Catalytic Asymmetric Synthesis of Unprotected $\beta^2$-Amino Acids

Chendan Zhu, Francesca Mandrelli, Hui Zhou, Rajat Maji, and Benjamin List*

ABSTRACT: We report here a scalable, catalytic one-pot approach to enantiopure and unmodified $\beta^2$-amino acids. A newly developed confined imidodiphosphorimidate (IDPi) catalyzes a broadly applicable reaction of diverse bis-silyl ketene acetics with a silylated aminomethyl ether, followed by hydrolytic workup, to give free $\beta^2$-amino acids in high yields, purity, and enantioselectivity. Importantly, both aromatic and aliphatic $\beta^2$-amino acids can be obtained using this method. Mechanistic studies are consistent with the enaminemethylation to proceed via silylum-based asymmetric counterion-directed catalysis (SI-ACDC) and a transition state to explain the enantioselectivity is suggested on the basis of density functional theory calculation.

Among the various classes of amino acids, $\beta^2$-amino acids hold a particularly prominent place and occur in an increasing number of pharmaceuticals, natural products, and drug candidates. However, while chemists, in recent years, have delivered several methods toward the asymmetric synthesis of $\beta^2$-amino acids, catalytic approaches that directly deliver the free, unmodified amino acid, without requiring separate redox- or protecting group manipulations, to our knowledge, have not yet been developed. Our inspirational blueprint to address this challenge is a hypothetical chiral acid catalyzed direct three-component-Mannich reaction of carboxylic acids with formaldehyde and ammonia (eq 1).

Unfortunately, except with malonic acid derivatives and nonenantioselectively so, such a “dream-reaction” has not yet been realized, arguably due to the current inability of chemists to catalytically enolize carboxylic acids. An attractive, even though less direct alternative would be a Mukaiyama-style reaction of preformed bis-silyl ketene acetics (bis-SKAs) with a formaldehyde imine equivalent. While this transformation has been described in a nonenantioselective fashion, asymmetric versions are entirely unknown. Encouraged by our recent studies on silylum-based asymmetric counterion-directed catalysis (SI-ACDC), we envisaged to apply this approach to a $\text{TMSX}^*$-catalyzed reaction of bis-SKAs with a silylated aminomethyl ether, followed by hydrolytic workup and extraction, which should deliver the free, unmodified $\beta^2$-amino acids and enable a simple catalyst $\text{HX}^*$ recovery (eq 2, $\text{X}^*^- = $ enaniopure counteranion). Here we report on the realization of this concept with a general and highly enantioselective imidodiphosphorimidate (IDPi) catalyzed Mukaiyama Mannich-type reaction that delivers free $\beta^2$-amino acids with either aromatic or aliphatic substituents.

We chose $\alpha$-benzyl bis-SKA 1a as our model substrate and commercially available $\alpha$-aminomethyl ether 2a as methylene imine equivalent to initiate our studies (Table 1). An initial catalyst exploration revealed that moderately acidic Brønsted acids, such as chiral phosphoric acids (CPAs), even upon warming, did not give any of the desired product, while imidodiphosphoric (IDP) acids promoted the reaction at 0 °C to give racemic product (see the Supporting Information). In contrast, more acidic IDPi catalysts provided both sufficient reactivity and promising enantioselectivity (at −40 °C in toluene). Among our IDPi libraries, spirocyclopentyl-3-fluorenyl substituted catalysts turned out to be particularly reactive and promising enantioselectivity (at −40 °C in toluene). Among our IDPi libraries, spirocyclopentyl-3-fluorenyl substituted catalysts 3 turned out to be particularly promising in terms of reactivity and enantioselectivity. Extending the perfluoroalkyl sulfonyl chains in the inner core further increased the enantioselectivity (entries 1–4). With catalyst 3d, temperature and solvent were further optimized. Lowering the temperature to −60 °C led to a slight increase in enantioselectivity (entry 5). Importantly, with pentane as the solvent instead of toluene, the enantiomeric ratio significantly increased (entry 6). Furthermore, we tested IDPi catalysts 3e–g, possessing an additional substituent at the fluorenyl group (entries 7–10). Ultimately, we identified the tert-butyl...
The scope of this transformation also includes simple, aliphatic β-amino acids. For example, bis-SKAs 1r−u, which were generated from propionic acid, butyric acid, valeric acid, and hexanoic acid, respectively, reacted smoothly, where the enantioselectivities increased with longer alkyl chains. Branched and cyclic alkyl groups (4v−x) and a methoxy- (4y) and an olefin-substituted alkyl chain (4z) were all tolerated and provided the desired products in good to excellent yields and enantioselectivity. Interestingly, the enantipure bis-SKA 1A and its enantiomer ent-1A reacted to products 4A and 4B in good yields and, in both cases, featuring excellent and catalyst-controlled diastereoselectivity. Limitations of our method include the use of bis-silyl ketene acetals derived from α,α-disubstituted carboxylic acids and of C-substituted imine sources, which display reduced reactivity and lead to lower diastereoselectivity and enantioselectivity (see the Supporting Information).

The absolute configuration of our obtained β-amino acids was determined from X-ray crystallographic analysis of products 4h, 4i, and 4j. Furthermore, bromoalkyl substituted bis-SKA 1C gave p-amino butyric acid uptake inhibitor (S)-(−)-nipeocatic acid30 5 in a one-pot operation in 84% yield and 97:3 e.r. when treating the initial reaction product with triethylamine. The absolute configuration of amino acid 5 was determined by converting it to the corresponding benzamide, 6, crystals of which were subjected to an X-ray crystallographic analysis.1H NMR investigation of the crude reaction mixture revealed the existence of silylated product 6a, which was subjected to X-ray crystallographic analysis. The practicality of our method was illustrated with two scale-up experiments, involving an extremely concise product purification and catalyst recovery. Using 1 mol % of catalyst 3h, 12 mmol of bis-SKA 1a and 10 mmol of imine precursor 2a gave 1.77 g of the free β-amino acid 4a in 99% isolated yield with an e.r. of 95.5:4.5. The workup of the reaction mixture included a simple extraction with water and washing with dichloromethane without further purification. Gratifyingly, catalyst 3h could be easily recovered in 96% yield from the organic phase via flash chromatography and acidification. Similarly, 2.84 g of the aliphatic free β-amino acid 4u was obtained in 98% isolated yield with an e.r. of 95:5 from 20 mmol of reagent 2a using only 0.5 mol % of catalyst 3h, which was recovered in 95% yield from the organic phase after flash chromatography and acidification.

Optionally, the crude products can be readily derivatized in situ into a variety of synthetically useful building blocks such as the corresponding N-Boc- or N-Fmoc-protected β-amino acids 8 and 9 by treating the reaction mixture with an appropriate derivatization reagent.
On the basis of the observation that the alkyl group of ethers had an insignificant effect on the enantioselectivity (Table 1, entries 11−14), coupled with literature results, we envision a catalytic cycle as shown in Figure 1a. Accordingly, the reaction commences with the in situ silylation of the IDPi catalyst by bis-SKA to furnish the N-silylated catalyst I and/or its diastereomeric O−Si-silatropomers. α-Amino-methyl ether 2 then reacts with catalyst I, generating the methylene iminium ion-IDPi anion pair II, simultaneously liberating TMSOMe. Subsequently, bis-SKA 1 reacts with the cationic methylene iminium ion in the anionic catalyst pocket to give ion pair III. Intra-ion-pair silyl transfer from the cationic product back onto its counteranion then furnishes the silylated product IV and re-establishes the silylated catalyst I.

Table 2. Substrate Scope

| Substrate | Yield | e.r.   |
|-----------|-------|--------|
| 4a        | 99%   | 96:4 a.r. |
| 4b        | 94%   | 95:5.5 e.r. |
| 4c        | 95%   | 95:5 e.r. |
| 4d        | 98%   | 95:5 e.r. |
| 4e        | 94%   | 95:5.5 e.r. |
| 4f        | 95%   | 98:5:1.5 e.r. |
| 4g        | 98%   | 98:2 e.r. |
| 4h        | 98%   | 98:2 e.r. |
| 4i        | 96%   | 98:2 e.r. |
| 4j        | 99%   | 97:3 e.r. |
| 4k        | 94%   | 95:5 e.r. |
| 4l        | 99%   | 96:4 e.r. |

Reactions were conducted on a 0.2 mmol scale: 1:2a = 1:2. Isolated yields with e.r. measured by HPLC. For derivatization, see Supporting Information. e.r. measured by HPLC after derivatization. 3 mol% 3h. BzCl, benzyol chloride; DCM, dichloromethane; TEA, triethylamine.

On the basis of the observation that the alkyl group of ethers 2 had an insignificant effect on the enantioselectivity (Table 1, entries 11−14), coupled with literature results, we envision a catalytic cycle as shown in Figure 1a. Accordingly, the reaction commences with the in situ silylation of the IDPi catalyst 3 by bis-SKA 1 to furnish the N-silylated catalyst I and/or its diastereomeric O−Si-silatropomers. α-Amino-methyl ether 2 then reacts with catalyst I, generating the methylene iminium ion-IDPi anion pair II, simultaneously liberating TMSOMe. Subsequently, bis-SKA 1 reacts with the cationic methylene iminium ion in the anionic catalyst pocket to give ion pair III. Intra-ion-pair silyl transfer from the cationic product back onto its counteranion then furnishes the silylated product IV and re-establishes the silylated catalyst I. Finally, hydrolytic workup and extraction of the reaction mixture delivers the free β-amino acid 4. On the basis of a detailed conformational search and subsequent Density Functional Theory (DFT) optimization of ion pair II, we tentatively propose a sterical hindrance-based selectivity model (Figure 1b), where re-facial addition of bis-SKA 1 to methylene iminium-IDPi anion pair II leads to the observed enantiomer (see the Supporting Information).
We have developed a traceless and scalable approach to enantiopure free β-amino acids via catalytic asymmetric aminomethylation of bis-silyl ketene acetics. A variety of aromatic and aliphatic bis-SKAs from carboxylic acids with diverse electronics and stericis were tolerated in this transformation and provided the corresponding amino acids in excellent yields and enantioselectivities. The purification process is extremely simple and concise and enables catalyst recovery. We conducted control experiments that are consistent with a mechanism that proceeds via Si-ACDC, while preliminary computational studies suggest steric effects to cause the observed enantioselectivity. As IDPi catalysts are currently being commercialized, the methodology reported here may facilitate the synthesis of pharmaceuticals, natural products, and peptidic foldamers.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00249.

Experimental details and analytical data for all new compounds, crystallographic data for compounds 4h, 4i, and 4j, HPLC traces, NMR spectra, computational studies, optimized structures, and Cartesian coordinates (PDF)

Accession Codes

CCDC 2056835–2056839 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Benjamin List – Max-Planck-Institut für Kohlenforschung, 45470 Mülheim an der Ruhr, Germany; orcid.org/0000-0002-9804-599X; Email: list@kofo.mpg.de

Authors

Chendan Zhu – Max-Planck-Institut für Kohlenforschung, 45470 Mülheim an der Ruhr, Germany
Francesca Mandrelli – Max-Planck-Institut für Kohlenforschung, 45470 Mülheim an der Ruhr, Germany
Hui Zhou – Max-Planck-Institut für Kohlenforschung, 45470 Mülheim an der Ruhr, Germany
Rajat Maji – Max-Planck-Institut für Kohlenforschung, 45470 Mülheim an der Ruhr, Germany; orcid.org/0000-0003-2614-1795

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c00249

Notes

The authors declare the following competing financial interest(s): We have a patent on the catalyst class.

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