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Forming All-Carbon Quaternary Stereocenters by Organocatalytic Aminomethylation: Concise Access to β^{2,2}-Amino Acids

Kai Wang, Jianliang Yu, Ying Shao, Shengbiao Tang and Jiangtao Sun*

Dedicated to the 100th anniversary of the School of Chemistry and Chemical Engineering, Nanjing University

Abstract: *The asymmetric synthesis of β^{2,2}-amino acids remains a formidable challenge in organic synthesis. We report here a novel organocatalytic enantioselective aminomethylation of ketenes with stable and readily available N,O-acetals, providing β^{2,2}-amino esters bearing an all-carbon quaternary stereogenic center in high enantiomeric ratios with a catalytic amount of chiral phosphoric acid. Typically, this transformation probably proceeds through an asymmetric counter-anion-directed catalysis. As a result, a concise, practical and atom-economy protocol toward rapidly access to β^{2,2}-amino acids has been developed.*

β-Amino acids are important chiral building blocks in organic synthesis and peptidic foldamers.[1] Spcially, the use of β-amino acids in constructing bioactive peptides is a promising strategy to obtain analogues that have beneficial effects to medicinal chemistry and pharmaceutical research.[2] For examples, β-amino acids can effectively enhance the stability of the peptides against proteolysis,[3] and are also compatible with ribosomal translation.[4] Thus, substantial effort has been made toward rapidly access to optically pure β-amino acids.[5] However, compared with the commercially available α- and β^3-amino acids,[6] the β^2-amino acids,[7] especially β^{2,2}-amino acids having an all-carbon quaternary stereogenic center,[8] are difficult to achieve (Figure 1). To date, the most common method to access β^{2,2}-amino acids is the utilization of chiral auxiliaries.[9] Several catalytic asymmetric approaches have also been developed, including enantioselective conjugate addition of aldehydes,[10] indoles[11] or arylboronic acids,[12] to β,β-disubstituted nitroalkenes, palladium-catalyzed intramolecular and intermolecular allylation of 4-substituted isoxazolidin-5-ones.[13] Despite these advances, the development of a concise and practical protocol for the catalytic enantioselective synthesis of β^{2,2}-amino, is still in highly demanded.

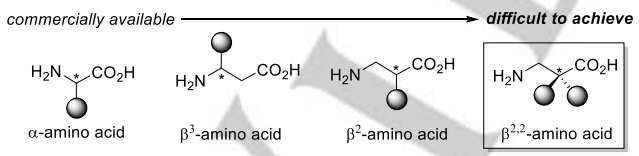

Figure 1. Synthetic difficulties to access α- and β-amino acids

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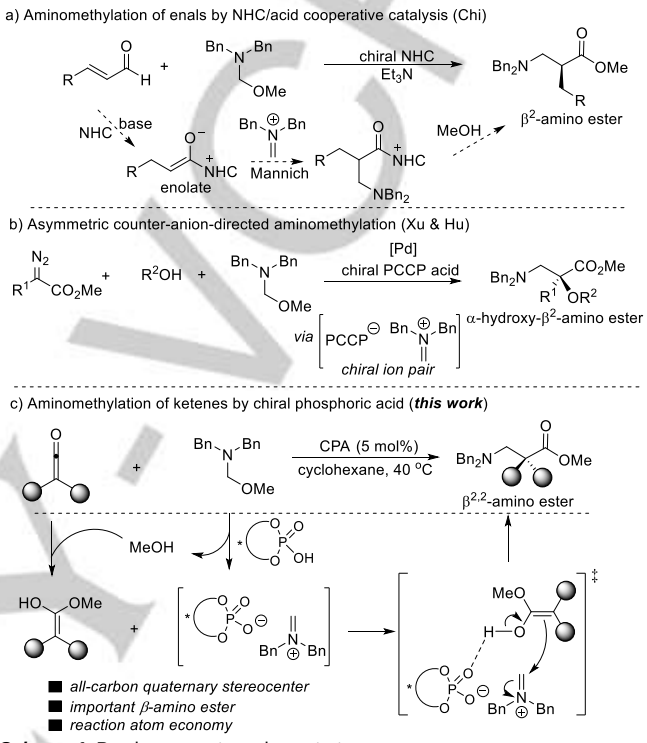

Scheme 1. Previous reports and our strategy

Recently, Chi and co-workers reported an asymmetric amino methylation of enals through N-heterocyclic carbene (NHC)-acid cooperative catalysis, yielding β^2-amino esters in high optical purity (Scheme 1a).[14] The enolate undergoes Mannich type reaction with electrophilic iminium ion (from N,O-acetal),[15] followed by trapping of the acyl azolium with methanol, to form the β^2-amino esters. Later, Xu, Hu and co-worker developed an asymmetric counter-anion directed[16] aminomethylation to form α-hydroxyl-β-amino esters (Scheme 1b).[17] This transformation probably proceeds through a Mannich-type reaction of enol intermediate with methylene iminium ion, and the asymmetric induction is enabled by the chiral pentacarboxycyclopentadiene (PCCP) anion. Inspired by these reports and in continuation with our interest in developing novel aminomethylation reactions,[18] we envision that the phosphoric acid anion and the electrophilic methylene iminium ion would form chiral ion pair. The subsequent convergent addition of enolate intermediate to the ion pair would give β^{2,2}-amino esters (Scheme 1c).

To validate the speculation, we commenced our studies by evaluating the reaction between ketene **1a** and N,O-acetal **2a** in dichloromethane at room temperature in the presence of a series of chiral phosphoric acid (CPA) catalysts (Table 1). A catalytic amount (5 mol%) of the BINOL-derived CPA **C1**, having a 2,4,6-triisopropylbenzene group at the 3,3'-position, afforded the desired β^{2,2}-amino ester **3a** in 32% yield with poor er (entry 1). Other BINOL-derived CPAs (**C2-C5**) exhibited similar results to

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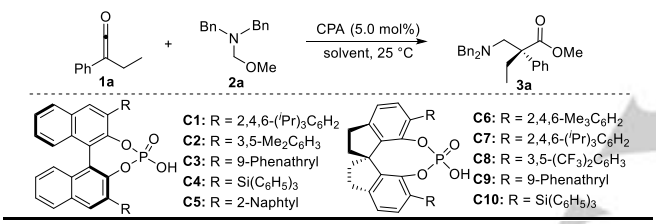
C1 (entries 2-5). To futher improve the reaction conditions, we then switched to evaluate the SPINOL-derived CPAs. The use of CPA **C6**, bearing a 2,4,6-trimethylbenzene group at the 6,6'-position, gave promising results. In this case, **3a** was isolated in 55% yield and a 72:28 er (entry 6). However, changing the substituents at the 6,6'-position (**C7-C10**) can not improve the reaction (entries 7-10). Using **C6** as the catalyst, several solvents were screened (entries 11-14). The reactions in toluene, chloroform, cyclopentane and cyclohexane all provided enhanced er values, and cyclohexane proved to be the best one (95.5:4.5 er; entry 14). It is believed that the non-polar solvent is benefical to the fomation of intimate ion pairs and thus helps stereocontrol (Scheme 1c). Then, evaluation of the temperature was performed. Decrease of the temperature to 10 °C resulted in a slight increase in enantiomeric ratio but with low yield (30%; entry 15). In contrast, the yield was improved to 74% at 40 °C without the loss of er (entry 16). Comparably, higher temperature gave inferior results (entry 17). Moreover, at dilute conditions (0.05 M), a slight increase in both the yield and the er was observed. As a result, **3a** could be obtained in 76% yield with 97:3 er value (entry 18).

***Table 1*:** Optimization of the reaction conditions.[a]

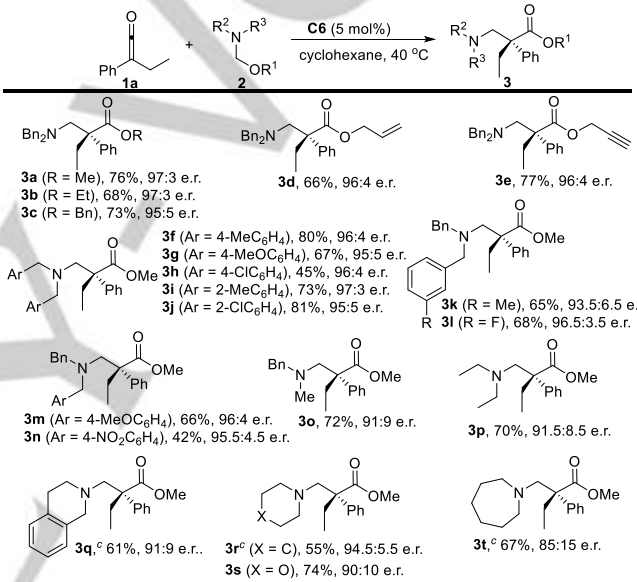


Entry	CPA	Solvent	T (°C)	Yield (%)[b]	e.r.[c]
1	**C1**	CH_2Cl_2	25	32	60:40
2	**C2**	CH_2Cl_2	25	20	51:49
3	**C3**	CH_2Cl_2	25	24	67:33
4	**C4**	CH_2Cl_2	25	21	52:48
5	**C5**	CH_2Cl_2	25	18	57:43
6	**C6**	CH_2Cl_2	25	55	72:28
7	**C7**	CH_2Cl_2	25	42	68:32
8	**C8**	CH_2Cl_2	25	33	65:35
9	**C9**	CH_2Cl_2	25	24	67:33
10	**C10**	CH_2Cl_2	25	30	60:40
11	**C6**	toluene	25	43	86:14
12	**C6**	$CHCl_3$	25	38	75:25
13	**C6**	cyclopentane	25	58	94.5:5.5
14	**C6**	cyclohexane	25	70	95.5:4.5
15	**C6**	cyclohexane	10	30	96.5:3.5
16	**C6**	cyclohexane	40	74	96.5:3.5
17	**C6**	cyclohexane	60	67	95:5
18[d]	**C6**	cyclohexane	40	76	97:3

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.1 mmol), catalyst (5.0 mol%) in 1 mL solvent, rt for 6 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out in 2 mL of solvent.

Having established the optimal reaction conditions, we next explored the scope of N,O-acetals (Table 2). Changing the R^1 group of N,O-acetals from methyl to ethyl, benzyl, allyl and propynyl, the desired products (**3b-3e**) were isolated in good yields and excellent er values. With respect to the amine moiety, the symmetric dibenzyl substituents containing either electron-donating or electron-withdrawing groups were all tolerated, providing the amino ester derivatives (**3f-3j**) in moderate to good yields and good er values. The amines containing unsymmetric dibenzyl substituents (**3k-3n**) were suitable substrates too. However, replacing one benzyl group with methyl group gave **3o** in decreased er (91:9). The similar phenomenon was observed for diethyl substituted N,O-acetals, and amino ester (**3p**) was obtained in 70% yield and 91.5:8.5 er. For acetals bearing a cyclic amine moiety, such as tetrahydroisoquinoline, piperidine, morpholine, and azepane, were also viable substrates, affording **3q-3t** in good yields and moderate stereoselectivities.

***Table 2*:** Substrate scope of N,O-acetals.[a],[b]



[a] Reaction conditions: **1a** (0.2 mmol, 2 equiv), **2** (0.1 mmol, 1 equiv), **C6** (5 mol%) in 2 mL cyclohexane, 40 °C, 6h. [b] Isolated yields were listed; the er values were determined by chiral HPLC analysis. [c] 10 mol% **C7** was used.

Further exploration of the reaction scope focused on the ketene substrates. An array of ketenes were examined by using **2a** as the reaction partner (Table 3). Generally, most of the reactions conducted were completed in 6 h with moderate to good yields (50-79%) and good er values (90:10-97.5:2.5). The electronic properties of the substituent on the phenyl ring had little or no effect on the enantioselectivity. Electron-donating (**3ba-3ca**) and electron-withdrawing (**3da-3ha**) groups substituted at para and meta positions on the phenyl ring are good substates. Even the steric hindered aromatic substrates were also amenable to this reaction, providing moderate yield and stereoselectivity of the corresponding products (**3ia-3ja**). A substrate with a thienyl group also reacted well, delivering **3ka** with good er value. Then, the variation of alkyl group R^2 of the ketenes was evaluated. The ketenes substituted with an alkyl group, such as methyl, *n*-butyl, *i*-butyl and *i*-pentenyl reacted well, affording the corresponding products (**3la-3oa**) in good yields and high er. The use of ketene bearing a tetrahydronaphthalene moiety furnished **3pa** in 65% yield with 96.5:3.5 er. However, the use of dialkyl-substituted

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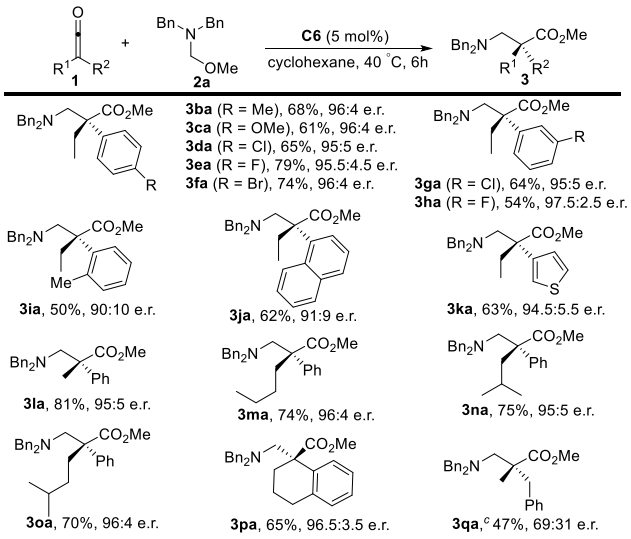
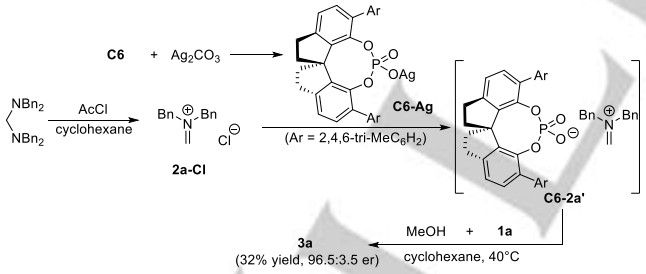
ketene provided product **3qa** in moderate yield and 69:31 er.

Table 3: Substrate scope of ketenes.[a],[b]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.1 mmol), **C6** (5 mol%) in 2 mL cyclohexane, 40 °C, 6h. [b] Isolated yields were listed; the er values were determined by chiral HPLC analysis. [c] 5 mol% **C9** was used.

To gain insight into the reaciton mechanism, we conducted control experiment by following Xu and Hu's procedure (Scheme 2).[17] Treatment of *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamine with acetyl chloride generated methylene iminium chloride **2a-Cl**. The anion exchange between chiral silver complex **C6-Ag** and **2a-Cl** gave the chiral ion pair **C6-2a′**. The addition of **C6-2a′** to a mixture of methanol and **1a** in cyclohexane produced **3a** in 32% yield and 96.5:3.5 er. This result indicates the chiral ion pair might be the key reaction intermediate and the asymmetric induction might result from the chiral phosphoric acid counteranion.



Scheme 2. Control experiment

Based on the above results and literature reports,[17] a possible mechanism is proposed (Figure 2). The reaction of **2a** with the acid catalyst generates methylene iminium ion pair **I** and releases a molecule of MeOH. The addition of MeOH to ketene **1a** forms the nucleophile enol **II**. This step likely favors the *E*-isomer due the severe steric repulsion encountered when methanol approaches the ketene from the same side of the phenyl group, as shown in the proposed transition state **TS1**.[19] Next, the enol reacts with the chiral iminium ion pair to deliver the observed product **3a** and regenrates the chiral acid catalyst. The transition state **TS2** is proposed to rationalize the stereochemcial outcome. In addition to the ion pairing interaction, a hydrogen bonding interaction between the phosphoryl oxygen and the enol hydroxy group is critical to the pseudo bifunctional stereocontrol. The enol plane is oriented such that its phenyl group is placed right above the mesitylene plane of the chiral catalyst, thereby effectively stablized by π-π interaction. Thus, the iminium electrophile aprroaches the *Si*-face of the enol molecule, resulting in (*R*)-**3a**, which is in agreement with the observed stereochemical outcome. Notably, the proposed π-π interaction is also consistent with the high enantioselectivity observed for aryl ketenes, but not for dialkyl ketenes which lack this interaction.

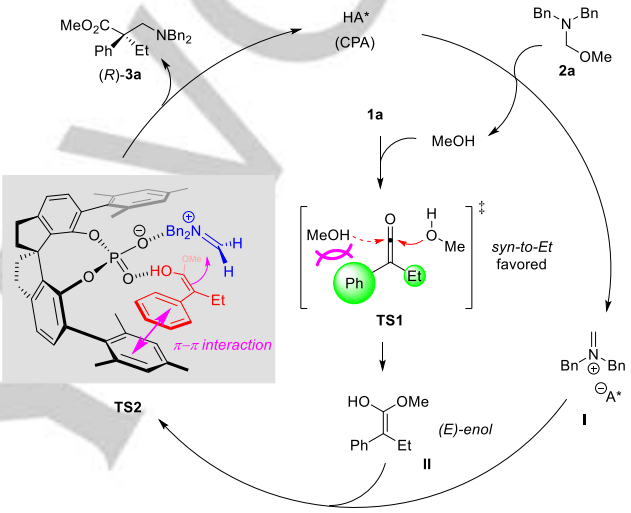


Figure 2. Proposed mechanism

In order to demonstrate the synthetic utility of this protocol, further elaboration has been conducted (Scheme 3). For 1 mmol scale reaction, **3a** was obtained in 75% yield and 97:3 er (Scheme 3a). Reduction of **3a** with lithium aluminum hydride in tetrahydrofura led to amino alcohol **4** in 95% yield without any erosion of the stereoselectivity (97:3 er). Hydrogenation of **3a** followed by acid-catalyzed hydrolysis produced β[2,2]-amino acid **5** in 95% yield. Then, a gram-scale reaction was performed in the presence of 1 mol% of **C6**, and **3a** was obtained in 72% yield with 96:4 er (Scheme 3b). Clearly, the low catalyst loading of CPA makes this reaction more practical. Next, hydrogenation of **3a** with Pd/C in a hydrogen atomosphere can remove the benzyl group and the amino group can be further proctected by a *tert*-butoxycarbonyl group to furnish compound **6** in 95% yield and 96:4 er. Moreover, after hydrogenation, the β-amino ester can be converted to β-lactam **7** in 62% yield with 99:1 er under basic reaction conditions. The absolute configuration of **7** was determined by X-ray analysis.[20] Furthermore, since ketenes can be obtained by photolytic Wolff rearrangement of *α*-diazo ketones,[21] we then performed the one-pot reaction of diazo ketone **8** and **2a** in the presence of **C6** under blue light irridation (Scheme 3c). **3a** was isolated in 26% yield with 95:5 er. The low yield probably attributed to the side carbene reactions. Moreover, we also tested the reaction of **1a** with substituted N,O-acetal **9** (Scheme 3d). However, the amide **10** was obtained in 29% yield

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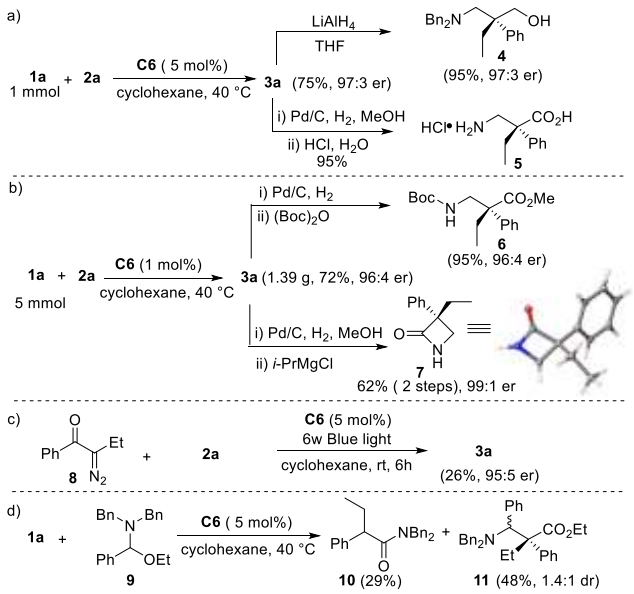
together with 48% yield of α-phenyl $\beta^{2,2}$-amino ester **11** with poor diastereoselectivity (1.4:1 dr).



Scheme 3. Synthetic applications

In summary, we have developed a novel phosphoric acid-catalyzed enantioselective aminomethylation reaction between ketenes and N,O-acetals under mild reaction conditions, providing $\beta^{2,2}$-amino esters bearing an all-carbon quaternary stereogenic center in high enantiomeric ratios. This transformation probably proceeds through the addition of in situ generated enol intermediate to methylene iminium ion in the presence of chiral phosphoric acid. Moreover, this protocol is concise, practical and atom economy. The $\beta^{2,2}$-amino esters can undergo further diversifications to synthesize enantiomerically pure $\beta^{2,2}$-amino acid and β-lactam.

Acknowledgements

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Keywords: amino acids • phosphoric acid • ketene • N,O-acetal• organocatalysis

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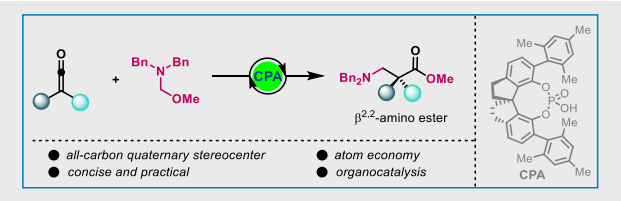

A novel organocatalytic enantioselective aminomethylation of ketenes with stable and readily available N,O-acetals has been developed, providing chiral $\beta^{2,2}$-amino esters bearing an all-carbon quaternary stereogenic center in high enantiomeric ratios.

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