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Organocatalytic Double Ugi Reaction with Statistical Amplification of Product Enantiopurity: A Linker Cleavage Approach To Access Highly Enantiopure Ugi Products

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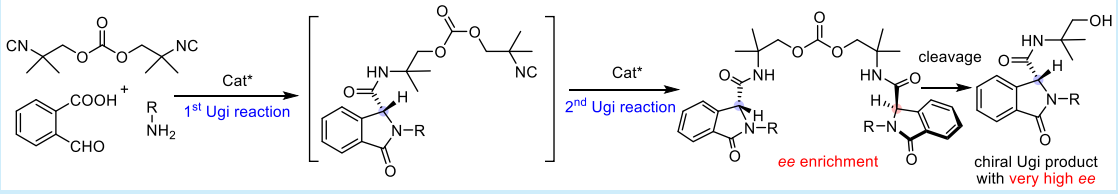
Supporting Information



ABSTRACT: Here we report an organocatalytic double Ugi reaction combining the enantioselective process and ee enhancement in a single operation to afford the chiral Ugi products with very high ee values. Both bisisocyanides and bisanilines tethered by carbonate and diester, respectively, were designed to accomplish this double multicomponent reaction that formed 10 new chemical bonds (4 C−N, 2 C−C, 2 C−O, and 2 N−H bonds). The strategy was further applied for the fast construction of an enantiomerically enriched macrocycle.

The Ugi four-component reaction (Ugi-4CR) converts an aldehyde, an amine, a carboxylic acid, and an isocyanide into an α-acetamidoamide with cocurrent creation of one stereocenter.[1] The reaction proceeds in a truly mix-and-go manner that poses a significant challenge for the development of its enantioselective version.[2] Indeed, the carboxylic acid acts as not only a substrate but also a promotor to catalyze imine formation and the subsequent nucleophilic addition of isocyanide. In developing a catalytic enantioselective Ugi-4CR, one would have to avoid the occurrence of this otherwise highly competitive background reaction. In addition, all four components of the Ugi-4CR are Lewis basic, rendering the selective activation by chiral Lewis and/or Brøsted acid catalysts, and hence the creation of a defined chiral environment, difficult to achieve. It is therefore not surprising to note that over the past 60 years since the Ugi reaction was first discovered in 1959, in spite of the dedicated efforts aimed at developing enantioselective Ugi-4CR,[3] the truly enantioselective Ugi-4CR has been developed only very recently by the group of Tan, which produced products with ee's in the range of 75−97%.[4] Nevertheless, rapid access to highly enantiopure Ugi products (ee > 98%) essential for the discovery and development of chiral drugs[5] remains challenging. A new research paradigm enabling the generation of enantiopure chiral compounds in a short time is in high demand.

Langenback[6] and Horeau[7] reported in 1970s a statistic enantiomeric enrichment method by reacting a scalemic compound with an achiral bifunctional linker to afford a mixture of a homochiral dimer and a heterochiral dimer. Isolation of the homochiral dimer pair followed by removal of the linker regenerates the starting materials with an increased enantiopurity. The cost paid associated with this duplication principle is material lost. Despite this obvious drawback, simple algebraic treatment indicated that the benefits of the duplication remain high, with the material lost being vanishingly small if the ee of the initial compound were sufficiently high (Scheme 1a).[8,9] Taking advantage of this, we have recently succeeded in combining a catalytic enantioselective process with ee enhancement in a single operation, allowing the rapid synthesis of pyrroloindoline without suffering from the loss of too much material.[10] The duplication approach is particularly useful for developing asymmetric reactions that are known to be highly challenging. We envision that if the strategy could be utilized in an enantioselective Ugi reaction, then rapid acquisition of chiral Ugi products with a more than decent ee could therefore not be a difficult-to-achieve goal; subsequently, cleavage of the linker could therefore form 2-fold or >2-fold highly enantiopure Ugi products (Scheme 1a).

We have been involved in the development of enantioselective Passerini-3CR[11] as well as Ugi-4CR and have reported a chiral phosphoric acid (CPA)-catalyzed enantioselective Ugi four-center, three-component reaction of 2-formylbenzoic acids, anilines, and isocyanides for the synthesis of

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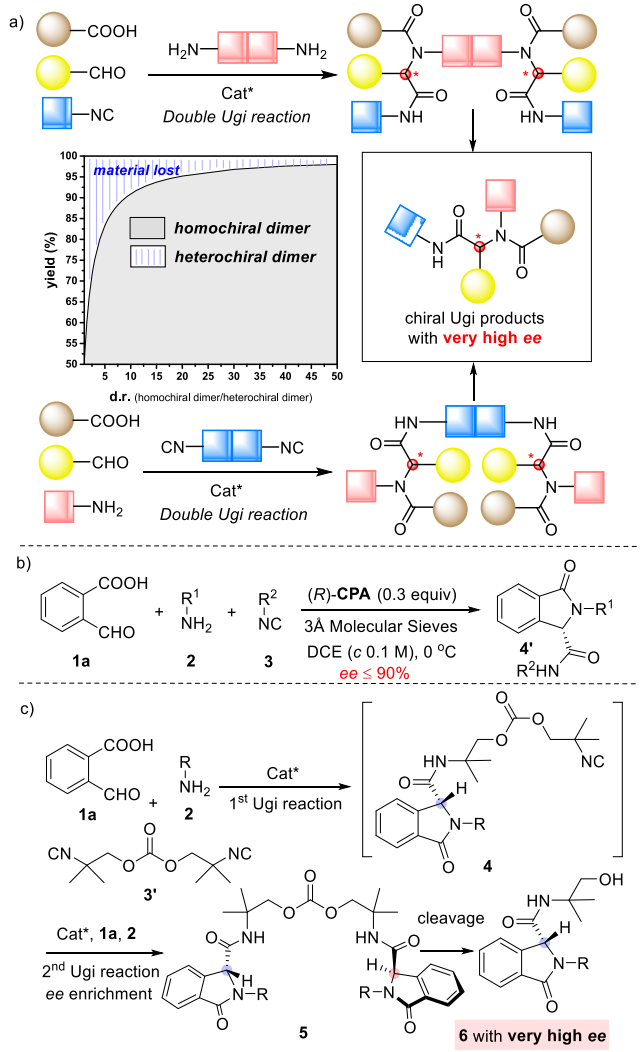
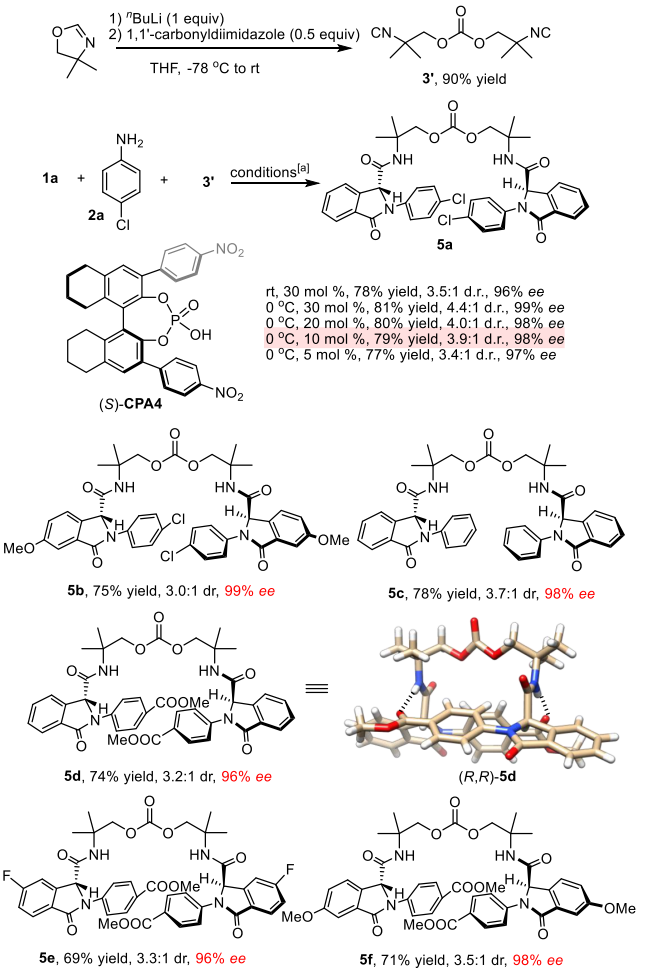
Scheme 1. Catalytic Double Ugi Reaction with Statistical Amplification of Product Enantiopurity (concept and reaction design)



enantioenriched 3-oxoisoindoline-1-carboxamides (Scheme 1b).[3f] The moderate application scope and the enantioselectivity rendered it an ideal candidate for the combined asymmetric transformation/ee amplification approach. We report herein that using bisisocyanides or bisanilines as the linker substrate, organocatalytic double Ugi reaction afforded the dimeric Ugi adducts via formation of 10 new chemical bonds (4 C−N, 2 C−C, 2 C−O, and 2 N−H) in high yields with excellent ee's. The monomeric isoindolines were readily prepared by cleavage of the linker without erosion of enantiopurity (Scheme 1c) and were found as a key structural motif in many bioactive natural products and medicinally relevant compounds,[12] such as (*R*)-pazinaclone, a sedative and anxiolytic drug.[13] We have also extended the method to an enantioselective synthesis of a highly enantiopure macrocycle from a chiral phosphoric acid-catalyzed reaction of a 2-formylbenzoic acid with a bisaniline and a bisisocyanide.

To upgrade the enantioselectivity to a record-breaking level, we first designed and tested double Ugi reaction of a novel carbonate-linked bisisocyanide **3′** with 2-formylbenzoic acid (**1a**) and 4-chloroaniline (**2a**). Bisisocyanide **3′** could be easily prepared in 90% yield from 4,4-dimethyl-2-oxazoline, which was first deprotonated with *n*BuLi to form lithium alcoholate and then captured with 1,1′-carbonyldiimidazole (Scheme 2).[14] The racemic product of **5a** was successfully isolated in a

Scheme 2. Development of Chiral Phosphoric Acid-Catalyzed Double Enantioselective Ugi Reaction Using Carbonate-Linked Bisisocyanide 3′ as a Linker



[a]**1a** (0.1 mmol), **2a** (0.1 mmol), **3′** (0.06 mmol), (*S*)-**CPA4** (10 mol %), DCE (*c* = 0.1 M), 3 Å molecular sieves (5 mg), 0 °C.

90% overall yield of the homo- and heterochiral dimer by using racemic BINOL-derived phosphoric acid (30 mol %) as a catalyst. Chiral phosphoric acids were next screened utilizing the dr value of products, easily measured by its ^{1}H NMR spectrum, as an indicator of the enantioselectivity (see the Supporting Information for details). On the basis of the mathematical equation of the duplication,[15] the enantiopurity of products can be estimated from the dr value of the dimers. Because the dr value is easily determined from the ^{1}H NMR spectrum of the crude reaction mixture, it avoids analysis of ee values using HPLC chromatographic methods, accelerating greatly the process of the optimization. Notably, after only a handful of catalysts had been tested, (*S*)-**CPA4** stood out as the best catalyst to afford dimerization product **5a** with a dr value of 3.5:1 (see the Supporting Information for details). Further fine-tuning of the conditions for the reaction that was carried out with ease under simple optimization by using the best catalyst candidate (*S*)-**CPA4** led to excellent enantioselectivity even with a decreased catalyst loading of 10 mol %

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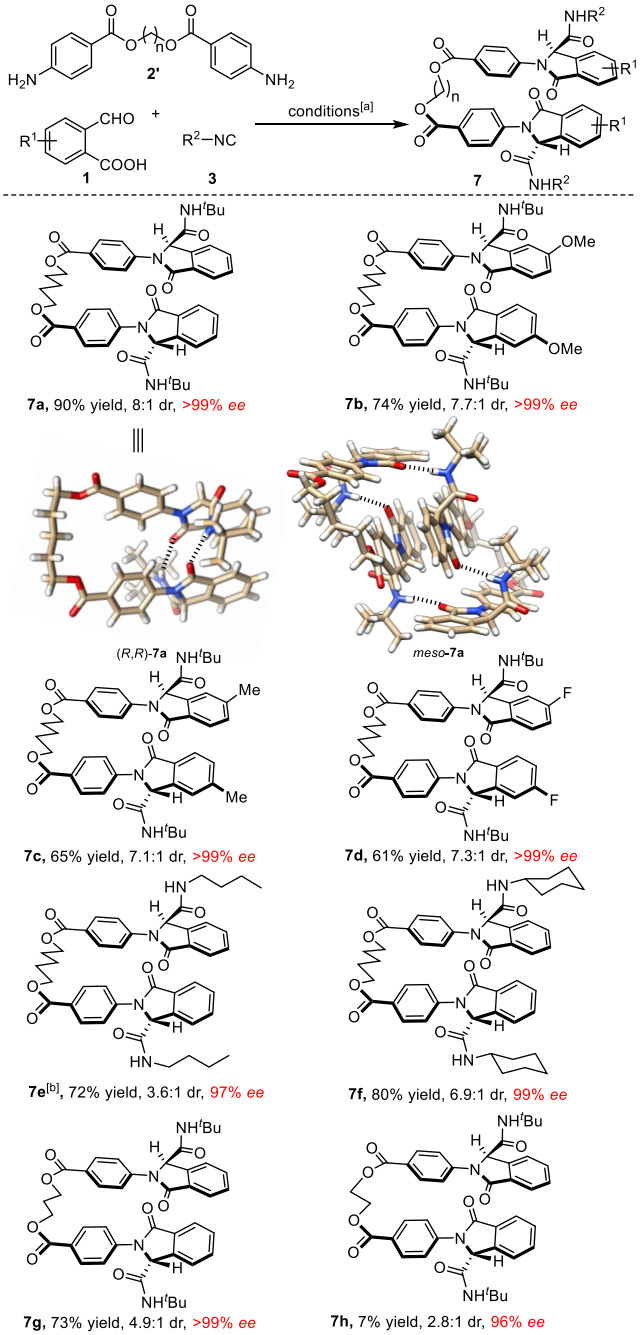
(Scheme 2). Thus, an ee value of ≤98% was achieved for Ugi product **5a** (79% yield, 3.9/1 dr) from the (*S*)-**CPA4**-catalyzed double Ugi reaction of **1a**, **2a**, and **3′**. The scope of this double enantioselective Ugi reaction by using carbonate-linked bisisocyanide **3′** was briefly examined (Scheme 2). 2-Formylbenzoic acids **1** and anilines **2** with different electronic properties participated in this reaction equally well to afford the 3-oxoisoindoline-1-carboxamide products **5** in good yields and excellent ee values. The absolute configuration of **5d** was determined to be (*R*,*R*) by X-ray crystallographic analysis.[16] Two 19-membered H-bonds between two NH and two ester functions forced the molecule to adopt an interesting folded structure. Dimer **5d** was easily hydrolyzed to afford 2 equiv of 3-oxo-isoindoline **6** in a 92% yield without erosion of enantiopurity (Scheme 4).

To further show the generality of the ee amplification strategy using a linker cleavage approach, double Ugi reaction of ester-linked bisanilines **2′** with 2-formylbenzoic acid **1** and isocyanide **3** was studied (Scheme 3). To our delight, by using the same chiral phosphoric acid catalyst with a slight change of reaction conditions, the reaction of **1**, **3**, and bisaniline **2′** proceeded straightforwardly forming the desired Ugi product **7** without any problem. The reaction had broad functional group tolerance. As illustrated in Scheme 3, yields of the double multicomponent reaction were generally good regardless of the electron-withdrawing or electron-donating groups. In general, the enantioselectivity and diastereoselectivity were even slightly higher compared with those of the cases of using carbonate-linked bisisocyanide **3′** (Scheme 2). The reaction proceeded equally well when the linker length was shortened to a three-carbon chain length (Scheme 3, **7g**). However, the yield decreased when the reaction was carried out with a two-carbon length chain as a linker (Scheme 3, **7h**). It was probably because of the odd−even effect that dramatically changed the solubility of the starting materials, intermediates, and the final product. It is worth mentioning that most of the products **7** yielded ee values exceeding 99%. The extremely high enantioselectivity of such a huge challenge-type multicomponent reaction is really astonishing. X-ray structures of both the enantiomer and the *meso* form of **7a** were obtained. In the crystals, the bis-Ugi products are rigidified by H-bonds.[17] Two intramolecular H-bonds were observed in (*R*,*R*)-**7a**, while the dimeric cyclic structure of *meso*-**7a** was formed through two intra- and two intermolecular H-bonds. Finally, **7a** was easily transformed into monomer **8** without a decrease in ee (Scheme 4), which made the carboxylic acid functional group accessible for further transformations.

Chiral macrocycles have found wide applications in supramolecular chemistry and in drug development due to their widespread occurrence in nature and their intrinsic three-dimensional structure. Ugi reaction has been widely used as a ring closure method in the construction of macrocyclic compounds, especially for peptide macrocyclization.[18] However, this multicomponent macrocyclization strategy was normally carried out in a racemic version or in a diastereoselective manner with the participation of chiral building blocks. To the best of our knowledge, enantioselective catalytic Ugi reaction for the synthesis of chiral macrocycles has never been reported. We speculated that the enantioselectivity of the chiral macrocycle should be increased spontaneously because of the inherent nature of the double asymmetric reaction mode of macrocyclization. As a demonstration, we attempted the catalytic enantioselective

Scheme 3. Scope of Double Enantioselective Ugi Reaction Using Ester-Linked Bisaniline 2′ as a Linker



[a]**1** (0.1 mmol), **2′** (0.05 mmol), **3** (0.15 mmol), (*S*)-**CPA4** (10 mol %), DCM (*c* = 0.1 M), 3 Å molecular sieves (5 mg), reflux. [b](*S*)-**CPA4** (15 mol %), 60 °C under otherwise optimized conditions.

synthesis of a chiral macrocycle **9** in 31% yield simply upon mixing the 2-formylbenzoic acid (**1a**), bisaniline **2′**, bisisocyanide **3′**, and (*S*)-**CPA4** (30 mol %) under the optimized conditions (Scheme 4). Two diastereomers (2.5:1 dr) were isolated and fully characterized. The ee of (*R*,*R*)-**9** was calculated to be 93% based on the dr value of diastereoisomers.[19] This chiral macrocycle was hardly soluble in most of the organic solvents except DMSO. However, its diastereoisomer *meso*-**9** was found to be quite soluble in a low-polarity solvent such as $CHCl_3$. The solid-state structure of

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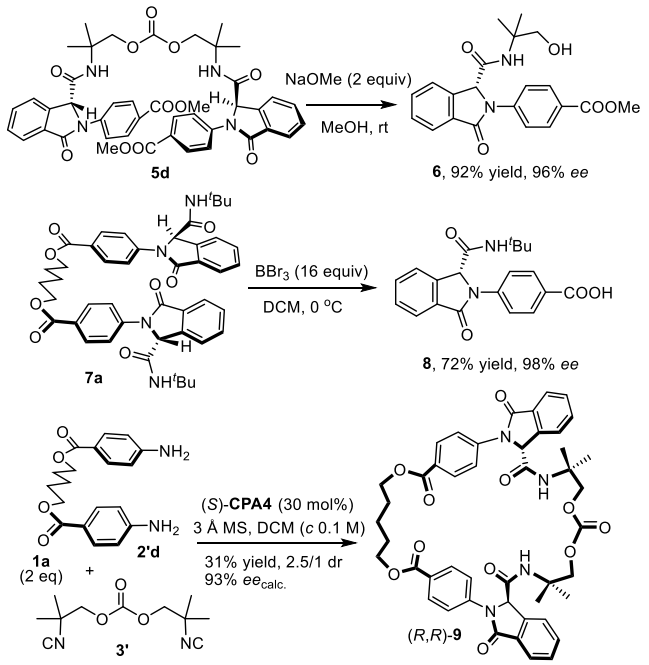
Scheme 4. Linker Cleavage To Form 2-fold Highly Enantiopure Ugi Products and Enantioselective Catalyst Double Ugi Reaction for the Synthesis of Chiral Macrocyclic Product 9



meso-**9** was determined by X-ray crystallography (Supporting Information).[20] The difference in solubility reflects the preferred interaction between the paired homoenantiomers of the macrocycles.

In summary, we have demonstrated a linker cleavage approach to access highly enantiopure Ugi products through a combination of an enantioselective process with statistical amplification of product enantiopurity. Utilizing this strategy, two divergent double enantioselective Ugi reactions, using different Ugi components as linkers, were successfully executed. The enantioselectivity was dramatically improved, and excellent ee values (96% to >99.5%) were determined for all chiral Ugi products. We have also shown the first example of the fast construction of an enantiomerically enriched macrocycle from catalytic enantioselective double Ugi reaction. We expect that the flexibility, reliability, and easy implementation of this strategy would make it applicable to many different organic reactions and impact the field of asymmetric synthesis and chiral macrocycle synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04239.

Reaction optimization, crystallographic data of (*R*,*R*)-**5d**, (*R*,*R*)-**7a**, *meso*-**7a**, and *meso*-**9**, and spectroscopic data [^{1}H and ^{13}C{^{1}H} spectra] of all new compounds (PDF)

Accession Codes

CCDC 1546340, 1941845−1941846, and 1941860 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(15) Find the details of the scheme description and algebraic solution of the duplication principle.
(16) CCDC 1546340 (**5d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(17) CCDC 1941845 (**7a**) and CCDC 1941846 (*meso*-**7a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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(19) Homodimer **9** could not be separated under current chiral HPLC conditions, most probably due to its poor solubility.
(20) CCDC 1941860 (*meso*-**9**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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