations Of α-Amino Esters

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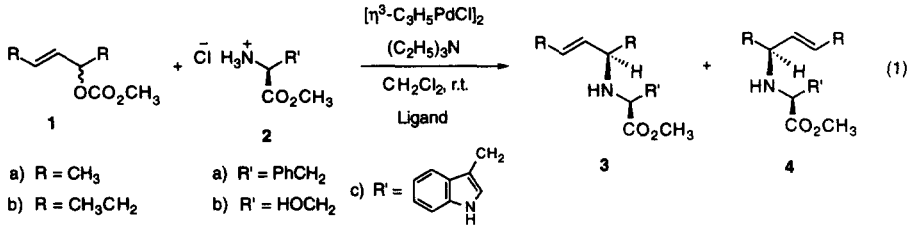
Summary: Asymmetric *N*-alkylation of α-amino esters in which a new stereogenic center is created at carbon is dictated by the catalyst and not the substrate.

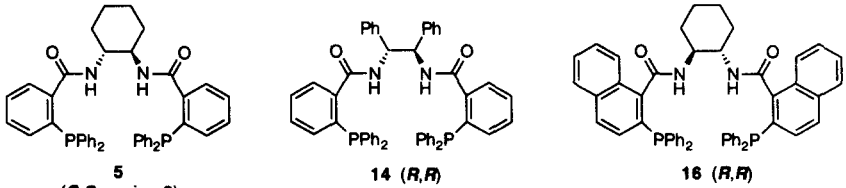
The design and synthesis of peptidomimetics constitutes one of the most important strategies for new drug discovery. *N*-Alkylated amino acid derivatives represent an interesting class. For example, the clinically important ACE inhibitors enalapril and lisinopril illustrate such structural types.[1,2] Similar compounds have also been found as unusual amino acids in crown-gall tumors induced by bacteria in higher plants.[3] Alkylations of the nitrogen of amino acid derivatives wherein a stereogenic center is created in a catalytic process raises the question whether the stereochemistry of the newly created center is dictated by the substrate or the catalyst. We report our preliminary results wherein this question is explored in the context of asymmetric allylic alkylation.[4]

The Pd catalyzed alkylation of the acyclic allyl carbonate **1a** with the methyl ester of phenylalanine (**2a**) using an achiral ligand, triphenylphosphine, gave a 3:1 mixture of the two diastereomers **3** and **4**. To probe the



(1)

ability of the catalyst to dictate the regioselectivity with respect to the π-allylpalladium intermediate (which corresponds to the diastereoselectivity in this case), the influence of chiral ligands was probed. With the *R,R*-ligand **5**, a 19:1 dr ratio of **3:4** was obtained; on the other hand, the *S,S*-ligand, under identical conditions gave a 1:3 ratio of **3:4**. Thus, the catalyst rather than the substrates dominated in determining the diastereoselectivity



in which there is a matched and a mismatched combination. Table **1** summarizes these results. The 1,3-diethyl substituted allyl substrate **1b** shows parallel behavior with the phenylalanine nucleophile **2a** (Table 1, entries 4 and 5).

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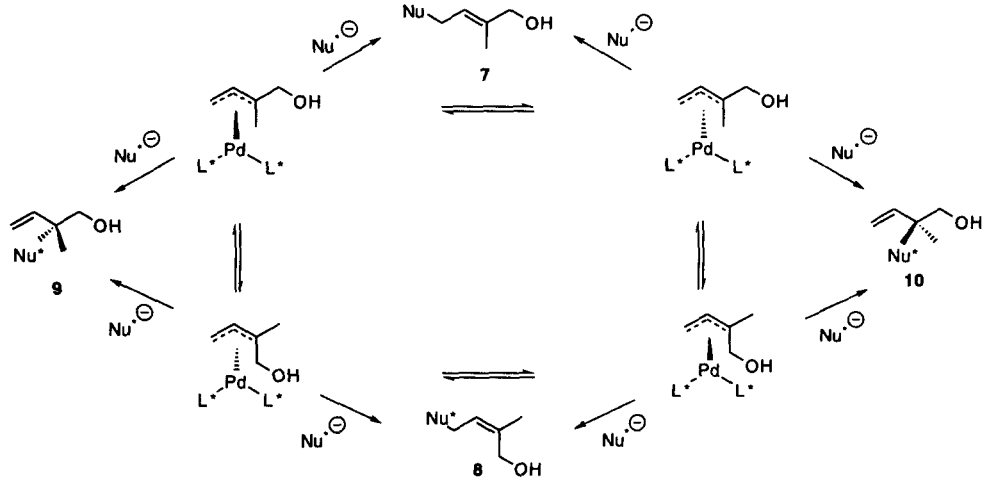
Table 1. Asymmetric Alkylation of Acyclic Allylic Esters with *S*-α-Amino Esters.[a]

Entry	R (**1**)	R' (**2**)	Ligand	Yield	dr (**3**:**4**)[b]
1	CH_3	$PhCH_2$	Ph_3P	36	3:1
2	CH_3	$PhCH_2$	**5**	78	19:1
3	CH_3	$PhCH_2$	**6**	60	1:3
4	CH_3CH_2	$PhCH_2$	Ph_3P	44	3.6:1
5	CH_3CH_2	$PhCH_2$	**5**	51	15.7:1
6	CH_3CH_2	$HOCH_2$	Ph_3P	78	1.9:1
7	CH_3CH_2	$HOCH_2$	**5**	60	49:1
8	CH_3CH_2	$HOCH_2$	**6**	60	1:3.8
9	CH_3CH_2	3-indolylmethyl	Ph_3P	78	1.9:1
10	CH_3CH_2	3-indolylmethyl	**5**	78	13.3:1
11	CH_3CH_2	3-indolylmethyl	**6**	65	1:1.2

a) All reactions run with 2.5 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$, 7.5 mol % **5** or **6** or 15 mol % Ph_3P, 2.4 equiv of triethylamine, 1 equiv of **1** and 1.2 equiv of **2** in methylene chloride at 0.3 M, 48 h. b) Determined by hplc using a Chiralpak AD column eluting with isopropanol in hexane.

The role of the structure of the amino acid on the diastereoselectivity was probed in the context of more functionalized substrates. The unprotected serine **2b** functions quite well with no discernible effect of the free hydroxyl group (Table 1, entries 6-8). Interestingly, even the unprotected indole of tryptophan does not interfere. The matched pair gave excellent selectivity (Table 1, entry 10), but the selectivity in the mismatched pair deteriorated somewhat. In all cases, the stereochemistry was assigned based upon analogous reactions of these allyl esters **1a** and **1b** with nucleophiles in the presence of ligands **5** and **6**.[5,6]

The reactions of diene monoepoxides are much more complicated[7] as illustrated in Scheme 1. Besides the issue of regioselectivity wherein no new stereogenic center is created as in formation of **7** and **8**, the



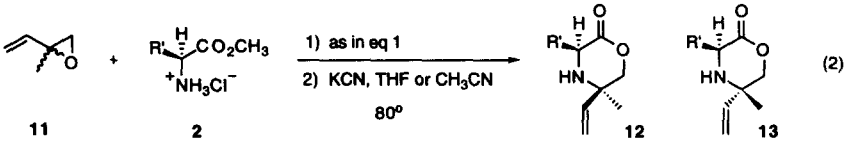
Scheme 1. Selectivity Issues in Reactions of Isoprene Monoepoxide

transition states for formation of **9** or **10** involves three chiral entities: the nucleophile, the ligands, and the allyl moiety. Thus, the selectivity in this case will be critically dependent on the nature of the nucleophile. The reactions of isoprene monoepoxide (**11**) with esters of amino acids were explored for the production of ketomorpholines as illustrated in eq 2 and summarized in Table 2.

Table 2. Catalyst Control of Diastereoselectivity of Isoprene Monoepoxide with α-Amino Acid Derivatives[a]

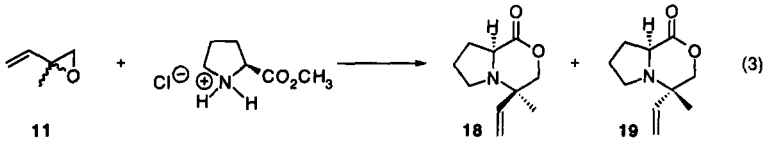
Entry	R' (2)	Ligand	Yield (2 steps)[b]	Ratio 12:13[c]
1	3-indolylmethyl	**5** (*R,R*)	39%	1:2.8
2	3-indolylmethyl	**6** (*S,S*)	51%	6.7:1
3	3-indolylmethyl	**14** (*R,R*)	50%	1:11.5
4	3-indolylmethyl	**15** (*S,S*)	45%	14:1
5	3-indolylmethyl	**16** (*R,R*)	75%	1:6.1
6	3-indolylmethyl	**17** (*S,S*)	75%	12.4:1
7	$HOCH_2$	**5** (*R,R*)	69%	1:2
8	$HOCH_2$	**14** (*R,R*)	28%	1:2.8
9	$HOCH_2$	**15** (*S,S*)	59%	3:1
10	$HOCH_2$	**16** (*R,R*)	85%	1:5
11	$HOCH_2$	**17** (*S,S*)	60%	4:1
12	CH_3	**5** (*R,R*)	30%	1:6
13	CH_3	**6** (*S,S*)	64%	13:1
14	CH_3	**14** (*R,R*)	36%	1:14.4
15	CH_3	**15** (*S,S*)	64%	22.7:1
16	H	**14** (*R,R*)	91%	1:13.6[d]
17	H	**15** (*S,S*)	73%	12.6:1[d]

a) All reactions run as follows: step 1, 1:1 epoxide:α-amino ester, 2.5 mol % $(\eta^3\text{-}C_3H_5PdCl)_2$, 3.75 mol % ligand, 1 equiv triethylamine, at 0.1 M in methylene chloride at room temperature, 24 h; step 2, 1% potassium cyanide in acetonitrile at 80° (or THF at reflux), 0.75-2 h. b) 1,2 vs. 1,4-addition examined by gas chromatography using Alltech AT-1 capillary column. c) Determined by hplc using a Chiralcel OD or AD column with isopropanol in heptane as eluting solvent. d) These represent enantiomeric ratios.



(2)

The reaction of tryptophan methyl ester with epoxide **11** using ligands **5** and **6** gave the hydroxy esters, which were smoothly cyclized in the presence of potassium cyanide to the morpholin-2-ones **12** and **13**.[6] Indeed, the regio- and diastereoselectivity were dominated by the catalysts (Table 2, entries 1 and 2). In all cases, excellent regioselectivity was observed. In order to enhance the diastereoselectivity, ligand variation was examined, focusing on the more flexible diphenyl ligand **14** (also its *S,S* version **15**) and the more conformationally restricted ligand **16** (also its *S,S* version **17**).[7] In both cases, the selectivity increased markedly. Somewhat better selectivity was observed with the diphenyl ligands **14** and **15** (Table 2, entries 3 and 4); better yields were obtained with the naphthalene linker ligands **16** and **17** (Table 2, entries 5 and 6).[6] With serine, best results were obtained with the naphthalene linker ligands **16** and **17** (cf. Table 2; entries 7-11).[6] Using a silyl ether of serine did increase the diastereoselectivity to 1:13.3 for ligand **14** but the yield decreased to 20% for inexplicable reasons. Alanine also gave good selectivities (Table 2, entries 12-15). The latter results inspired us to examine glycine methyl ester in which enantioselectivities would result. As shown in Table 2, entries 16 and 17, excellent results were obtained in this case as well. These reactions proceeded satisfactorily with 0.13 mol % of $[\eta^3\text{-}C_3H_5PdCl]_2$ and 0.38 mol % of chiral ligand. A secondary amine in the form of the methyl ester of proline was also examined as shown in eq 3. Satisfactory results were obtained with both the "parent ligands" **5** (**18:19**, 1:19) and **6** (4:1, 56% yield) as well as the diphenyl ligands **14** (1:7.6, 77 yield) and **15** (7.0:1, 72% yield). The diastereoselectivity was assigned by analogy to the established enantioselectivity of reactions of **11** with amines[4,5] and NOE studies, i.e., an enhancement between the vinyl group and the ring H but not between the quaternary methyl group and this hydrogen in **19**.



Using the concept of chiral pockets for asymmetric induction in allylic alkylation allows access to diastereoselective *N*-alkylation of amino acids to generate building blocks to peptidomimetics. These results stand in contrast to the common use of amino acids and their derivatives as chiral auxiliaries wherein they impose their stereochemical imprint on a prostereogenic center.[10] The reactions of isoprene monoepoxide are particularly noteworthy. Even though the mechanism for chiral discrimination is much more complicated, better selectivity is observed compared to the simpler type of substrate involving meso like π-allyl intermediates. We focused on creating a quaternary center to distinguish this methodology from approaches involving asymmetric reduction of imines and enamines.[11] It should be noted that the reactions are preferably run using the hydrochloride salts of the α-amino esters with triethylamine rather than the free α-amino esters in the absence of the external amine. The presence of a weak acid catalyst clearly accelerates and facilitates the reaction, while excess tertiary amine does retard the reaction. The success of these results encourages the use of other chiral nucleophiles wherein catalyst control of diastereoselectivity may be anticipated.

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