A fully-telescoped, aqueous, auxiliary-mediated asymmetric transformation

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Dedicated to Professor Eusebio Juaristi on the occasion of his 55th birthday
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Abstract

A fully-telescoped, aqueous, auxiliary-mediated Diels-Alder cycloaddition in moderate selectivity is reported. The auxiliary is prepared from L-asparagine and trimethylacetaldehyde, and coupled without isolation to the acryloyl substrate. Direct addition of cyclopentadiene generates the cycloadduct, which is cleaved from the heterocycle upon mild treatment with acid and heat. A significantly reduced selectivity is observed relative to the two-pot synthesis in which the acrylamide is precipitated and washed prior to the cycloaddition. Vacuum-assisted removal of the acrylic acid contaminant prior to the cycloaddition substantially remedies the reduced selectivities achieved in the one-pot transformation relative to the two-step sequence. Four chemical transformations, not including acid/base reactions, are accomplished in this one-pot synthesis.

Keywords: Aqueous, auxiliary, asymmetric, Diels-Alder cycloaddition, one-pot, telescoped

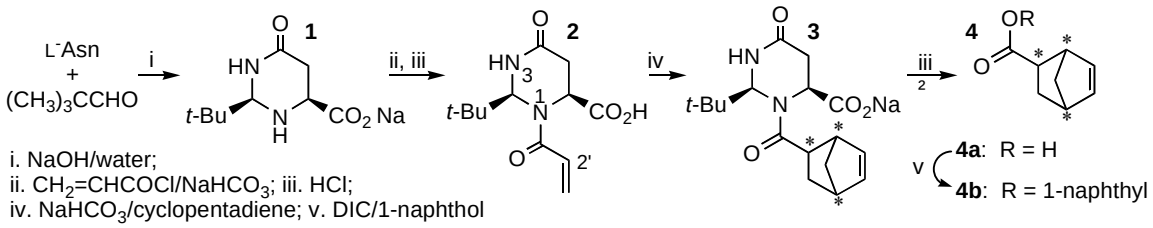
Introduction

The auxiliary-mediated Diels-Alder reaction is a powerful technique for assembling complex organic frameworks with regio- and stereochemical control.[2] Extensive efforts have been directed at developing the conventionally applied approach, which requires multiple discrete steps for auxiliary synthesis and application, and the use of environmentally problematic solvents, reagents, and catalysts.[3] Much less work has been directed at aqueous auxiliary variants[4] or sequential, one-pot synthetic approaches (e.g. telescoping syntheses[5]) that would address environmental concerns. We recently reported the development of an aqueous, asparagine-based Diels-Alder cycloaddition[6] with promising features for "greening"[7] auxiliary-mediated asymmetric transformations. The *in situ* assembly of the auxiliary and its attachment to

an acryloyl dienophile occurred in one pot. In a second one-pot procedure the chiral dienophile was dissolved in sodium bicarbonate, reacted with cyclopentadiene, and the auxiliary was cleaved hydrolytically. Mention was made that the entire process could be conducted in a one-pot sequence, which conforms to current research thrusts aimed at realizing the efficiency of telescoped sequences. However, experimental yields and cycloaddition stereoselectivity in the previous work were significantly diminished and not reported. Here we report details of the adaptation of this system to a one-pot preparation that substantially alleviates previous deficiencies.

Results and Discussion

In these studies, the *tert*-butyl-substituted auxiliary (**1**; Scheme 1) was employed to simplify the proton NMR spectral interpretation of optimization studies necessary to implement a fully-telescoped synthesis. In the previously reported two-pot synthesis,[6] auxiliary **1** was prepared by sequential treatment of L-asparagine monohydrate (10 mmol) with aqueous base (1 M, 1 equiv, rt) and trimethylacetaldehyde (1 equiv). After overnight stirring, the dienophile unit was appended to the auxiliary upon treatment with sodium bicarbonate (1.5 equiv) and acryloyl chloride (1.3 equiv, 0 °C) followed by 24 h stirring to generate **2** (M = Na). This mixture was acidified and the resulting precipitate was filtered, washed with water, and dried overnight at 0.1 mmHg to generate **2** (M = H) as an amorphous white solid in 54% yield. In the second single-pot reaction sequence, the acrylamide was dissolved in sodium bicarbonate (1M, 1.5 equiv), treated with cyclopentadiene (6 equiv), and stirred for 24 h to generate cycloadduct **3**. The product was cleaved from the auxiliary upon acidification (10% HCl, 1.5 equiv) and heating (3 h at 100 °C), steam distilled, and isolated upon ethyl acetate extraction to give 2-norbornenecarboxylic acid **4a** (53% overall yield from asparagine, 64% ee, 15:1 endo/exo).[6] After extractive isolation of the distillate, the product was derivatized to the 1-naphthyl ester (**4b**: DIC, DMAP, CH_2Cl_2) and analyzed by chiral phase HPLC.



Scheme 1. Asparagine-based, aqueous, auxiliary-mediated cycloaddition.

Initial attempts at implementing a one-pot sequence employing the same conditions as described above gave products in significantly reduced yield and selectivity. In these trials, the sodium salt of acrylamide **2** was identically prepared and directly treated with cyclopentadiene.

After incubation as above, the mixture was acidified, hydrolyzed upon heating, and the product was isolated as described. The yield and stereochemical mixture of the product of this telescoped sequence was significantly reduced for the several preparations attempted (averages: 21% overall yield from asparagine, 33% ee, 12:1 endo/exo) compared to that obtained from the two-pot sequence in which acrylamide **2** had been isolated and processed prior to exposure to $NaHCO_3$ and cyclopentadiene.

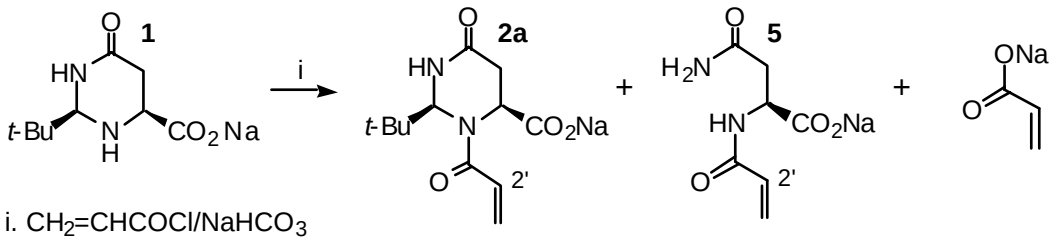
We reasoned that the poor yield in the telescoped preparation occurred from an inefficient synthesis of acrylamide **2**, which was also likely to have impacted the poor selectivity of the two-step sequence. Also, the reduced cycloaddition stereoselectivity of the one-pot sequence may have resulted from cycloadditions to acryloyl chloride or its hydrolyzed byproduct, either of which may have been removed during the isolation process of **2** (e.g. aqueous washing of the precipitate) in the two-pot sequence. This stereochemical analysis is consistent with the significantly reduced selectivity observed for the telescoped sequence, which apparently reflects contributions from the asymmetric auxiliary-mediated cycloaddition and the racemic formation of endo and exo products from cycloadditions to acryloyl chloride or its hydrolyzed product. Accordingly, we examined each step of the telescoped sequence with the goal of optimizing the overall process.

To address the problems associated with the poor yield, the synthesis of acrylamide **2** was examined. Proton NMR was employed to monitor the cyclocondensation of asparagine and trimethylacetaldehyde in $NaOH/D_2O$ over 12 h. Spectral interpretation of the sample removed at 15 min indicated that an imine formed in several minutes, followed by a much slower cyclization to **1**, as indicated by the disappearance of the imine singlet (7.6 ppm) and the emergence of the diastereotopic C2 proton signals (of **1**) centered at 4.1 ppm. The product was cleanly formed in 4 h and exhibited a strong prevalence of trans heterocycle **1** (93% major isomer based on integration), [8] a much smaller amounts of aldehyde (4%), an imine intermediate (2%), and no evidence of the asparagine.

Factors impacting the acryloylation were investigated by preparative studies and proton NMR experiments. Optimization studies, which examined the stoichiometry, temperature, and time requirements for each step, provided the basis for the following standard preparation of acrylamide **2**: asparagine was stirred 15 minutes with NaOH (2.0 M, 1 equiv) and trimethylacetaldehyde (1.1 equiv) was added with stirring. Agitation was maintained 4 h after which the mixture is treated with sodium bicarbonate (1.5 equiv). The mixture was stirred for 15 min, cooled to ice bath temperature, and acryloyl chloride was slowly added (1.3 equiv in four portions over 30 min) with stirring. The mixture was allowed to gradually warm to ambient temperature over 2 h. Acidification induced a precipitate, which was filtered, washed with cold water, and dried *in vacuo* to deliver an amorphous white solid (55-60% yield). Attempted recovery of additional product from the aqueous layer gave a compound identified as asparagyl acrylamide **5** by proton NMR.[9]

Proton NMR studies were also performed to examine the formation and distribution of byproducts in the reaction of **1** with acryloyl chloride. In these studies, aliquots of a standard

preparation of **2** were removed at selected time points, evaporated, taken up in D_2O, and examined by ^1H NMR. For each sample, relative integration values for the C2' protons of acrylamides **2a** and **5** (Scheme 2) together with the value for the C2 proton of sodium acrylate were used to determine the relative amounts of products in the mixtures. At all time points the product, which comprised 73% of the mixture, was significantly contaminated with the salt of asparagyl acrylamide **5** (7%) and sodium acrylate (20%).



Scheme 2. Product formation during the aqueous acryloylation of **1**.

For telescoping purposes, it had been planned to acidify the mixture and remove the acrylic acid upon exposure to high vacuum. Such a protocol was unlikely to remove **5**. However, product **5** can also be considered an auxiliary-appended acrylate and may induce cycloaddition stereoselectivity compatible with the desired process.[4b] If cycloadditions to **5** significantly reduced with the overall selectivity of the telescoped process (for example, if the minor endo product was promoted by **5**), we reasoned that the product mixture may be precipitated upon the usual exposure to acid, decanted, and contaminant **5** triturated from the solid. This would parallel the removal of **5** in the two step reaction in which **5** is analogously removed from product **2** in the aqueous washes, though such manipulations would diminish the elegance of the one-step procedure. Alternatively, the negative impact of cycloadditions to **5** may be remedied upon chemoselective hydrolysis of the Diels-Alder product. Our expectation for a more facile hydrolysis of the cycloadducts of **2** versus the cycloadducts of **5** was bolstered by the ease of the hydrolysis of the former compared to either other tertiary amides[10] or the Diels-Alder cycloadduct of the corresponding cysteine-based auxiliary cycloadduct.[11] Thus, we proceeded with efforts to remove acrylic acid from the telescoped sequence as the initial approach to improving the stereoselectivity of this sequence.

Efforts were next directed at implementing a telescoped variant of this procedure, employing acid and vacuum to remove acrylic acid (bp at ambient pressure = 132°C) prior to cycloaddition. Accordingly, **2a** (1 mmol, 0.2 M) was prepared from asparagine, treated with dilute HCl (1 M, 1 equiv), and evacuated (0.1 mmHg, 24 h) with mild heating (39-40 °C). The evaporated water was replenished in order to maintain the original concentration. The preparations were treated with $NaHCO_3$ (1.5 equiv) followed by cyclopentadiene (6 equiv/24 hr stirring/rt), and the resulting cycloadducts were routinely processed and analyzed. Comparison of the data suggested that the endo product ee increased as expected for evacuated samples

(vacuum: 54% ee, 30:1 endo/exo) compared to that obtained without evacuation (44% ee, 30:1 endo/exo). It should be noted that the selectivity with vacuum is comparable to that obtained in the two-pot sequence, suggesting that the undesired acrylic acid was removed upon submission to strong vacuum. Subsequent experiments at 5 mmol scale provided an acceptable yield of cycloadduct with reproducible efficiency and stereoselectivity (35%; 54% ee, 30:1 endo/exo).

It is not clear from these studies if acrylamide **5** undergoes cycloadditions or if cycloadducts of **5** are, indeed hydrolyzed and subsequently analyzed in the product mixture. Further studies will examine the suitability of these derivatives for auxiliary-mediated, asymmetric Diels-Alder transformations.

Summary

We report a completely telescoped variant of an aqueous, auxiliary-mediated asymmetric transformation. This system employs asparagine, a non-toxic and economical amino acid that is commercially available in either optical series. Each step, including auxiliary formation, substrate attachment, asymmetric transformation, and auxiliary cleavage is incorporated in a single-pot sequence. Preparative experiments partially remedied the modest efficiency of this system. A diminution of selectivity in the sequential process was substantially improved by acidification and low-pressure removal of the acrylic acid contaminant. To our knowledge, this is the first example of an auxiliary-mediated, asymmetric process that has been fully-telescoped. This system thus constitutes a promising avenue for coaxing chiral auxiliary technology toward the more verdant end of organic synthesis. Studies are ongoing to optimize the cycloaddition selectivity,[12] elucidate its origin, increase the overall efficiency of this process, and examine the influence of acryloylated asparagine in this cycloaddition.

Experimental Section

General Procedures. Proton NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz (Varian Inova), respectively in water-d_2 or $CDCl_3$ as indicated at 25°C. Chemical shift values are reported in ppm with TMS as an internal reference. *J* values are given in Hz. Reactions were routinely effected in capped vials with magnetic stirring. Cyclopentadiene was fractionally distilled on the day of its use. All other chemicals were purchased from the Sigma-Aldrich Chemical Company (St. Louis, MO) and used without purification.

(2*S*,4*R*)-3-Acryloyl-2-*tert*-butyl-6-oxo-hexahydropyrimidine-4-carboxylic acid (2). Into a 100 mL flask was added L-asparagine monohydrate (7.51 g, 50 mmol) and aq NaOH (2.0 M, 1 equiv). The mixture was stirred 15 min and trimethylacetaldehyde (1 equiv) was added via syringe over 5 min. The mixture was stirred 4 h, treated with solid sodium bicarbonate

(1.5 equiv), cooled in an ice bath, and acryloyl chloride (1.3 equiv) was added slowly (four portions over 1 h) to the vigorously stirred solution. Cooling and stirring were maintained 2 h, after which the mixture was precipitated upon treatment with HCl (10%, 1.6 equiv), washed with cold water, and dried overnight under reduced pressure. The product **(2**) was obtained as a white solid (55%) and exhibited the reported physical and spectral properties.[12] In addition, a minor byproduct of this transformation exhibited extraneous signals in the proton NMR spectrum. An analytical sample was obtained by washing precipitated **2** and evaporating the combined aqueous washes under high vacuum. The contaminant exhibited proton NMR values that are identical to those previously reported for *N*-acryloylasparagine **5**,[9b] though these data were collected at higher field and revealed previously obscured coupling information: ^{1}H NMR (sat. $NaHCO_3$ in D_2O): δ 2.99 (dd, *J* = 8.8, 15.1 Hz, 1H), 3.08 (dd, *J* = 4.9, 15.1 Hz, 1H), 4.84 (dd, *J* = 4.9, 8.8 Hz, 1H), 6.08 (dd, *J* = 1.0, 10.3 Hz, 1H), 6.48 (dd, *J* = 1.0, 17.1 Hz, 1H), 6.62 (dd, *J* = 10.3, 17.1 Hz, 1H); ^{13}C NMR (sat. $NaHCO_3$ in D_2O): δ 38.3 (t), 52.5 (d), 128.7 (t), 130.4 (d), 168.4 (s), 175.0 (s), 178.0 (s).

General procedures for cycloadditions and hydrolyses

Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (4a), prepared as a mixture of stereoisomers from 2 via the two-pot proced**ure.** Acrylamide **2** (1 mmol) was prepared as described above, was dissolved in aqueous $NaHCO_3$ (1.5 equiv) and treated with cyclopentadiene (3 equiv). The mixture was stirred 24 h and treated with HCl (10%, 1.5 equiv). For spectral observation, an aliquot was removed, extracted with ethyl acetate (2x5 mL), and dried over sodium sulfate. Removal of solvent left behind a slightly yellow solid that exhibited a forest of signals in the ^{1}H NMR spectrum (sat. $NaHCO_3$ in D_2O), which is consistent with a complex mixture of diastereomers and their corresponding syn and anti amide conformers. The bulk solution was treated with HCl (3 M, 1.6 equiv) and heated to 70°C for 24 h. The resulting clear solution was extracted twice with ethyl acetate (5 mL) and the combined organic phases were washed with brine (3 mL) and dried with sodium sulfate (anh). Removal of drying agent and solvent left behind a colorless oil (54%) that exhibited the expected physical and spectral properties.[12]

Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (4a), prepared as a mixture of stereoisomers via the one-pot procedure. Into a 10 mL culture tube was added L-asparagine monohydrate (750 mg, 5.0 mmol) and aq NaOH (2.0 M, 1 equiv). The mixture was stirred 15 min and trimethylacetaldehyde was added via syringe over 5 min. The mixture was stirred 4 h, treated with solid sodium bicarbonate (1.5 equiv), cooled in an ice bath, and acryloyl chloride (1.3 equiv) was added slowly to the vigorously stirred solution over 20 min. Cooling and stirring were maintained an additional 2 h, after which the mixture was treated HCl (10%, 0.3 equiv) and evacuated (0.1 mmHg, 16 h). Water was added to re-establish the original concentrations and subsequently the mixture was treated with cyclopentadiene (6 equiv), and stirred 24 h. The mixture was heated to 70 °C for 24 h, extracted with ethyl acetate, dried, and concentrated to yield the title compound (35% yield), which exhibited proton and carbon NMR signals identical to the known mixture of endo and exo products.

1-Naphthyl bicyclo[2.2.1]hept-5-ene-2-carboxylate (4b, mixture of stereoisomers). The stereoisomeric mixture of carboxylic acid **4a** (34.5 mg, 0.25 mmol) was converted to the 1-naphthyl esters (DIC/DMAP/CH_2Cl_2) and analyzed for stereochemical content by chiral phase HPLC profiles (Regis Pirkle Type 1, RR; 95/5 hexanes/isopropanol, 1.0 mL/min) as described elsewhere.[12] The endo products, as measured by HPLC integrations of the well separated endo enantiomers, and the exo antipodes, which partially co-eluted but were well separated from the endo products, revealed the diastereoselectivity of the endo products and endo/exo ratios, respectively.

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References and Notes

1. Current address: Chemical Diversity, Inc., San Diego, CA, 92121.
2. (a) Nicolaou, K. C.; Snyder, S. A. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11929. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. (c) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304.
3. Rück-Braun, K.; Kunz, H. *Chiral Auxiliaries in Cycloadditions*; Wiley-VCH: Weinheim, Germany, 1999.
4. Aqueous, auxiliary-mediated Diels-Alder cycloadditions are attractive from an environmental point of view but few other examples of auxiliaries specifically designed for aqueous application have been reported. See: (a) Fringuelli, F.; Matteucci, M.; Piermatti, O.; Pizzo, F.; Burla, M. C. *J. Org. Chem.* **2001**, *66*, 4661. For an example of the use of amino acids as chiral auxiliaries in water/alcohol mixtures see: (b) Waldmann, H.; Braun, M. *Gazz. Chim. Ital.* **1991**, *121*, 277.
5. (a) Rouh, A. M. *Chem. & Eng. News* **2002**, *80*, 30. (b) Stinson, S. C. *Chem. & Eng. News* **2001**, *79*, 65.
6. Lakner, F. J.; Negrete, G. R. *Synlett* **2002**, 643.
7. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press, New York, N.Y. 1998.
8. Heterocycle **1** and several analogs have been previously reported: (a) Chu, K. S.; Negrete, G. R.; Konopelski, J. P.; Lakner, F. J.; Woo, N.-T.; Olmstead, M. M. *J. Am. Chem. Soc.*

1992, *114*, 1800. (b) Juaristi, E.; Quintana, D.; Balderas, M.; García-Pérez, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2233.

9. Acrylamide derivatives of asparagine have been reported as adhesives: (a) Heilmann, S. M.; Smith II, H. K. *J. Appl. Polymer Sci.* **1979**, *24*, 1551. (b) Heilmann, S. M. *US Patent* 4,172,934 (*Chemical Abstracts* **1979**, *92*, 43083).
10. For example note the harsh conditions required to hydrolyze the tertiary amide in reference 8a.
11. This product resisted hydrolysis, even under severe conditions. Bakthadoss, M.; Quiñones, B. A.; Recio III, A.; Negrete, G. R. *unpublished data.*
12. Mahindaratne, M. P. D.; Quiñones, B. A.; Recio III, A.; Rodriguez, E. A.; Lakner, F. J.; Negrete, G. R. *Tetrahedron* **2005**, *61*, 0000.