Enhanced Diastereoselectivity in the Asymmetric Ugi Reaction Using a New "Convertible" Isonitrile

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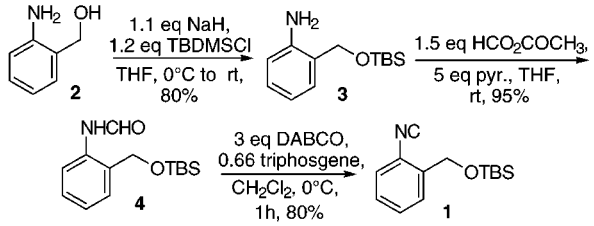
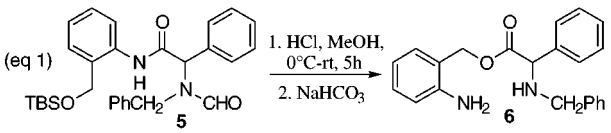
Multicomponent condensation (MCC) reactions, and in particular the Ugi four-component coupling reaction,[1] have recently appeared as efficient methods for the synthesis of diverse libraries of small organic molecules such as benzodiazepines, pyrroles, lactams, and diketopiperazines.[2] The Ugi reaction has also been applied in the asymmetric synthesis of amino acids. In early work, Ugi and co-workers determined that use of a chiral acid or isonitrile in the Ugi MCC reaction did not provide any degree of diastereoselectivity.[1,3] In contrast, chiral ferrocenylamine inputs resulted in the synthesis of nonracemic amino acid derivatives with low to modest levels of diastereoselectivity.[4] Kunz and Pfrengle developed more versatile chiral auxiliaries for the Ugi MCC reaction using carbohydrate derivatives.[5] High diastereomeric ratios of (*R*)-amino acids were obtained in reactions employing a galactosylamine derivative.[5a] A drawback of this asymmetric Ugi reaction was the fact that high levels of diastereoselectivity were only observed for reactions using *tert*-butyl isonitrile. The asymmetric synthesis of (*S*)-amino acid acids via the Ugi reaction was achieved using an arabinosylamine derivative; however, the diastereoselectivity was not as high as that observed in the synthesis of the corresponding (*R*)-enantiomer.[5b] A single variant on the chemistry developed by Kunz has been reported by Ugi.[6] A 2-acetamido glucosylamine derivative provided high levels of stereoselectivity for the (*R*)-amino acid derivative in the Ugi reaction, even if nonsterically demanding isonitriles were employed. However, no hydrolysis of the amide product was reported, and a complementary method for the synthesis of the (*S*)-amino acid was not achieved.

The chemical conversion of an Ugi product is a limitation in the application of the Ugi reaction to the synthesis of small molecules.[2a] Post-Ugi modification is restricted by the need to selectively hydrolyze a secondary amide functional group, a nontrivial task in functionalized substrates.[7] Armstrong and co-workers have addressed this problem by the design of a "convertible" isonitrile, cyclohexenyl isocyanide.[8] Armstrong has shown that the cyclohexenyl amide Ugi product can be hydrolyzed to the free acid, or be converted to a different amide, an ester, or a thioester derivative via a munchnone intermediate. Although the "convertible" isonitrile is a significant advance toward a solution for the post-Ugi conversion problem, cyclohexenyl isocyanide introduces additional difficulties. The isonitrile can be difficult to prepare and is quite unstable, requiring storage at −30 °C. We report here an alternative "convertible" isonitrile which not only provides a means for milder hydrolysis of the Ugi amide product, but results in improved diastereoselectivities of both (*R*)- and (*S*)-amino acids via the asymmetric Ugi reaction using the Kunz chiral auxiliaries.

Scheme 1



Our design of a convertible isonitrile envisioned an acid-catalyzed intramolecular conversion of an amide to an ester. Evans and Takacs demonstrated that chiral amides obtained via alkylation of a prolinol derivative were easily hydrolyzed under acidic conditions without racemization of the adjacent chiral center.[9] We chose to prepare isonitrile **1**, Scheme 1, bearing a silyl ether functionality suitable for conversion of the derived Ugi amide product to an ester via a six-centered transition state. A potential advantage of isonitrile **1** compared to cyclohexenyl isocyanide is the application of this sterically demanding isonitrile in the asymmetric Ugi reaction. Chemoselective O-silylation of 2-amino benzyl alcohol **2** was achieved using sodium hydride and *tert*-butyldimethylsilyl chloride. Formation of the *N*-formyl intermediate **4** via the mixed anhydride and subsequent dehydration with DABCO and triphosgene[8b] generates **1**. Isonitrile **1** can be purified by chromotography on deactivated silica gel or by Kugelrohr distillation. Although isonitrile **1** is quite stable and can be prepared on a reasonable scale, we routinely prepare and store larger quantities of formamide **4** rather than the isonitrile. The Ugi reaction using isonitrile **1**, benzylamine, benzaldehyde, and formic acid at 0 °C to obtain amide **5** was carried out. The amide exhibited an IR stretch at 1670 cm^{-1} for the secondary amide CO. Upon treatment with methanolic HCl, the silyl protecting group was cleaved, and the expected amide/ester exchange reaction took place to provide ester **6** in quantitative yield (after basification), eq 1. The amide CO stretch was no longer present, and only the ester CO stretch at 1722 cm^{-1} was observed.



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Scheme 2

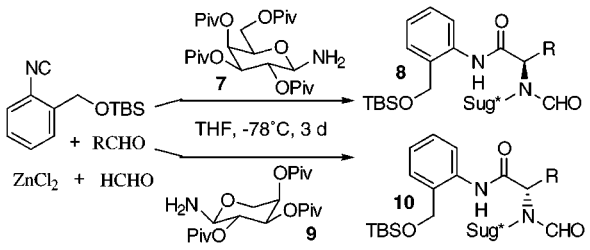
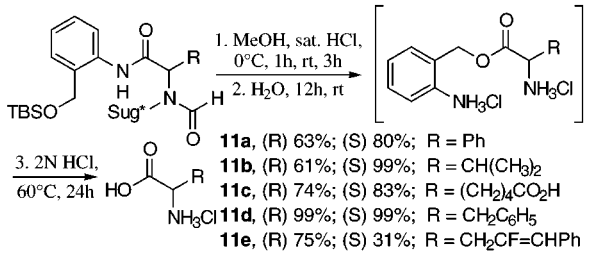


Table 1. Asymmetric Amino Acids via the Ugi MCC Reaction using Isonitrile 1

aldehyde, R =	yield (%)	dr	yield (%)	dr
Ph	**8a**, 61	90:10	**10a**, 48	90:10
$CH(CH_3)_2$	**8b**, 80	97:3	**10b**, 76	90:10
$(CH_2)_4CO_2CH_3$	**8c**, 80	98:2	**10c**, 71	96:4
CH_2Ph	**8d**, 85	98:2	**10d**, 66	93:7[a]
$(CH_2)_2CF{=}CHC_6H_5$	**8e**, 65	98:2	**10e**, 76	95:5

[a] Reaction temperature reached −70 °C resulting in a diminished dr.

Scheme 3



We then examined the application of isonitrile **1** in the asymmetric Ugi reaction using the galactosylamine auxiliary **7** under the conditions reported by Kunz,[5a] Scheme 2. As previously reported, the asymmetric Ugi reaction is fairly slow, requiring up to 72 h at −78 °C. Nevertheless, we were extremely gratified to note that the reaction did indeed provide the (*R*)-valine derivative **8b** in 80% yield with excellent diastereoselectivity, 97:3 dr. The diastereoselectivity of the reaction is rapidly degraded at increased reaction temperatures. While benzaldehyde provided the lowest yield and diastereoselectivity in the reaction, Table 1, the amino acid amides **8b**−**e** are obtained with excellent diastereomeric ratios. It is interesting to note that the formamide proton is not only distinguishable as pairs of diastereomers, but also as rotamers. Integration of the formamide proton signal provides a reliable method for determination of the diastereomeric ratio; however, all of the ratios reported herein were verified by HPLC analysis. In nearly all cases, the minor diastereomer is not observed by NMR in reactions carried out at −78 °C, but can be readily detected in reactions carried out at higher temperatures. More significantly, Ugi reaction of isonitrile **1** with the arabinosylamine auxiliary **9**, Scheme 2, provides the (*S*)-amino acid in excellent yield with greater degrees of diastereoselectivity than those reported by Kunz for similar asymmetric Ugi reactions using *tert*-butyl isonitrile. The results of the synthesis of several (*S*)-amino acids are also given in Table 1.

The amides **8a**−**e** and **10a**−**e** were converted to the free amino acids **11** as shown in Scheme 3. The amides were converted to the acid via hydrolysis without isolation of the intermediate ester. Hydrolysis of the sugar and formyl groups occurs concomitantly. The chiral auxiliary sugar is isolated by pentane extraction of the crude hydrolysis reaction mixture. Purification of the amino acid can then be accomplished by ion exchange chromatography. Yields reported in Scheme 3 were determined by NMR integration of the mixture of the free amino acid and 2-aminobenzyl alcohol. Separation of the 2-aminobenzyl alcohol byproduct can be problematic. More highly functionalized amino acid products, such as diacid **11c**, are easily separated by ion exchange chromatography while separation of simpler products such as phenylalanine **11d** is difficult. We are currently examining several alternative aryl groups in the isonitrile to alleviate this problem.

Table 2. Asymmetric Synthesis of 8c′ and 10c′ via the Ugi MCC Reaction Using Silyl Ether Analogs of Isonitrile 1

isonitrile, OR =	yield (%) (*R*)-**8c′**	dr	yield (%) (*S*)-**10c′**	dr
$SiEt_3$	87	94:6	75[a]	90:10
$Si(iPr)_3$	76	98:2	81	99:1
$Si(Ph)_2CH_3$	52	>99:1	80[a]	98:2
$Si(Ph)_2tBu$	54	98:2	69	98:2

[a] Yield of amide corrected for isolated benzyl ester derivative formed by amide/ester exchange under the Ugi reaction conditions.

The improvement realized by the incorporation of an intramolecular amide/ester exchange process is illustrated by the synthesis of the (*R*) and (*S*) vinyl fluoride containing amino acid **11e**.[10] The acid-catalyzed hydrolysis of *tert*-butyl amide amino acid derivatives required 6 N HCl at 80 °C for 6 days![5] We have found that vinyl fluorides are very susceptible to acid-catalyzed hydrolysis. Normal hydrolysis conditions for an amide (6 N HCl) result in complete destruction of the vinyl fluoride within 12 h. We obtained (*R*) vinyl fluoride **11e** in 75% yield from amide **8e**. The lower yield for the (*S*) enantiomer of **11e** was attributed to solubility problems encountered during hydrolysis of the arabinosyl derivative.

We have also been able to demonstrate that the size of the silyl ether can influence the diastereoselectivity of the reaction. We have prepared a series of silyl ether derivatives of isonitrile **1** and carried out the asymmetric Ugi reaction leading to amide **8c′** and **10c′**, Table 2.

The triethyl silyl ether provided the lowest dr while all of the other ether derivatives provided comparable dr. The yield of the reaction is somewhat lower with the phenyl silyl ether derivatives, but the yields in Table 2 have not been optimized. For practical purposes, the *tert*-butyldimethyl silyl ether isonitrile **1** is the reagent of choice for the asymmetric Ugi reaction reported here. In all of the cases examined, the Ugi product minor diastereomer is easily removed by flash chromatography, and *diastereomerically pure products* can be obtained prior to hydrolysis.

In summary, we have developed an alternative easily hydrolyzable isonitrile which can be applied to the asymmetric Ugi reaction, providing functionalized unnatural amino acids such as **11e** in excellent dr.

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Supporting Information Available: Experimental procedures for isonitrile synthesis, the Ugi reaction, and hydrolysis of the amide products; characterization data for all new compounds.

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