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Organocatalytic Enantioselective One-Pot Four-Component Ugi-Type Multicomponent Reaction for the Synthesis of Epoxy-tetrahydropyrrolo[3,4-*b*]pyridin-5-ones

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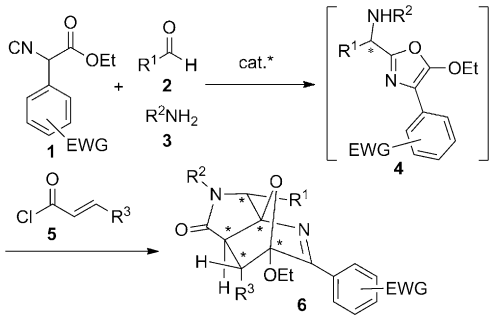
The development of catalytic asymmetric reactions has been one of the major research activities for the past twenty-five years and nowadays remains a mainstream chemical technology. While many uni- or bimolecular reactions can currently be performed under catalytic conditions to provide products in high yields with excellent enantioselectivities,[1] the development of asymmetric multicomponent reactions (MCRs) is still in its infancy.[2] In this context, the development of asymmetric isocyanide-based MCRs is known to be particularly challenging. While intensive efforts have led to the development of a catalytic asymmetric Passerini-type reaction[3] for the synthesis of α-acetoxy (α-hydroxy) amides[4] and enantiomerically enriched chiral nonracemic heterocycles,[5] enantioselective Ugi-4CR remains unknown.[6]

Recently, we demonstrated that isocyanoacetates[7] bearing an additional electron-withdrawing group at the α position (**1**) display a different reactivity profile relative to the parent one[8] and developed a three-component synthesis of 5-alkoxyoxazoles (**4**) by its reaction with aldehydes **2** and amines **3**.[9] As a continuation of our work[10] on organocatalytic enantioselective MCRs,[11] we report herein a Brønsted acid[12] catalyzed enantioselective Ugi-type three-component synthesis of **4** and the one-pot four-component synthesis of epoxy-tetrahydropyrrolo[3,4-*b*]pyridin-5-ones **6** (Scheme 1). Six chemical bonds (one C–O, two C–N, and three C–C) and five contiguous stereogenic centers including two quaternary ones were created in this four-component reaction with good to excellent diastereoselectivity and enantioselectivity.



Scheme 1. Enantioselective one-pot four-component synthesis of epoxy-tetrahydropyrrolo[3,4-*b*]pyridin-5-ones.

Reasoning that the absolute configuration of 2-(1-aminoalkyl)-5-alkoxyoxazoles **4** will dictate those of the remaining stereogenic centers in **6**, we initiated our studies on the chiral phosphoric acid-catalyzed enantioselective synthesis of **4** using ethyl α-(*p*-nitrophenyl)-α-isocyanoacetate (**1a**), pivalaldehyde (**2a**), and aniline (**3a**) as test substrates. As summarized in Table 1, the optimum conditions consisted of performing the three-component reaction at −35 °C in CH_2Cl_2 (*c* 0.25 M) in the presence of a bulky chiral phosphoric acid (*R*)-TRIP (**7g**, 0.1 equiv; see Figure 1). Under these conditions, **4a** was isolated in 83% yield with 87% *ee* (Table 1, entry 10).

The scope of the reaction was examined next (Table 2). Anilines bearing electron-donating (Me, OMe) or electron-

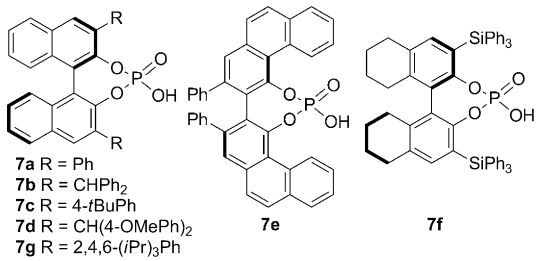


Figure 1. Structure of phosphoric acids used for catalyzing the reaction of **1a**, **2a**, and **3a**.

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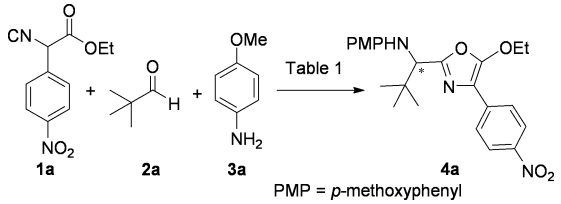
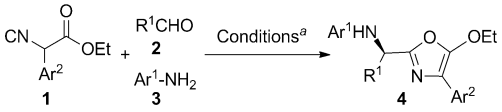
Table 1. Optimization of the three-component reaction.[a]



Entry	Cat (equiv)	Solvent	T [°C]	Yield [%][b]	*ee* [%][c]
1	**7a** (0.2)	toluene	−78	61	0
2	**7b** (0.05)	toluene	−78	53	18
3	**7c** (0.05)	toluene	−78	49	0
4	**7d** (0.05)	toluene	−78	47	12
5	**7e** (0.1)	toluene	−78	53	6
6	**7f** (0.1)	toluene	−78	57	6
7	**7g** (0.1)	toluene	−78	21	31
8	**7g** (0.1)	toluene	−30	72	60
9[d]	**7g** (0.1)	toluene	−30	81	76
10[d]	**7g** (0.1)	CH_2Cl_2	−35	83	87

[a] Reaction conditions: **1a**/**2a**/**3a** = 1.0/1.1/1.1; c = 0.10 M; aldehyde **2a** and aniline **3a** were stirred at room temperature for 1 h followed by addition of phosphoric acid **7** and isocyanoacetate **1a** at −78 °C. Stirring was continued for 24 h at given temperature. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] c = 0.25 M.

Table 2. Scope of the three-component synthesis of **4**.[a]



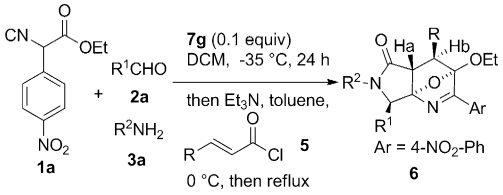
Entry	R^1	Ar^1	Ar^2	**4**	Yield [%][b]	*ee* [%][c]
1	*t*Bu	4-Me-C_6H_4	4-NO_2-C_6H_4	**4b**	78	87
2[d]	*t*Bu	C_6H_5	4-NO_2-C_6H_4	**4c**	76	92
3[d]	*t*Bu	4-F-C_6H_4	4-NO_2-C_6H_4	**4d**	80	93
4[d]	*t*Bu	4-Cl-C_6H_4	4-NO_2-C_6H_4	**4e**	76	92
5[d]	*t*Bu	4-Br-C_6H_4	4-NO_2-C_6H_4	**4f**	84	91
6[d]	*t*Bu	3-OMe-C_6H_4	4-NO_2-C_6H_4	**4g**	94	92
7[d]	*t*Bu	3-Me-C_6H_4	4-NO_2-C_6H_4	**4h**	93	92
8[d]	*t*Bu	3-Cl-C_6H_4	4-NO_2-C_6H_4	**4i**	65	92
9	*t*Bu	3,4-$(Me)_2$-C_6H_3	4-NO_2-C_6H_4	**4j**	95	89
10[d]	*t*Bu	3,5-$(Me)_2$-C_6H_3	4-NO_2-C_6H_4	**4k**	95	90
11[d]	*t*Bu	3-Br-4-OMe-C_6H_3	4-NO_2-C_6H_4	**4l**	87	92
12	*c*hex	C_6H_5	4-NO_2-C_6H_4	**4m**	83	84
13	*c*hex	4-F-C_6H_4	4-NO_2-C_6H_4	**4n**	80	84
14	*t*Bu	C_6H_5	4-CN-C_6H_4	**4o**	77	94

[a] Reaction conditions: **1**/**2**/**3** = 1.0/1.1/1.1; c = 0.25 M in dichloromethane; aldehyde **2** and aniline **3** were stirred at room temperature for 1 h followed by addition of phosphoric acid **7g** and isocyanoacetate **1** at −78 °C. Stirring was continued for 5 min at −78 °C, then 24 h at −35 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction time: 48 h.

withdrawing groups (F, Cl, Br) in both *meta*- and *para*-position underwent the reaction smoothly to afford the three-component adduct **4** in high yields with excellent *ee* values. Cyclohexanecarboxaldehyde behaved well in this reaction (Table 2, entries 12 and 13), but linear aldehydes afforded adducts with lower *ee* values. Finally, ethyl α-(*p*-cyanophenyl)-α-isocyanoacetate (**1b**) participated equally well in this reaction to afford **4o** in good yield and excellent *ee* (Table 2, entry 14). The (*R*)-absolute configuration of oxazole **4** was assigned based on X-ray crystallographic analysis of compound **4f**[17] bearing a bromine atom (see the Supporting Information for details).

With the conditions for the enantioselective synthesis of 5-alkoxyoxazoles in hand, we next turned our attention to a one-pot four-component synthesis of epoxytetrahydropyrrolo[3,4-*b*]pyridin-5-ones **6**. Eventually, stirring a CH_2Cl_2 solution of **1a**, **2a**, and **3a** in the presence of chiral phosphoric acid **7g** at −35 °C for 24 h followed by addition of cinnamoyl chloride **5a** (R = Ph) and refluxing the resulting solution for 5 h afforded adduct **6a** as a single detectable diastereomer in 94% yield with 89% *ee* (Table 3, entry 1).

Table 3. Enantioselective four-component synthesis of epoxytetrahydropyrrolo[3,4-*b*]pyridin-5-ones.



Entry	R^1	R^2	R	**6**, Yield [%][a]	*ee* [%][b]
1	4-MeO-Ph	*t*Bu	Ph	**6a**, 94	89
2	4-MeO-Ph	*t*Bu	COOEt	**6b**, 76	91
3	4-Me-Ph	*t*Bu	Ph	**6c**, 76	87
4	4-Me-Ph	*t*Bu	COOEt	**6d**, 81	86
5	Ph	*t*Bu	Ph	**6e**, 81	94
6	Ph	*t*Bu	COOEt	**6f**, 75	92
7	4-F-Ph	*t*Bu	Ph	**6g**, 59	94
8	4-F-Ph	*t*Bu	COOEt	**6h**, 41	93
9	3-Br-4-MeO-Ph	*t*Bu	Ph	**6i**, 69	94
10	3-Br-4-MeO-Ph	*t*Bu	COOEt	**6j**, 35	93
11	Ph	*c*hex	Ph	**6k**, 84	94[c]
12	Ph	*c*hex	COOEt	**6l**, 81	81[d]
13	4-F-Ph	*c*hex	Ph	**6m**, 80	84[e]
14	4-F-Ph	*c*hex	COOEt	**6n**, 87	84[c]

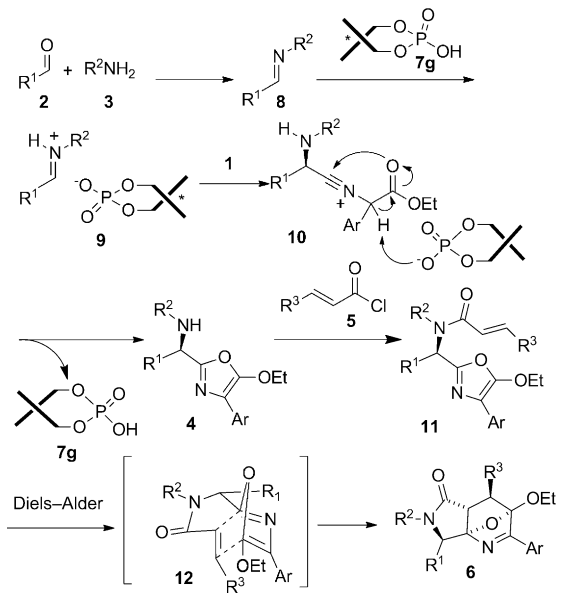
[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase. [c] d.r. = 9/1. [d] d.r. = 6/1. [e] d.r. = 12/1.

Similarly, using 3-chlorocarbonylacrylic acid ethyl ester **5b** (R = COOEt) as the fourth component, compound **6b** was isolated in 76% yield with 91% *ee* (Table 3, entry 2). A sequence involving oxazole formation followed by intermolecular acylation of the resulting secondary amine and intramolecular hetero Diels–Alder reaction could account for the formation of the observed product.[13] Interestingly, in this one-pot four-component reaction, five stereogenic centers were created and 16 pairs of enantiomers can be expected theoretically. However, only one stereoisomer was obtained in excellent yield and enantiomeric excess. The relative stereochemistry of **6b** was confirmed by its X-ray crystallographic analysis[17] (see the Supporting Information). The coupling constant between H_a and H_b (J_{Ha-Hb} = 4.0 Hz) indicated a *gauche* relationship between these two protons, in

accordance with the X-ray structure determined. Since the oxazole intermediate is *R*-configured, the absolute configuration of **6** was therefore determined as shown in Table 3.

The scope of this novel four-component reaction is shown in Table 3. Excellent yields and enantiomeric excesses are obtained for most of the oxa-bridged tricyclic adducts. The diastereoselectivity was slightly reduced when cyclohexanecarboxaldehyde was used and the formation of a minor diastereomer was detected (**6k**–**6n**). However, the major product shown in Table 3 has the same relative stereochemistry as proven by X-ray structure analysis of compound **6b** and **6k**[17] (see the Supporting Information) as well as the characteristic J_{Ha-Hb} (4.0 Hz) throughout these examples. When electron-poor anilines were used, the acylation reaction was less effective leading to the low conversion of the oxazole intermediate. However, this can be remedied by filtration of the catalyst after the initial oxazole formation followed by addition of a solution of acyl chloride **5** in toluene.

A possible reaction sequence leading to the enantioselective formation of heterocycles **6** is shown in Scheme 2. Condensation of aldehydes **2** and amines **3** led to imines **8**,



Scheme 2. Proposed mechanism for the formation of epoxy-tetrahydropyrrolo[3,4-*b*]pyridin-5-ones.

which would be protonated by the chiral Brønsted acid **7g** to form an ion pair **9**.[14] Nucleophilic attack of the divalent carbon atom of isonitrile to the *si*-face of iminium would afford the nitrilium intermediates **10**. Deprotonation of the α-proton by phosphate followed by the attack of the resulting enolate oxygen atom at the nitrilium carbon atom would afford oxazole **4** with the concurrent regeneration of the catalyst **7g**. Following addition of acyl chloride **5** and triethylamine, acylation of the secondary amine would take place to produce **11**, which would undergo intramolecular Kondrat′eva type Diels–Alder reaction to afford epoxy-tetrahydropyrrolo[3,4-*b*]pyridin-5-ones **6**.[15] From the stereochemical outcome that we observed, it was assumed that the cycloaddition went through a concerted amide-*exo*/R^3-*endo* mode and that the bulky R^1 group adopted a pseudo-equatorial position to avoid the steric interference with both oxygen and the *N*-R^2 group.

In summary, we developed an organocatalytic enantioselective three-component synthesis of 5-alkoxyoxazoles **4** and the four-component synthesis of epoxy-tetrahydropyrrolo[3,4-*b*]pyridin-5-ones **6**. These MCRs are highly efficient leading to products in high yields with high *ee* values. While the use of α-isocyanoacetate in enantioselective transformation has attracted much attention recently, all these reported catalytic asymmetric reactions are initiated by the nucleophilic addition of its α-carbanion to the polarized C=C and C=X bonds leading to formal [3+2] cycloadducts.[16] To the best of our knowledge, the present work represents the first examples of the enantioselective transformation of α-isocyanoacetates wherein the stereogenic center was generated by the nucleophilic addition of the divalent isocyanide carbon atom to the electrophiles (imines). Together with our previous report on the α-isocyano acetamides,[6b,13] we expect further development of this approach for the synthesis of complex enantioenriched polyheterocycles, which are among the most medicinally relevant compounds.

Experimental Section

Four-component synthesis of epoxy-tetrahydropyrrolo[3,4-*b*] pyridin-5-ones: To a flame-dried round-bottom flask equipped with a stir bar were added aniline (0.05 mmol), aldehyde (1.1 equiv), and dry CH_2Cl_2 (0.1 mL). The solution was stirred at room temperature for 1 h. The phosphoric acid (0.1 equiv) was then introduced and the resulting mixture was cooled to −78 °C. A solution of ethyl α-isocyanoacetate (1.1 equiv) in CH_2Cl_2 (0.1 mL) was injected slowly by using a syringe pump (addition time 5 min), and the resulting reaction mixture was stirred at −35 °C for 24 h. Then, the reaction mixture was cooled to 0 °C and was diluted with toluene (1.0 mL). Et_3N (6.0 equiv) was added followed by acyl chloride (2.5 equiv). The reaction mixture was then heated to reflux until the complete consumption of the intermediate amide. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (heptane/EtOAc = 6/1) to afford the desired product.

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Keywords: brønsted acid · multicomponent reactions · organocatalysis · Ugi reaction · α-isocyanoacetate

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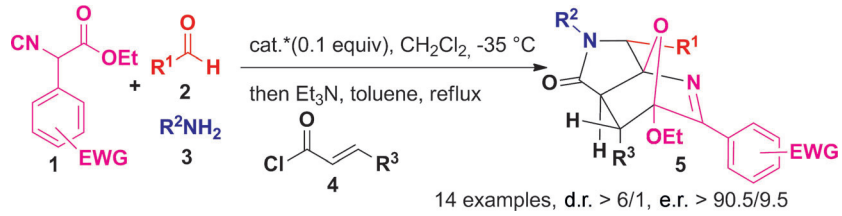

Enantioselective multicomponent reaction: In the presence of a catalytic amount of chiral BINOL-derived phosphoric acid (TRIP), reaction of an α-isocyanoacetate (**1**), an aldehyde (**2**), and an aniline (**3**), followed by addition of a toluene solution of α,β-unsaturated acyl chloride **4** afforded the oxa-bridged tricycle **5** in excellent yield, diastereoselectivity, and enantioselectivity. Six chemical bonds, five stereogenic centers, and three cycles were formed in this one pot four-component reaction.

Multicomponent Reactions

Y. Su, M. J. Bouma, L. Alcaraz, M. Stocks, M. Furber, G. Masson, J. Zhu** ..... ▮▮▮▮–▮▮▮▮

Organocatalytic Enantioselective One-Pot Four-Component Ugi-Type Multicomponent Reaction for the Synthesis of Epoxy-tetrahydropyrrolo[3,4-*b*]pyridin-5-ones