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Catalytic Mannich-type reactions of α-aminoacetonitrile using fluorenylidene as a protecting and activating group

Yasuhiro Yamashita, Masatoshi Matsumoto, Yi-Jing Chen, Shū Kobayashi *

Department of Chemistry, School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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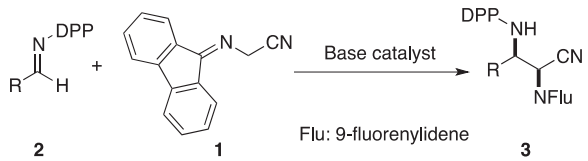
ABSTRACT

Catalytic Mannich-type reactions of 9-fluorenylidene-protected α-aminoacetonitrile with imines were investigated. The desired reactions proceeded smoothly to afford the Mannich-type adducts in high yields with high diastereoselectivities in the presence of a catalytic amount of 1,1,3,3-tetramethylguanidine (TMG). A chiral guanidine catalyzed the reaction with good enantioselectivity.

1. Introduction

α-Aminoacetonitrile is a useful reactant for the synthesis of nitrile compounds bearing a nitrogen functionality on the α-position.[1] It can be activated to form a reactive carbanion at the α-position for carbon–carbon bond forming reactions via deprotonation by a base,[2] although the corresponding α-hydrogen is less reactive because of the electron donating effect of the neighboring amino group. Use of a protecting group for the amino group is one way to solve the problem. Benzylidene or diphenylmethylene group is used as a typical imino protecting group (Schiff base), which can enhance acidity of the α-hydrogen via conjugated stabilization of the formed carbanion, and they can be removed under weak acidic conditions.[3] Up till now, carbon–carbon bond forming reactions using *N*-alkylidene-protected α-aminoacetonitrile have been well-investigated,[4–8] however, a stoichiometric amount of a strong base has been employed in many cases, and only a few examples using a catalytic amount of base species have been reported.[2d,9]

Recently we have shown that 9-fluorenylidene is a good protecting and activating group for primary amine compounds, and that *N*-fluorenylidene-protected glycine esters or α-aminophosphonates reacted with imines to afford Mannich adducts in high yields with high stereoselectivities in the presence of a weak base, such as metal phenoxide or guanidine.[10] Moreover, we have found that simple primary aminoalkanes such as ethyl- or methylamine could be activated for catalytic carbon–carbon bond forming reactions.[11] These results indicate that the fluorenylidene group is a very promising protecting and activating group for primary amine compounds. We then decided to apply this methodology to the activation of α-aminoacetonitrile. Here we report a catalytic, highly stereoselective Mannich-type reaction of *N*-fluorenylidene-protected α-aminoacetonitrile (**1**) using a base catalyst (Scheme 1).



Scheme 1. Catalytic Mannich-type reaction of α-aminonitrile with 9-fluorenylidene group (**1**).

2. Results and discussion

N-Fluorenylidene-protected α-aminoacetonitrile (**1**) was easily prepared from 9-fluorenone imine and α-aminoacetonitrile (Scheme 2). 9-Fluorenone imine was prepared by the reaction of 9-

* Corresponding author. E-mail address: shu_kobayashi@chem.s.u-tokyo.ac.jp (S. Kobayashi).

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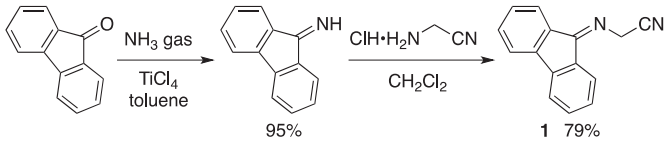
fluorenone and ammonia gas in the presence of titanium(IV) chloride. The imine was then treated with α-aminoacetonitrile hydrochloric acid salt to afford the desired product **1** in good yield.[12]



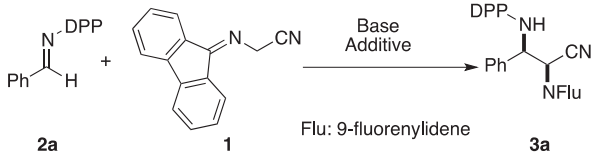
Scheme 2. Preparation of **1**.

The Mannich-type reaction of **1** with diphenylphosphinylimine (DPP imine) **2a** prepared from benzaldehyde in the presence of potassium *tert*-butoxide (KO^{t}Bu) was first investigated using our previous reaction conditions.[11] The desired reaction proceeded in THF at room temperature to afford the corresponding Mannich product in moderate yield with low *syn*/*anti* selectivity (Table 1, entry 1). When 18-crown-6 ether was used for activation of KO^{t}Bu, the yield was improved, but the selectivity was still moderate (entry 2). The reaction using weaker potassium bases was then investigated. While potassium phenoxide prepared from KO^{t}Bu and 2,6-dimethylphenol did not work well (entry 3), the yield dropped but the diastereoselectivity was improved when potassium carbonate was used (entry 4). These results indicated that the use of weaker bases was a key for high diastereoselectivity. On the other hand, organobases were found to be promising (entries 5–7). Whereas triethylamine did not work at all, DBU or 1,1,3,3-tetramethylguanidine (TMG) promoted the reaction successfully, and TMG especially was the best base to obtain the desired product (94% yield, entry 7). In the current reaction system, the fluorenylidene part was crucial; the aminoacetonitrile protected with a diphenylmethylene group did not work well (12% yield, entry 8). The effect of solvents was then examined (entries 9–12), and it was found that Et_2O gave the highest diastereoselectivity among the solvents employed (entry 12). Interestingly, investigation of the temperature effect suggested that the reaction at around room temperature showed the most promising result (entry 12 vs entries 13 and 14). The reactions using lower catalyst loadings also proceeded well, and a good yield was obtained even using 2.5 mol % of TMG (entry 16).

The scope of substrates was then examined (Table 2). A Et_2O/CH_2Cl_2 (9:1) mixed solvent was used to improve the solubility of DPP imine **2** in the solvent. The aminoacetonitrile **1** successfully reacted with aromatic or aliphatic DPP imines, and the desired products were obtained in high yields with good to high diastereoselectivities. Reactions of aromatic imines with electron-withdrawing (entry 2) or -donating groups (entries 3 and 4) did not affect the reactivity significantly, and high diastereoselectivities were also obtained. Large steric bulkiness on the aromatic part was found to affect the selectivity. Whereas the reaction of *ortho*-tolyl or 2-naphthyl DPP imine gave similar good results (entries 5 and 6), a somewhat lower diastereoselectivity was obtained in the case of 1-naphthyl DPP imine (entry 7). Heteroaromatic DPP imines also reacted with **1** smoothly, and good to high yields with high diastereoselectivities (except for the 2-thienyl imine) were obtained (entries 8–10). We also conducted the reactions using aliphatic imines, which were sometimes less stable and less reactive compounds compared with aromatic imines. The reaction of DPP imines with secondary aliphatic groups, cyclohexyl or *iso*-propyl, proceeded smoothly to afford the desired products in high yields with high selectivities (entries 11 and 12). On the other hand, a primary aliphatic imine also reacted, however, the selectivity decreased (entry 13). It should be noted that the current reaction system using TMG has a wide substrate scope for the synthesis of α,β-diaminonitriles **3**.

Transformation of Mannich product **3** was then conducted. Both protecting groups were selectively removed under different acidic

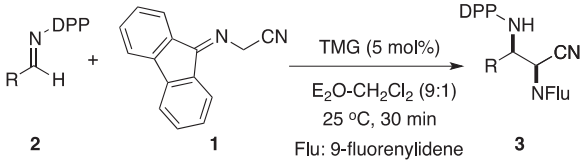
Table 1
Stereoselective Mannich-type reactions of *N*-fluoronylidene-protected α-amino-acetonitrile (**1**)[a]



Entry	Base	Additive	Solvent	Yield[b] (%)	*syn*/*anti*[b]
1	KO^{t}Bu	—	THF	68	60:40
2	KO^{t}Bu	18-Crown-6	THF	91	64:36
3	KO^{t}Bu	2,6-Me$_2$–phenol	THF	62	59:41
4	K_2CO_3	—	THF	33	72:28
5	Et_3N	—	THF	Trace	—
6	DBU	—	THF	90	63:37
7	TMG	—	THF	94	78:22
8[c]	TMG	—	THF	12	76:24
9	TMG	—	CH_3CN	91	95:5
10	TMG	—	CH_2Cl_2	95	60:40
11	TMG	—	Toluene	96	86:14
12	TMG	—	Et_2O	89	97:3
13[d]	TMG	—	Et_2O	91	91:9
14[e]	TMG	—	Et_2O	76	77:23
15[f]	TMG	—	Et_2O	90	97:3
16[g]	TMG	—	Et_2O	77	97:3

[a] The reaction of **1** (0.24 mmol) with **2a** (0.20 mmol) was performed in the presence of base (10 mol %) at 25 °C for 30 min in 0.05 M unless otherwise noted. TMG=1,1,3,3-tetramethylguanidine.
[b] Yield and selectivity were determined by ^{1}H NMR spectroscopic analysis of the crude product using an internal standard (benzyl).
[c] Diphenylmethylene-protected α-aminoacetonitrile was used instead of **1**.
[d] At 0 °C.
[e] At −20 °C.
[f] Catalyst of 5 mol % was used.
[g] Catalyst of 2.5 mol % was used.

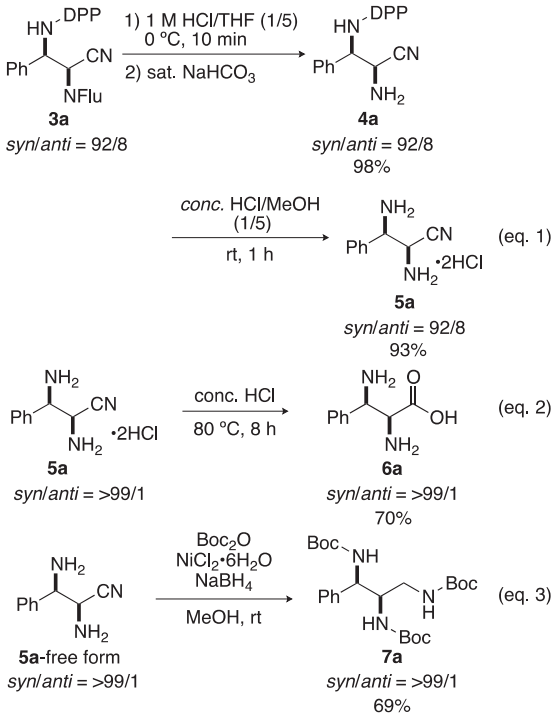
Table 2
Substrate scope[a]



Entry	R^1	Isolated yield (%)	*syn*/*anti*[b]
1	Ph (**2a**)	90	97:3
2	4-BrC_6H_4 (**2b**)	99	92:8
3	4-MeOC_6H_4 (**2c**)	85	95:5
4	4-MeC_6H_4 (**2d**)	95	96:4
5	2-MeC_6H_4 (**2e**)	84	96:4
6[c]	2-Naphthyl (**2f**)	92	93:7
7	1-Naphthyl (**2g**)	99	86:14
8	3-Pyridyl (**2h**)	70	94:6
9	2-Furyl (**2i**)	93	94:6
10	2-Thienyl (**2j**)	92	73:27
11[d]	Cyclohexyl (**2k**)	99	93:7
12[d]	*iso*-Propyl (**2l**)	97	89:11
13[d]	*n*-Hexyl (**2m**)	85	74:26

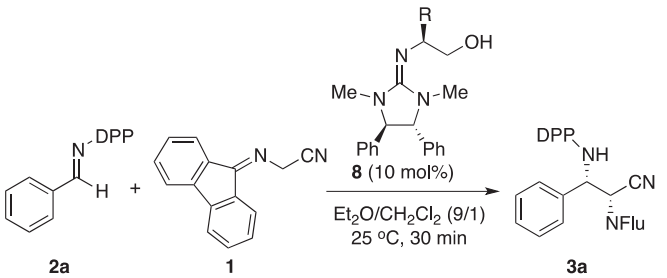
[a] The reaction of **1** (0.24 mmol) with **2** (0.20 mmol) was performed in the presence of TMG (5 mol %) in a Et_2O/CH_2Cl_2 (9:1) mixed solvent system at 25 °C for 30 min in 0.05 M unless otherwise noted. The crude product was purified by using preparative TLC (CH_2Cl_2/MeOH=100:3).
[b] *syn*/*anti* selectivity was determined by ^{1}H NMR spectroscopic analysis of the crude product.
[c] The crude product was purified by using silica gel column chromatography (CH_2Cl_2/MeOH=100:3).
[d] Compounds **1** (0.20 mmol) and **2** (0.30 mmol) were employed for the reaction.

conditions (Scheme 3, Eq. 1). The fluorenylidene group of **3a** was first cleaved immediately under mild acidic conditions to afford mono-protected product **4a**, and 1,2-diaminonitrile **5a** was obtained as a hydrochloric acid salt after concd HCl/MeOH treatment. Further hydrolysis of the nitrile part of **5a** could be achieved by additional acid treatment to afford 1,2-diaminocarboxylic acid in high yield without loss of stereoselectivity.[13] Moreover, the acid free form of 1,2-diaminonitrile **5a** was converted into the corresponding 1,2,3-triamine under reducing conditions using $NiCl_2$ and $NaBH_4$ in the presence of Boc_2O,[14] and the desired compound **7a** was obtained as a Boc-protected form in 69% yield.



Scheme 3. Transformations of the Mannich adduct **3a**.

The catalytic asymmetric Mannich-type reaction of **1** was then investigated (Scheme 4). In our previous study, chiral guanidine derivative **8a**[15] was found to be a good catalyst for Mannich-type reactions of a glycine ester protected by 9-fluorenylidene.[10] It was found that **8a** was also successfully employed in the Mannich-type reaction of **1**, and the desired product **3a** was obtained in high yield with good *syn* selectivity and moderate enantioselectivity. Further improvement of the enantioselectivity was achieved by modifying the chiral guanidine structure, and good selectivity was obtained using **8b** bearing the ^{i}Pr group on the chiral side chain of **8**.



8a (R = Ph): 92% yield, *syn/anti* = 88/12, 60% ee (*syn*)
8b (R = ^{i}Pr): 62% yield, *syn/anti* = 87/13, 73% ee (*syn*)

Scheme 4. Asymmetric Mannich-type reaction of **1**.

3. Conclusion

Catalytic Mannich-type reactions of 9-fluorenylidene-protected α-aminoacetonitrile (**1**) with DPP-protected imines were developed. The desired reactions proceeded smoothly to afford the Mannich adducts **3** in high yields with high diastereoselectivities in the presence of a catalytic amount of TMG. Deprotection and further transformations of the product obtained were successfully achieved, and 1,2-diaminonitrile and 1,2,3-triamine derivatives were obtained in high yields. The catalytic asymmetric Mannich-type reaction was also investigated to afford the desired adduct in high yield with good diastereo- and enantioselectivities.

4. Experimental section

4.1. General

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on JEOL JNM ECX400, JNM ECX500, and JNM-ECX600 spectrometers in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard (δ=0) for ^{1}H NMR, and $CDCl_3$ (δ=77.0) was used as internal standard for ^{13}C NMR. In ^{13}C NMR analysis, detectable peaks were written in cases of the DPP imine adducts. IR spectra were measured on a JASCO FT/IR-610 or JASCO FT/IR-4200 spectrometer. Specific rotations were recorded with a JASCO P-1200 polarimeter. High-resolution mass spectrometry was recorded with a JEOL JMS-T100TD (ESI or DART®). Column chromatography was conducted on Silica gel 60N (spherical, neutral, Kanto Chem. Co., Inc.), and preparative thin-layer chromatography (PTLC) was carried out using plates with Wakogel B-5F. All reactions were carried out under argon atmosphere in well-dried glassware. All solvents were dried and distilled by following standard procedures. 9-Fluorenylidene-protected α-aminoacetonitrile (**1**) was prepared according to a literature method.[10] *N*-Diphenylphosphinyl imines were prepared according to the reported method.[16] The chiral guanidines (**8a** and **8b**) were prepared using a literature method.[15] Relative configuration of **3a** was determined by comparison of ^{1}H NMR spectra of **6a** and the reported compound after acid hydrolysis.[13] The others were determined by analogy to **3a** by ^{1}H NMR spectroscopic analysis.

4.2. General procedure for the preparation of 9-fluorenylidene-protected α-aminoacetonitrile (1)

9*H*-Fluoren-9-imine (fluorenone imine, 1.00 g, 5.58 mmol) and α-aminoacetonitrile hydrochloric acid salt (5.58 mmol) were combined in CH_2Cl_2 (30 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was filtered to remove the ammonium salt and concentrated in vacuo to remove all volatile materials, and the residue was dissolved in Et_2O. The ether solution was then washed with H_2O and dried over anhydrous Na_2SO_4. The desired product was obtained in a pure form after filtration and concentration of the ether solution (full conversion). The product was further purified by recrystallization (AcOEt/hexane) before use.

*4.2.1. 2-(9H-Fluoren-9-ylideneamino)acetonitrile (**1**).* Yellow fine needles, mp 170 °C (dec); IR (neat): 3154, 3063, 2986, 2924, 2313, 2254, 1648, 1453, 1098; ^{1}H NMR ($CDCl_3$, 399.78 MHz): δ 7.82 (d, *J*=7.3 Hz, 1H), 7.63 (dd, *J*=10.3, 7.6 Hz, 2H), 7.54 (d, *J*=7.3 Hz, 1H), 7.50–7.40 (m, 2H), 7.31–7.29 (m, 2H), 5.00 (s, 2H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.6, 144.1, 141.2, 137.4, 132.6, 132.0, 131.0, 128.8, 128.1, 127.3, 123.2, 120.9, 119.6, 117.4, 40.9; HRMS (DART®): exact mass calcd for $C_{15}H_{11}N_2$ $[M+H]^+$ 219.09222, found 219.09325.

4.3. General procedure for the catalytic Mannich-type addition of 1 to DPP imines 2

Compounds **1** (0.24 mmol) and **2** (0.20 mmol) were placed in a flame-dried 30 mL round-bottom flask. Anhydrous Et_2O (3.6 mL) was added to the flask. 1,1,3,3-Tetramethylguanidine (0.020 mmol) was then added to the mixture at room temperature, and CH_2Cl_2 (0.4 mL) was added. The resulting yellow solution was stirred at 25 °C for 30 min under Ar and quenched with a saturated aqueous NH_4Cl solution. The mixture was extracted with CH_2Cl_2, and the organic layers were combined and dried over Na_2SO_4. After filtration and concentration in vacuo, the obtained crude product was purified by PTLC or silica gel column chromatography ($CHCl_3$/MeOH) to afford the desired product.

*4.3.1. (1R,2S)-syn-3-Diphenylphosphinylamino-2-(9H-fluoren-9-ylidene)amino-3-phenylpropanenitrile (**3a**).* Yellow fine needles, mp 200 °C (dec); IR (neat): 3401, 3165, 3058, 2917, 2361, 2344, 1646, 1597, 1451,1436, 1309, 1178, 1124, 1108,1072; ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 8.01–7.94 (m, 4H), 7.80 (d, J=7.9 Hz, 1H), 7.63–7.38 (m, 13H), 7.32–7.22 (m, 5H), 5.61 (d, J=3.4 Hz, 1H), 4.82–4.77 (m, 1H), 4.65 (dd, J=10.2, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.6, 144.3, 141.4, 138.5, 137.5, 132.8, 132.5, 132.5, 132.4, 132.3, 132.2, 132.2, 132.1, 132.0, 131.7, 131.2, 130.7, 128.8, 128.7, 128.6, 128.6, 128.6, 128.5, 128.3, 127.8, 127.5, 123.2, 120.7, 119.6, 117.1, 57.9, 57.7 (J_{PC}=5.7 Hz); ^{31}P NMR ($CDCl_3$, 161.83 MHz): δ 23.5; HRMS (DART®): exact mass calcd for $C_{34}H_{27}N_3OP$ $[M+H]^+$ 524.18917, found 524.19125; chiral HPLC: Daicel Chiralcel AD-H: hexane/*i*PrOH=2:1, flow rate=0.7 mL/min; t_R=15.9 min (1*R*,2*S*), 47.7 min (1*S*,2*R*). $[\alpha]_D^{20}$ +9.6 (*c* 0.50, CH_2Cl_2) 73% ee.

*4.3.2. syn-3-(p-Bromophenyl)-3-diphenylphosphinylamino-2-(9H-fluoren-9-ylidene)aminopropanenitrile (**3b**).* Yellow fine needles, mp 210 °C (dec); IR (neat): 3054, 2986, 2685, 2372, 2348, 2308, 1698, 1636, 1421, 1265; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.93–7.88 (m, 4H), 7.71 (d, J=7.6 Hz, 1H), 7.56–7.30 (m, 12H), 7.26–7.17 (m, 5H), 5.47 (d, J=3.4 Hz, 1H), 4.68–4.66 (m, 1H), 4.57 (dd, J=10.3, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 169.0, 144.3, 141.6, 141.4, 137.6, 137.4, 133.0, 132.4, 132.4, 132.3, 132.3, 132.3, 132.2, 131.6, 131.6, 131.5, 131.5, 130.0, 129.2, 128.8, 128.8, 128.7, 128.7, 128.6, 128.6, 128.6, 128.3, 127.8, 123.2, 122.5, 120.8, 119.7, 116.8, 57.4, 57.4; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.4; HRMS (ESI): exact mass calcd for $C_{34}H_{26}BrN_3OP$ $[M+H]^+$ 602.09914, found 602.09948.

*4.3.3. syn-3-Diphenylphosphinylamino-2-(9H-fluoren-9-ylideneamino)-3-(p-methoxyphenyl)propanenitrile (**3c**).* Yellow fine needles, mp 204 °C (dec); IR (neat): 2921, 2851, 2363, 2328, 1698, 1682, 1649, 1456, 1273; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.93–7.92 (m, 4H), 7.78 (d, J=7.6 Hz, 1H), 7.62–7.36 (m, 10H), 7.30–7.21 (m, 5H), 6.81 (d, J=8.9 Hz, 2H), 5.57 (d, J=3.4 Hz, 1H), 4.73 (m, 1H), 4.55 (m. 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.5, 159.4, 144.2, 141.4, 137.5, 132.8, 132.6, 132.5, 132.4, 132.2, 132.2, 132.2, 132.1, 131.7, 131.2, 130.8, 130.6, 129.4, 128.7, 128.6, 128.6, 128.6, 127.8, 123.2, 120.7, 119.6, 117.2, 113.8, 113.7, 57.9 (J_{PC}=5.8 Hz), 57.4, 55.2; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.4; HRMS (ESI): exact mass calcd for $C_{35}H_{29}N_3O_2P$ $[M+H]^+$ 554.19974, found 554.19886.

*4.3.4. syn-3-Diphenylphosphinylamino-2-(9H-fluoren-9-ylideneamino)-3-(p-tolyl)propanenitrile (**3d**).* Mp 200 °C (dec); IR (neat): 3161, 2361, 1772, 1646, 1600, 1449, 1435, 1179, 1106; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.94 (m, 4H), 7.77 (d, J=10.0 Hz, 1H), 7.59–7.34 (m, 10H), 7.28–7.17 (m, 5H), 7.07 (d, J=7.6 Hz, 2H), 5.56 (d, J=4.1 Hz, 1H), 4.73–4.70 (m, 1H), 4.57 (dd, J=10.3, 6.9 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.5, 144.2, 141.3, 138.0, 137.5, 135.6, 132.8, 132.5, 132.4, 132.3, 132.2, 132.2, 132.1, 132.1, 130.7, 129.1, 128.7, 128.7, 128.6, 128.6, 128.6, 127.8, 127.3, 123.2, 120.7, 119.6, 57.9 (J_{PC}=4.2 Hz), 57.7, 21.1; ^{31}P NMR ($CDCl_3$, 242.83 MHz): δ 23.4; HRMS (ESI): exact mass calcd for $C_{35}H_{29}N_3OP$ $[M+H]^+$ 538.20482, found 538.20692.

*4.3.5. syn-3-Diphenylphosphinylamino-2-(9H-fluoren-9-ylideneamino)-3-(o-tolyl)propanenitrile (**3e**).* Yellow fine needles, mp: 195 °C (dec); IR (neat): 3168, 3051, 2788, 2373, 2349, 1764, 1694, 1641, 1597, 1436, 1288, 1211, 1180, 1012; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.85 (m, 4H), 7.71 (d, J=8.2 Hz, 1H), 7.65 (d, J=7.6 Hz, 1H), 7.50–7.29 (m, 11H), 7.23–7.10 (m, 4H), 7.01 (d, J=7.6 Hz, 1H), 5.53 (d, J=4.1 Hz, 1H), 4.99 (dt, J=9.3, 4.1 Hz, 1H), 4.49 (dd, J=10.3, 7.6 Hz, 1H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.7, 144.2, 141.3, 137.5, 137.1, 135.5, 132.8, 132.5, 132.4, 132.4, 132.2, 132.2, 132.1, 132.0, 132.0, 131.3, 130.7, 130.2, 128.7, 128.6, 128.6, 128.6, 128.6, 128.5, 128.1, 127.8, 126.7, 126.4, 123.2, 120.7, 119.6, 117.0, 57.4 (J_{PC}=6.0 Hz), 53.1, 19.4; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.7; HRMS (ESI): exact mass calcd for $C_{35}H_{29}N_3OP$ $[M+H]^+$ 538.20482, found 538.20229.

*4.3.6. syn-3-Diphenylphosphinylamino-2-(9H-fluoren-9-ylideneamino)-3-(2-naphthyl)propanenitrile (**3f**).* Yellow fine needles, mp 206 °C (dec); IR (neat): 3054, 2986, 2373, 2348, 2306, 1698, 1649, 1436, 1421, 1265, 1203, 1174, 1157; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.99–7.94 (m, 4H), 7.82–7.79 (m, 5H), 7.61 (d, J=7.6 Hz, 1H), 7.56–7.20 (m, 15H), 5.67 (d, J=3.4 Hz, 1H), 4.94 (m, 1H), 4.75 (dd, J=10.7, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 174.3, 144.3, 141.4, 137.5, 136.1, 135.1, 134.3, 133.2, 133.0, 132.9, 132.5, 132.4, 132.3, 132.2, 132.2, 132.2, 132.0, 131.7, 128.8, 128.7, 128.6, 128.6, 128.2, 127.9, 127.8, 127.6, 126.7, 126.7, 126.3, 126.2, 125.2, 123.2, 120.7, 119.6, 117.1, 58.1, 57.9 (J_{PC}=4.2 Hz); ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.6; HRMS (ESI): exact mass calcd for $C_{38}H_{29}N_3OP$ $[M+H]^+$ 574.20482, found 574.20844.

*4.3.7. syn-3-Diphenylphosphinylamino-2-(9H-fluoren-9-ylideneamino)-3-(1-naphthyl)propanenitrile (**3g**).* Yellow fine needles, mp 210 °C (dec); IR (neat): 3149, 2373, 2348, 1701, 1646, 1599, 1509, 1436, 1261, 1182, 1111; ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 8.13 (d, J=6.7 Hz, 1H), 7.94 (dd, J=2.7, 12.4 Hz, 1H), 7.90–7.71 (m, 8H), 7.65 (d, J=18.7 Hz, 1H), 7.58–7.15 (m, 14H), 5.87 (dt, J=3.9, 10.2 Hz, 1H), 5.76 (d, J=4.4 Hz, 1H), 4.29 (dd, J=7.9, 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 173.3, 145.2, 139.2, 137.8, 137.0, 134.2, 134.3, 133.2, 133.0, 132.6, 132.4, 132.4, 132.2, 132.2, 132.2, 131.6, 128.8, 128.7, 128.6, 128.5, 128.2, 128.2, 127.8, 127.6, 126.7, 126.7, 126.3, 126.2, 125.3, 123.2, 120.7, 120.0, 117.1, 58.1, 57.0 (J_{PC}=4.2 Hz); ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.7; HRMS (ESI): exact mass calcd for $C_{38}H_{29}N_3OP$ $[M+H]^+$ 574.20482, found 574.20459.

*4.3.8. syn-3-Diphenylphosphinylamino-2-(9H-fluoren-9-ylideneamino)-3-(3-pyridyl)propanenitrile (**3h**).* Yellow fine needles, mp: 130 °C (dec); IR (neat): 3055, 2374, 2349, 2316, 1757, 1693, 1645, 1591, 1435, 1187, 11s09; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 8.48 (d, J=4.8 Hz, 1H), 7.86–7.83 (m, 4H), 7.63–7.33 (m, 11H), 7.23–7.13 (m, 6H), 5.84 (d, J=5.5 Hz, 1H), 4.96 (dt, J=10.1, 5.7 Hz, 1H), 4.58 (dd, J=5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.1, 157.0, 149.2, 144.2, 141.4, 136.8, 132.6, 132.5, 132.4, 132.1, 132.1, 132.2, 132.0, 131.9, 131.9, 130.7, 128.6, 128.5, 128.5, 128.5, 128.4, 128.4, 127.9, 123.3, 123.3, 123.2, 120.6, 119.5, 117.2, 58.9, 57.6 (J_{PC}=7.2 Hz); ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 24.9; HRMS (ESI): exact mass calcd for $C_{33}H_{26}N_4OP$ $[M+H]^+$ 525.18442, found 525.18497.

*4.3.9. syn-3-Diphenylphosphinylamino-2-(9H-fluoren-9-ylideneamino)-3-(2-furyl)propanenitrile (**3i**).* Yellow fine needles, mp 115 °C (dec): IR (neat): 2360, 2340, 1646, 1598, 1437, 1191, 1107; ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 7.95–7.90 (m, 4H), 7.83 (d, J=7.9 Hz, 1H),

7.44–7.30 (m, 15H), 6.51 (s, 1H), 5.70 (d, J=3.4 Hz, 1H), 4.69–4.64 (m, 1H), 4.18 (dd, J=11.1, 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 124.51 MHz): δ 168.3, 144.2, 143.2, 141.4, 140.8, 137.5, 132.8, 132.4, 132.3, 132.3, 132.3, 132.2, 132.1, 132.0, 132.0, 131.1, 130.6, 128.8, 128.8, 128.7, 128.7, 128.7, 128.6, 127.9, 123.8, 123.8, 123.2, 120.7, 119.6, 117.2, 109.6, 57.9 (J_{PC}=4.7 Hz), 51.0; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.7; HRMS (ESI): exact mass calcd for $C_{32}H_{25}N_3O_2P$ $[M+H]^+$ 514.16844, found 514.16835.

*4.3.10. syn-3-Diphenylphosphinylamino-2-(9H-fluoren-9-ylideneamino)-3-(thiophen-2-yl)propanenitrile (**3j**).* Yellow fine needles, mp 120 °C (dec); IR (neat): 2360, 2340, 1647, 1541, 1437, 1186, 1107; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.95–7.90 (m, 1H), 7.79 (m, 2H), 7.71–7.66 (m, 2H), 7.50–7.15 (m, 14H), 7.04 (d, J=3.4 Hz, 1H), 6.93 (dd, J=3.6, 4.8 Hz, 1H), 5.67 (d, J=3.4 Hz, 1H), 5.17 (dt, J=3.6, 7.6 Hz, 1H), 4.12 (dd, J=11.0, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 170.2, 144.3, 144.2, 141.5, 141.4, 132.9, 132.6, 132.6, 132.3, 132.0, 131.5, 130.7, 128.7, 128.7, 128.5, 128.5, 128.5, 128.2, 127.9, 127.3, 126.6, 126.2, 123.5, 120.7, 119.6, 116.6, 115.9, 58.2 (J_{PC}=4.4 Hz), 54.4; ^{31}P NMR ($CDCl_3$, 242.95 MHz) δ 24.8; HRMS (ESI): exact mass calcd for $C_{32}H_{25}N_3OPS$ $[M+H]^+$ 530.14425, found 530.14464.

*4.3.11. syn-3-Cyclohexyl-3-diphenylphosphinylamino-2-(9H-fluoren-9-ylideneamino)propanenitrile (**3k**).* Yellow amorphous solid, mp 187 °C (dec); IR (neat): 3054, 2986, 2372, 2348, 2308, 1748, 1733, 1716, 1698, 1540, 1508, 1455, 1421, 1374; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 8.03–7.96 (m, 4H), 7.74 (d, J=7.6 Hz, 1H), 7.61 (d, J=7.6 Hz, 1H), 7.56 (d, J=7.6 Hz, 1H), 7.48–7.32 (m, 9H), 7.23–7.17 (m, 2H), 5.54 (d, J=3.4 Hz, 1H), 3.33 (m, 1H), 2.18 (d, J=12.4 Hz, 1H), 1.79–1.69 (m, 3H), 1.57–1.48 (m, 3H), 1.19–0.97 (m, 5H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 167.8, 144.3, 141.3, 137.6, 133.1, 132.7, 132.6, 132.5, 132.5, 132.2, 132.2, 132.0, 131.9, 131.0, 130.7, 128.7, 128.6, 128.6, 128.5, 128.5, 127.7, 123.2, 120.7, 119.6, 118.1, 58.7, 54.6 (J_{PC}=5.7 Hz), 41.0 (J_{PC}=3.0 Hz), 30.3, 28.8, 26.3, 26.1, 26.0; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 22.6; HRMS (ESI): exact mass calcd for $C_{34}H_{33}N_3OP$ $[M+H]^+$ 530.23612, found 530.23378.

*4.3.12. syn-3-Diphenylphosphinylamino-2-(9H-fluoren-9-ylideneamino)-3-iso-propylpropanenitrile (**3l**).* Yellow amorphous solid, mp 186 °C (dec); IR (neat): 3057, 2962, 2360, 2340, 1645, 1598, 1451, 1308, 1188; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 8.00 (m, 1H), 7.88 (dd, J=11.7, 7.6 Hz, 2H), 7.73 (m, 3H), 7.56 (d, J=7.6 Hz, 1H), 7.39–7.26 (m, 11H), 5.46 (d, J=4.8 Hz, 1H), 3.58–3.54 (m, 1H), 3.34 (dd, J=10.9, 6.8 Hz, 1H), 2.23 (m, 1H), 1.13 (d, J=6.8 Hz, 3H), 1.09 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 168.8, 144.3, 141.4, 137.8, 132.9, 132.7, 132.5, 132.5, 132.4, 132.4, 132.2, 132.1, 132.0, 132.0, 131.8, 131.7, 130.7, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.0, 123.2, 120.7, 119.6, 117.2, 58.9, 55.2 (J_{PC}=4.4 Hz), 31.0 (J_{PC}=5.9 Hz), 21.2, 18.0; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 24.5; HRMS (ESI): exact mass calcd for $C_{31}H_{29}N_3OP$ $[M+H]^+$ 490.20482, found 490.20612.

*4.3.13. syn-3-Diphenylphosphinylamino-2-(9H-fluoren-9-ylideneamino)nonanenitrile (**3m**).* Yellow amorphous solid, mp 179 °C (dec); IR (neat): 2926, 2857, 2361, 1644, 1599, 1451, 1438, 1309, 1192, 1123, 1108, 1027; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.93 (m, 4H), 7.85 (d, J=7.6 Hz, 1H), 7.60 (d, J=7.6 Hz, 1H), 7.50 (d, J=6.9 Hz, 1H), 7.47–7.13 (m, 11H), 5.67 (d, J=4.1 Hz, 1H), 3.65 (dd, J=7.6, 11.0 Hz, 1H), 3.45–3.44 (m, 1H), 1.22–1.13 (m, 10H), 0.81 (t, J=6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 167.7, 144.0, 141.0, 141.3, 137.6, 132.5, 132.4, 132.2, 132.1, 132.1, 132.0, 132.0, 132.0, 131.9, 131.5, 131.5, 130.6, 128.7, 128.6, 128.5, 128.4, 127.8, 123.1, 123.0, 120.5, 119.5, 119.4, 117.7, 57.0 (J_{PC}=2.9 Hz), 54.6, 32.5 (J_{PC}=5.7 Hz), 31.5, 28.8, 26.0, 22.5, 14.0; ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 23.3; HRMS (ESI): exact mass calcd for $C_{34}H_{35}N_3OP$ $[M+H]^+$ 532.25177, found 532.25399.

4.4. Synthesis of *syn*-3-diphenylphosphinylamino-2-amino-3-phenylpropanenitrile (4a)

A solution of **3a** (100 mg, 0.183 mmol) in a mixture of THF (9 mL) and 0.5 M HCl (1 mL) was stirred at 0 °C for 10 min and then diluted with H_2O (15 mL), and the aqueous layer was separated and washed with Et_2O (10 mL×3). The aqueous layer was basified with saturated $NaHCO_3$ (5 mL), and then the aqueous phase was extracted with EtOAc (15 mL×3). The organic layers were combined, then dried over Na_2SO_4 and evaporated under reduced pressure to afford **4a** (69 mg, 98%).

*4.4.1. syn-3-Diphenylphosphinylamino-2-amino-3-phenylpropanenitrile (**4a**).* Colorless fine needles, mp 165 °C; IR (neat): 2922, 2368, 2351, 2326, 1716, 1698, 1635, 1619, 1557, 1473, 1456, 1264; ^{1}H NMR ($CDCl_3$, 495.13 MHz): δ 7.84–7.65 (m, 5H), 7.48–7.25 (m, 10H), 4.27–4.23 (m, 1H), 4.10–4.06 (m, 1H), 1.7 (br, 2H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 132.5, 132.5, 132.3, 132.2, 131.7, 131.6, 131.4, 129.0, 128.9, 128.8, 128.7, 128.7, 128.7, 128.6, 128.6, 128.5, 127.3, 120.3, 57.8, 50.7 (J_{PC}=3.6 Hz); ^{31}P NMR ($CDCl_3$, 242.95 MHz): δ 24.8; HRMS (DART®): exact mass calcd for $C_{21}H_{21}N_3OP$ $[M+H]^+$ 362.14222, found 362.14189.

4.5. Synthesis of *syn*-2,3-diamino-3-phenylpropanenitrile bishydrochloric acid salt (5a·2HCl)

A solution of **4a** (60.0 mg, 0.146 mmol) in a mixture of MeOH (4 mL) and concd HCl (1 mL) was stirred at room temperature for 1 h, and then diluted with H_2O (10 mL). After the aqueous phase was washed with EtOAc (10 mL×3), the aqueous layers were combined and evaporated under reduced pressure to afford **5a** (31.8 mg, 93% yield).

*4.5.1. syn-2,3-Diamino-3-phenylpropanenitrile bishydrochloric acid salt (**5a**·2HCl).* Colorless fine needles, mp 123 °C (dec): IR (neat.): 3434, 2522, 1661, 1641, 1585, 1442, 1204; ^{1}H NMR (CD_3OD, 600.17 MHz): δ 7.81–7.48 (m, 5H), 5.53 (d, J=6.2 Hz, 1H), 5.43–4.83 (br, 5H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 133.3, 132.3, 130.9, 129.7, 113.8, 55.2, 45.6; HRMS (DART®): exact mass calcd for $C_9H_{12}N_3$ $[M-H-2Cl]^+$ 162.1026, found 162.1029.

4.6. Neutralization of 5a·2HCl

A saturated $NaHCO_3$ aqueous solution was added to a stirred solution of **5a**·2HCl (11.8 mg, 0.078 mmol) in MeOH (10 mL). The solution was then stirred for 10 min at ambient temperature. CH_2Cl_2 was added, and the reaction mixture was extracted with CH_2Cl_2, then the organic layers were combined and dried over Na_2SO_4. The desired product was obtained in a pure form after filtration and concentration of the CH_2Cl_2 solution (5.3 mg, 67% yield).

*4.6.1. syn-2,3-Diamino-3-phenylpropanenitrile (**5a**).* Colorless amorphous solid, mp 155 °C; IR (neat): 2922, 2326, 1698, 1264; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.34–7.30 (m, 5H), 4.10 (d, J=6.2 Hz, 1H), 3.75 (d, J=6.2 Hz, 1H), 1.75 (s, 4H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 139.5, 128.8, 127.2, 126.6, 120.6, 58.6, 50.6; HRMS (DART®): exact mass calcd for $C_9H_{12}N_3$ $[M+H]^+$ 162.1312, found 162.10369.

4.7. Synthesis of *syn*-2,3-diamino-3-phenylpropanoic acid (6a)

Compound **5a**·2HCl (207.9 mg, 0.89 mmol) was dissolved in concd HCl at 0 °C, and the solution was heated at 80 °C for 12 h. After being cooled to ambient temperature, the solution was diluted with water and extracted with Et_2O. The separated aqueous

layer was evaporated under reduced pressure and the residue was dissolved in EtOH. Propylene oxide was then added and the mixture was stirred at room temperature for 30 min. A white solid precipitated, which was collected by filtration and washed with cold EtOH and Et_2O to give the desired diamino acid (112 mg, 70% yield).

*4.7.1. syn-2R,3S-Diamino-3-phenylpropanoic acid (**6a**).*[13] Colorless fine needles, mp 202 °C (dec); ^{1}H NMR (D_2O, 600.17 MHz): δ 7.40–7.29 (m, 5H), 4.61 (m, 1H, overlap with D_2O peaks, 1H), 4.09 (s, 1H), ^{13}C NMR (D_2O, 150.92 MHz standard: MeOH δ 4.95): δ 172.2, 132.4, 132.2, 131.3, 129.4, 55.9, 55.13. $[\alpha]_D^{20}$ −18.0 (*c* 0.50, H_2O) (Ref. 13, $[\alpha]_D^{26}$ +39 (*c* 0.52, H_2O) (99% ee, 2*S*,3*R*-form)).

4.8. Synthesis of *syn*-1-phenyl-1,2,3-tris(*tert*-butoxycarbonylamino)propane (7a)

Boc_2O (95.6 mg, 0.44 mmol) and $NiCl_2 \cdot 6H_2O$ (17.3 mg, 0.073 mmol) were added to a stirred solution of diaminonitrile (11.8 mg, 0.078 mmol) in dry methanol (20 mL) in a 50 mL round-bottom flask and cooled to 0 °C. $NaBH_4$ (19.3 mg, 0.51 mmol) was then added in small portions over 30 min. The reaction was exothermic and effervescent. The resulting reaction mixture containing a finely divided black precipitate was allowed to warm to room temperature and stirred for a further 1 h, at which point diethylenetriamine (15.7 μL, 0.14 mmol) was added. The mixture was stirred for 30 min before solvent evaporation. The purple residue was dissolved in CH_2Cl_2 and extracted with saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to yield a residue, which was purified by column chromatography to give desired tricarbamate as colorless liquid (23.4 mg, 69% yield).

*4.8.1. syn-1-Phenyl-1,2,3-tris(tert-butoxycarbonylamino)propane (**7a**).*[17] Colorless liquid, IR (neat): 2977, 2933, 2249, 1698, 1519, 1479, 1414, 1392, 1249, 1174, 1068, 1038; ^{1}H NMR ($CDCl_3$, 600.17 MHz): δ 7.75–7.72 (m, 2H), 7.47 (d, *J*=6.1 Hz, 1H), 7.40–7.37 (m, 2H), 5.07 (br, 1H), 4.96 (br, 1H); 3.70 (d, *J*=10.9 Hz, 2H), 3.38 (br, 1H), 3.26 (br, 1H), 3.19 (br, 1H), 1.42–1.35 (m, 27H); ^{13}C NMR ($CDCl_3$, 150.92 MHz): δ 156.16 (br), 131.6, 131.5, 128.5, 128.4, 80.2, 50.5, 39.5, 28.3, 28.3. HRMS (DART®): exact mass calcd for $C_{24}H_{40}N_3O_6$ $[M+H]^+$ 466.2912, found 466.2915.

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