A Sequential C–N, C–C Bond-Forming Reaction: Direct Synthesis of α-Amino Acids from Terminal Alkynes

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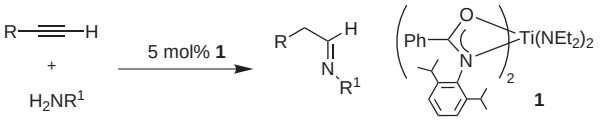
Abstract: Catalytic hydroamination is combined with the Strecker reaction to yield a one-pot synthesis of α-cyanoamines from terminal alkynes. This methodology is further applied to the synthesis of α-amino acids and α-amino esters.

Key words: amino acids, catalysis, hydroamination, Strecker reaction, synthesis

Sequential one-pot reactions, such as catalytic C–N and subsequent C–C bond formation, are very desirable in synthetic chemistry due to their efficiency and synthetic facility.[1] Such an approach leading to the synthesis of important organic building blocks, such as α-amino acids, represents an important contribution to synthetic methodology.[2] Furthermore, new routes for the direct synthesis of these highly functionalized molecules from alternative synthetic precursors provide enhanced flexibility in synthetic approaches. Here we report a sequential one-pot synthesis of α-cyanoamines, (also known as α-amino nitriles), ready precursors to α-amino acids, from easily accessible terminal alkynes using a modified Strecker reaction.

The most efficient and atom-economical way of forming C–N bonds is through catalytic hydroamination,[3] the addition of nitrogen and hydrogen atoms across a carbon-carbon multiple bond (Equation 1). Our research group has developed group 4 bis(amidate) complexes for the hydroamination of alkynes.[4] In particular, the bis-amidate, bis-amido titanium(IV) complex **1** has been shown to be very active in the *anti*-Markovnikov regioselective intermolecular hydroamination of terminal alkynes with a wide range of primary amines to yield exclusively aldimine products.[5] This easily prepared catalyst is, to the best of our knowledge, the only generally applicable *anti*-Markovnikov selective catalyst that has been reported to date.[6]



Equation 1

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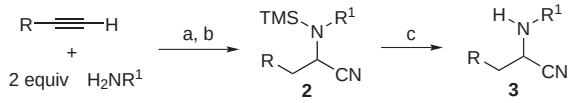
Though imines are found in natural products and pharmaceuticals,[7] one of their most important uses is as synthetic intermediates in further transformations.[8] Hydroamination-generated imines are particularly attractive in this regard as there are no side products formed in the reaction.

Importantly, imines are invoked as intermediates in the Strecker reaction (Equation 2), a well established method for the synthesis of racemic amino acids.[9] More recent contributions in this area have focused on enantioselective versions of this reaction.[10] As shown in Equation 2, carbonyl containing starting materials are used for either the in situ preparation of the requisite imines or alternatively, for the preparation of isolable imine substrates. In the latter case, the required isolation of these easily hydrolyzed functional groups can limit the reaction scope to more stable imines, such as aryl-substituted imines.

Equation 2

Here we demonstrate that the combination of the facile catalytic synthesis of a wide range of aldimines from terminal alkynes can be used in a modified Strecker reaction for the synthesis of alkyl-substituted α-cyanoamines (Scheme 1). This approach complements existing methodology and provides flexibility in synthetic strategy by taking advantage of the fact that terminal alkynes are easily installed and can be carried through synthetic manipulations with ease.

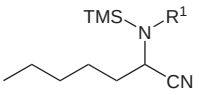
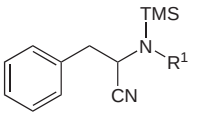
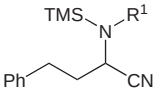


Scheme 1 Synthesis of α-cyanoamines. *Reagents and conditions*: a) **1** (5 mol%), C_6H_6, 65 °C, 12 h; b) TMSCN (1 equiv), r.t., 3 h; c) sat. NH_4Cl.

Initial investigations focused on the reaction of 1-hexyne and isopropyl amine, using NMR spectroscopy to monitor reaction progress. 1-Hexyne and 2 equivalents of isopropyl amine were combined with 5 mol% of precatalyst **1** in benzene-d_6 within a sealed NMR tube and heated at 65 °C for 12 hours. Appearance of a triplet at δ = 7.40 ppm in the ^{1}H NMR spectrum as well as the complete disappearance of the alkyne signal at δ = 1.78 ppm signified

imine formation. This observation was further confirmed by the diagnostic imine signal at δ = 161 ppm in the ^{13}C NMR spectrum. The cyano moiety was then added to the imine using 1 equivalent of TMSCN administered via syringe under an inert atmosphere at room temperature. Disappearance of the imine signals in both the ^{1}H and ^{13}C NMR spectra within three hours signified its consumption, and the appearance of a peak at δ = 120 ppm in the ^{13}C NMR spectrum indicated the formation of the desired cyanoamine. The TMS-protected cyanoamines **2** were spectroscopically characterized in situ and isolable α-cyanoamines **3** were prepared to obtain corroborating mass spectrometric data. Table 1 demonstrates that the reaction conditions are amenable to both aliphatic and aromatic alkynes, as well as amines with different steric properties. Most importantly, these reactions work well with benzyl amine, a challenging aliphatic amine substrate for alkyne hydroamination.[11] This benzyl group is a desirable substituent due to the fact that it can be used as a protecting group for the amine functionality.

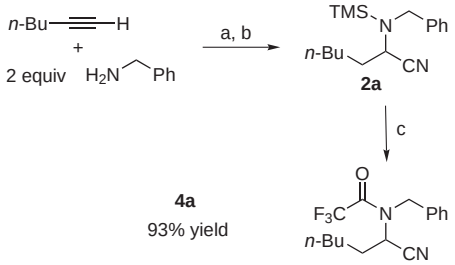
Table 1 TMS-Protected Cyanoamines Formed from Tandem Reaction Sequence (Scheme 1)

Compound	Cyanoamine	R^1	Yield (%)
2a		Bn	Quant.[a]
2b		*i*-Pr	Quant.[a]
2c		Bn	90[b]
2d		*i*-Pr	89[b]
2e		Bn	98[b]
2f		*i*-Pr	86[b]

[a] Conversion based on consumption of imine starting material calculated from ^{1}H NMR spectroscopy.
[b] Yield calculated by ^{1}H NMR spectroscopy using 2,4,6-trimethoxybenzene as an internal standard.

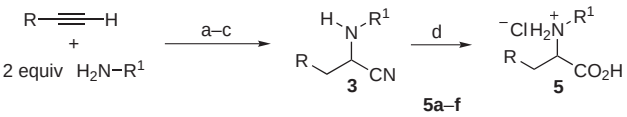
The reactions proceed cleanly with no spectroscopically discernible side products. α-Cyanoamines can be unstable towards common purification methods such as chromatography,[10b] and as such, removal of the amide proligand from the cyanoamine product was problematic. Thus, the yield was determined using ^{1}H NMR spectroscopy with an internal standard, and the tandem reaction sequence was shown to be high yielding over the two steps (Table 1). It is interesting to note that the use of *tert*-butyl amine in the above reaction sequence fails to produce any α-cyanoamine, even though successful formation of the imine is observed. Presumably this is due to the overwhelming steric interactions present between the TMSCN and the *tert*-butyl groups.

Though it is known that α-cyanoamines **3** can be unstable, Jacobsen and co-workers have shown with numerous examples that treatment of TMS-protected α-cyanoamines with trifluoroacetic anhydride yield trifluoroacetate-protected α-cyanoamines.[12] These compounds are more stable than **3** and are amenable to purification. In this case, for example, compound **4a** was formed by the addition of 2.5 equivalents of trifluoroacetic anhydride to the TMS-protected cyanoamine **2a** (Scheme 2) and was purified via column chromatography to give the desired product in 93% yield. Thus, as demonstrated by both the ^{1}H NMR spectroscopic yield determination and the isolation of **4a**, both the hydroamination step and the addition of the cyano moiety are high-yielding reactions.



Scheme 2 Synthesis of trifluoroacetate-protected α-cyanoamines. *Reagents and conditions*: a) **1** (5 mol%), C_6H_6, 65 °C, 12 h; b) TMSCN (1 equiv), r.t., 3 h; c) TFAA (2.5 equiv), 5 min.

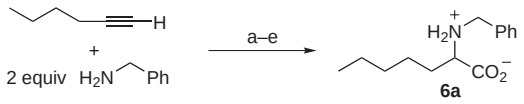
α-Cyanoamines are extremely useful as precursors in the formation of α-amino acids. To demonstrate the utility of this reaction methodology, a number of α-amino acids were synthesized by refluxing the α-cyanoamine **3** in concentrated hydrochloric acid (Scheme 3).



Scheme 3 Synthesis of α-amino acids. *Reagents and conditions*: a) **1** (5 mol%), C_6H_6, 65 °C, 12 h; b) TMSCN (1 equiv), r.t., 3 h; c) sat. NH_4Cl; d) concd HCl, reflux, 12 h.

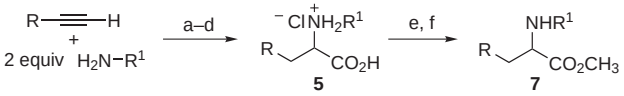
The progress of this reaction was monitored by mass spectrometry, and the corresponding α-amino acid was isolated as HCl salt **5** after completion of the reaction in 6–12 hours. Again, this conversion is clean, and only the presence of the amide proligand and the desired product are observed by ^{1}H NMR and ^{13}C NMR spectroscopy, using methanol-d_4 as an NMR solvent. Amino acid formation was further supported by high-resolution mass spectrometry. Moreover, the amino acid salts can be obtained directly from the TMS-cyanoamines **2** by omitting the reaction quench with saturated ammonium chloride and simply heating to reflux in concentrated hydrochloric acid. This leads to a one-pot synthesis of α-amino acids from terminal alkynes. The desired products were obtained in quantitative amounts; though the isolation of analytically pure materials proved challenging (likely due to residual water or salts) and thus accurate yield determinations could not be obtained for this step in the reaction sequence.

However, if the amino acid–HCl salt was treated with propylene oxide in water and ethanol, the free amino acid was formed[13] and could be separated from the amide proligand by precipitation from water (Scheme 4). For example, this methodology yielded the zwitterionic species **6a** in analytically pure form in modest (<30%) yields.



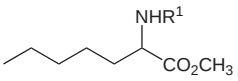
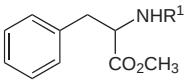
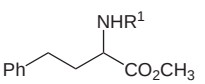
Scheme 4 Synthesis of free amino acid. *Reagents and conditions*: a) **1** (5 mol%), C_6H_6, 65 °C, 12 h; b) TMSCN, r.t., 3 h; c) sat. NH_4Cl; d) concd HCl, reflux, 12 h; e) propylene oxide, EtOH, H_2O.

A more generally useful reaction for the quantification of α-amino acid derivatives is the preparation of the corresponding α-amino methyl esters **7** (Scheme 5). The amino acid salts were dissolved in acidic methanol (made from methanol and thionyl chloride) and then heated to reflux. Formation of the α-amino methyl ester salts was monitored by mass spectrometry, and the reactions were complete in 3–5 hours. After removal of the volatile components, the α-amino methyl esters were obtained by treatment of the salts with a saturated sodium bicarbonate solution and extraction into organic solvent. These compounds are amenable to column chromatography and yield analytically pure product that is free of the amide proligand in good overall yields for the entire reaction sequence (Table 2). Though this reaction sequence can be performed in one pot, thereby avoiding the isolation of **5**, the isolated yields of the final α-amino methyl esters were somewhat lower in this case (i.e. **7c** was formed in 48% yield using a one-pot synthesis).



Scheme 5 Synthesis of α-amino methyl esters. *Reagents and conditions*: a) **1** (5 mol%), C_6H_6, 65 °C, 12 h; b) TMSCN (1 equiv), r.t., 3 h; c) sat. NH_4Cl; d) concd HCl, reflux, 12 h; e) $SOCl_2$, MeOH, reflux, 5 h; f) sat. $NaHCO_3$.

Table 2 Synthesis of Amino Methyl Esters (Scheme 5)

Compound	Amino methyl ester	R^1	Yield (%)[a]
7a		Bn	58
7b		*i*-Pr	61
7c		Bn	58
7d		*i*-Pr	54
7e		Bn	58
7f		*i*-Pr	69

[a] Isolated yield calculated from terminal alkyne.

In summary, we report the combination of catalytic hydroamination with the Strecker reaction to give a high yielding one-pot synthesis of α-cyanoamines from terminal alkynes. Importantly, terminal alkynes are easily installed and can be carried through synthetic manipulation with ease. Furthermore, the utility of this reaction sequence has been demonstrated by the further conversion of these versatile α-cyanoamines to both α-amino acids and α-amino esters. This approach yields α-cyanoamines **3** and their α-amino acid derivatives **5** and **7** with a methylene group α to the tertiary carbon. This spacer is a rare structural motif for amino acid derivatives synthesized via other Strecker reaction methods reported. Ongoing investigations focus on the development of reaction protocols for the stereoselective preparation of amino acid derivatives.

General Method Provided for Trifluoroacetate-Protected Cyanoamine 4a

An oven-dried Schlenk flask was charged with 0.16 g (2.0 mmol) of 1-hexyne, 0.42 g (3.9 mmol) of benzyl amine, 0.07 g (0.10 mmol) of **1**, and 4 mL of benzene in the glove box. The solution was stirred at 65 °C for 12 h before it was cooled to r.t. and 0.26 mL (2.0 mmol) of TMSCN was added via syringe. The solution stirred for a further 3 h and then 0.68 mL (4.9 mmol) of TFAA was added. After stirring for 5 min, 10 mL of Et_2O was added, and the organic phase was washed with a sat. $NaHCO_3$ solution (4 × 10 mL). The organic portion was dried over $MgSO_4$, and concentrated to a dark brown oil. It was purified by silica gel column chromatography (3:2 hexanes–Et_2O) and concentrated to provide **4a** as a pale yellow oil (0.57 g, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 7.2 Hz, 3 H), 1.23 (m, 5 H), 1.37 (m, 1 H), 1.56 (m, 1 H), 1.75 (m, 1 H), 4.64 (d, *J* = 16.0 Hz, 1 H), 4.73 (t, *J* = 6.0 Hz, 1 H), 4.85 (d, *J* = 16.0 Hz, 1 H), 7.34 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.3, 25.6, 30.8, 31.1, 48.9, 51.3, 116.1, 116.3 (q, *J* = 286 Hz), 128.0, 129.2, 129.4, 133.7, 157.2 (q, *J* = 37 Hz). MS (ESI): *m/z* = 335.2 [M + Na]. HRMS (ESI): *m/z* calcd for $C_{16}H_{19}F_3N_2NaO$: 335.1347 [M + Na]; found: 335.1346. Anal. Calcd for $C_{16}H_{19}N_2OF_3$: C, 61.53; N, 8.97; H, 6.13. Found: C, 61.93; N, 9.10, H, 6.35.

Free Amino Acid 6a

^{1}H NMR (300 MHz, CD_3OD): δ = 0.93 (t, *J* = 6.6 Hz, 3 H), 1.39 (m, 6 H), 1.84 (m, 2 H), 3.50 (t, *J* = 6.0 Hz, 1 H), 4.12 (d, *J* = 13.0 Hz, 1 H), 4.24 (d, *J* = 13.0 Hz, 1 H), 7.48 (m, 5 H). ^{13}C NMR (75 MHz, CD_3OD): δ = 14.3, 23.4, 25.9, 31.6, 32.7, 51.7, 63.5, 130.2, 130.6, 131.2, 132.8, 173.3. MS (ESI): *m/z* = 236.1 [M + 1], 190.1 [M – CO_2H]. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; N, 5.95; H, 8.99. Found: C, 71.66; N, 6.19; H, 9.18.

α-Amino Methyl Esters 7

Compound **7a**: 58% yield (1:16:1 EtOAc–hexane–Et_3N). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3 H), 1.29 (m, 6 H), 1.60 (m, 2 H), 1.82 (br s, 1 H), 3.25 (t, *J* = 6.8 Hz, 1 H), 3.61 (d, *J* = 13.0 Hz, 1 H), 3.70 (s, 3 H), 3.79 (d, *J* = 13.0 Hz, 1 H), 7.26 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.6, 25.6, 31.8, 33.7, 51.8, 52.4, 60.9, 127.2, 128.4, 128.5, 140.1, 176.3. MS (ESI): *m/z* = 272.3 [M + Na], 250.3 [M + H]. HRMS (EI): *m/z* calcd for $C_{15}H_{23}NO_2$ [M^+]: 249.17288; found: 249.17325. Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; N, 5.62; H, 9.30. Found: C, 72.30; N, 6.00; H, 9.00.

Compound **7b**: 61% yield (1:16:1 EtOAc–hexane–Et_3N). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.4 Hz, 3 H), 0.95 (d, *J* = 6.0 Hz, 3 H), 0.99 (d, *J* = 6.0 Hz, 3 H), 1.26 (m, 6 H), 1.54 (m, 3 H), 2.64 (sept, *J* = 6.0 Hz, 1 H), 3.27 (t, *J* = 6.8 Hz, 1 H), 3.66 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.2, 22.6, 24.0, 25.6, 31.8, 34.2, 47.2, 51.7, 59.2, 176.8. MS (ESI): *m/z* = 202.3 [M + H]. HRMS (ESI): *m/z* calcd for $C_{11}H_{24}NO_2$ [M + H]: 202.1807; found: 202.1809. Anal. Calcd for $C_{11}H_{23}NO_2 \cdot 0.5H_2O$: C, 62.82; N, 6.66, H, 11.50. Found: C, 62.89; N, 7.08; H, 11.27.

Compound **7c**: 58% yield (1:15:1 EtOAc–hexane–Et_3N).[14] ^1H NMR (300 MHz, $CDCl_3$): δ = 1.85 (br s, 1 H), 2.95 (d, *J* = 7.1 Hz, 2 H), 3.53 (t, *J* = 6.9 Hz, 1 H), 3.62 (d, *J* = 13.0 Hz, 1 H), 3.63 (s, 3 H), 3.80 (d, *J* = 13.0 Hz, 1 H), 7.20 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.8, 51.6, 52.0, 62.1, 126.7, 127.0, 128.2, 128.3, 128.4, 129.3, 137.4, 139.7, 175.0. MS (ESI): *m/z* = 270.3 [M + H].

Compound **7d**: 54% yield (1:17:1 EtOAc–hexane–Et_3N).[14] ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.2 Hz, 3 H), 0.99 (d, *J* = 6.2 Hz, 3 H), 1.60 (br s, 1 H), 2.68 (sept, *J* = 6.2 Hz, 1 H), 2.88 (m, 2 H) 3.57 (m, 4 H), 7.19 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 23.6, 40.0, 47.1, 51.5, 60.6, 126.6, 128.3, 129.1, 137.2, 175.4. MS (ESI): *m/z* = 244.2 [M + Na], 222.3 [M + H].

Compound **7e**: 58% yield (1:10:1 EtOAc–hexane–Et_3N). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.97 (br s, 1 H), 2.05 (m, 2 H), 2.82 (m, 2 H), 3.37 (t, *J* = 6.6 Hz, 1 H), 3.71 (d, *J* = 13.0 Hz, 1 H), 3.76 (s, 3 H), 3.91 (d, *J* = 13.0 Hz, 1 H), 7.34 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.0, 35.0, 51.6, 52.1, 60.0, 125.9, 127.0, 128.3, 128.4, 128.5, 139.4, 141.4, 175.7. MS (ESI): *m/z* = 306.1 [M + Na], 284.2 [M + H]. HRMS (ESI): *m/z* calcd for $C_{18}H_{22}NO_2$ [M + H]: 284.1651; found: 284.1649. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; N, 4.94; H, 7.47. Found: C, 76.43; N, 5.00; H, 7.56.

Compound **7f**: 69% yield (1:10:1 EtOAc–hexane–Et_3N). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.0 Hz, 3 H), 1.02 (d, *J* = 6.4 Hz, 3 H), 1.55 (br s, 1 H), 1.88 (m, 2 H), 2.67 (m, 3 H), 3.30 (t, *J* = 6.8 Hz, 1 H), 3.65 (s, 3 H), 7.18 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 23.8, 32.0, 35.5, 47.0, 51.5, 58.3, 125.9, 128.3, 128.4, 141.4, 176.4. MS (ESI): *m/z* = 258.3 [M + Na], 236.3 [M + H]. HRMS (ESI): *m/z* calcd for $C_{14}H_{22}NO_2$ [M + H]: 236.1651; found: 236.1651. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; N, 5.95; H, 8.99. Found: C, 71.47; N, 6.00; H, 9.00.

Acknowledgment

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