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Facile Synthesis of Enantioenriched C^{γ}-Tetrasubstituted α-Amino Acid Derivatives via an Asymmetric Nucleophilic Addition/Protonation Cascade

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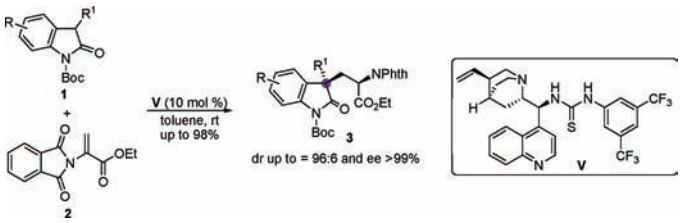
ABSTRACT



An asymmetric nucleophilic addition/protonation reaction of 3-substituted oxindoles and ethyl 2-phthalimidoacrylate has been described. This strategy can give direct access to C^{γ}-tetrasubstituted α-amino acid derivatives bearing 1,3-nonadjacent stereocenters with up to 98% yield, 94:6 dr, and >99% ee. Dual activation is proposed in the transition state, and the opposite enantiomers can be obtained simply by changing cinchonidine-derived catalyst to the cinchonine analogue.

C^{γ}-Tetrasubstituted α-amino acid derivatives are structural motifs often found in a number of natural products and medicinally important agents.[1] For instance, (+)-alantrypinone[1d,e] and (−)-serantrypinone[1c,d] have been shown to be effective insecticidal reagents against green peach aphids, while mollenine A[1f] has been proven to have cytotoxic and antibacterial activity (Figure 1). As a result, the development of methods for the catalytic asymmetric construction of C^{γ}-tetrasubstituted α-amino acids and their derivatives is of widespread interest in synthetic organic chemistry.[2] In contrast to the facile construction of C^{α}- and C^{β}-tetrasubstituted α-amino acids,[3,4] the de novo synthesis of C^{γ}-tetrasubstituted α-amino acids is much more difficult, especially the one bearing 1,3-nonadjacent stereocenters with control of absolute stereochemistry.[5] Very recently, an elegant formal [3 + 2] cycloaddition reaction of C(3)-substituted indoles with 2-amidoacrylates was developed by Reisman and co-workers representing, to our knowledge, the first successful one-step strategy to pyrroloindolines containing C^{γ}-tetrasubstituted α-amino acid motifs with excellent stereoselectivities.[6]

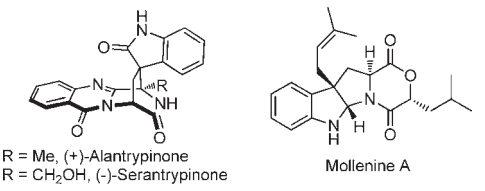


Figure 1. Examples of biologically important molecules containing C^{γ}-tetrasubstituted α-amino acid motifs.

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On the other hand, asymmetric cascades or domino reactions, which combine two or more reactions together, are highly efficient pathways that allow the synthesis of complex molecules from simple substrates.[7] Different from a stepwise strategy toward a target molecule, this process represents an advance of synthetic efficiency, operational simplicity, and atom economy. As part of our recent research program to develop new cascade methodologies,[8] we envisaged that the enantioselective nucleophilic addition/diastereoselective protonation between prochiral trisubstituted nucleophiles and α-aminoacrylates would probably be a potential method to achieve C^{γ}-tetrasubstituted α-amino acid derivatives.[9−11] However, there are two problems that possibly counteract the success of this process, including: (1) the steric hindrance for the formation of the quaternary stereocenter and (2) the difficulty in diastereoselectivity control during asymmetric protonation. Owing to the significance of C^{γ}-tetrasubstituted α-amino acid derivatives and in continuation from our recent investigation on unnatural amino acids,[12] we present herein an enantioselective nucleophilic addition/diastereoselective protonation cascade between a wide range of C(3)-substituted oxindoles[13] and ethyl 2-phthalimidoacrylate, affording C^{γ}-tetrasubstituted α-amino acid derivatives bearing 1,3-nonadjacent stereocenters in one pot. By giving high stereoselectivities (up to 94:6 dr and > 99% ee) with easily accessible thiourea as the catalyst under operationally simple conditions, the current reaction provides a complementary method to a series of unnatural amino acids with excellent structural diversity. Notably, the procedure allows the construction of the opposite enantiomers by changing the cinchonidine-derived thiourea catalyst to its cinchonine analogue.

In view of the fact that the reaction of 3-phenyloxindole **1a** and ethyl 2-phthalimidoacrylate **2** catalyzed by tetramethylguanidine (TMG) proceeded very quickly at room temperature to give the racemic compounds, our investigation started with the screening of various kinds of chiral tertiary amine catalysts. Although only trace amounts of the Michael adduct were obtained using Takemoto's catalyst or the cinchonine-derived catalyst **II** after 5 days on the basis of TLC analysis (Table 1, entries 1 and 2), the chiral multihydrogen bonding catalyst **III** could give the desired product in moderate yield with moderate stereoselectivities (Table 1, entry 3). Encouraged by these results, we surveyed the more basic cinchona-derived thioureas for this reaction.

As shown in Table 1, IV was found to be the best catalyst to give the C^{γ}-tetrasubstituted α-amino acid derivative **3a** with good stereoselectivity and yield after 10 h at room temperature (Table 1, entry 4). These results indicated that a cinchona alkaloid proved suitably basic to enolize the 3-phenyloxindole; the thiourea moiety was indispensable to activate the ethyl 2-phthalimidoacrylate. Significantly, simply by changing catalyst from cinchonidine-derived thiourea to its cinchonine analogue, the opposite enantiomer could be produced with even slightly better diastereoselectivity (Table 1, entry 5, 94:6 dr, 93% ee). Further optimization of

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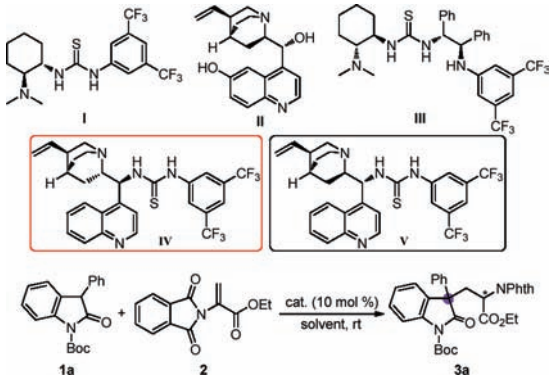
Table 1. Conditions Optimization[a]



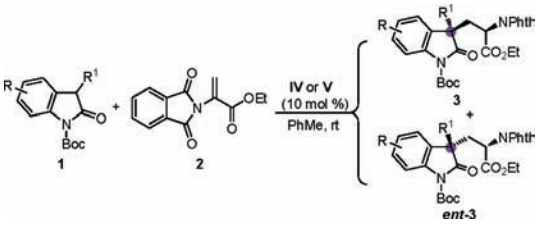
entry	cat.	solvent	time	yield[b] (%)	dr[c]	ee[c] (%)
1	**I**	PhMe	5 d	trace		
2	**II**	PhMe	5 d	trace		
3	**III**	PhMe	3 d	79	67:33	75
4	*IV*	*PhMe*	*10 h*	*93*	*91:9*	*95*
5	*V*	*PhMe*	*10 h*	*95*	*94:6*	*−93*
6	**IV**	CH_2Cl_2	3 d	63	64:36	84
7	**IV**	Et_2O	16 h	92	74:26	95
8	**IV**	xylenes	16 h	93	89:11	94
9	**IV**	DMF	24 h	94	54:46	0
10	**IV**	DMSO	10 h	99	58:42	0
11[d]	**IV**	PhMe	16 h	88	92:8	92
12[e]	**IV**	PhMe	16 h	92	85:15	97

[a] The reaction was carried out with **1a** (0.24 mmol), **2** (0.2 mmol), and cat. (0.02 mmol) in solvent (1.0 mL) at rt. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 10 equiv of H_2O was added. [e] 30 mg of 4 Å MS was added.

the reaction medium revealed that less polar solvents, such as toluene and xylenes, were superior to polar solvents which dramatically depressed the selectivity (Table 1, entries 9−10). Water had little effect on this asymmetric procedure, since using H_2O or 4 Å MS as an additive gave comparable results regarding the yields and stereoselectivities (Table 1, entries 11 and 12).

The scope of this cascade reaction was then investigated with **IV** and **V** as the catalysts under optimized conditions. As summarized in Table 2, this procedure provided a facile approach to a range of C^{γ}-tetrasubstituted α-amino acid derivatives with the generation of 1,3-nonadjacent stereocenters in high enantiomeric excess. The stereoselectivity was found to be nearly independent of the electronic properties of the oxindoles. Consistently high diastereoselectivities (89:11 to 94:6 dr) and enantioselectivities (93 to >99% ee) were observed for both the electron-rich and electron-deficient 3-aryl oxindoles. The reactions completed within 2 h for a series of oxindoles substituted with electron-withdrawing groups at the C5−C7 positions (Table 2, entries 3−16). Importantly, different aryl groups at the C3 position, including the 4-Me phenyl, 4-F phenyl, and 2-naphthyl groups, could be well tolerated, and excellent enantioselectivities (93 to >99% ee) for both enantiomers were achieved in the presence of **IV** or **V** (Table 2, entries 17−22). Notably, the 3-benzyloxindole

Table 2. Substrate Scope Examination[a]



entry	R	R^1	yield[b] (%)		dr[c]	ee[c] (%)
1	H	Ph	**3a**	93	91:9	94
2			*ent*-**3a**	95	94:6	93
3	5-Me	Ph	**3b**	90	89:11	93
4			*ent*-**3b**	93	93:7	95
5	5-F	Ph	**3c**	96	91:9	96
6			*ent*-**3c**	96	90:10	97
7	5-Br	Ph	**3d**	94	89:11	97
8			*ent*-**3d**	96	93:7	98
9	5-OCF_3	Ph	**3e**	95	91:9[d]	97
10			*ent*-**3e**	94	93:7[d]	98
11	6-Cl	Ph	**3f**	93	92:8	97
12			*ent*-**3f**	98	93:7	97
13	6-Br	Ph	**3g**	94	90:10	96
14			*ent*-**3g**	95	94:6	97
15	7-F	Ph	**3h**	95	93:7	95
16			*ent*-**3 h**	96	93:7	>99
17	H	4-FPh	**3i**	94	90:10	>99
18			*ent*-**3i**	95	93:7	95
19	H	4-MePh	**3j**	94	89:11	94
20			*ent*-**3j**	92	92:8	93
21	H	2-naphth	**3k**	94	91:9[d]	>99
22			*ent*-**3k**	93	91:9[d]	98
23	H	Bn	*ent-3 L*	90	52:48	87

[a] The reaction was carried out with **1** (0.24 mmol), **2** (0.2 mmol), and **IV** or **V** (0.02 mmol) in PhMe (1.0 mL) at rt. [b] Isolated yield. [c] Determined by chiral HPLC analysis unless noted. [d] Determined by ^{1}H NMR.

could also provide the desired product **3l** in 90% yield with good enantioselectivity, although with a prolonged reaction time (Table 2, entry 23). Furthermore, the absolute configuration of the 1,3-nonadjacent stereocenters was confirmed to be (*S*,*R*) by X-ray crystallographic analysis of **3d** (Figure 2). On the basis of this observation, we proposed a dual activation model for the transition state, wherein the Michael donor was enolized by a tertiary amine and the thiourea motif directed the Michael acceptor through a hydrogen bonding interaction.[14] The enolic Michael donor approached the acceptor with its *Si* face

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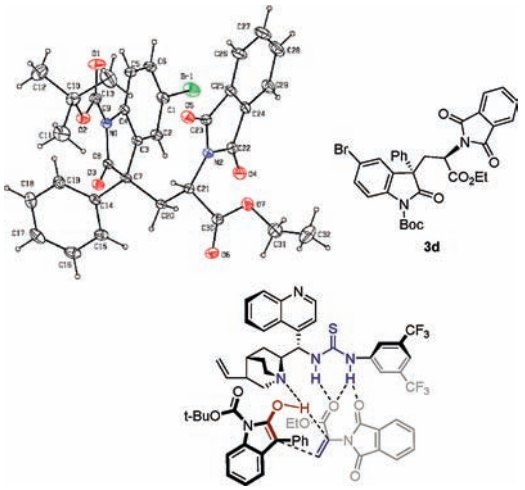
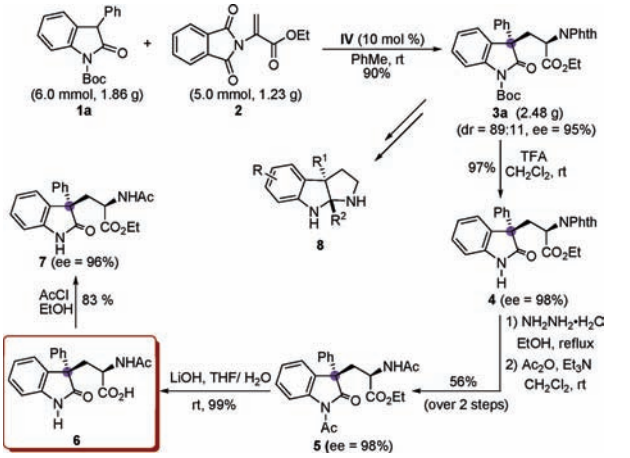


Figure 2. Absolute configuration of **3d** and proposed transition state.

followed by diastereoselective protonation to give the corresponding chiral product.

The significance of this nucleophilic addition/asymmetric protonation cascade reaction was demonstrated in the synthesis of C^{γ}-tetrasubstituted α-amino acids from the adducts. As shown in Scheme 1, a gram-scale reaction of *tert*-butyl 2-oxo-3-phenylindoline-1-carboxylate **1a** with ethyl 2-phthalimidoacrylate **2** was accomplished in 90% yield with 89:11 dr and 95% ee using **IV** within 10 h. The major diastereoisomer was then separated by SiO_2 chromatography. The deprotection of of the adduct **3a** afforded **4** in 97% yield, which was directly converted to **5** through a sequential hydrazinolysis and acylation in order to avoid unnecessary purification. The hydrolysis of **5** provided **6** in high yield without loss in optical purity, which was confirmed by HPLC analysis of its corresponding ester **7**. In addition, the synthesis of pyrroloindoline natural product **8** starting from this kind of C^{γ}-tetrasubstituted α-amino acid derivatives is currently underway.

Scheme 1. Derivatization of the Cascade Adduct **3a**



In conclusion, we have developed a novel procedure to achieve both enantiomers of C^{γ}-tetrasubstituted α-amino acid derivatives with high stereoselectivities and yields. This strategy allows for rapid and facile access to a series of unnatural amino acids bearing 1,3-nonadjacent stereocenters through an enantioselective nucleophilic addition/distereoselective protonation cascade under operationally simple conditions.

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Supporting Information Available. Experimental procedures and compound characterization data including X-ray crystal data (CIF) for **3d**. This material is available free of charge via the Internet at http://pubs.acs.org