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Exploring the Unique Reactivity of Diazoesters: An Efficient Approach to Chiral β-Amino Acids

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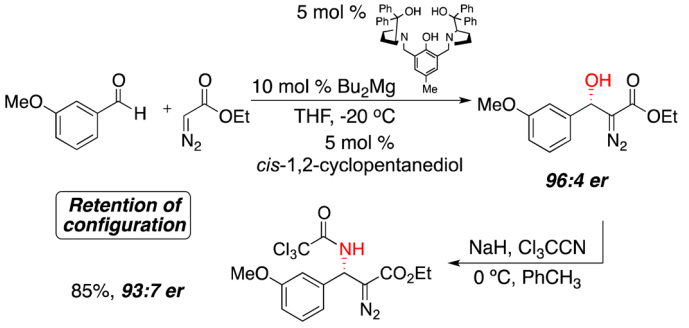
ABSTRACT



The development of a highly stereospecific process for the C−O to C−N exchange with retention of configuration is described. This transformation enables access to optically enriched β-amido-α-diazoesters. These products are transformed to β-amino acids not readily accessible using known methods.

Optically enriched β-amino acids (β-AA) belong to a family of privileged structural motifs that are commonly used in the discovery of small-molecule pharmaceuticals and are present in several natural products.[1] Incorporation of β-AAs in peptide frameworks has led to novel tertiary structures possessing greater stability toward proteolysis thereby elevating our understanding of several biological mechanisms.[2] Taxol[3] and sitagliptin,[4] both possessing a β-AA motif, exemplify the importance of these motifs in cancer chemotherapeutics and as agents for the treatment of type 2 diabetes mellitus respectively.

The significance of β-AA substructures in advancing novel therapeutics and natural product analogs led us to explore alternate ways of accessing these structural motifs, in particular those that cannot be readily accessed by current methods. Our work on the asymmetric addition of ethyl diazoacetate to aldehydes employing a dinuclear Mg-based chiral catalyst[5] prompted us to first investigate the nucleophilic addition to activated imines; however, in our hands, low reactivity and enantioselectivity were obtained although the addition to the N-Boc imine of furfural in

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10.1021/ol303011f

62% yield and 84% ee has recently been reported.[6] In contrast, the use of a Brønsted acid catalyzed process developed by Terada[7] and Maruoka[8a,b] proved to be more successful in accessing enantiomerically enriched β-AA precursors, although this method was limited to aryl imines (Figure 1, eq 1). Maruoka et al. have recently reported a method to address this limitation via the use of azomethine imines.[8c]

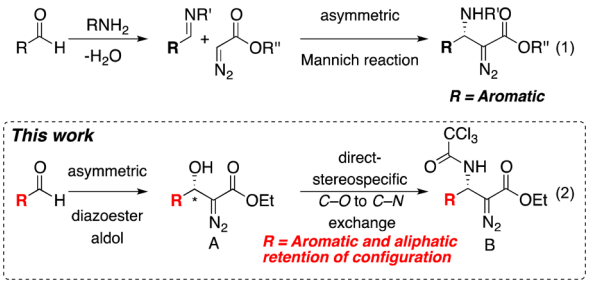

Figure 1. Synthesis of β-amido-α-diazoesters.

Our interest in exploring the synthetic utility of both aromatic and aliphatic β-amido-α-diazoesters as β-AA precursors led to the exploration of an alternate strategy. Given that the synthesis and purification of imines can be problematic, having a route that does not require such substrates would be beneficial. Wang et al. initially reported that the treatment of β-hydroxy-α-diazoesters in the presence of sodium hydride and trichloroacetonitrile (TCA) proceeds with an in situ C−O to C−N exchange (Figure 1, eq 2).[9] In one example employing a benzylic alcohol (Figure 1, R = Ph, eq 2), they showed that an enantioenriched substrate (84:16 er) gave the product of 77:23 er although the stereochemical course of the reaction remained undefined.[9a] Our ability to access a broad array of enantiomerically enriched β-hydroxy-α-diazoesters, an interest in determining the stereochemical outcome of this C−O to C−N exchange which proved to be quite surprising, and evaluation of the range of substrates permitting this transformation inspired the further exploration of this process. Herein we report that both aliphatic and aromatic β-hydroxy-α-diazoesters undergo C−O to C−N exchange remarkably with retention in absolute configuration and with high stereospecificity. The resulting products enabled the asymmetric synthesis of the enantiomer of the natural product cytoxazone and cyclopropanated β-AA via a unique 1,3-C−H insertion reaction.[10,11]

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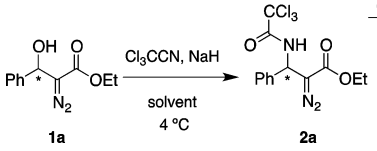
Initial evaluation of the C−O to C−N exchange on benzylic alcohol **1a** initially investigated by Wang et al. led to the finding that solvents such as dioxane and dimethoxyethane led to the greatest erosion of optical purity. Conversely, less polar solvents such as toluene, benzene, and hexanes gave enantiomeric ratios up to 93:7 er (entry 5, Table 1). Furthermore, a dramatic temperature dependence was observed where conducting the reaction at rt instead of 4 °C afforded amide **2a** as a racemate (entries 5 and 6, Table 1).

Table 1. Initial Solvent and Temperature Screen

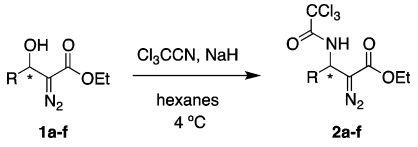


entry	solvent	product er[a]
1	$PhCH_3$	90:10
2	PhH	89:11
3	1,4-dioxane	75:25
4	DME	88:12
5	hexanes	93:7
6	hexanes	50:50[b]

[a] Starting material er = 95:5. [b] Room temperature.

Conditions optimized for the C−O to C−N exchange using alcohol **1a** enable the direct exchange of both aromatic and heteroaromatic α-hydroxy-β-diazoesters (Table 2). Significant variations on the electronic properties of the aromatic group are well tolerated. Inductively withdrawing *m*-methoxyphenyl and electron-donating *p*-methoxyphenyl furnished trichloroamides **2b** and **2c** in 93:7 er and 91:9 er. Electron-withdrawing *m*- and *p*-fluorobenzenes afford amides **2d** and **2e** in 94:6 er and 94:6 er respectively. Electron-rich furan possessing a differential steric disposition compared to the carbocyclic rings previously studied resulted in the formation of amide **2f** in 90:10 er.

Table 2. Reaction Scope with Aromatic and Heteroaromatic Alcohols



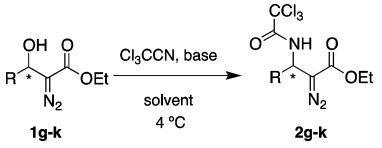
entry[a]	R	product	% yield	er[b]
1	Ph(**1a**)	**2a**	92	93:7
2	*m*-$CH_3OC_6H_4$(**1b**)	**2b**	85	93:7
3	*p*-$CH_3OC_6H_4$(**1c**)	**2c**	77	91:9
4	*m*-FC_6H_4(**1d**)	**2d**	66	94:6
5	*p*-FC_6H_4(**1e**)	**2e**	78	94:6
6	2-Furyl(**1f**)	**2f**	69	90:10

[a] Reactions using 1.0 equiv of substrate, 2.0 equiv of NaH, and 3.0 equiv of trichloroacetonitrile. [b] Enantimeric ratio of resulting product.

To probe whether the aromatic group was essential for the highly stereospecific C−O to C−N exchange, alcohols **1g**−**k** were employed (Table 3). Treatment of alcohol **1g** with sodium hydride and TCA in hexanes afforded amide **2g** in 39% yield (59% brsm) where the desired product was

isolated in 92:8 er. Further optimization revealed that higher enantiomeric ratios can be obtained by switching the counterion to potassium and the yield can be enhanced to 53% using 6.0 equiv of TCA. Switching the solvent to toluene afforded amide **2g** in a higher 74% yield affording the desired product in 89:11 er. With two sets of conditions in hand, one where products with higher stereospecificities can be accessed, and the other where higher yields can be obtained, we explored the scope using the latter set of conditions. As presented in Table 3, branched cyclic and acyclic and unbranched aliphatic substrates afforded the desired products in respectable yields and enantiomeric ratios.

Table 3. Reaction Scope with Aliphatic Alcohols

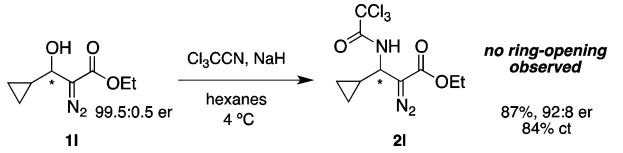


entry[a]	R	solvent	base	% yield	er[b]
1	*n*-Bu (**2g**)	Hexanes	NaH	39(59)[b]	92:8
2	*n*-Bu (**2g**)	Hexanes	KH	48	96:4
3	*n*-Bu (**2g**)	Hexanes	KO*t*-Bu	48	93:7
4[c]	*n*-Bu (**2g**)	Hexanes	KO*t*-Bu	53	92:8
5	*n*-Bu (**2g**)	$PhCH_3$	NaH	74	89:11
6	$PhCH_2CH_2$ (**2h**)	$PhCH_3$	NaH	62	90:10
7	*i*-Pr (**2i**)	$PhCH_3$	NaH	35	89:11
8	cyclohexyl (**2j**)	$PhCH_3$	NaH	58	89:11
9	Me-(CH2)2 (**2k**)	$PhCH_3$	NaH	56	93:7

[a] Reactions using 1.0 equiv of alcohol, 2.0 equiv of base, and 3.0 equiv of TCA unless otherwise specified. [b] Yield based on recovered starting material at 66% conversion. [c] 6.0 equiv of TCA used.

The high stereospecificity observed in the C−O to C−N exchange employing alcohol **1l** suggests the absence of a radical fragmentation and recombination pathway (Scheme 1). Treatment of this alcohol **1l** with sodium hydride and TCA in hexanes at 4 °C afforded amide **2l** in 87% yield and 92:8 er without the formation of any ring opened products.

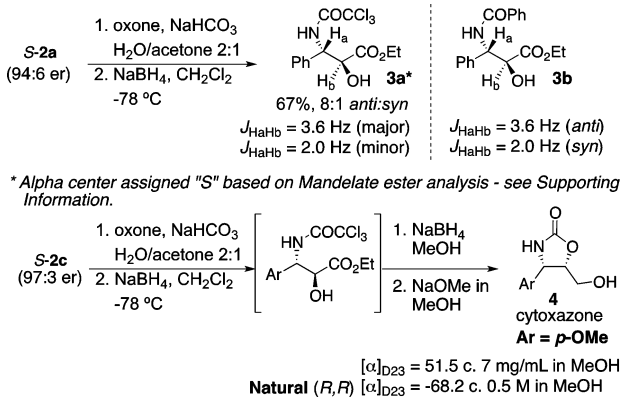
Scheme 1. Transformation of Alcohol **1l** to Amide **2l**



The resulting aromatic and aliphatic β-amido-α-diazoesters presented the enantio- and diastereoselective synthesis of both $\beta^{2,3}$- and $\beta^{2,2,3}$-AA analogs and revealed the stereochemical course of the C−O to C−N transfer. Oxidation of diazoester *S*-**2a** using oxone in acetone followed by reduction with sodium borohydride furnished protected amino alcohol (2*S*,3*S*)-**3a** (Scheme 2).[12] The relative configuration of the product was assigned via comparison of the coupling constants with a closely related analog **3b** and its corresponding diastereoisomer.[13] The relative configuration observed in this reduction is consistent with the diastereocontrol observed by Maruoka et al. for a related β-amido-α-diazoester.[8] The mandelate ester derived from this alcohol revealed the absolute configuration at the α-center. Collectively, these results suggested that the C−O to C−N exchange proceeds via net retention.

To reinforce this assignment, oxidation of diazoester *S*-**2c** followed by reduction afforded an intermediary alcohol. Sodium borohydride reduction of the resulting α-hydroxy ester followed by treatment with sodium methoxide afforded the enantiomer of the natural product cytoxazone **4**, thereby reinforcing the assignment of both the relative and absolute configuration of **3a**. Based on this finding, we propose that the C−O to C−N transfer proceeds via a tight ion pair to afford the product from the net retention of stereochemistry in the exchange reaction. The initial formation of the trichloroacetimidate is followed by rapid recombination to the trichloroamide. The hypothesis of a tight ion pair is supported by the observation that nonpolar solvents (which minimize the separation of charge) furnish the desired product in high enantiomeric ratios.

Scheme 2. Elucidation of the Relative and Absolute Configuration



The synthesis of highly functionalized amino alcohol **5** was accomplished using a recently described protocol for the synthesis of 1,2-diols bearing a tertiary center. Here the oxidation of *S*-**2a** using oxone in acetone followed by the direct treatment of the resulting β-amido-α-ketoester with allyl iodide in the presence of indium metal afforded amino alcohol **5** in 79% yield, 93:7 er, and 5:1 diastereoselectivity.

(12) The conversion of the diazo group to the carbonyl group can be accomplished without the preparation of DMDO as described previously. The two-step protocol involving the oxidation of the diazo group followed by the reduction to the secondary alcohol has been described previously (see ref 7).

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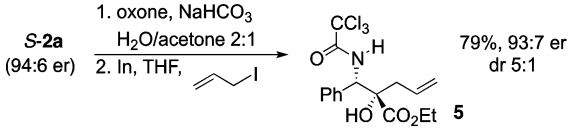
It is noteworthy that under these conditions minimum racemization of the transient β-amido-α-ketoester is observed (Scheme 3).

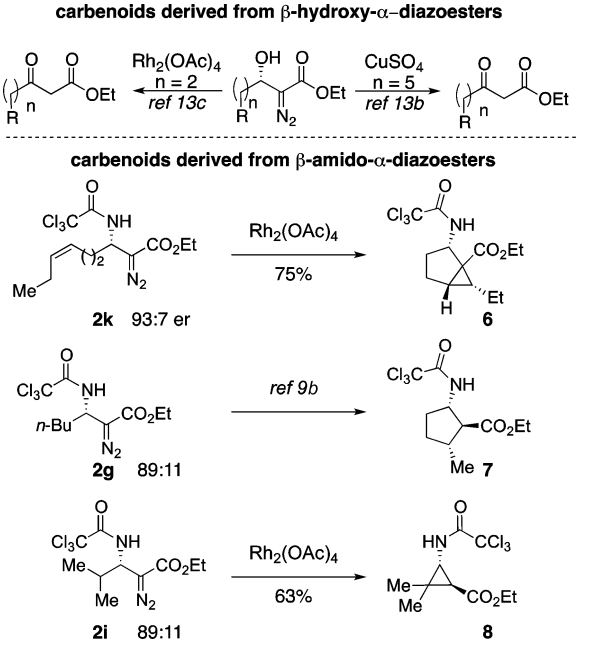
Scheme 3. Asymmetric Synthesis of Amino Alcohol **5**



Of great significance is the question of the effect of the β-substituent on the reactivity of a carbenoid derived from diazo precursors such as compounds **2g**, **2i**, and **2k**. Rhodium carbenoids derived from β-hydroxy-α-diazoesters undergo a rapid 1,2-shift (Scheme 4).[14] Conversely, treatment of β-amido-α-diazoesters derived from aliphatic aldehydes[15] such as **2g**, **2i**, and **2k** with $Rh_2(OAc)_4$ afford products consistent with traditional carbenoid chemistry such as intramolecular C−H insertion and cyclopropanation.[16,17] As illustrated in Scheme 4, subjecting the β-amido-α-diazoester **2k** bearing an olefin afforded cyclopropane **6**, a novel bicyclo[3.1.0]hexane β-amino acid. Wang et al. have previously demonstrated that treatment of **2g** with $Rh_2(OAc)_4$ affords the 1,5-C−H insertion product affording cyclopentane **7**; this work enables the synthesis of the same compound in enantiomerically enriched form.[9a,18,19] Importantly, the treatment of geometrically constrained β-amido-α-diazoester **2i** with Rh catalysts affords cyclopropane **8** via an unusual Rh-catalyzed 1,3-C−H insertion process with high diastereocontrol.[20]

In conclusion, we have developed conditions that exploit a reactivity pattern unique to diazo esters to form enantioenriched β-amino acid building blocks. These studies revealed that the C−O to C−N exchange proceeds via net retention and that nonpolar solvents, those that prevent the separation of charge, afford products with the greatest enantiomeric ratios. This stereochemical course is in complete contrast to the normal behavior of trichloroimidates which invariably proceeds with inversion during substitution.[21] The ability of both aromatic and aliphatic substrates to participate in this transformation with high stereospecificity enhances the utility of this method. The ability to access the β-amido-α-diazoester **2i** allowed typical subsequent carbenoid chemistry to access cyclic β-amido-esters including the enantio- and diastereoselective synthesis of the cyclopropanated product by an unusual 1,3-C−H insertion reaction in contrast to the behavior of β-hydroxy-α-diazoesters. Further, studies will focus on trapping the putative carbocation intermediate with other nucleophilic species.

Scheme 4. Effect of β-Substituent on Carbenoid Chemistry



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Supporting Information Available. Experimental procedures, product characterization data, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The treatment of **2a** with $Rh_2(OAc)_4$ affords the product derived from the 1,2-phenyl shift. See: (a) Jiang, N.; Qu, Z.; Wang, J. *Org. Lett.* **2001**, *3*, 2989. (b) Jiang, N.; Ma, Z.; Qu, Z.; Xing, X.; Xie, L.; Wang, J. *J. Org. Chem.* **2003**, *68*, 893. (c) Shi, W.; Jiang, N.; Zhang, S.; Wu, W.; Du, D.; Wang, J. *Org. Lett.* **2003**, *5*, 2243.

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(17) Recent reports demonstrate that β-hydride transfer can be avoided using bulkier rhodium carboxylates; however, these catalysts were not investigated in the present work. For selected examples, see: (a) DeAngelis, A.; Shurtleff, V. W.; Dmitrenko, O.; Fox, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 1650. (b) Sambasivan, R.; Ball, Z. T. *J. Am. Chem. Soc.* **2010**, *132*, 9289. (c) DeAngelis, A.; Panne, P.; Yap, G. P. A.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 1435. (d) Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22.

(18) Zhang, Z.; Shi, W.; Zhang, J.; Zhang, B.; Liu, B.; Liu, Y.; Fan, B.; Xiao, F.; Xu, F.; Wang, J. *Chem.—Asian J.* **2010**, *5*, 1112.

(19) For a review highlighting the significance of such products, see: Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181.

(20) For a selectd example for this process, see: Shi, W.; Zhang, B.; Zhang, J.; Liu, B.; Zhang, S.; Wang, J. *Org. Lett.* **2005**, *7*, 3103.

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The authors declare no competing financial interest.