Synthetic Methods

International Edition: DOI: 10.1002/anie.201600751
German Edition: DOI: 10.1002/ange.201600751

Chiral Phosphoric Acid Catalyzed Asymmetric Ugi Reaction by Dynamic Kinetic Resolution of the Primary Multicomponent Adduct

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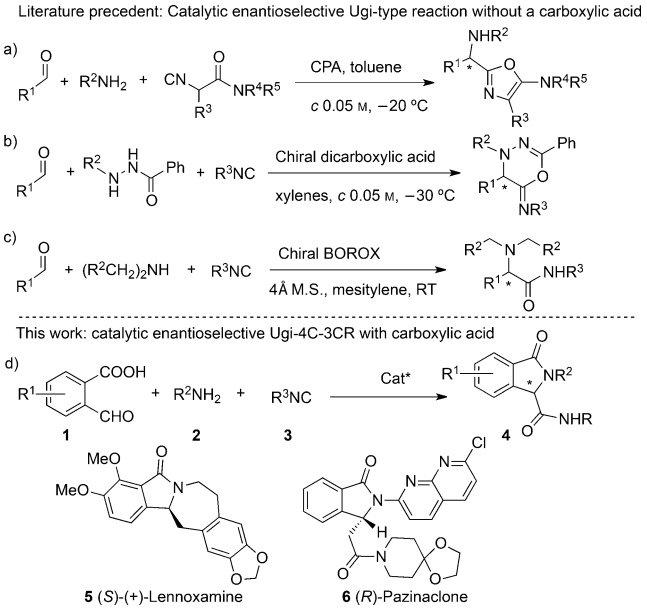
Abstract: *Reaction of isonitriles with 3-(arylamino)isobenzofuran-1(3H)-ones in the presence of a catalytic amount of an octahydro (R)-binol-derived chiral phosphoric acid afforded 3-oxo-2-arylisoindoline-1-carboxamides in high yields with good to high enantioselectivities. An enantioselective Ugi four-center three-component reaction of 2-formylbenzoic acids, anilines, and isonitriles was subsequently developed for the synthesis of the same heterocycle. Mechanistic studies indicate that the enantioselectivity results from the dynamic kinetic resolution of the primary Ugi adduct, rather than from the C–C bond-forming process. The resulting heterocycle products are of significant medicinal importance.*

The Ugi 4CR converts an aldehyde, an amine, an acid, and an isonitrile into an α-acetamidoamide at room temperature under catalyst (promoter)-free conditions and is therefore one of the rare chemical transformations that proceeds in a truly mix-and-go manner.[1] The reaction generates one C–C, one C=O, and two C–N bonds with water as the only by-product. While the prototypical Ugi 4CR provides a linear peptide-like adduct, many heterocycles[2] and even macrocycles[3] are now readily accessible by modification of this versatile and powerful reaction. Since one stereogenic center is generated in this transformation, the ability to control the stereochemical outcome would expand significantly its synthetic utilities. However, the development of a catalytic, enantioselective Ugi reaction remains an unsolved problem in spite of the progress recorded in the field of asymmetric Passerini reactions,[4–9] a closely related three-component condensation of an aldehyde, carboxylic acid, and isonitrile.[10]

Our group[11] and that of Maruoka[12] have independently reported chiral phosphoric acid (CPA) and chiral dicarboxylic acid catalyzed Ugi-type three-component reactions in which the transient nitrilium intermediate was trapped by an internal carboxamide function (Scheme 1 a,b). Very recently,



Scheme 1. Enantioselective Ugi-type multicomponent reaction. M.S. = molecular sieves.

Wulff and co-workers described a chiral BOROX-catalyzed reaction of aldehydes, secondary amines, and isonitriles for the synthesis of enantioenriched α-aminoacetamides (Scheme 1 c).[13] List and Pan have also examined the CPA (TRIP)-catalyzed reaction of benzaldehyde, 4-methoxyaniline, and *tert*-butylisonitrile, however, the three-component adduct was obtained in low yield and *ee* value.[14] In all these truncated Ugi reactions, the carboxylic acid is notably absent. Indeed, its presence renders the development of an enantioselective process extremely difficult since carboxylic acid is not only a reactant, but also a catalyst for the classic Ugi reaction. We report herein a novel CPA-catalyzed enantioselective reaction between isonitriles (**3**) and 3-(arylamino)isobenzofuran-1(3*H*)-ones (**7**), as well as the first examples of the Ugi four-center three-component reaction of 2-formylbenzoic acids (**1**), anilines (**2**), and isonitriles (**3**) for the synthesis of enantioenriched 3-oxoisoindoline-1-carboxamides (**4**).[15] We also document that the observed enantioselectivity results from the dynamic kinetic resolution (DKR) of the primary Ugi adduct, rather than from the C–C bond-forming step. The heterocycle **4** is known for its analgesic properties[16] and has

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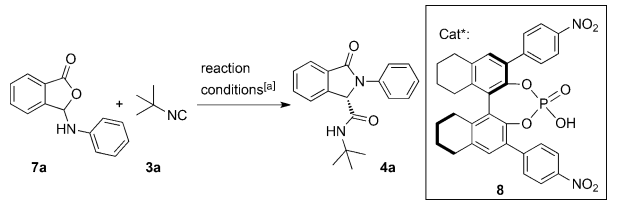
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201600751.

been found, as a key structural motif, in many bioactive natural products [for example, (*S*)-(+)-lennoxamine (**5**)][17] and medicinally relevant compounds, such as (*R*)-pazinaclone, a sedative and anxiolytic drug.[18]

As a prelude to the development of enantioselective Ugi four-center three-component reaction, we began our studies by examining the two-component reaction between the isonitrile **3a** and 3-(phenylamino) isobenzofuran-1(3*H*)-one (**7a**: see Table 1). The latter is easily synthesized from 2-formylbenzoic acid (**1a**) and aniline (**2a**). The reaction itself was unknown, but we assumed that **7a** could serve as a latent iminium species under mild acidic conditions. Therefore, the reaction was expected to follow the Ugi pathway involving nucleophilic addition of the isonitrile to the iminium species as a key step. After initial screening of different (*R*)-binol-derived CPAs,[19,20] the phosphoric acid **8** stood out as the catalyst of choice in terms of both the reactivity and selectivity (see the Supporting Information for a list of CPAs screened). The results of a survey of reaction conditions using **8** as the catalyst are summarized in Table 1. As expected, the racemic **4a** was isolated in 89% yield when the reaction was performed in MeOH, one of the preferred solvents for the Ugi 4CR (entry 1). Other polar solvents capable of forming hydrogen bonds with CPA were equally inefficient (entries 2–5), although a reasonable *ee* value (50%) was obtained in EtOAc (entry 4). More rewarding results were obtained when the reaction was carried out in chlorinated solvents, with DCE affording the best results (entry 9). A slightly higher *ee* value was observed when performing the reaction in toluene. However, there was a solubility issue with this solvent and DCE was chosen for further optimization. Adding molecular sieves (M.S.) improved significantly the enantioselectivity of the reaction (entries 12–16), with 3 Å M.S. (10 mg per 0.2 mmol of substrate) being optimum (entry 15). The reverse molar ratio (**3a**/**7a** = 1.2:1) increased the yield of the product without affecting the enantioselectivity (entry 16). Finally, both decreasing and increasing the catalyst loading had a negative effect on the *ee* value of the product (entries 17 and 18), whereas a similar result was obtained when the reaction was carried out at −20 °C.

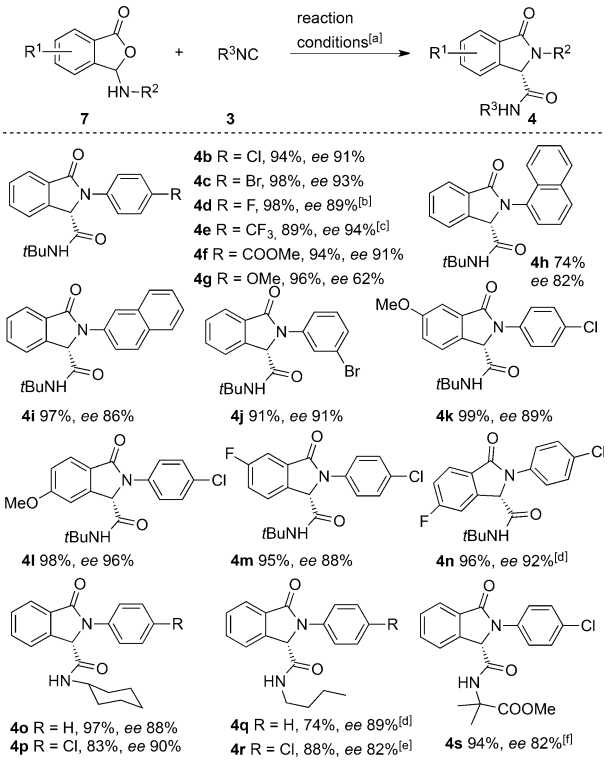
With optimal reaction conditions in hand [molar ratio **3a**/**7a** = 1.2:1, **8** (0.1 equiv) and 3 Å M.S., DCE (c = 0.1 M), 0 °C], the generality of the reaction was next examined (Scheme 2). Anilines with different electronic properties participated in this reaction. Electron-poor anilines afforded the 3-oxoisoindoline-1-carboxamides **4** in excellent yields and *ee* values (**4b–f**). However, **7** bearing an electron-rich aniline afforded the desired product **4g** with a reduced *ee* value. The compounds **4h** and **4i** with 1-naphthyl and 2-naphthyl substituents, respectively, were similarly prepared in high yields and *ee* values. Both electron-withdrawing and electron-donating groups on the aromatic ring of **7** were also well tolerated (**4k–**

Table 1: Two-component version: Optimization of the reaction conditions.[a]



Entry	Solv	M.S. (mg)	T [°C]	t [h]	Yield [%][b]	*ee* [%][c]
1	MeOH	–	20	1.5	89	0
2	MeCN	–	20	1.5	77	12
3	THF	–	20	48	trace	n.d.[d]
4	EtOAc	–	20	20	68	50
5	$MeNO_2$	–	20	3	96	26
6	CH_2Cl_2	–	20	1.5	79	67
7	$CHCl_3$	–	20	6.5	74	52
8	CCl_4	–	20	24	75	59
9	DCE	–	20	3	97	73
10	toluene	–	20	36	65	75
11	DCE	–	0	6	95	79
12	DCE	3 Å (20)[e]	0	3	98	86
13	DCE	4 Å (20)[e]	0	2	90	80
14	DCE	3 Å (40)	0	0.4	95	84
15	DCE	3 Å (10)	0	3	93	87
16[f]	DCE	3 Å (10)	0	1	99	87
17[g]	DCE	3 Å (10)	0	52	81	69
18[h]	DCE	3 Å (10)	0	0.5	87	84
19	DCE	3 Å (10)	−20	7	95	87

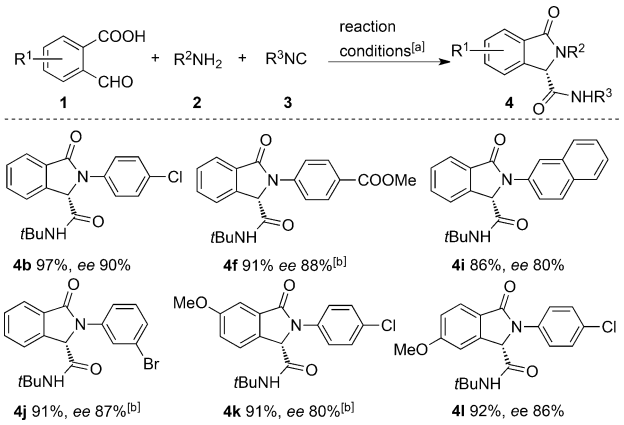
[a] Reaction conditions: **7a** (0.24 mmol), **3a** (0.2 mmol), **8** (0.02 mmol, 0.1 equiv), solvent (2.0 mL). [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] n.d. = not determined. [e] Used without preactivation. [f] Used **7a** (0.24 mmol), **3a** (0.24 mmol). [g] Used 0.05 equiv of **8**. [h] Used 0.2 equiv of **8**. DCE = 1,2-dichloroethane, THF = tetrahydrofuran.



Scheme 2. Scope of the catalytic enantioselective synthesis of isoindolinones. [a] **7** (0.2 mmol), **3a** (0.24 mmol), **8** (0.02 mol, 0.1 equiv), DCE (c = 0.1 M), 3 Å M.S. (10.0 mg), 0 °C. [b] Reaction was performed at −10 °C. [c] With 0.15 equiv of **8**. [d] With 0.2 equiv of **8**. [e] With 0.3 equiv of **8**. [f] With 0.4 equiv of **8**.

n). With regard to the isonitrile, tertiary, secondary, and primary alkyl isonitriles, including α-isocyanoacetate, were all tolerated to afford the corresponding isoindolinones (**4o–s**). The absolute configuration of **4j** was determined by X-ray crystallographic analysis[21] and that of other isoindolinones was assigned accordingly since all these compounds have very similar CD spectra.

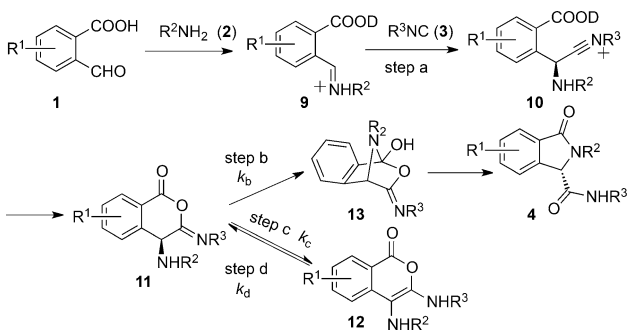
With the aforementioned results in hand, the development of a catalytic enantioselective Ugi four-center three-component reaction of **1**, **2**, and **3** was straightforward. As illustrated in Scheme 3, yields of the three-component



Scheme 3. Enantioselective four-center three-component reaction. [a] **1** (0.1 mmol), **2** (0.1 mmol), **3** (0.12 mmol), **8** (0.03 mol, 0.3 equiv), DCE ($c = 0.1$ M), 3 Å MS (5.0 mg), 0 °C. [b] With 0.4 equiv of **8**.

reaction were generally excellent considering that four chemical bonds were generated in this operationally simple process. The enantioselectivity was slightly decreased and a higher catalyst loading was needed relative to the two-component version. To the best of our knowledge, this represents the first example of an enantioselective Ugi reaction in which a carboxylic acid was incorporated as one of the participating functional groups.[22]

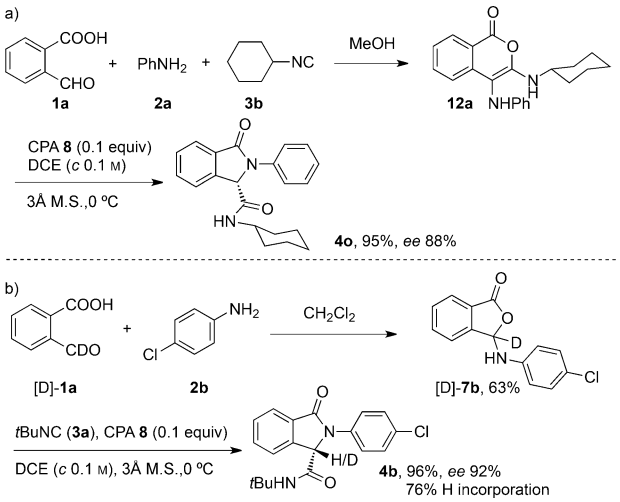
Possible reaction pathways accounting for the formation of **4** from **1**, **2**, and **3** are depicted in Scheme 4. Condensation of **1** with **2** affords the iminium salt **9**. Intermolecular nucleophilic addition of the divalent carbon atom of **3** to **9** can provide the nitrilium **10** (step a, Scheme 4), which can be trapped by the tethered carboxylate to provide **11**. Mumm rearrangement of **11** via the bridged intermediate **13** can furnish the isoindolinone **4**. However, **11** is known to undergo facile isomerization to the isocoumarine **12** by prototropic tautomerization.[23] While this equilibrium is transparent in a racemic process, it would have an important consequence in our catalytic enantioselective version. In light of the observed enantioselectivity, two scenarios could be advanced: a) the Mumm rearrangement (step b) is much faster than the imine–enamine isomerization (step c/d; $k_b \gg k_c$, k_d). In this case, the C–C bond-forming step (step a) leading to **10** would determine the absolute configuration of the final adduct; b) imine–enamine isomerization (step c/d) is much faster than the Mumm rearrangement (step b; k_c, $k_d \gg k_b$). In this case, the DKR of **12** would be responsible for the observed enantioselectivity.



Scheme 4. Possible reaction pathway. The role of CPA in these steps was not illustrated for the sake of clarity.

To gain insight on the reaction mechanism, control experiments were performed (Scheme 5). Submitting the isocoumarine **12a**, prepared following literature procedure,[23a] to our standard reaction conditions afforded the isoindolinone **4o** (Scheme 5a) in 95% yield with 88% *ee*, and is a perfect match with the result of the direct CPA **8**-catalyzed condensation between **3b** and **7a**. Reaction of the C3-deuterated isobenzofuranone [D]-**7b**, synthesized by condensation between 2-(formyl-D)benzoic acid ([D]-**1a**)[24] and 4-chloroaniline (**2b**), with *t*BuNC (**3a**) under our standard reaction conditions afforded **4b** with 76% loss of deuterium. Once again, the *ee* value of **4b** (92%; Scheme 5b) matched that obtained from the reaction of **7b** and **3a**. The results of these two control experiments clearly indicate that the imine–enamine equilibrium occurs (Scheme 4, steps c, d) and that the overall transformation involves a DKR of **12** which is formed in situ. This mechanistic interpretation is also in accord with our experimental observation that electron-rich aniline, hence increased rate of Mumm rearrangement of **11** (step b, Scheme 4), afforded product in low enantioselectivity (see **4g**, Scheme 2). That the deuterium is not completely exchanged is understandable and may reflect the kinetic isotopic effect in the prototropic tautomerization step.

In summary, we have developed a novel chiral phosphoric acid catalyzed enantioselective reaction between isonitriles (**3**) and 3-(arylamino)isobenzofuran-1(3*H*)-ones (**7**) to afford



Scheme 5. Control experiments.

3-oxo-2-arylisoindoline-1-carboxamides (**4**) in high yields with good to high enantioselectivities. A catalytic enantioselective Ugi reaction of 2-formylbenzoic acids (**1**), anilines (**2**), and isonitriles (**3**) was subsequently developed for the first time and lead to the same heterocycles **4**. Mechanistic studies indicate that the observed enantioselectivity results from a DKR of the primary Ugi adduct rather than from the C–C bond-forming process. While a great number of DKRs have been developed dealing with specific substrates,[25] DKR of a reaction intermediate as a means to achieving enantioselectivity remains an underexploited field.[26]

Acknowledgments

Financial supports from National Natural Science Foundation of China (21320102002, 21502202) and the EPFL (Switzerland) are gratefully acknowledged.

Keywords: asymmetric synthesis · kinetic resolution · multicomponent reaction · organocatalysis · reaction mechanisms

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 5282–5285
Angew. Chem. **2016**, *128*, 5368–5371

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Received: January 22, 2016
Published online: March 21, 2016

