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Catalytic Asymmetric Alkylation of Nucleophiles: Asymmetric Synthesis of α-Alkylated Amino Acids**

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Modified peptides not only open a major avenue to understanding biological phenomena, but also offer opportunities for drug discovery.[1] Incorporating conformational constraints probes the molecular structure of receptors. By preorganizing the optimum conformation for binding, significant enhancements of biological activity can be expected. Introduction of alkyl groups at the α-carbon of amino acids introduces such conformational constraints and, furthermore, enhances metabolic stability. As a result, the synthesis of α-alkylated amino acids has attracted considerable attention.[2–6] Virtually all methods involve controlling diastereoselectivity—either by use of a chiral auxiliary[3] or by involving what is termed self-reproduction of chirality (also termed self-regeneration of stereocenters).[4] Methods in which the asymmetric inducing unit is required only catalytically are lacking. The major method for catalytic asymmetric synthesis of simple amino acids,[7a] hydrogenation of dehydroamino acids, is not applicable. We report a new strategy for the synthesis of α-alkylated amino acids, which are important building blocks for peptide synthesis.

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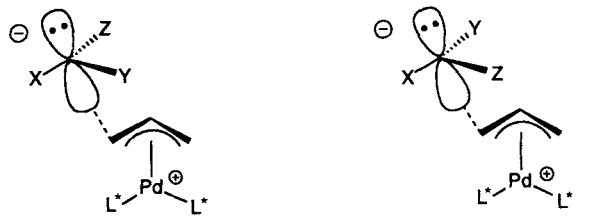
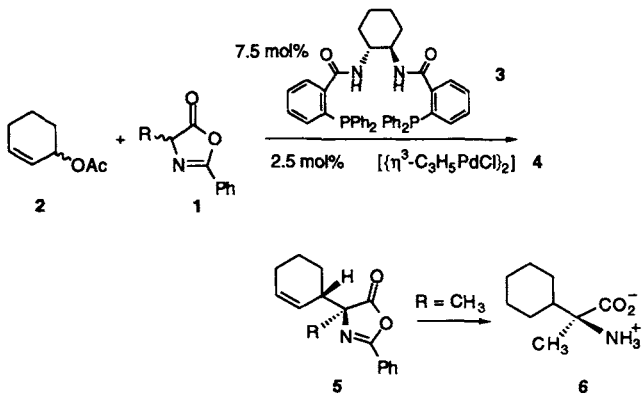
The question relates to the broader one of inducing absolute stereochemistry at an enolate carbon. No reaction is as ubiquitous as alkylations of enolates and related intermediates. The major current approach to effect such reactions asymmetrically involves use of stoichiometric amounts of chiral auxiliaries.[3] Catalytic processes, outside of aldol-like reactions, are rare.[7b,8] An approach based upon palladium-catalyzed allylic alkylations faces the difficult obstacle, illustrated in Scheme 1, that the attacking nucleophile is very remote from the chiral inducing units L*—in fact, the nucleophile is insulated from these chiral ligands by the allyl moiety. It is not surprising that examination of such



Scheme 1. Two competing arrangements for the approach in the asymmetric allylic alkylation at a nucleophilic carbon atom.

reactions to date have been disappointing.[9] Modest success stems from ligands with functional arms that appear to reach beyond the allyl barrier to help direct an incoming nucleophile. We have been exploring a different concept borrowed from the basic principles of an active site of an enzyme.[10] In this model, primary chirality in terms of structural units that contain stereogenic centers induces conformational chirality, which, in turn, creates chiral space. The ability of the reactants to "fit" into the "active site" then defines the molecular recognition and, consequently, the asymmetric induction.

One way to apply this concept to the asymmetric synthesis of α-alkylated amino acids invokes the allylation of the readily available azlactones.[11] The initial studies examined the reaction of the alanine-derived azlactone **1** (R = CH_3) and 3-acetoxycyclohexene (**2**) by using ligand **3** and a palladium complex **4** as a precatalyst (Scheme 2). On use of cesium



Scheme 2. Asymmetric alkylation of azlactones **1** with 3-acetoxycyclohexene **2**.

carbonate as base in dichloromethane at room temperature, a 2.5:1 diastereomeric ratio (d.r.) of alkylation product was obtained in 96% yield. Gratifyingly, the enantiomeric ex-

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cesses (*ee*) were 94% and 92% for the major and minor diastereomers, respectively.[12] The major diastereomer is assigned as depicted in **5**, based on chemical correlation with the known amino acid **6**[13] and analogy to asymmetric alkylations of the allylic ester.[14] Variation to less polar (e.g., benzene) or more polar solvents (e.g., THF or DMSO) failed to improve the diastereomeric ratio or affect the *ee*. With dichloromethane as the standard solvent, the base was varied. Other inorganic or organometallic bases did not prove beneficial. Employing triethylamine, however, did enhance the d.r. to 2.8:1 and the *ee* to 99%. This result prompted our re-examination of the solvent effect with this base. In DMSO or DMF the diastereomeric ratio increased to greater than 4:1. The best diastereoselectivity was observed in acetonitrile. In this case a 90% yield of alkylated product with 8.7:1 d.r. and 99% *ee* of the major diastereomer was obtained. Since the minor diastereomer can be removed by column chromatography, **5** ($R = CH_3$) can be isolated diastereomerically and enantiomerically pure. Table 1 summarizes the alkylation for

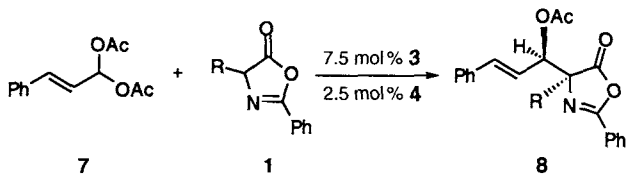
Table 1. Results of the asymmetric alkylation of **1** with 3-acetoxycyclohexene (**2**).

Entry	R	Yield[%]	d.r.[a]	*ee*[%][a]
1	CH_3	90	8.7:1	99
2	CH_2Ph	74	12.4:1	99
3	$CH_2CH(CH_3)_2$	77[b]	13.3:1[c]	99[d]
4	$CH(CH_3)_2$	91	>19:1	95

[a] Determined by HPLC on a Chiralcel OD column with heptane/2-propanol mixtures unless stated otherwise. [b] Yield of pure major isomer only. [c] Determined by HPLC on a Microsorb Si 80-125-C5 column with a heptane/ethyl acetate mixture. [d] Determined by HPLC on a Chiralpak AD column.

a range of azlactones. Expectedly, as the size of the R group of the azlactone increased, the diastereoselectivity increased. 3-Acetoxycyclopentene behaved similarly. The tentative assignment of configuration is based upon analogy to that for **5** ($R = CH_3$).

An interesting approach to serine analogues is illustrated in Scheme 3. Palladium-catalyzed allylic alkylation of geminal dicarboxylates serves as a synthetic equivalent to an aldol



7 1 8

Scheme 3. Asymmetric alkylation of azlactones **1** with *gem*-dicarboxylate **7**.

reaction but for stablized pronucleophiles that do not normally provide stable adducts.[15] Thus, asymmetric desymmetrizations of such compounds function as the equivalent of an asymmetric addition of stabilized nucleophiles to carbonyl groups.[16] In this case the chiral recognition with respect to the allyl unit differs from that of Scheme 2, in which the attack of the nucleophile on the π-allylpalladium intermediate is the enantiodiscriminating step with respect to both partners. In Scheme 3 the configuration with respect to the allyl fragment is established in the ionization step, whereas that with respect to the nucleophiles is obviously fixed in the alkylation step. As shown in Table 2, entry 1, our standard conditions gave reasonable d.r. and *ee* values but not as high as those of Scheme 2. In our studies of desymmetrization of the geminal dicarboxylates with achiral nucleophiles, sodium hydride in DME proved to be effective.[16] Indeed, application of these conditions improved both the d.r. and *ee* value (Table 2,

Table 2. Conditions and results of the asymmetric alkylation of **1** with the *gem*-dicarboxylate **7**[a].

Entry	R	*T*	Yield[%][b]	d.r.[c]	*ee*[%][d]
1[e]	CH_3	RT[f]	73 (16)	4.4:1	83 (40)
2	CH_3	RT[f]	60 (9)	6.6:1	99 (96)
3	CH_2Ph	RT[f]	67 (7)	7.8:1	98 (94)[g]
4	CH_2Ph	0–5°C	75 (6)	9.7:1	99 (96)
5	$CH_2CH(CH_3)_2$	0–5°C	91 (6)	15:1	99 (95)[g]
6	$CH(CH_3)_2$	0–5°C	88 (4)	>19:1	99 (–)

[a] All reactions were performed with sodium hydride in DME unless stated otherwise. [b] Yields of isolated products for the major and minor (in parentheses) diastereomers. [c] Determined by ^1H NMR on the crude mixture. [d] Determined by HPLC on a Chiralcel OD column with heptane/2-propanol mixtures unless stated otherwise. Numbers in parentheses correspond to *ee* values for the minor diastereomer. [e] Performed with triethylamine in dichloromethane. [f] RT = room temperature. [g] Determined by HPLC on a Chiralpak AD column with heptane/2-propanol mixtures.

entry 2). Temperature also has an effect. In the case of the phenylalanine derivative (Table 2, entries 3 and 4), simply lowering temperature from room temperature to 0°C increases the diastereomeric ratio; the *ee* value also increased. Expectedly, increasing the size of the R group increases the diastereomeric ratio (entries 4–6). The configuration of these serine analogues is assigned based upon precedent in the desymmetrization reaction with achiral nucleophiles and the established configuration on alkylation of the azlactones **1** with **2**, and an X-ray crystal structure of **8** ($R = CH_2Ph$).

This new method for synthesis of α-alkylated amino acids is the first catalytic asymmetric reaction to yield members of this important family of compounds. Hydrolysis provides the amino acids (cf. Scheme 2) without danger of racemization. Furthermore, the azlactones can be used to construct constrained peptides by directly coupling them with a second amino acid unit.[11] By making available greater diversity in such novel amino acids, generation of libraries of peptidomimetics by combinatorial chemistry is facilitated. More generally, inducing chirality at a prochiral nucleophilic center by this mechanism may have broader applications. An important question to address is: why does the family of catalysts employing ligands like **3** function so well? Although detailed structural information is still lacking despite significant effort, the model in which a chiral pocket is envisioned as depicted in the cartoon of Scheme 4 does rationalize the result.[17]

Experimental Section

Alkylation of **2**: 3-Acetoxycyclohexene (**2**, 28 μg, 200 μmol) was added to a solution of Et_3N (56 μL, 400 μmol) and 4-alkyl-2-phenyl-2-oxazolin-5-one (450 μmol) in acetonitrile (1 mL, dry and oxygen free). A prepared solution of **4** (1.8 mg, 4.9 μmol) and chiral ligand **3** (10.4 mg, 15.1 μmol) in acetonitrile (1 mL) was added by cannula under N_2. The reaction mixture was quenched (2–6 h) with aqueous phosphate buffer (pH 7, 40 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/EtOAc).

Alkylation of **7**: A solution of **1** (450 μmol) in DME (1 mL, dry and oxygen free) was added to NaH (95% in oil, 10.1 mg, 400 μmol) at –78°C and allowed to warm to room temperature. When gas evolution stopped, a solution of **4** (1.8 mg, 4.9 μmol) and ligand **3** (10.4 mg, 15.1 μmol) in DME (0.5 mL) was added. Finally a solution of **7** (46.9 mg, 200μmol) in DME (1 mL) was added at the desired

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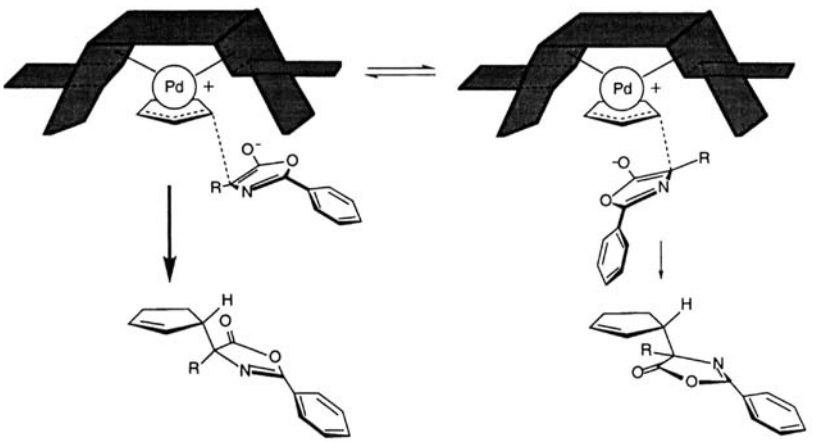

Scheme 4. Cartoon depicting the sense of asymmetric induction at an azlactone-derived nucleophile.

temperature (see Table 2). The reaction mixture was quenched (2–24 h) with aqueous phosphate buffer (pH 7, 40 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/EtOAc).

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A Highly Efficient Aminohydroxylation Process**

A. Erik Rubin and K. Barry Sharpless*

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

Stereospecific transformations of olefins to 1,2-diols[1,2] and β-amino alcohols[3,4] are very important due to the ready availability of the starting materials and the significance of the products as building blocks in the syntheses of drugs and natural products, ligands for asymmetric catalysis, and chiral auxiliaries.[1–5] The recently discovered catalytic asymmetric aminohydroxylation (AA) of olefins,[4] a close "relative" of the highly reliable catalytic asymmetric dihydroxylation (AD),[1] stereospecifically provides N-protected β-amino alcohols with the added benefit of good to excellent regio- and enantioselectivities. However, in the absence of cinchona alkaloid ligands (i. e., in the achiral mode, which yields racemic products if the olefin is prochiral), the reaction is plagued by the formation of large amounts of diol and suffers from a significant decrease in regioselectivity.[4,6]

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