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Asymmetric Wolff Rearrangement Reactions with α-Alkylated-α-diazoketones: Stereoselective Synthesis of α-Substituted-*β*-amino Acid Derivatives[†]

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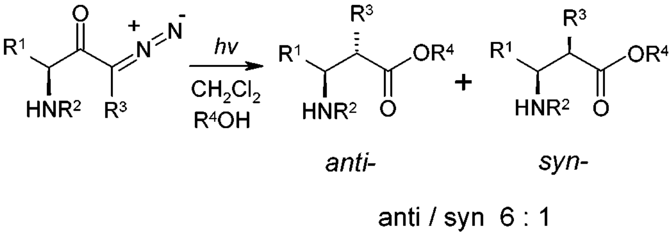
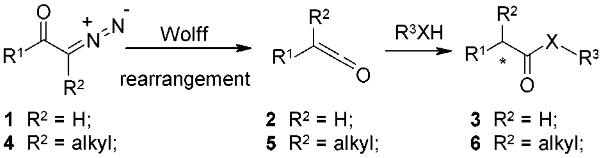
ABSTRACT



Photoinduced asymmetric Wolff rearrangement reactions were performed with α-amino-α′-methyl-α′-diazoketones to afford α-methyl-*β*-amino acid esters with good stereoselectivity. Factors that may influence the stereochemistry were examined, including steric effects and temperature dependence, which had a great impact on the stereochemistry.

Wolff rearrangements are one of the most practical reactions for one-carbon (methylene) extension methods in organic synthesis.[1] α-Diazoketone **1** may undergo a Wolff rearrangement to intermediate ketene **2** which may be trapped with a nucleophile giving product **3**, after CH_2 insertion (Scheme 1).[2] It is conceivable that α-alkylated-α-diazoketone **4** may also undergo a Wolff rearrangement to prochiral ketene **5**, resulting in the chiral product **6**.[3] There are potentially numerous ways available to control the stereochemistry at the α position.[4] Therefore, the Wolff rearrangement reactions with α-alkylated-α-diazoketones may provide an alternate route to molecules with one carbon atom extended, incor-

Scheme 1



[†] This paper is dedicated to Professor Stephen Hanessian on the occasion of his 65th birthday.

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(2) Newman, M. S.; Arkell, A. *J. Org. Chem.* **1959**, *24*, 385.

(3) a) Lopez-Herrera, F. J.; Sarabia-Garcia, F. *Tetrahedron Lett.* **1993**, *34*, 3467. (b) Lopez-Herrera, F. J.; Sarabia-Garcia, F. *Tetrahedron Lett.* **1994**, *35*, 2929.

(4) a) *Asymmetric Synthesis*; Morrison, D. D., Ed.; Academic Press: Orlando, FL, 1983−1986; Vols. 1−5. (b) Hanessian, S. *Total Synthesis of Natural Products: the Chiron Approach;* Baldwin, J., Ed.; Pergamon Press: New York, 1983.

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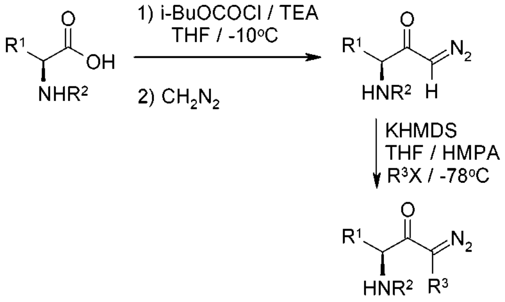
porating a new chiral center, introduced in a one-pot synthesis. To test the concept, we prepared the α-alkylated-α-diazoketones from α-amino acids and assumed that the chiral center residing in the α-amino acid could influence the stereochemistry of the newly established chiral center of the Wolff rearrangement product. Herein we would like to communicate our preliminary results of the *asymmetric Wolff rearrangement*.

α-Alkyl-α-diazoketones, precursors to the new Wolff rearrangement reactions, were readily prepared from the corresponding α-amino acids via the two-step sequence of diazomethane coupling followed by anionic alkylation reactions. Thus, the N-protected α-amino acids were treated with i-BuOCOCl at −10 °C in THF followed by the addition of diazomethane to afford the α-diazoketones,[5] which were subsequently deprotonated using a base and then trapped with electrophiles at −78 °C in THF, in the presence of HMPA, to give the α-alkyl-α-diazoketones (Scheme 2).

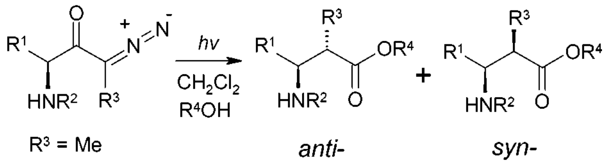
Scheme 2



The Wolff rearrangement reactions were effected using UV light at −78 °C in dichloromethane to give intermediate ketenes which were then trapped with, for example, alcohols to furnish the α-methyl-*β*-amino acid derivatives (Table 1). The stereochemistry of the major diastereoisomer was determined to be *anti by* a single-crystal X-ray crystallographic analysis and chemical correlations.[6]

The steric size of the substituents in the Wolff rearrangement precursor appears to have a great influence on the stereochemistry of the reaction. The diastereomeric ratios increased significantly from 2:1 to 6:1 with the size of R1 when the nitrogen atom was protected with Fmoc (entries 1−3, Table 1). Interestingly, when *tert*-butoxycarbonyl was utilized as the nitrogen protecting group, in all the cases studied so far, high diastereomeric ratios > 5:1 were observed (entries 4−9, Table 1). This discrepancy in stereoselection between Fmoc and Boc groups could be due to the steric difference, that the *tert*-butyl group of the Boc is bulkier than that of the Fmoc. When the bulkiness of the trapping reagent was changed from MeOH to i-PrOH, however, no improvement on the stereoselectivity was observed (entry 10 Table 1). Further experiments indicated that the stereoselectivity of the Wolff rearrangement was temperature-dependent. Better diastereoselectivity was obtained with decreasing reaction temperature.[6] The best ratios were obtained when the reactions were run at −78 °C, although the reaction yields were relatively low.

Table 1. Wolff Rearrangement with α-Diazoketones

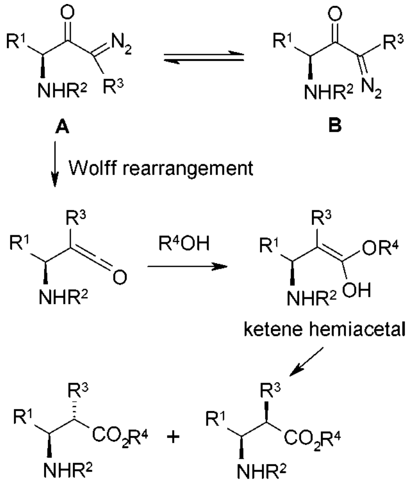


entry	R^1	R^2	R^4	ratio[b,c] (*anti*/*syn*)	yield[d] (%)
1	Me	Fmoc	Me	1.5:1	37
2	i-Pr	Fmoc	Me	6:1	33
3	1-naphthylmethyl	Fmoc	Me	5:1	43
4	Me	Boc	Me	6:1	25
5	i-Pr	Boc	Me	>10:1	48
6	Bn	Boc	Me	6:1[e]	49
7	Ph_2CH	Boc	Me	6:1	45
8	1-naphthylmethyl	Boc	Me	6:1	77
10	Me	Fmoc	i-Pr	1:1	38

[a] All reactions run at −78 °C in a photochemical reaction apparatus purchased from Aldrich, with nitrogen gas bubbling through the reaction mixture. [b] Ratio determined by ^1H NMR and/or HPLC analysis prior to purification. [c] Stereochemistry determined by comparison with the compound in entry 6. [d] Isolated yield. [e] Stereochemistry determined by X-ray analysis of a single crystal and chemical correlations.[6]

Photoinduced Wolff rearrangement of α-diazoketones most likely proceeds via an excited singlet state.[7] It has been suggested that the migrating group be *anti* to the diazo leaving group in order for the Wolff rearrangement to take place efficiently.[7,8] Decreasing the size of R^3 would favor the Wolff rearrangement reaction since the equilibrium would move toward the isomer **A**, leading to the desired rearranged products (Scheme 3). Thus, the Wolff rearrangement, in the

Scheme 3



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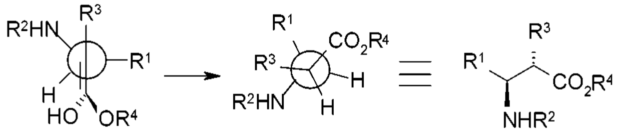
(5) Pizey, J. S. In *Synthetic Reactions*; Halsted: New York, 1974; Vol. 2, Chapter 4.

(6) For details, see the Supporting Information.

extreme case, where $R^3 = H$, gave better yields (54−87%). An X-ray crystallographic analysis of a single crystal structure of a diazoketone (R^1 = Bn, R^2 = Boc, and $R^3 = H$) clearly indicated that the migrating group is *anti* to the diazo group, which should favor the Wolff rearrangement. In contrast, when R^3 = Bn, a group which is sterically larger than H and Me, the Wolff rearrangement reaction gave a complex mixture at various temperatures, suggesting that the predominant population is rotomer **B**, which is less inclined toward the Wolff rearrangement reactions[8] (Scheme 3). The fact that a higher yield can be obtained at a higher temperature[6] implies the relative ease of rotation of the diazo group around the C1−C2 bond at higher temperatures (Scheme 3).[7]

The ketenes generated from the Wolff rearrangement reactions are trapped with electrophiles to give the desired products. It is at this stage that a new chiral center is created. It is most likely that an intermediate ketene hemiacetal is generated[9] and then tautomerized to the final product (Scheme 3). We tentatively assume that the most stable conformation of the transition state of tautomerization is the one resembling the lowest energy conformation of the final product, as shown in Scheme 4.[10,11] The proton may approach from one side of the ketene hemiacetal such that the strain between R^1 and R^3, as well as between R^2 and R^3 could be released to the maximum extent in the transient state. Hence, the larger R^1, R^2, and R^3, the higher the diastereomeric ratio is. Furthermore, R^4 points away from the R^1 and R^2 groups and consequently imposes much less influence on the prochiral center than R^1 and R^2 do. The model we have proposed here is in harmony with the experimental results obtained so far.

Scheme 4



In summary, we have developed a novel method to extend one carbon atom with concomitant introduction of one chiral center using the Wolff rearrangement reaction. The new chiral center is controlled by the chiral resident group in the molecules. The stereochemistry of the reactions could also potentially be controlled by chiral auxiliaries[4a,12] and chiral ligands.[4a] The results of these efforts will be reported in due course. In short, the methodology described in this Letter is complementary to existing methods[13,14] and will find a variety of applications in synthetic organic chemistry and medicinal chemistry.

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Supporting Information Available: Experimental procedures, characterization data, chemical correlations, X-ray structures, and the temperature effects. This information is available free of charge via the Internet at http://pubs.acs.org.

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(7) Kaplan, F.; Meloy, G. K. *J. Am. Chem. Soc.* **1966**, *88*, 950.

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(9) For some recent discussions about the regioselectivity of additions to ketenes, see: (a) Sung, K.; Tidwell, T. T. *J. Am. Chem. Soc.* **1998**, *120*, 3043. (b) Allen, A. D.; Tidwell, T. *J. Org. Chem.* **1999**, *64*, 266.

(10) Solution NMR studies and a single-crystal *X*-ray crystallography analysis[6] suggest that the most likely lowest energy conformation of the *anti* product is the one as shown in Scheme 4.

(11) Molecular modeling studies of the ketene hemiacetal and the *anti* and *syn* products suggest that the most likely transition state may be the one resembling the lowest energy conformation of the final product, as shown in Scheme 4, i.e., a later-transition state. The molecular modeling studies were performed using a Sybyl software package, version 6.0, with a SiliconGraphics workstation.

(12) For trapping of ketenes generated from acid chlorides, with chiral alcohols to control the stereochemistry, see: Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1989**, *111*, 7650.

(13) For recent reviews on synthesis of β-amino acids, see: (a) Cole, D. *Tetrahedron* **1994**, *50*, 9517. (b) Enders, D.; Beltray, W.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 1322.

(14) For a stereoselective synthesis of α-alkylated-β-amino acid derivatives using anionic chemistry, see: Podlech, J.; Seebach, D. *Liebigs Ann.* **1995**, 1217, and references therein. For a stereoselective synthesis of α-alkylated-β-amino acid derivatives using free radical chemistry, see: Hanessian, S.; Yang, H.; Schaum, R. *J. Am. Chem. Soc.* **1996**, *118*, 2507, and references therein.