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Nucleophile Generation via Decarboxylation: Asymmetric Construction of Contiguous Trisubstituted and Quaternary Stereocenters through a Cu(I)-Catalyzed Decarboxylative Mannich-Type Reaction

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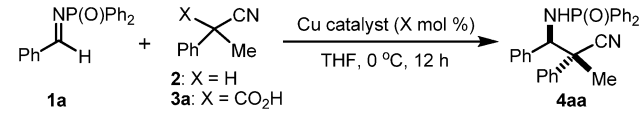
Catalytic asymmetric construction of contiguous trisubstituted and all-carbon quaternary stereocenters represents a particularly difficult challenge.[1,2] For the success of such a catalytic methodology, carbon−carbon bond formation with high diastereo- and enantiocontrol using sterically congested substrates is a prerequisite. With the aim of expanding the scope of asymmetric catalysis,[3] we investigated the asymmetric synthesis of linear β-amino-α,α-disubstituted carboxylic acids ($\beta^{2,2,3}$-amino acids) containing contiguous α-quaternary and β-trisubstituted chiral carbons. These amino acids and their derivatives are important chiral building blocks for biologically active molecules, but there are few examples of their catalytic asymmetric synthesis.[1a,b,4] We report herein a general method for accessing $\beta^{2,2,3}$-amino acid derivatives through the development of a Cu-catalyzed decarboxylative asymmetric Mannich-type reaction.

Our previous studies revealed that Cu(I)-catalyzed transmetalation of silylated reagents and deprotonation of nitriles are two valuable nucleophile activation methods for asymmetric C−C bond formation at sterically hindered positions (tetrasubstituted carbon synthesis).[3] Because it is difficult to control the enolate geometry in α,α-disubstituted silicon enolate synthesis,[1c] we initially studied a catalytic asymmetric direct Mannich-type reaction[5] between aldimine **1a** and 2-phenylpropionitrile (**2**: racemic) using nucleophile generation via chiral CuO^{t}Bu complex-catalyzed deprotonation.[6] Products (**4aa** + its diastereomer) were obtained in moderate to high yields, but the diastereo- and enantioselectivity were quite low (up to 1:1.6 dr and less than 5% ee of **4aa**) using various chiral phosphines (Table 1, entries 1 and 2).[7]

Thus, we next examined the Cu(I)-catalyzed extrusion of CO_2 from carboxylic acids as an alternative nucleophile-generation method that proceeds under neutral to weakly acidic conditions. Although this type of nucleophile generation is a well-known process in nature,[8] it has not been utilized in artificially catalyzed asymmetric carbon−carbon bond formation.[9−12] Currently, there is an intensive focus on this method as a novel catalytic nucleophile-activation method that does not require stoichiometric organometallic reagents.[13−15]

Using 10 mol % CuOAc−(*S*)-tol-BINAP complex as a catalyst, we studied the decarboxylative Mannich-type reaction between **1a** and racemic cyanocarboxylic acid **3a** (Table 1, entry 3).[16] Products were obtained in 83% combined yield with a 3.5:1 dr, with the major diastereomer **4aa** in 37% ee. Subsequent phosphine-ligand screening indicated that DTBM-SEGPHOS (**5**) was the best ligand in terms of diastereo- and enantioselectivity (7:1 dr and 87% ee; entry 4). The yield, however, decreased to 30%. A significant amount of **2**, generated through decarboxylative protonation of **3a**, was recovered in this case. Therefore, we tried slow addition of **3a** to a mixture of the catalyst and **1a**. As expected, the yield improved to 91% while the high enantio- and diastereoselectivity were maintained (entry 5). The reaction successfully proceeded in the presence of lower catalyst loading (5 mol %) using 2.5 equiv of **3a** (entry 6).

Table 1. Optimization of the Reaction Conditions



entry	Cu catalyst (X mol %)	2/3a	yield (%)	dr[a]	ee (%)[b]
1[c]	CuO^{t}Bu−(*S*)-Ph-Taniaphos (10)	**2**	87	1:1.6	<5
2[c]	CuO^{t}Bu−(*R*)-**5** (10)	**2**	58	1:1.3	<5
3[d]	CuOAc−(*S*)-tol-BINAP (10)	**3a**	83	3.5:1	37[g]
4[d]	CuOAc−(*R*)-**5** (10)	**3a**	30	7.0:1	87
5[e]	CuOAc−(*R*)-**5** (10)	**3a**	91	7.0:1	87
6[f]	CuOAc−(*R*)-**5** (5)	**3a**	98	7.0:1	87

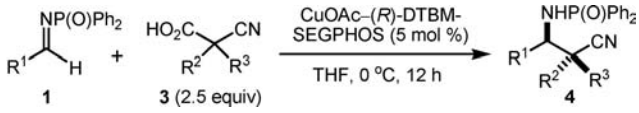
[a] Diastereomeric ratio determined by ^{1}H NMR. [b] Enantiomeric excess of **4aa** determined by chiral HPLC. [c] Using 1.5 equiv of **2**. [d] Using 1.5 equiv of **3a**. [e] With syringe-pump addition of 1.5 equiv of **3a** over 7 h. Total reaction time = 12 h. [f] With syringe-pump addition of 2.5 equiv of **3a** over 7 h. Total reaction time = 12 h. [g] The enantiomer of **4aa** was obtained.

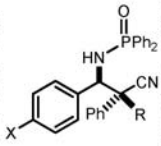
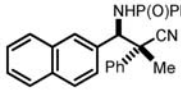
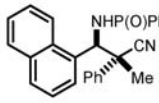
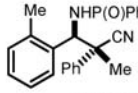
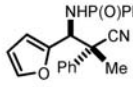
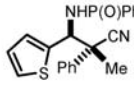
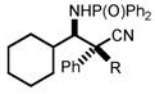
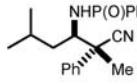
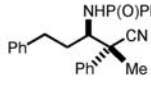
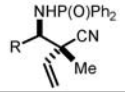
The optimized reaction conditions were evaluated using a range of combinations of imines and cyanocarboxylic acids (Table 2). In regard to imines, aromatic imines containing either electron-donating or -withdrawing substituents at the para position were tolerated, as were heteroaromatic imines (entries 1−12). The reaction proceeded with complete chemoselectivity to the imine functionality in the presence of a ketone group (entry 7). Sterically congested ortho-substituted aromatic imines afforded excellent enantioselectivity, although the yield and diastereoselectivity were slightly decreased (entries 9 and 10). Remarkably, aliphatic imines containing acidic α-protons and thus sensitive to basic conditions were competent substrates in this decarboxylative Mannich-type reaction (entries 13−17) because of the mild reaction conditions. The diastereoselectivity, however, was moderate for aliphatic imines, which must be overcome in future studies. As for the cyanocarboxylic acids, the enantio- and diastereoselectivity decreased slightly according to the size of the α-substituents (entries 1−3, 13−15). Nevertheless, products containing a synthetically useful allyl group at the quaternary center were produced with meaningful efficiency (entries 3 and 15). It is also noteworthy that this method was applicable to cyanoacetic acid without an aromatic substituent, affording the products with reasonable enantioselectivity (entries 18 and 19). To our knowledge, this is the first general catalytic asymmetric method to access $\beta^{2,2,3}$-amino acid derivatives with both aromatic and aliphatic substituents at the α- and/or β-position.

The products were converted to enantiomerically enriched $\beta^{2,2,3}$-amino acid derivatives without any racemization and epimerization

10.1021/ja9036675 CCC: $40.75

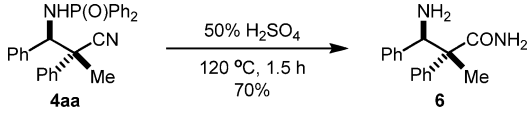
Table 2. Catalytic Asymmetric Decarboxylative Mannich-Type Reaction



entry	product (major isomer)		yield (%)[a]	dr[b]	ee (%)[c]
1		X = H, R = Me (**4aa**)	94	7.1 : 1	87
2		X = H, R = Et (**4ab**)	96	6.5 : 1	81
3		X = H, R = allyl (**4ac**)	90	5.4 : 1	80[d]
4		X = MeO, R = Me (**4ba**)	93	7.4 : 1	97
5		X = MeO, R = Et (**4bb**)	93	6.0 : 1	80
6		X = Br, R = Me (**4ca**)	96	6.4 : 1	82
7		X = MeCO, R = Me (**4da**)	95	7.4 : 1	80
8		**4ea**	51	9.1 : 1	84
9		**4fa**	63	4.0 : 1	90
10		**4ga**	62	5.2 : 1	93
11		**4ha**	94	8.9 : 1	85
12		**4ia**	93	8.4 : 1	83
13		R = Me (**4ja**)	82	2.1 : 1	95
14		R = Et (**4jb**)	72	2.7 : 1	83
15		R = allyl (**4jc**)	71	1.6 : 1	80
16		**4ka**	75	2.4 : 1	84
17		**4la**	83	2.5 : 1	85
18		R = Ph (**4ad**)	70	4.5 : 1	70
19		R = *c*-Hex (**4jd**)	73	2.1 : 1	80

[a] Isolated, combined yield of diastereomers. [b] Diastereomeric ratio determined by ^{1}H NMR. [c] Enantiomeric excess of **4** determined by chiral HPLC. [d] The absolute and relative configurations were determined by X-ray crystallography (see the Supporting Information).

Scheme 1. Conversion to $\beta^{2,2,3}$-Amino Acid Derivatives



through hydrolysis of the *N*-diphenylphosphinoyl moiety and the cyano group under acidic conditions (Scheme 1).

In conclusion, we have developed a catalytic asymmetric decarboxylative Mannich-type reaction involving nucleophile generation via Cu(I)-catalyzed extrusion of CO_2 from cyanocarboxylic acids. This method affords $\beta^{2,2,3}$-amino acid precursors containing contiguous trisubstituted and all-carbon quaternary stereocenters with synthetically useful enantio- and diastereoselectivity. Detailed mechanistic studies and expansion of this catalytic nucleophile-activation method to other asymmetric reactions are ongoing.

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Supporting Information Available: Experimental procedures, characterization of the products, and crystallographic data (CIF) for **4ac**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The low enantio- and diastereoselectivity observed in entries 1 and 2 of Table 1 were due to the existence of a retro-Mannich reaction under the direct reaction conditions. When a 7:1 mixture of **4aa** (87% ee) and its diastereomer **4aa′** was subjected to the conditions of entry 2 (10 mol % CuO′Bu−DTBM-SEGPHOS at 0 °C for 24 h), **4aa** and **4aa′** were recovered in 73% yield with 1:1.3 dr, along with imine **1a** in 27% yield. The enantiomeric excess of recovered **4aa** was less than 5%.

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(16) **3a** was readily synthesized from commercially available ethyl phenylcyanoacetate in two steps. Cyanoacetate derivatives were utilized on the basis of our hypothesis that the soft−soft interaction between Cu(I) and nitriles would facilitate decarboxylation (see ref 6). *N*-Phosphinoyl imines produced better results than *N*-sulfonyl and *N*-Boc imines.

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