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Catalytic Asymmetric Synthesis of Trifluoromethylated γ -Amino Acids via Umpolung Addition of Trifluoromethyl Imines to Carboxylic Acid Derivatives

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Abstract

Enabled by the discovery of novel cinchona alkaloid-derived chiral phase-transfer catalysts, highly chemo-, regio-, diastereo- and enantioselective umpolung additions of trifluoromethyl imines to α , β -unsaturated *N*-acylpyrroles were realized. With a catalyst loading ranging from 0.2 to 5.0 mol%, this new catalytic asymmetric transformation provides facile and high-yield access to highly enantiomerically enriched chiral trifluoromethylated γ -amino acids and γ -lactams.

Graphical Abstract

Enabled by the discovery of novel cinchona alkaloid-derived chiral phase-transfer catalysts, highly chemo-, regio-, diastereo- and enantioselective umpolung additions of trifluoromethyl imines to α , β -unsaturated *N*-acylpyrroles were realized. This new catalytic asymmetric transformation provides facile and high-yield access to highly enantiomerically enriched chiral trifluoromethylated γ -amino acids and γ -lactams.

Keywords

Amino acids; Asymmetric catalysis; C-C forming; Phase-transfer catalyst; Umpolung

Chiral γ -amino acids as a structural motif are presented in a wide variety of natural products and synthetic compounds of biological interests and pharmaceutical importance.^[1–2]

Accordingly, the development of new catalytic methodology for the efficient asymmetric synthesis of γ -amino acid derivatives continues to attract great attention.^[3] Recently, γ -

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trifluoromethylated γ -amino acid motifs began to appear in pharmaceutically significant compounds (Figure 1).^[4] On the other hand, a general enantioselective access toward these chiral building blocks is not yet available. Herein, we wish to report the discovery and development of new catalysts to enable an unprecedented asymmetric umpolung addition of trifluoromethyl imines to α , β -unsaturated *N*-acylpyrroles, thereby establishing a general synthetic strategy for the asymmetric synthesis of trifluoromethylated γ -amino acid derivatives.

While numerous approaches towards α/β -substituted γ -amino acids have been successfully established,^[5–7] the catalytic asymmetric generation of γ -substituted γ -amino acids from achiral starting materials remains underdeveloped. One approach focuses on the development of enantioselective C–N bond forming γ -aminations of carbonyl derivatives with nitrogen-based electrophilic or nucleophilic reagents. Ye and coworkers^[8] reported the use of a cinchona alkaloid-derived chiral nucleophilic catalyst to mediate a highly enantioselective γ -amination of α , β -unsaturated acyl chlorides with azodicarboxylates, after which the products were transformed into enantiomerically enriched γ -substituted γ -amino acids (Scheme 1a). By exploring phosphine nucleophilic catalysis, Fu and coworkers^[9] developed a chiral phosphine catalyst to realize an efficient enantioselective γ -amination of allenates with 2,2,2-trifluoroacetamide to generate optically active α , β -unsaturated γ -amino esters (Scheme 1a). Jacobsen and coworkers^[10] designed a chiral phosphinothiourea bifunctional catalyst for the asymmetric γ -amination of allenyl esters with *N*-methoxy carbamates (Scheme 1a). Chiral metal complex-catalyzed asymmetric allylic aminations of γ , δ or δ , ϵ -unsaturated esters constitute another enantioselective C–N bond forming approach for the generation of γ -amino acid derivatives. Helmchen and coworkers^[11] reported an iridium-catalyzed highly enantioselective allylic amination of allylic carbonates with diacylamides (Scheme 1b). By employing the imido-sulfur compounds as the nitrogen source, Tambar and coworkers^[12] established a palladium-catalyzed highly enantioselective allylic functionalization of methyl hexenoate via an ene reaction/[2,3]-rearrangement (Scheme 1b). More recently, Hartwig and coworkers^[13] disclosed a one-pot sequence of palladium catalyzed allylic C–H bond oxidation followed by the enantioselective iridium-catalyzed allylic amination of methyl hexenoate with phthalimide to form optically active γ -vinyl γ -amino acids (Scheme 1b).

The catalytic activation of imines as 2-azaallylanions for asymmetric C–C bond forming reactions has recently emerged as a new strategy for the design and development of efficient asymmetric access to chiral amines.^[14–15] These latest advances in asymmetric catalysis pointed to the development of nucleophilic addition of imines to α , β -unsaturated carboxylic acid derivatives as a conceptually distinct C–C bond forming strategy for the direct generation of optically active γ -substituted γ -amino acids. With this strategy direct enantioselective synthesis of chiral γ -amino acids not yet accessible by existing enantioselective C–N bond forming methods, such as γ , γ -disubstituted and β , γ -disubstituted γ -amino acids, is possible. Zhang and coworkers^[16] reported the development of a phosphine nucleophilic catalyst for the activation of a Morita-Baylis-Hillman carbonate for the nucleophilic addition of trifluoromethyl imines to generate enantiomerically enriched α -methylene γ -trifluoromethylated γ -amino acids (Scheme 1c).

Our group recently discovered that cinchonium salts bearing an *N*-terphenyl substituent such as **C-1a** could efficiently activate imines for asymmetric nucleophilic additions to enals and enones.^[17] Thus, we commenced our studies with an investigation of **C-1a** as a catalyst for the model reaction of methyl trifluoromethyl imine **1A** and α , β -unsaturated *N*-acylpyrrole **3a**. However, this attempt to extend the application of catalyst **C-1a** proved to be unsuccessful. Specifically, the model reaction with 1.0 mol% of **C-1a** was found to proceed with virtually no enantioselectivity and poor regioselectivity, affording the desirable adduct **4Aa** in only 5% ee and the undesirable regioisomer **5Aa** as a significant side product, although no isomerization product **6A** (< 1%) was detected (Table 1, entry 1). We next examined two additional *N*-terphenyl catalysts **C-1b** and **C-1c**, and found that the latter, with a sterically less bulky electron-donating substituent, afforded a significantly improved regioselectivity albeit little enhancement in enantioselectivity (**4Aa/5Aa** = 89/11, Table 1, entry 3 vs 1).

These initial results, though disappointing from the view point of developing an efficient catalyst, led us to formulate the working hypothesis that a further decrease of the steric bulk of the *N*-substituent might provide a catalyst to afford further improved regioselectivity. To test this working hypothesis, catalyst **C-2** bearing *N*-benzyl as a substituent was applied to our model reaction. To our delight, the **C-2** mediated reaction proceeded with essentially perfect regioselectivity although in virtually no enantioselectivity (Table 1, entry 4). Although we were not able to address the issue of enantioselectivity at this point, this result directed us to a new focus in catalyst development; namely focusing on extending the spatial reach of the pi-moiety in the *N*-substituent without drastically increasing its steric bulk.

Following this consideration, we prepared and examined catalysts **C-3** and **C-4**, respectively. While the reaction with **C-3** proceeded in essentially the same fashion as that mediated by **C-2** (Table 1, entry 5), a dramatic leap in enantioselectivity was observed from the reaction mediated by catalyst **C-4** (Table 1, entry 6). Importantly, **C-4** afforded this improved enantioselectivity without compromising the perfect regioselectivity. We next tested **QD-4**, the quinidium analogue of **C-4**, and found it to afford even higher enantioselectivity (Table 1, entry 7). Subsequent optimization studies identified the mixed solvent of toluene/chloroform (4/1) to be the optimal solvent (Table 1, entry 8). Lygo and Maruoka previously demonstrated that the additions of phenol derivatives could significantly improve the reaction conversion and yield of phase transfer catalyst-mediated C-C bond forming reactions.^[18] We also found the addition of 10 mol% mesitol resulted in a significantly accelerated reaction rate and slightly improved stereoselectivity, allowing a complete reaction to occur with perfect regioselectivity and high enantioselectivity in only 15 minutes with 1.0 mol% **QD-4** (Table 1, entry 9). Notably, the reaction also went to completion in 10 hours with only 0.2 mol% catalyst without deterioration in either regioselectivity or enantioselectivity (Table 1, entry 10).

Under the optimized conditions, we investigated the substrate scope of this new reaction. As summarized in Table 2, the trifluoromethyl imines bearing simple and functionalized linear aliphatic alkyl groups (**1A-1D**) reacted with **3a** in not only high enantioselectivity but also perfect chemo- and regioselectivity to furnish the desired products **4Aa-4Da** in 93–96% yields and 91–93% ee (Table 2, entries 1–4). Similarly, excellent enantioselectivities and

high yields were obtained from reactions with α , β and γ -branched alkyl groups (entries 5–8). Such highly efficient catalytic control could also be extended to the reaction with an alkenyl substituted trifluoromethyl imine **1I** (entry 9). Trifluoromethyl aldimine **1J** was shown to be a more active substrate, allowing a complete reaction in one hour with only 0.5 mol% **QD-4**. However, this reaction occurred in a decreased enantioselectivity (entry 10).

A variety of aryl substituted trifluoromethyl imines were also examined. These imines, in comparison to aliphatic trifluoromethyl imines, appeared to be more challenging substrates. In particular, the reactions with imines bearing electron-deficient aryl groups proceeded in compromised chemoselectivity and regioselectivity. Importantly, these side reactions could be efficiently suppressed in the presence of an increased amount of mesitol (1.0–2.0 equiv.). Consequently, reactions with trifluoromethyl imines with para-substituted phenyls of varying electronic properties proceeded in useful yield and high enantioselectivity (Table 2, **1L-1Q**, entries 12–17). Moving the substituent from the para- to the meta-position appeared to have little influence on the reaction outcome (entries 18–19). The presence of a more extended aromatic group such as naphthyl was readily tolerated by the catalyst (entry 20).

We next focused our attention to expand the scope of the electrophiles to β -substituted α , β -unsaturated *N*-acylpyrroles **3a-d**. The β -methyl- α , β -unsaturated *N*-acylpyrrole **3b** turned out to be completely inactive in an attempted reaction with imine **1A** in the presence of **QD-4** (Table 3, entry 1). By incorporating an electron-withdrawing cyano group on *N*-acylpyrrole moiety, the β -alkyl and β -aryl α , β -unsaturated *N*-acylpyrroles such as **3c** and **3d** became suitably active electrophiles. As summarized in Table 3, the additions of trifluoromethyl imines **1A**, **1B** and **1J** to **3c-d** proceeded in useful chemo-, regio-, diastereo-, and enantioselectivity (entries 2–5). To our knowledge, these results represent the first examples of highly diastereoselective and enantioselective formations of β , γ -disubstituted γ -amino acid derivatives from achiral precursors. Interestingly, we found that TBAB could also catalyze a racemic reaction of trifluoromethyl imine **1A** and **3c**, producing **4Ac** in high diastereoselectivity (> 95/5) but moderate regioselectivity (**4Ac/5Ac** = 70/30).^[19]

We carried out a gram-scale reaction of **1A** with **3a** (Scheme 2). With only 0.2 mol% of **QD-4** the reaction went to completion in 24 hours to afford the desired product **4Aa** in 92% yield and 91% ee. In addition, the straightforward and high-yield respective conversions of **4Aa** and **4Ka** to γ -amino ester **8Aa** and γ -lactam **9Ka** illustrated the utility of **4** as versatile chiral building blocks. The absolute configuration of **9Ka** was further established by the X-ray crystallographic analysis.^[20]

To provide experimental data to support our hypothesis that the quinidium unit of **QD-4** interacted with 2-azaallylanion **2** via a pi-pi interaction between the anthracene and the 4-nitrophenyl groups, we prepared ion-pair complex **I** by replacing the bromide anion in **QD-4** with 4-nitrophenoxide (Figure 2). The 4-nitrophenoxide was selected to mimic the unstable 2-azaallylanion **2** in that both contain a 4-nitrophenyl group in conjugation with an anionic moiety. We were able to determine the structure of ion-pair complex **I** by X-ray crystallographic analysis.^[21] Significantly, a face-to-face pi-stacking interaction between the anthracene ring and the 4-nitrophenoxide was observed. Our structural studies were inspired by the X-ray crystallographic structural determination of an *N*-(9-methylanthracene)

cinchonidumphenoxy complex. Interestingly, no π -stacking interaction was observed in that complex.^[22] These experimental results suggested that a π - π interaction between the anthracene ring in QD-4 and 2-azaallyanion **2** is feasible, which was a key hypothesis in our catalyst development studies.

In conclusion, we have developed a new chiral phase-transfer catalyst to realize an unprecedented asymmetric umpolung reaction of trifluoromethyl imines with α , β -unsaturated *N*-acylpyrroles. This catalyst addressed the issues of inadequate regioselectivity and poor enantioselectivity encountered by existing catalysts. By complementing existing methods toward optically active γ -amino acids derivatives and γ -lactams, this new asymmetric imine umpolung reaction should be valuable for asymmetric synthesis of chiral amino compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Biologically active and medically important trifluoromethylated γ -amino acids.

Figure 2.

Single crystal X-ray structure of ion-pair complex **I**. The phenyl ring of 4-nitrophenoxide is highlighted. The protons and solvent molecules have been hid for clarity (C: grey, O: red, N: blue, Cl: green).

(a) γ -Amination of carbonyl derivatives with nitrogen-based reagents

(b) Chiral metal complex-catalyzed allylic aminations

(c) Phoshyne-catalyzed addition of trifluoromethyl imines to Morita-Baylis-Hillman Carbonate

(d) Present work: Catalytic umpolung addition of trifluoromethyl imines to α , β -unsaturated *N*-acylpyrroles **Scheme 1.**Catalytic asymmetric approaches to γ -substituted γ -amino acid derivatives

Scheme 2.
Gram-scale reactions and synthetic applications

Table 1.

Development of phase transfer catalysts.^[a]

entry	cat. (x mol%)	time (h); conv.(%) ^[b]	4Aa/5Aa ^[b]	ee of 4Aa (%) ^[c]
1	C-1a (1.0)	1; 100	73/27	−5
2	C-1b (1.0)	1; 100	80/20	5
3	C-1c (1.0)	1; 100	89/11	9
4	C-2 (1.0)	1; 100	>99/1	2
5	C-3 (1.0)	1; 100	>99/1	0
6	C-4 (1.0)	1; 100	>99/1	85
7	QD-4 (1.0)	1; 100	>99/1	89
8 ^[d]	QD-4 (1.0)	1; 100	>99/1	90
9 ^[d,e]	QD-4 (1.0)	1/4; 100	>99/1	93
10 ^[d,e]	QD-4 (0.2)	10; 98	>99/1	91

^[a] Unless noted, reactions were performed with **1A** (0.025 mmol), **3a** (0.05 mmol), aqueous KOH (0.22 μ L, 50 wt%, 10 mol%) in PhMe (0.25 mL) with catalyst (x mol%).

^[b] Determined by ¹⁹F NMR analysis.

^[c] Determined by HPLC analysis.

^[d] PhMe/CHCl₃ (4/1) was used as solvent.

^[e] 10 mol% mesitol was added.

Table 2.

Substrate scope of trifluoromethyl imines with α , β -unsaturated *N*-acylpyrrole **3a**.^[a]

entry	R ¹	cat. (x mol%)	mesitol (y mol%)	T (°C)	4/5; 4/6 ^[b]	Yield of 4 (%) ^[c]	ee of 4 (%) ^[d]
1	Me; 1A	1.0	10	−20	>99/1; >99/1	96 (4Aa)	93
2	Et; 1B	2.0	10	−20	>99/1; >99/1	95 (4Ba)	92
3	n-Bu; 1C	2.0	10	−20	>99/1; >99/1	94 (4Ca)	92
4	CH ₂ =CH(CH ₂) ₃ ; 1D	2.0	10	−20	>99/1; >99/1	93 (4Da)	91
5	Cy; 1E	5.0	10	−20	>99/1; >99/1	90 (4Ea)	92
6	CyCH ₂ ; 1F	5.0	10	−20	>99/1; >99/1	90 (4Fa)	94
7	Bn; 1G	2.0	10	−20	>99/1; >99/1	93 (4Ga)	92
8	PhCH ₂ CH ₂ ; 1H	2.0	10	−20	>99/1; >99/1	94 (4Ha)	90
9	PhCH=CH ₂ ; 1I	2.0	200	−50	>99/1; >99/1	93 (4Ia)	95
10	H; 1J	0.5	10	−20	>99/1; >99/1	90 (4Ja)	76
11	Ph; 1K	3.0	100	−20	99/1; 96/4	80 (4Ka)	93
12	<i>p</i> -FC ₆ H ₄ ; 1L	5.0	200	−30	99/1; 96/4	77 (4La)	93
13	<i>p</i> -ClC ₆ H ₄ ; 1M	5.0	200	−40	99/1; 97/3	75 (4Ma)	93
14	<i>p</i> -BrC ₆ H ₄ ; 1N	5.0	200	−40	99/1; 97/3	70 (4Na)	93
15	<i>p</i> -CF ₃ C ₆ H ₄ ; 1O	5.0	200	−40	98/2; 95/5	78 (4Oa)	91
16	<i>p</i> -MeOC ₆ H ₄ ; 1P	5.0	100	−20	98/2; 94/6	79 (4Pa)	92
17	<i>p</i> -MeC ₆ H ₄ ; 1Q	5.0	100	−20	98/2; 97/3	77 (4Qa)	94
18	<i>m</i> -MeOC ₆ H ₄ ; 1R	5.0	100	−20	98/2; 97/3	78 (4Ra)	91
19	<i>m</i> -MeC ₆ H ₄ ; 1S	5.0	100	−20	98/2; 96/4	70 (4Sa)	92
20	2-Naphthyl; 1T	5.0	200	−30	98/2; 96/4	78 (4Ta)	93

^[a] Unless noted, reactions were performed with **1** (0.2 mmol), **3a** (0.4 mmol), mesitol (y mol%) and aqueous KOH (2.2 μ L, 50 wt%, 10 mol%) in PhMe/CHCl₃ (4/1, totally 2.0 mL) with catalyst QD-4 (x mol%) at indicated temperature. For entries 9, 11–20, PhMe (2.0 mL) was used as the solvent.

^[b] Determined by ¹⁹F NMR analysis.

^[c] Isolated yield of product.

^[d] Determined by HPLC analysis.