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Enamide Synthesis

The Synthesis of Ketone-Derived Enamides by Elimination of HCN from Cyanoamides

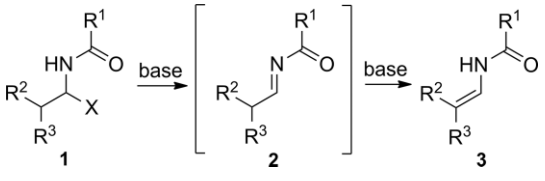
Guilhem Coussanes,[a][‡] Katharina Gaus,[a] and Anthony C. O'Sullivan*[‡‡]

Abstract: Treatment of easily available ketone-derived cyanoamides with NaO*t*Bu leads to enamides in a simple, scalable, and inexpensive one-step operation in good yield. Enamides not stabilized by conjugation or by inclusion in a ring can also be prepared. An E1cB mechanism consistent with all results and observations, is proposed. The *Z* geometry of the product enamide is highly favoured, and the regioselectivity can be directed by one's choice of protecting group.

Introduction

Enamides are reactive and versatile building blocks.[1] Their electrophilicity at the α-centre (after protonation to generate acyl iminium ions) and nucleophilicity at the β-centre have been exploited recently through the use of chiral reagents and catalysts in a number of one-step enantioselective syntheses of highly functionalized compounds.[2] Furthermore, the enantioselective hydrogenation of enamides is probably the most widely used method for the synthesis of chiral amines in both academic and industrial settings.[3] A high yielding, cheap, and scalable methodology for the synthesis of enamides would clearly further their synthetic utility.[4]

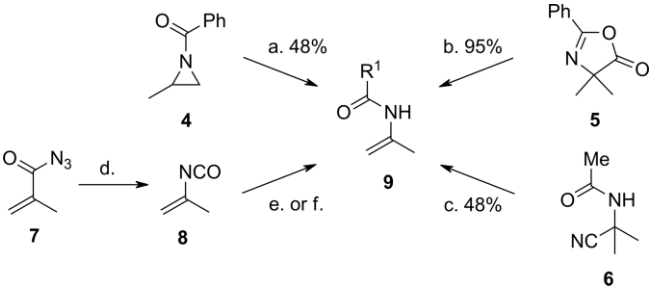
The synthesis of aldehyde-derived enamides is straightforward in view of the ready accessibility of precursor amidoacylating agents **1**, in which X can be Cl, Br, OH, OR, OCOR, SR, SO_2R, NHCOR, or benzotriazole.[5] (Scheme 1) Treatment of these compounds with base leads to highly reactive acylimines **2**, which tautomerise readily to the desired enamides.[6–8] Further developments in the field have been achieved during the synthesis of natural products containing aldehyde-derived enamide functionalities, wherein enamide formation is the key step.[9]



Scheme 1. Synthesis of aldehyde-derived enamides using amidoacylating agents.

An analogous access to enamides derived from ketones is not feasible because ketone-derived amidoacylating agents have not been described,[5] in some or all cases, due to their instability. Consequently, access to ketone-derived enamides has been achieved using other approaches. In particular, the reductive acylation of oximes, using Ac_2O/pyridine,[10] $Cr(OAc)_2$ and $Ti(OAc)_3$,[11] Fe,[12] $Fe(OAc)_2$,[13] $RuCl_2/NaHSO_3$,[14] Et_3P,[15] H_2,[16] and $CuI/NaHSO_3$[17] as reducing agents, provides easy access. However, in nearly all cases,[13] only enamides stabilized by conjugation with aromatic moieties and/or ring formation have been generated. In addition, a synthesis of enamides directly from ketones via a proposed titanium imine intermediate has recently been reported by Boehringer Ingelheim; again though, only stabilized enamides were reported.[18]

Several methods for the preparation of unstabilised ketone-derived enamides (shown in Scheme 2 with acetone-derived enamides as examples) have been reported but are inconvenient for the following reasons: i) palladium-catalyzed rearrangement of acyl aziridine **4** starts from carcinogenic aziridines;[19] ii) the pyrolysis of dimethylazlactone **5** is high yielding but requires the use of special equipment, and provides the product mixed with its tautomeric acyl imine;[20] and iii) gas phase ther-



Scheme 2. Known methods for the synthesis of isopropenyl amides/carbamates. Reagents and conditions: a) $Pd_2(dba)_3/PCy_3$, toluene, 40 °C, 7 h, R^1 = Ph. b) 550 °C, R^1 = Ph. c) 500–600 °C, 12 Torr, R^1 = Me. d) approx. 100 °C. e) ROH for R^1 = RO. f) RMgBr for R^1 = R.[24]

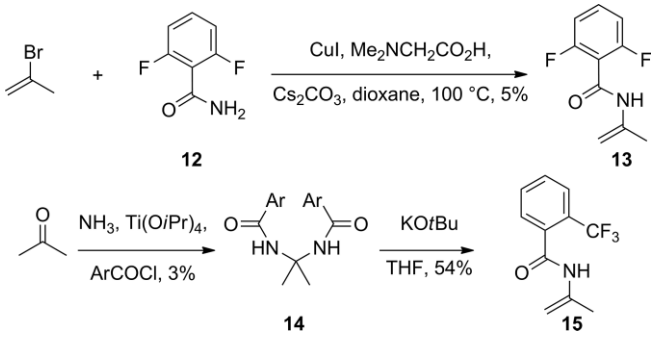
[a] *Process Research Chemistry, Syngenta Crop Protection AG, Schaffhauserstrasse 101, 4332 Stein, Switzerland*
E-mail: anthony.osullivan@syngenta.com
www.syngenta.com
[‡] University of Barcelona (most of this work was performed by G. C. when he was in a traineeship from Uni Montpelier).
[‡‡] Present address Carbogen-Amcis AG, 5001 Aarau, Switzerland
E-mail: anthony.osullivan@carbogen-amcis.com

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201600638.

molysis of readily available amidonitrile **6** also requires pyrolysis apparatus.[21] The most commonly used route to enecarbamates involves Curtius degradation of methacroyl azide **7** to isopropenyl isocyanate **8**.[22] Although the yield is high, there are safety issues as methacroyl azide is volatile, unstable and explosive. Another limiting consideration is that isopropenyl isocyanate is volatile, toxic and unstable.[23] Nevertheless it is possible to prepare and use kilogram amounts of vinyl isocyanate using the Curtius degradation, if the proper safety measures are in place.[23b,23c] This method is easier to apply safely with non-volatile substrates.

Results and Discussion

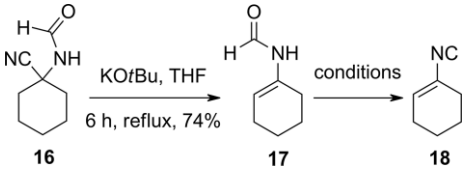
We required access to a small amount of acetone derived enamide **15**, but considered the methods described above in Scheme 2 to be sub-optimal. Unfortunately, attempts to apply methods described for stabilised enamides proved to be unfruitful (Scheme 3). Reductive acylation of acetone oxime **10** with iron powder in acetic anhydride gave only traces of **11**.[12b] Copper-catalyzed cross coupling of isopropenyl bromide with amide **12** gave desired **13** in 5 % yield.[25] The Boehringer Ingelheim method[18] led to low yields of *gem*-bis-amide **14**, and none of the desired enamide **15**.



Scheme 3. Attempts towards the synthesis of isopropenyl amides in the present work.

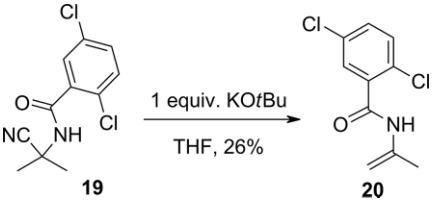
Thermolysis of **14** at 200 °C under vacuum[26] led to a mixture of products containing no enamide, but treatment of **14** with base[27] was more rewarding. The use of 1 equiv. of strong base such as *n*BuLi, *i*PrMgBr or KO*t*Bu at room temperature led to partial conversion to desired enamide **15**. The best conversion were achieved with KO*t*Bu, providing enamide **15** in 54 % yield, accompanied by 26 % of recovered starting material **14**. Despite this promising result, the lack of direct methods to access ketone-derived *gem*-bis-amides render this approach impractical as a general method.[28]

The successful base-mediated synthesis of isopropenyl amide **15** from 1,1-diamide **14** suggested that elimination of other leaving groups might also be feasible. As mentioned above, ketone-derived amidoacylating agents analogous to **1** are unknown, but the use of cyanide as a leaving group would be highly attractive in view of the stability of cyanoamines and their ready accessibility via the Strecker reaction. There is some precedent for this reaction. Ugi and co-workers demonstrated that KO*t*Bu at reflux brought about the elimination of cyanide from 1-cyano-cyclohexyl-formamide **16** (Scheme 4). Enamide **17** was not isolated but was transformed further to isocyanide **18** upon in situ treatment with $POCl_3$.[29] Later, Keating and Armstrong modified Ugi's protocol to isolate and characterize intermediate enamide **17**.[30a] Besidsky et al. demonstrated the elimination of HCN from a cyanoamide embedded in a quinuclidine ring system using KH in THF.[30b] Kurtz and Disselnkötter showed that gas phase pyrolysis of cyanoamides is faster with marble as a packing material rather than with non-basic packing materials, indicating base catalysis as a viable mechanism.[21] Herein, we now describe the scope and limitations of the Ugi method, which turns out to be applicable to ketone-derived enamides including those not stabilized by being part of a cyclohexenyl ring. In addition to its wide scope, the reaction shows high and directable regio- and stereo-selectivity, in the absence of functional groups associated with influencing selectivity.



Scheme 4. Ugi's synthesis of cyclohexenyl isonitrile, involving the elimination of cyanide from **16**.

Cyanoamide **19** was selected for initial screening and optimization of the methodology (Scheme 5). Initial screening of bases showed promising results. KO*t*Bu (1 equiv.) in THF or *t*BuOH at room temperature gave 26 % and 22 % conversion, respectively, to desired enamide **20**, with no by-products observable in the NMR. On the other hand, the use of *i*PrMgCl gave only 8 % conversion, and attempts to use BuLi led only to recovered starting material.[41] A small solvent screen showed THF to deliver higher yields than *t*BuOH, DMF, and MeCN, and running the reaction with a wider series of bases identified KO*t*Bu as the best base of those screened.[41]



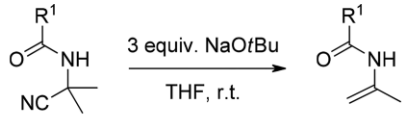
Scheme 5. Reaction used as model system to optimize conditions.

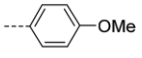
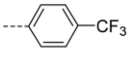
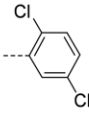
On examining the effects of counter ion, it was found that the less expensive NaO*t*Bu reacted a little faster than KO*t*Bu and much faster and more cleanly than LiO*t*Bu.[41] Led by the notion that silver cation could assist in the removal of the cyanide, a series of silver salts was screened, but to no avail. It was found that the soluble salts AgOTs, AgO_2CCF_3, AgOTf, and $AgSbF_6$ inhibit the reaction and that only the insoluble $AgNO_3$ and Ag_2SO_4 allow the reaction to take place.[31] An excess of base was found to be necessary, but more than three equivalents of NaO*t*Bu offered no advantage.

Quenching the reaction mixture appropriately proved to be very important. Considering that enamide product **20** will be almost completely deprotonated under the reaction conditions (see below), an acid quench is necessary to isolate the neutral enamide. However, enamides, although stable to base, are very acid sensitive. A series of quenching conditions with mild acids[41] revealed that $NaHCO_3$, either as a solid or more conveniently as a 1 M aqueous solution, gave a cleaner product than NH_4Cl (solid or aqueous solution) or AcOH. $NaHCO_3$ has the advantage of being acidic enough to protonate the enamide anion and that the subsequently formed Na_2CO_3 serves to maintain a pH basic enough to stabilize the enamide. The method used for further purification of the crude products is also very important. Direct crystallization is favoured with little or no loss due to decomposition.[32] As ketone-derived enamides are unstable or only partially stable to chromatography,[33] a number of chromatographic methods and stationary phases were screened.[41] The best results were achieved with chromatography on silica using eluents containing Et_3N, but there were, on occasion, unpredictable losses even using these conditions.

Using these now optimised reaction conditions (i.e. with 3 equiv. NaO*t*Bu in THF), the reaction of a series of cyanoamides derived from acetone was studied (Table 1). Most substrates reacted fully and cleanly over the course of 24 h at ambient temperature, with electron-donating groups accelerating the reaction (Table 1, Entries 1–6). The table (Table 1) is ordered according to reactivity, with the pK_a values of the corresponding carboxylic acids also provided to illustrate this point.[34]

Table 1. Conversion of a series of cyanoamides derived from acetone to the corresponding enamides.



Entry	Cyanoamide - R_1		Pka	Time (h)	Enamide	Yield
1	**21**	*t*Bu	5.01	1	**22**	64%
2	**23**		4.47	3	**24**	80%
3	**6**	Me	4.76	24	**11**	80%
4	**25**		3.79	29	**26**	84%
5	**19**		–	40	**20**	60%
6	**27**	CF_3	3.07	47	**28**	0%
7	**29**	NHPh	–	6	**30**	0%
8	**31**	OCH_2Ph	–	28	**32**	0%
9	**33**	O*t*Bu	–	3	**34**	78%

TFA analog **27** (Table 1, Entry 6) did not react at room temperature, and urea **29** (Table 1, Entry 7) decomposed nonspecifically. Benzyl carbamate **31** (Table 1, Entry 8) gave a mixture of products, presumably because the known base-catalyzed elimination of carbamate to isocyanate,[35] competes with enamide formation. It was anticipated that a poorer leaving group such as *tert*-butoxide would be less prone to elimination to isocyanate, and indeed substrate **33** (Table 1, Entry 9), provided **34** in 78 % yield under the standard conditions.

Having established the scope of the reaction with acetone-derived cyanoamides, we studied a larger panel of cyanoamides, to examine the compatibility of functional groups with the reaction and to ascertain the regio- and stereo-selectivity of these more substituted compounds (Table 2). Cyanoamides with a simple series of substituents (Me, Et, *i*Pr, cPr) as well as several with diverse functionalities were chosen.

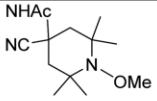
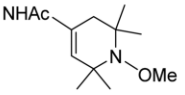
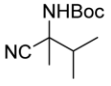
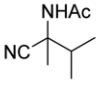
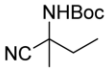
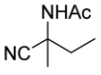
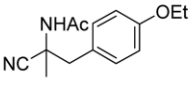
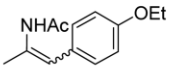
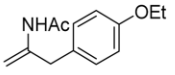
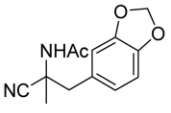
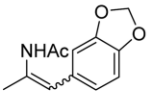
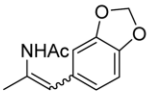
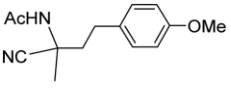
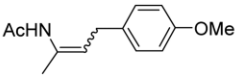
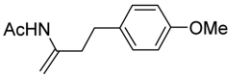
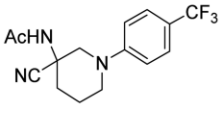
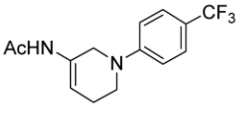
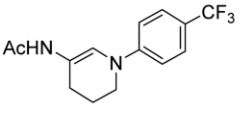
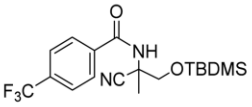
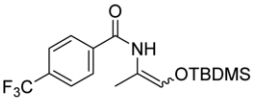
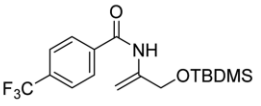
Under the standard conditions most of the substrates examined provided enamides in good to high yields. The products were obtained in nearly pure form, and in some cases as mixtures of regio- and stereo-isomers. An exception was **64** (Table 2, Entry 11), which gave **65** and **66** in low yield as a mixture of isomers after chromatography.

Cyclic compound **35** (Table 2, Entry 1) is symmetric, and leads to a single compound **36** in high yield. The regioselectivity of elimination in the formation of **38** (Table 2, Entry 2) is unsurprising, having taken place away from the cyclopropyl group, thus avoiding ring strain.

The reaction of simple open chain cyanoamides shows surprisingly high regio- and stereo-selectivity. The effect of the *N*-acyl group was unforeseen and striking. Cyanoamides **39**, **43**, **46**, and **49** (Table 2, Entries 3–6) derived from butanone and methyl butanone served as models. In each case, the Boc derivative preferentially afforded the more substituted enamide (product of Zaitsev elimination) and the acetamide underwent Hoffmann elimination in the direction of the methyl group. Also noteworthy was that the butenyl amide **47*Z*** was formed exclusively as its *Z*-isomer. To demonstrate that these simple unstabilised enamides are the kinetic products, **43** was heated under the reaction conditions at 60 °C overnight, which provided the same result as when the reaction was performed at room temperature. Hoffman enamide **45** was formed as the major product along with trace amounts of the presumably more stable Zaitsev product **44**.

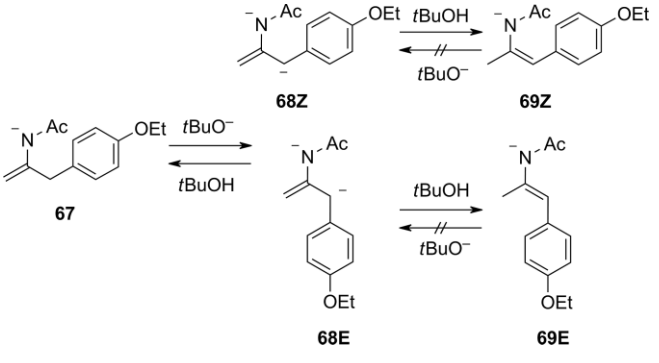
The reactions of **52** and **55** (Table 2, Entries 7 and 8) invoke elimination from the cyanoamides derived from benzyl methyl ketones. The reactions at room temperature were not regioselective. In each case, a mixture of Hoffman (**54** and **57**) and Zaitsev products (**53** ***E***+***Z*** and **56** ***E***+***Z***) were formed. It was considered possible that the initially formed Hofmann elimination product (**54** and **57**) isomerized partly to more stable isomers (**53** ***E***+***Z*** and **54** ***E***+***Z***).[36] Indeed, heating **52** overnight at 60 °C under the reaction conditions resulted in full conversion of initially formed **54** to the more stable Zaitzev isomer **53** ***E***+***Z*** in high yield. These isomers (**53*E*** and **53*Z***) were separately con-

Table 2. Conversion of a series of diverse cyanoamides to the corresponding enamides.

Entry		Cyanoamide	Time	Yield	Zaitsev enamide		Hoffman enamide	
1	**35**		131 h, r.t.	96%	**36**			
2	**37**		131 h, r.t.	77%			**38**	
3	**39**		131 h, r.t.	78% **40**:**41** 96:4	**40**		**41**	
4	**43**		18 h, r.t.	93% **44**:**45** 7:93	**44**		**45**	
5	**46**		131 h, r.t.	80% **47Z**:**48** 96:4	**47**		**48**	
6	**49**		17 h, r.t.	70% **50E**:**50Z**:**51** 7:11:82	**50**		**51**	
7	**52**		20 h, r.t. 20 h, 60 °C	85% **53E**:**53Z**:**5** 27:24:49 98% **53E**:**53Z**:**5** 66:33:0	**53**		**54**	
8	**55**		20 h, r.t.	100% **56E**:**56Z**:**5** 27:20:53	**56**		**57**	
9	**58**		20 h, r.t.	89% **59E**:**59Z**:**60** 8:10:82	**59**		**60**	
10	**61**		16 h, 60 °C	90% **62**:**63** 55:45	**62**		**63**	
11	**64**		122 h, r.t.	17% **65**:**66** 86:14	**65**			

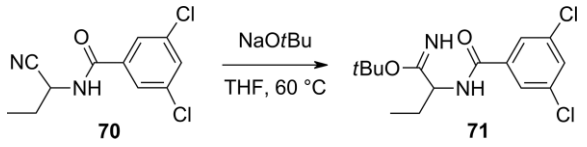
firmed to be stable on heating under the reaction conditions. This particular behavior of benzyl compounds **52** and **55** is compatible with the mechanism shown in Scheme 6. Compound **67** can be transiently deprotonated with NaO*t*Bu to form conjugated dianion **68**,[36] which on reprotonation, can lead to **67**, **69*E*** or **69*Z***. The charge in both **69*E*** and **69*Z*** is conjugated from the phenyl ring through to the carbonyl oxygen; deprotonation leading to **68** would interrupt this conjugation, and consequently, is not observed. Phenethyl analog **58** (Table 2, Entry 9) led, as expected, predominantly to Hofmann product **60**, and cyclic compound **61** (Table 2, Entry 10) reacted unselectively to yield a mixture of regioisomers.

Aldehyde-derived cyanoamides were so slow to react that imidate formation took precedence (Scheme 7). Despite heating overnight **70** remained largely unreacted; partial conversion to



Scheme 6. Isomerization of initially formed **67** to the conjugated enamide anions **69*E*** and **69*Z***.

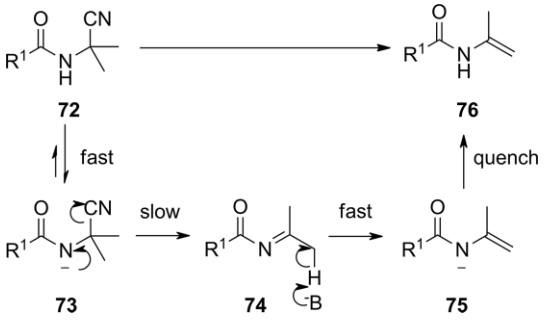
imidate **71**, which appeared to be in equilibrium with **70**, was observed. Compound **71** reverted slowly to **70** after workup, but could be isolated in low yield after chromatography and repeated crystallization.[37]



Scheme 7. Reaction of aldehyde-derived cyanohydrin **70** with NaO*t*Bu: formation of imidate.

The method was validated with **45** on a 168 mmol scale providing identical results to the 3 mmol scale reaction.

All results and observations are compatible with the E1cB mechanism shown in Scheme 8.[38] The first step, the deprotonation of NH, is expected to be fast. Simple amides have a pK_a of approx. 15–16[39] for the NH protons and would be rapidly and almost completely deprotonated by NaO*t*Bu (pK_a 19)[40] The NH protons of cyanoamide **72** and enamide **76** are even more acidic. A deuteration study was undertaken to demonstrate this fact.[41] The third step, conversion of acyl imine **74** to enamide **75**, is fast;[7] so much so that ketone-derived acyl imines have rarely been detected.[8,42] The second step, the elimination of cyanide from **73** to **74**, is thus the rate determining step, which explains, and is in accord with, the following results. Firstly the rate of the reaction is increased by electron-donating substituents, which is evidenced by the series in Table 1, and the differences in reactivity of ketone- and aldehyde-derived substrates. Secondly the effect of the counterion on rate decreases in the order $Na^+ \approx K^+ > MgCl^+ > Li^+ \approx Ag^+$. And finally, the reaction is independent of base concentration. In all, two equivalents of base are needed, one to deprotonate starting cyanoamide **72**, and one to deprotonate acyl imine intermediate **74**. The use of three equivalents of base gave a small improvement in rate and yield over two equivalents, but the use of five or more equivalents brought no further increase in rate, as expected since the conversion of **73** to **74** does not involve base.



Scheme 8. Proposed mechanism for conversion of cyanoamides to enamides.

Although the evidence supporting an E1cB mechanism is conclusive, there are details of the mechanism which remain obscure. Although the remarkable dependence of the degree and direction of regio- and stereo-selectivity on the amine protecting group is predictive and useful, we offer no model for its mechanistic origin. The selectivity may arise in the stereoselective formation of *E* or *Z* acylimines **74**, or by their regioselective elimination. Analogy with the deprotonation of ketones to their enolates is pertinent, because the factors influencing regio- and stereo-selectivity are only partially understood, despite considerable study.[43]

Conclusions

In conclusion, we have shown that acid-sensitive ketone-derived enamides can be prepared starting from the easily accessible cyanoamides using a simple, cheap, and scalable procedure in high yields. The protecting group has a useful directing effect on the regioselectivity, with Boc protection leading to Hoffmann elimination and *N*-acetylation leading to Zaitsev regioselectivity, with selective formation of *Z*-enamides in the latter case.

Experimental Section

Synthesis of Starting Materials – Acylation of Aminonitriles

For known acylaminonitriles the acylations were performed following the reported literature conditions. For new compounds one of these procedures was applied. In some cases, acylation conditions gave moderate or low yields. Due to the main focus of these studies, attempts to optimise these low yielding reactions were not made.

***N*-(1-Cyano-1-methylethyl)acetamide (6):**[44] 2-Amino-2-methylpropanenitrile (1 g, 11.88 mmol) and acetic anhydride (1.35 mL, 14.26 mmol, 1.2 equiv.) were stirred at room temperature without any solvent. After 19 h, the reaction mixture was diluted with Et_2O and washed 3 times with a 1 M solution of $NaHCO_3$, followed by 2 M HCl and then by saturated brine. The resulting organic layer was dried with $MgSO_4$, filtered and concentrated to afford cyanoamide **6** (337 mg, 23 % yield, white solid), m.p. 100–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65 (br. s, 1 H), 2.0 (s, 3 H), 1.7 (s, 6 H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 120.7, 46.4, 27.2, 23.4 ppm. MS (ES): *m/z* = 149 $[M + Na]^+$. HRMS (ESI+): calcd. for $C_6H_{11}N_2O$ $[M + H]^+$ 127.0871, found 127.0870.

***N*-(1-Cyano-1-methyl-ethyl)-2,2-dimethylpropanamide (21):**[45] Pivaloyl chloride (430 mg, 3.57 mmol, 1.0 equiv.) was added to a mixture of K_2CO_3 (498 mg, 3.57 mmol, 1.0 equiv.) and 2-amino-2-methylpropanenitrile (300 mg, 3.57 mmol) in EtOAc (5 mL) and stirred at room temperature for about 48 h. The reaction was then quenched with water, and washed with saturated brine. The resulting organic layer was concentrated to afford cyanoamide **21** (474 mg, 79 % yield, yellow solid), m.p. 119–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.6 (br. s, 1 H), 1.75 (s, 6 H), 1.25 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 120.9, 46.3, 38.9, 27.6, 27.4; 27.2 ppm. MS (CI): *m/z* = 169 $[M + H]^+$. HRMS (ESI^+): calcd. for $C_9H_{17}N_2O$ $[M + H]^+$ 169.1341, found 169.1336.

***N*-(1-Cyano-1-methyl-ethyl)-4-methoxybenzamide (23):**[46] 2-Amino-2-methylpropanenitrile (1 g, 5.95 mmol) was dissolved in THF (5 mL) and the solution was then cooled down to 0 °C. TEA (2.45 mL, 17.5 mmol, 3.0 equiv.) was then added, stirred for 15 min,

followed by 4-methoxybenzoyl chloride (1 g, 5.86 mmol, 0.98 equiv.), the reaction mixture was then warmed up to room temperature and stirred for about 48 h. The reaction was then quenched with 2 M HCl, followed by a solution of $NaHCO_3$, and then saturated brine. The crude product was purified by silica chromatography with a gradient cyclohexane/EtOAc to afford cyanoamide **23** (298 mg, 24 % yield, white solid), m.p. 140–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 10 Hz, 2 H), 6.92 (d, J = 10 Hz, 2 H), 6 (br. s, 1 H), 3.88 (s, 3 H), 1.8 (s, 6 H) ppm. MS (ES): m/z = 219 $[M + H]^+$.

***N*-(1-Cyano-1-methylethyl)-4-(trifluoromethyl)benzamide (25):** This compound was prepared following the procedure described for **23** using 4-(trifluoromethyl)benzoyl chloride (1 g, 4.79 mmol) to afford cyanoamide **25** (712 mg, 58 % yield, white solid), m.p. 208–211 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.9 (d, J = 9 Hz, 2 H), 7.72 (d, J = 10 Hz, 2 H), 6.15 (br. s, 1 H), 1.85 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 127.6, 125.9, 125.8, 120.4, 47.0, 27.3 ppm. HRMS (ESI^+): calcd. for $C_{12}H_{12}F_3N_2O$ $[M + H]^+$ 257.0902, found 257.0897.

***N*-(1-Cyano-1-methylethyl)-2,2,2-trifluoroacetamide (27):** This compound was prepared following the procedure described for **6** using trifluoroacetic anhydride (1.99 mL, 14.27 mmol) to afford cyanoamide **27** (2.04 g, 87 % corrected yield for remnants of solvent, brown oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (br. s, 1 H), 1.8 (s, 6 H) ppm. MS (ES): m/z = 181: $[M + H]^+$.

1-(1-Cyano-1-methylethyl)-3-phenylurea (29):[47] *2*-Amino-2-methylpropanenitrile (705 mg, 8.40 mmol) was dissolved in dichloromethane (5 mL) and the solution was then cooled down to 0 °C. Phenyl isocyanate (1 g, 8.40 mmol, 1.0 equiv.) was added followed by TEA (1.5 mL, 10.91 mmol, 1.3 equiv.), the reaction mixture was then warmed up to room temperature and stirred for 22 h. The reaction mixture was then quenched with 2 M HCl, followed by a solution of Na_2CO_3, and then saturated brine. The resulting organic layer was concentrated, then crystallized with a mixture of dichloromethane/cyclohexane/MeOH, 60:40:1. The solid was filtered, washed with Et_2O and then dried. The resulting solid was purified by silica chromatography with a gradient cyclohexane/EtOAc to afford cyanoamide **29** (83 mg, 5 % yield, white solid), m.p. 120–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (m, 2 H), 7.31 (m, 2 H), 7.00 (m, 1 H), 6.35 (bs, 1 H), 5.71 (bs, 1 H), 1.52 (s, 6 H) ppm. MS (ES): m/z = 204 $[M + H]^+$.

Benzyl *N*-(1-Cyano-1-methylethyl)carbamate (31):[48] 2-Amino-2-methylpropanenitrile (700 mg, 8.32 mmol) was dissolved in *t*BuOMe (5 mL) and the solution was then cooled down to 0 °C. Benzyl chloroformate (1.71 g, 9.99 mmol, 1.2 equiv.) was added followed by iPr$_2$NEt (1.85 mL, 10.82 mmol, 1.3 equiv.), the reaction mixture was then warmed up to room temperature and stirred for 20 h. The reaction mixture was then washed with water (3 × 10 mL), followed by saturated brine. The crude product was crystallized with a mixture cyclohexane/*t*BuOMe, 90:10 to afford cyanoamide **31** (1.18 g, 65 % yield, white solid), m.p. 100–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (m, 5 H), 5.65 (s, 2 H), 4.9 (br. s, 1 H), 1.7 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 133.7, 128.7, 128.5, 128.5, 120.9, 67.4, 47.1, 27.5 ppm. MS (ES): m/z = 241 $[M + Na]^+$. HRMS (ESI^+): calcd. for $C_{12}H_{15}N_2O_2$ $[M + H]^+$ 219.1134, found 219.1128.

***tert*-Butyl *N*-(1-Cyano-1-methylethyl)carbamate (33):**[49] 2-Amino-2-methylpropanenitrile (500 mg, 5.95 mmol) was dissolved in dichloromethane (5 mL) and *i*PrNEt (2.09 mL, 11.90 mmol, 2.0 equiv.) was then added, followed by Boc-anhydride (1.95 g, 8.90 mmol, 1.5 equiv.) and stirred at room temperature for about 48 h. The reaction was then quenched with 2 M HCl, followed by a solution of $NaHCO_3$, and then saturated brine. The resulting organic layer was concentrated to afford cyanoamide **33** (310 mg, 28 % yield, colorless liquid). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.6 (br. s, 1 H), 1.65 (s, 6 H), 1.5 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 121.2, 46.8, 28.3, 27.7 ppm. HRMS (ESI^+): calcd. for $C_9H_{17}N_2O_2$ $[M + H]^+$ 185.1290, found 185.1287.

***N*-(4-Cyano-1-methoxy-2,2,6,6-tetramethyl-4-piperidyl)acetamide (35):** 4-Amino-1-methoxy-2,2,6,6-tetramethylpiperidine-4-carbonitrile (1.05 g, 5 mmol) was dissolved in EtOAc (5 mL), followed by K_2CO_3 (0.768 mg, 5.5 mmol, 1.1 equiv.) and acetic anhydride (0.52 mL, 5.5 mmol, 1.1 equiv.). The reaction mixture was quenched with water and washed with a saturated brine. The resulting organic layer was dried with $MgSO_4$, filtered and concentrated to afford cyanoamide **35** (742 mg, 59 % yield, white solid), m.p. 166–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (br. s, 1 H), 3.6 (s, 3 H), 2.6 (d, J = 15 Hz, 2 H), 1.93 (s, 3 H), 1.65 (d, J = 15 Hz, 2 H), 1.45 (s, 6 H), 1.22 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 121.3, 65.7, 58.9, 46.9, 46.0, 44.2, 33.7, 32.8, 23.4, 22.5, 19.9 ppm. MS (CI): m/z = 254 $[M + H]^+$. HRMS (ESI^+): calcd. for $C_{13}H_{24}N_3O_2$ $[M + H]^+$ 254.1869, found 254.1861.

***N*-(1-Cyano-1-cyclopropylethyl)acetamide (37):** This compound was prepared following the procedure described for **35** using 2-amino-2-cyclopropylpropanenitrile (0.51 g, 5 mmol) to afford cyanoamide **37** (0.760 g, 76 % corrected yield for remnants of solvent, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (br. s, 1 H), 2.25 (s, 1 H), 2.05 (s, 3 H), 0.7 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 167.5, 115.7, 51.0, 22.7, 21.2, 18.6, 17.3 ppm. MS (CI): m/z = 153 $[M + H]^+$. HRMS (ESI^+): calcd. for $C_8H_{13}N_2O$ $[M + H]^+$ 153.1027, found 153.1023.

***tert*-Butyl *N*-(1-Cyano-1,2-dimethylpropyl)carbamate (39):** 2-Amino-2,3-dimethylbutanenitrile (1 g, 8.92 mmol) was added to a round bottom flask with Boc-anhydride (10.7 mmol, 1.2 equiv.). The solution was then heated up to 80 °C for 17 h. The reaction mixture was cooled to room temperature and 2 M ammonia/methanol solution (1 mL, 0.2 equiv.) was added, and stirred for 10 min. The reaction mixture was then concentrated to afford cyanoamide **39** (1.839 g, white solid), m.p. 88–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.6 (br. s, 1 H), 2.25 (septet, J = 7 Hz, 1 H), 1.6 (s, 3 H), 1.5 (s, 9 H), 1.15 (d, J = 7 Hz, 3 H), 1.05 (d, J = 7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 120.2, 81.2, 55.1, 35.2, 28.2, 21.7, 17.6, 16.5 ppm.

***N*-(1-Cyano-1,2-dimethylpropyl)acetamide (43):** This compound was prepared following the procedure described for **6** using 2-amino-2,3-dimethylbutanenitrile (2 g, 17.8 mmol) to afford cyanoamide **43** (1.72 g, 63 % yield, yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.31 (br. s, 1 H), 2.35 (septet, J = 7 Hz, 1 H), 2.05 (s, 3 H), 1.6 (s, 3 H), 1.15 (d, J = 7 Hz, 3 H), 1.05 (d, J = 7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 119.9, 54.8, 34.4, 23.1, 21.0, 17.7, 16.3 ppm. HRMS (ESI+): calcd. for $C_8H_{15}N_2O$ $[M + H]^+$ 155.1184, found 155.1180.

***tert*-Butyl *N*-(1-Cyano-1-methylpropyl)carbamate (46):** This compound was prepared following the procedure described for **39** using 2-amino-2-methylbutanenitrile (0.5 g, 5.1 mmol) to afford cyanoamide **46** (982 mg, 100 % yield, yellow solid), m.p. 48–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.65 (br. s, 1 H), 1.95 (m, 2 H), 1.65 (s, 3 H), 1.5 (s, 9 H), 1.1 (t, J = 7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7, 120.4, 81.2, 51.3, 32.8, 28.3, 24.8, 8.4 ppm. HRMS (ESI+): calcd. for $C_{10}H_{19}N_2O_2$ $[M + H]^+$ 199.1446, found 199.1442.

***N*-(1-Cyano-1-methylpropyl)acetamide (49):** This compound was prepared following the procedure described for **6** using 2-amino-2-methylbutanenitrile (0.5 g, 5.1 mmol) to afford cyanoamide **49**

(303 mg, 42 % yield, yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.5 (br. s, 1 H), 2 (m, 2 H), 2 (s, 3 H), 1.65 (s, 3 H), 1.1 (t, J = 7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 120.1, 51.0, 32.2, 24.9, 23.3, 8.4 ppm. HRMS (ESI+): calcd. for $C_7H_{13}N_2O$ $[M + H]^+$ 141.1028, found 141.1024.

***N*-[1-Cyano-2-(4-ethoxyphenyl)-1-methylethyl]acetamide (52):** This compound was prepared following the procedure described for **35** using 2-amino-3-(4-ethoxyphenyl)-2-methylpropanenitrile (1.02 g, 5 mmol) to afford cyanoamide **52** (1.178 g, 75 % corrected yield for remnants of solvent, orange oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, J = 10 Hz, 2 H), 6.85 (d, J = 10 Hz, 2 H), 5.5 (br. s, 1 H), 4.14 (q, J = 6 Hz, 2 H), 3.30 (d, J = 15 Hz, 1 H), 3.15 (d, J = 15 Hz, 2 H), 2.05 (s, 3 H), 1.95 (s, 3 H), 1.62 (s, 3 H), 1.4 (t, J = 6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 158.7, 131.5, 125.2, 120.2, 114.7, 63.5, 50.7, 43.0, 24.9, 23.5, 14.8 ppm. MS (EI): m/z = 247 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{14}H_{19}N_2O_2$ $[M + H]^+$ 247.1446, found 247.1445.

***N*-[2-(1,3-Benzodioxol-5-yl)-1-cyano-1-methylethyl]acetamide (55):** This compound was prepared following the procedure described for **35** using 2-amino-3-(1,3-benzodioxol-5-yl)-2-methylpropanenitrile (0.41 g, 2 mmol) to afford cyanoamide **55** (0.380 g, 75 % corrected yield for remnants of solvent, orange oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (m, 3 H), 5.95 (s, 2 H), 5.45 (br. s, 1 H), 3.3 (d, J = 15 Hz, 1 H), 3.15 (d, J = 15 Hz, 2 H), 2 (s, 3 H), 1.68 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 147.9, 147.4, 127.7, 124.1, 120.2, 110.6, 108.5, 101.2, 53.4, 43.4, 24.8, 23.4 ppm. MS (EI): m/z = 247 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{13}H_{15}N_2O_3$ $[M + H]^+$ 247.1083, found 247.1075.

***N*-[1-Cyano-3-(4-methoxyphenyl)-1-methylpropyl]acetamide (58):** This compound was prepared following the procedure described for **35** using 2-amino-4-(4-methoxyphenyl)-2-methylbutanenitrile (1.02 g, 5 mmol) to afford cyanoamide **58** (0.936 g, 58 % corrected yield for remnants of solvent, pale yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, J = 10 Hz, 2 H), 6.85 (d, J = 10 Hz, 2 H), 5.55 (br. s, 1 H), 3.8 (s, 3 H), 2.8 (m, 2 H), 2.2 (m, 2 H), 1.9 (s, 3 H), 1.7 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 158.3, 131.8, 129.3, 120.0, 114.2, 55.3, 50.6, 40.7, 29.8, 25.2, 23.3 ppm. MS (EI): m/z = 247 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{14}H_{18}N_2O_2$ $[M + H]^+$ 247.1447, found 247.1445.

***N*-{3-Cyano-1-[4-(trifluoromethyl)phenyl]-3-piperidyl}acetamide (61):** This compound was prepared following the procedure described for **35** using 3-amino-1-[4-(trifluoromethyl)phenyl]piperidine-3-carbonitrile (1.34 g, 5 mmol) to yield cyanoamide **61** (643 mg, 25 % corrected yield for remnants of solvent, brown oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.5 (d, J = 10 Hz, 2 H), 6.95 (d, J = 10 Hz, 2 H), 5.7 (br. s, 1 H), 4 (d, J = 15 Hz, 1 H), 3.5 (d, J = 15 Hz, 1 H), 3.3 (m, 2 H), 2.15 (t, J = 10 Hz, 2 H), 2.05 (s, 3 H), 1.9 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 152.5, 126.6, 126.5, 118.6, 116.0, 56.0, 49.9, 48.2, 33.2, 23.3, 21.0 ppm. MS (EI): m/z = 312 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{15}H_{17}F_3N_3O$ $[M + H]^+$ 312.1324, found 312.1318.

General Procedure – Formation of Enamides

Cyanoamide was dissolved in dry THF (1 M) and NaO*t*Bu (2 M in THF, 3 equiv.) were added with stirring under argon. The reaction was followed by TLC and/or HPLC-MS. After stirring and heating for the time indicated, the mixture was diluted with *t*BuOMe and poured into a stirred mixture of *t*BuOMe, $NaHCO_3$ (1 M), and ice. On a large scale it was not necessary to dilute the reaction mixture with *t*BuOMe before quenching. The organic phase was dried with $MgSO_4$ and evaporated to yield the enamide. Apart from isomeric mixtures there were usually very few, or no, observable by-products. The isomers were separated by chromatography. This resulted in a greater or smaller loss of material. The optimization of chromatographic separations is described below, and as discussed, the best solutions were not perfect.

WARNING: Cyanide in the aqueous phase can be destroyed by oxidation, for example with hypochlorite.[50] The aqueous phase is basic and should not be acidified, which would generate HCN, which may escape the vessel as a gas.

***N*-Isopropenylacetamide (11):** Following the general procedure with **6** (100 mg, 0.79 mmol) afforded enamide **11** (59 mg, 80 % yield, white solid), m.p. 72–77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (br. s, 1 H), 5.4 (s, 1 H), 4.45 (s, 1 H), 2.1 (s, 3 H), 1.9 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 137.5, 98.8, 24.5, 22.1 ppm. MS (CI): 99 $[M + H]^+$. HRMS (ESI+): calcd. for $C_5H_{10}NO$ $[M + H]^+$ 100.0762; found 100.0767.

2,4-Dichloro-*N*-isopropenylbenzamide (20): Following the general procedure with **19** (256 mg, 1 mmol) yielded a crude mixture, which was purified by chromatography with a gradient of cyclohexane/EtOAc, each containing 1 % Et_3N to afford **20** (138 mg, 60 % yield, white solid), m.p. 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (s, 1 H), 7.48 (s, 2 H), 7.15 (br. s, 1 H), 5.6 (s, 1 H), 4.62 (s, 1 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 137.1, 136.5, 133.4, 131.5, 130.2, 128.7, 100.7, 22.1 ppm. MS (ES): 230 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{10}H_{10}Cl_2NO$ $[M + H]^+$ 230.0139, found 230.0139.

***N*-Isopropenyl-2,2-dimethylpropanamide (22):** Following the general procedure with **21** (256 mg, 1 mmol), yielded **22** (44 mg, 63 % yield, pale yellow solid), m.p. 66–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.6 (br. s, 1 H), 5.42 (s, 1 H), 4.45 (s, 1 H), 1.92 (s, 3 H), 1.22 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 137.5, 98.7, 39.6, 27.6, 22.3 ppm. HRMS (ESI+): calcd. for $C_8H_{16}NO$ $[M + H]^+$ 142.1232, found 142.1229.

***N*-Isopropenyl-4-methoxybenzamide (24):** Following the general procedure with **23** (100 mg, 0.45 mmol) yielded **24** (87 mg, 80 % corrected yield for remnants of solvent, pale yellow solid), m.p. 40–43 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 10 Hz, 2 H), 7.05 (br. s, 1 H), 6.92 (d, J = 10 Hz, 2 H), 5.5 (s, 1 H), 4.55 (s, 1 H), 3.88 (s, 3 H), 1.6 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 162.6, 162.4, 138.0, 131.4, 129.3, 113.8, 101.5, 55.4, 28.3 ppm. MS (ES): 192 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{11}H_{14}NO_2$ $[M + H]^+$ 192.1025, found 192.1020.

***N*-Isopropenyl-4-(trifluoromethyl)benzamide (26):** Following the general procedure with **25** (115 mg, 0.45 mmol) yielded enamide **26** (90 mg, 84 % yield, pale yellow solid), m.p. 100–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 10 Hz, 2 H), 7.70 (d, J = 10 Hz, 2 H), 7.1 (br. s, 1 H), 5.55 (s, 1 H), 4.62 (s, 1 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 137.4, 133.9, 138.4, 127.8, 127.6, 125.8, 122.2, 100.5, 22.1 ppm. MS (ES): 230 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{11}H_{11}F_3NO$ $[M + H]^+$ 230.0793, found 230.0788.

2,2,2-Trifluoro-*N*-isopropenylacetamide (28): Following the general procedure with **27** (144 mg, 0.80 mmol). Starting material **27** was recovered.

1-Isopropenyl-3-phenylurea (30): Following the general procedure with **29** (65 mg, 0.32 mmol). ^{1}H NMR of the crude product mixture indicated a complex mixture of products.

Benzyl *N*-Isopropenylcarbamate (32): Following the general procedure with **31** (70 mg, 0.32 mmol). NMR of the crude product showed a complex mixture of products.

***tert*-Butyl *N*-Isopropenylcarbamate (34):** Following the general procedure with **33** (92 mg, 0.5 mmol) yielded **34** (66 mg, 78 % yield, pale yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.8 (br. s, 1 H), 5.08 (s, 1 H), 4.27 (s, 1 H), 1.87 (s, 3 H), 1.48 (s, 9 H) ppm.

***N*-(1-Methoxy-2,2,6,6-tetramethyl-3*H*-pyridin-4-yl)acetamide (36):** Following the general procedure with **35** (253 mg, 1 mmol) yielded **36** (217 mg, 96 % yield, white solid), m.p. 109–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.2 (br. s, 1 H), 6.85 (s, 1 H), 3.53 (s, 3 H), 2.45 (d, J = 15 Hz, 1 H), 2 (s, 3 H), 1.95 (d, J = 15 Hz, 1 H), 1.3 (br. s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 127.2, 119.4, 65.4, 59.7, 58.4, 42.4, 32.6, 30.1, 24.5, 23.1, 21.3 ppm. HRMS (ESI+): calcd. for $C_{12}H_{23}N_2O_2$ $[M + H]^+$ 227.1760, found 227.1759.

***N*-(1-Cyclopropylvinyl)acetamide (38):** Following the general procedure with **37** (152 mg, 1 mmol) yielded **38** (97 mg, 77 % yield, orange oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.6 (br. s, 1 H), 5.62 (s, 1 H), 4.55 (s, 1 H), 2.05 (s, 3 H), 0.7 (m, 2 H), 0.55 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 142.0, 97.4, 21.2, 10.7, 9.3 ppm.

40 and 41: Following the general procedure with **39** (500 mg, 2.4 mmol) yielded **40** (340 mg, 78 % yield, pale yellow oil). Small signals were observed in the ^{1}H NMR spectrum, which are tentatively assigned to **41** integrating as a 4 % contaminant.

***tert*-Butyl *N*-(1,2-Dimethylprop-1-enyl)carbamate (40):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.5 (br. s, 1 H), 1.9 (s, 3 H), 1.7 (s, 3 H), 1.65 (s, 3 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 124.0, 122.6, 79.4, 28.3, 19.6, 19.3, 17.3 ppm. HRMS (ESI+): calcd. for $C_{10}H_{20}NO_2$ $[M + H]^+$ 186.1494, found 186.1492.

***tert*-Butyl *N*-(2-Methyl-1-methylenepropyl)carbamate (41):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.7 (br. s, 1 H), 5.3 (s, 1 H), 4.4 (s, 1 H), 1.45 (s, 9 H) ppm. Some peaks were presumably occluded by the much larger ones of **40**.

44 and 45: Following the general procedure with **43** (515 mg, 3.3 mmol) yielded **44**/**45** in a ratio of 7:93 (340 mg, 94 % yield).

***N*-(1,2-Dimethylprop-1-enyl)acetamide (44):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.4 (br. s, 1 H), 5.6 (s, 1 H), 2.3 (septet, J = 7 Hz, 1 H), 2.05 (s, 3 H), 1.1 (d, J = 7 Hz, 6 H) ppm.

***N*-(2-Methyl-1-methylenepropyl)acetamide (45):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.9 (br. s, 1 H), 2.05 (s, 3 H), 1.75 (s, 3 H), 1.7 (s, 3 H), 1.65 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 146.7, 96.8, 33.6, 21.0, 18.1 ppm. HRMS (ESI+): calcd. for $C_7H_{14}NO$ $[M + H]^+$ 128.1075, found 128.1074.

47 and 48: Following the general procedure with **46** (500 mg, 2.5 mmol) yielded **47*Z*/48** in a ratio of 94:6 (347 mg, 80 % yield, pale yellow oil).

***tert*-Butyl *N*-[(*Z*)-1-Methylprop-1-enyl]carbamate (47*Z*):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (br. s, 1 H), 4.74 (q, J = 6.85 Hz, 1 H), 2 (s, 3 H), 1.55 (d, J = 6.85 Hz, 3 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 132.0, 109.0, 79.6, 28.3, 21.0, 11.6 ppm.

tert*-Butyl *N*-(1-Methylenepropyl)carbamate (48):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65 (br. s, 1 H), 5.2 (s, 1 H), 4.3 (s, 1 H), 1.45 (s, 9 H) ppm. Some peaks were obscured by the much larger ones of **47*Z.

50 and 51: This compound was prepared following the procedure described for **22** using substrate cyanoamide **49** (67 mg, 0.47 mmol) to afford **50*E*/50*Z*/51** in a 7:11:82 ratio (38 mg, 70 % yield, pale yellow oil). Chromatography with a gradient of EtOAc/cyclohexane, with each component containing 1 % Et_3N, yielded 18 mg of **51** and 1 mg of a mixture of **50*E*/50*Z*** in ratio of 58:42.

***N*-[(*E*)-1-Methylprop-1-enyl]acetamide (50*E*):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.4 (br. s, 1 H), 5.7 (q, J = 7 Hz, 1 H), 2.05 (s, 3 H), 1.9 (s, 3 H), 1.65 (s, 3 H) ppm.

***N*-[(*Z*)-1-Methylprop-1-enyl]acetamide (50*Z*):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.4 (br. s, 1 H), 5 (q, J = 7 Hz, 1 H), 2.1 (s, 3 H), 2 (s, 3 H), 1.55 (s, 3 H) ppm.

***N*-(1-Methylenepropyl)acetamide (51):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (br. s, 1 H), 4.74 (q, J = 6.85 Hz, 1 H), 2 (s, 3 H), 1.55 (d, J = 6.85 Hz, 3 H), 1.45 (s, 9 H) ppm.

53 and 54, a: At room temperature. Following the general procedure with **52** (246 mg, 1 mmol) yielded 188 mg (86 % yield) of a brown oil (ratio **53*E*/53*Z*/54** = 27:20:53). This was chromatographed with a gradient of EtOAc/cyclohexane, with each component containing 1 % Et_3N, to yield 83 mg (38 %) of a mixture of **53*Z*/54** in a 28:72 ratio, and 36 mg (16 %) of **53*E*** as a yellow solid. A sample of the mixture of **53*Z*/54** was separated by RP-HPLC to yield 10 mg of **53*Z*** and 2 mg of **54**.

b: At 60 °C As above but heating the reaction mixture for 16 h at 60 °C before workup yielded 214 mg (98 %) of a 2:1 *E*/*Z* mixture which was chromatographed with a gradient of EtOAc/cyclohexane, with each component containing 1 % Et_3N, to yield **53*Z*** (92 mg, 42 % yield) and **53*E*** (50 mg, 23 % yield).

***N*-[(*Z*)-2-(4-Ethoxyphenyl)-1-methylvinyl]acetamide (53*Z*):** M.p. 111–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, J = 10 Hz, 2 H), 6.95 (br. s, 1 H), 6.88 (d, J = 10 Hz, 2 H) 5.65 (s, 1 H), 4.05 (q, J = 10 Hz, 2 H), 2.28 (s, 3 H), 2 (s, 3 H), 1.4 (t, J = 10 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 157.7, 133.1, 129.6, 128.1, 114.8, 63.5, 24.3, 21.4, 14.8 ppm. MS (EI): 219 [M+ H]$^+$. HRMS (ESI+): calcd. for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.1337, found 220.1331.

***N*-[(*E*)-2-(4-Ethoxyphenyl)-1-methylvinyl]acetamide (53*E*):** M.p. 102–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, J = 11 Hz, 2 H), 6.88 (s, 1 H), 6.84 (d, J = 11 Hz, 2 H), 4.02 (q, J = 7 Hz, 2 H), 2.10 (s, 3 H), 2.08 (s, 3 H), 1.41 (t, J = 10 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.4, 114.4, 63.5, 14.8 ppm. MS (EI): 219 [M+ H]$^+$. HRMS (ESI+): calcd. for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.1337, found 220.1332.

***N*-{1-[(4-Ethoxyphenyl)methyl]vinyl}acetamide (54):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, J = 10 Hz, 2 H), 6.85 (d, J = 10 Hz, 2 H), 6.25 (br. s, 1 H), 5.7 (s, 1 H), 4.65 (s, 1 H), 4.05 (q, J = 10 Hz, 2 H), 3.4 (s, 2 H), 1.95 (s, 3 H), 1.4 (t, J = 10 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.6, 130.1, 114.2, 63.4, 14.9 ppm. MS (EI): 219 [M+ H]$^+$. HRMS (ESI+): for $C_{13}H_{18}NO_2$ $[M + H]^+$ calcd. 220.1337, found 220.1334.

56 and 57: Following the general procedure with **57** (123 mg, 0.5 mmol) yielded 135 mg of product containing **56*E*/56*Z*/57** in a ratio of 27:20:53, which was chromatographed with a gradient of EtOAc/cyclohexane, with each component containing 1 % Et_3N, to yield a mixture **56*Z*/57** in a 20:80 ratio (41 mg, 37 % yield) and **56*Z*** (15 mg, 14 % yield).

***N*-[(*Z*)-2-(1,3-Benzodioxol-5-yl)-1-methylvinyl]acetamide (56*Z*):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (br. s, 1 H), 6.75 (m, 3 H), 5.95 (s, 2 H), 5.6 (s, 1 H), 2.28 (s, 3 H), 2 (s, 3 H) ppm. MS (EI): 219 [M + H]$^+$.

***N*-[(*E*)-2-(1,3-Benzodioxol-5-yl)-1-methylvinyl]acetamide (56*E*):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (s, 1 H), 6.67–6.79 (m, 3 H), 6.56 (br. s, 1 H), 5.93 (s, 2 H), 2.08 (s, 3 H), 2.06 (s, 3 H) ppm. MS (EI): 219 [M + H]$^+$.

***N*-[1-(1,3-Benzodioxol-5-ylmethyl)vinyl]acetamide (57):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (m, 3 H), 6.3 (br. s, 1 H), 5.95 (s, 2 H), 5.7 (s, 1 H), 4.65 (s, 1 H), 1.95 (s, 3 H) ppm. MS (EI): 219 [M + H]$^+$.

59 and 60: Following the general procedure with **58** (246 mg, 1 mmol) yielded **59*E*/59*Z*/60** in a ratio of 4:5:40 (197 mg, 90 % yield). Chromatography with a gradient of EtOAc/cyclohexane, with each component containing 1 % Et_3N, afforded **60** (88 mg, 40 % yield) and a 50:50 mixture of **59*E*/59*Z*** (10 mg, 5 % yield).

***N*-[(*Z*)-3-(4-Methoxyphenyl)-1-methylprop-1-enyl]acetamide (59*Z*):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, J = 10 Hz, 2 H), 6.85 (d, J = 10 Hz, 2 H), 6.6 (br. s, 1 H), 5.15 (s, 1 H), 3.25 (d, J = 10 Hz, 1 H), 2.00 (s, 3 H) ppm. MS (EI): 219 $[M + H]^+$.

***N*-[(*E*)-3-(4-Methoxyphenyl)-1-methylprop-1-enyl]acetamide (59*E*):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, J = 10 Hz, 2 H), 6.85 (d, J = 10 Hz, 2 H), 6.6 (br. s, 1 H), 5.9 (s, 1 H), 3.35 (d, J = 10 Hz, 1 H), 2 (s, 3 H) ppm. MS (EI): 219 $[M + H]^+$.

***N*-[3-(4-Methoxyphenyl)-1-methylenepropyl]acetamide (60):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.1 (d, J = 10 Hz, 2 H), 6.85 (d, J = 10 Hz, 2 H), 6.2 (br. s, 1 H), 5.5 (s, 1 H), 4.5 (s, 1 H), 3.7 (s, 3 H), 2.75 (t, J = 7 Hz, 2 H), 2.43 (t, J = 7 Hz, 2 H), 1.95 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 158.0, 141.0, 133.0, 129.3, 113.9, 99.2, 55.3, 37.8, 33.7, 22.6 ppm. MS (EI): 219 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.1338, found 220.1336.

62 and 63: Following the general procedure with **61** (264 mg, 0.848 mmol) yielded a 55:45 mixture of **62/63** (216 mg, 90 % yield). This mixture was chromatographed using a gradient of EtOAc/cyclohexane, with each component containing 1 % Et_3N, to yield **62** (75 mg, 31 %) and a 40:60 mixture of **62/63** (62 mg).

***N*-{1-[4-(Trifluoromethyl)phenyl]-3,6-dihydro-2*H*-pyridin-5-yl}acetamide (62):** ^{1}H NMR (400 MHz $CDCl_3$): δ = 7.47 (d, J = 10 Hz, 2 H), 6.92 (d, J = 10 Hz, 2 H), 6.63 (br. s, 1 H), 5.42 (s, 1 H), 3.98 (s, 2 H), 3.45 (t, J = 5 Hz, 2 H), 2.82 (br. s, 2 H), 2.06 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 152.2, 131.5, 126.5, 126.1, 120.1, 114.0, 112.1, 48.4, 44.6, 24.2, 23.7 ppm. MS (CI): 285 [M+ H]$^+$. HRMS (ESI+): calcd. for $C_{14}H_{16}F_3N_2O$ $[M + H]^+$ 285.1209, found 285.1206.

***N*-{1-[4-(Trifluoromethyl)phenyl]-3,4-dihydro-2*H*-pyridin-5-yl}acetamide (63):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 10 Hz, 2 H), 7.30 (s, 1 H), 6.90 (d, J = 10 Hz, 2 H), 6.28 (br. s, 1 H), 3.51 (t, J = 7 Hz, 2 H), 2.29 (t, J = 7 Hz, 2 H), 2.08 (s, 3 H), 2.05 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 148.5, 128.8, 127.0, 123.1, 121.8, 120.6, 120.3, 44.4, 25.1, 24.0, 21.8 ppm. MS (CI): 285 [M+ H]$^+$. HRMS (ESI+): calcd. for $C_{14}H_{16}F_3N_2O$ $[M + H]^+$ 285.1209, found 285.1204.

65 and 66: Following the general procedure with **64** (386 mg, 1 mmol) yielded crude **65** and **66** (487 mg), which was chromatographed with a gradient of EtOAc/cyclohexane, with each component containing 1 % Et_3N, to yield **65/66** in a ratio of 80:20 (64 mg, 18 % yield).

***N*-[(*Z*)-2-Hydroxy-1-methyl-vinyl]-4-(trifluoromethyl)benzamide (65):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 10 Hz, 2 H), 7.85 (br. s, 1 H), 7.72 (d, J = 10 Hz, 2 H), 5.78 (s, 2 H), 2.18 (s, 3 H), 0.96 (s, 9 H), 0.18 (s, 6 H) ppm. MS (CI): 360 [M+ H]$^+$.

***N*-[1-(Hydroxymethyl)vinyl]-4-(trifluoromethyl)benzamide (66):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 10 Hz, 2 H), 7.72 (d, J = 10 Hz, 2 H), 7.11 (s, 1 H), 6.86 (br. s, 1 H), 5.94 (s, 1 H), 4.73 (s, 1 H), 4.29 (s, 2 H), 0.96 (s, 9 H), 0.18 (s, 6 H) ppm. MS (CI): 360 [M+ H]$^+$.

Synthesis of Enamide 45 on 168 mmol Scale: A solution of NaO*t*Bu (2 M in THF, 252 mL, 505 mmol, 3 equiv.) was added in one portion to a solution of **43** (25 g, 168 mmol) in THF (77mL) with stirring at room temperature. There was no exotherm. During the addition a smeary precipitate appeared, but after complete addition a clear solution was formed. After 60 h the mixture was poured into a stirred mixture of $NaHCO_3$ (1 M, 1 L) and *t*BuOMe (300 mL) to which ice had been added to bring the temperature down to approx. 5–10 °C. There was a weak exotherm and the mixture did not quite reach room temperature. The ethereal phase was dried with $MgSO_4$, and evaporated down to yield **45** (18.17 g, 85 % yield), with a ^{1}H NMR spectrum identical to that obtained from the 3 mmol reaction. Although it was not crystalline, **45** was stable for several months at 4 °C in the refrigerator.

Attempts Using Modified Literature Methods

***N*-(1-Methyl-1-{[2-(trifluoromethyl)benzoyl]amino}ethyl)-2-(trifluoromethyl)benzamide (14):** A solution of acetone (10 g, 172 mmol) in toluene (40 mL) was stirred at 0 °C under argon. Ammonia (7 M in MeOH, 36.9 mL, 258 mmol, 1.5 equiv.) and then Ti(O*i*Pr)$_4$ (108 mL, 100.9 g, 344.5 mmol, 2 equiv.) were added, the mixture warmed to room temperature, stirred for 18 h and cooled again to 0 °C. Triethylamine (97 mL, 70.4 g, 688 7 mmol, 4 equiv.) and then 2-(trifluoromethyl)benzoyl chloride (51.23 mL, 72.5 g, 344 mmol, 2 equiv.) were added. During the addition of the acid chloride a thick suspension was formed, so more toluene was added to keep the mixture mobile. After stirring for 2 h at room temperature, *N*,*N*,*N*′,*N*′-tetrakis(2-hydroxyethyl)ethylenediamine (75.6 mL, 85.4 g, 361 mmol, 2.1 equiv.) in a little toluene was added, the mixture was stirred at 60 °C for 15 min, cooled to room temperature, then poured into a mixture of water (500 mL) and 7 M NH_3 (aq.). The mixture was extracted with EtOAc, and the organic phase washed with water and brine, dried with Na_2SO_4 and evaporated to give a semi-solid mass. This was stirred with ether and the solid filtered off. The filtrate was evaporated to yield 41 g of an oil, which appeared, upon NMR analysis, to be a complex mixture of products containing little or no **15**. The solid was a mixture of **14** and 2-(trifluoromethyl)benzamide. This mixture was chromatographed with EtOAc/cyclohexane to yield 2.3 g (3 %) of **14** as white crystals, m.p. 214–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, J = 9.0 Hz, 2 H), 7.55 (m, 6 H), 6.59 (br. s, 2 H, NH), 1.90 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 135.8, 132.1, 130.0, 128.7, 125.0, 120.0, 66.8, 27.0 ppm. MS (CI): 441 $[M + Na]^+$. HRMS (ESI+): calcd. for $C_{19}H_{17}F_6N_2O_2$ $[M + H]^+$ 419.1189, found 419.1186.

***N*-Isopropenyl-2-(trifluoromethyl)benzamide (15):** A solution of KO*t*Bu in THF (1 M, 4.4 mL, 4.39 mmol, 1.2 equiv.) was added to a solution of **14** (1.53 g, 3.66 mmol) in THF (10 mL). After 16 h at room temperature the mixture was cooled to 0 °C, acetic acid (0.5 mL) added, and the mixture shaken between EtOAc and water, washed with a 1 M solution of $NaHCO_3$, brine, dried with $MgSO_4$ and evaporated to yield 1.48 g of crude product which contained about 20 % starting material. Chromatography with EtOAc/cyclohexane yielded 451 mg (54 %) *N*-isopropenyl-2-(trifluoromethyl)benzamide, m.p. 95–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 9 Hz, 1 H), 7.60 (m, 3 H), 6.72 (br. s, 1 H, NH), 5.53 (s, 1 H), 4.61 (s, 1 H) 1.99 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 137.4, 132.1, 130.1, 128.6, 126.3, 100.5, 82.7, 28.3, 21.9 ppm. MS (CI): 230 $[M + H]^+$. HRMS (ESI+): calcd. for $C_{11}H_{11}F_3NO$ $[M + H]^+$ 230.0787, found 230.0788.

Initial Base Screen to Establish Proof of Principle: Cyanoamide **19** (256 mg, 1 mmol) was dissolved in dry THF (1 mL) under argon, and 1 equiv. of the bases [BuLi (1.6 M in hexane, 0.625 mL, 1 mmol); *i*PrMgCl (1.3 M in THF, 0.769, 1 mmol); KO*t*Bu (1 M in THF, 1 mL, 1 mmol); KO*t*Bu (1 M in *t*BuOH) (1 mL, 1 mmol)] was added. After 30 min, TLC showed traces of a less polar product. Silver sulfate (155 mg, 0.5 mmol) was then added and the reaction mixtures were left for about 48 h at room temperature. Following reaction, the mixtures were diluted with EtOAc and shaken with a 1 M solution of $NaHCO_3$, washed with a saturated solution of brine, dried with

$MgSO_4$, and concentrated. The crude product mixture containing **20** was analyzed by ^{1}H NMR spectroscopy (Table 3).

Table 3. Initial screen of four strong bases.

Base	SM remaining [%]	Product yield [%]
*n*BuLi	100	0
*i*PrMgCl	92	8
KO*t*Bu in THF	74	26
KO*t*Bu in *t*BuOH	78	22

Screening of Silver Salts: Cyanoamide **19** (256 mg, 1 mmol) was dissolved in dry THF (1 mL) under argon and KO*t*Bu (1 M in THF, 2 mL, 2 mmol) was added. Silver salts [Ag_2SO_4 (232 mg, 0.75 mmol); $AgNO_3$ (253 mg, 1.5 mmol); AgOTs (416 mg, 1.5 mmol); $AgSbF_6$ (513 mg, 1.5 mmol); AgO_2CCF_3 (330 mg, 1.5 mmol); AgOTf (384 mg, 1.5 mmol)] were then added and the reaction mixture was stirred at room temperature overnight. Reactions were then were diluted with EtOAc and agitated with a 1 M solution of $NaHCO_3$. They were then washed with a saturated solution of brine, dried with $MgSO_4$, concentrated and analyzed by ^{1}H NMR spectroscopy (Table 4).

Table 4. Effect of silver salts on conversion and yields of reaction.

Silver salt	Equiv.	SM remaining [%]	Product yield [%]
Ag_2SO_4	0.75	72	28
$AgNO_3$	1.5	71	29
AgOTs	1.5	100	0
$AgSbF_6$	1.5	100	0
AgO_2CCF_3	1.5	100	0
AgOTf	1.5	100	0

Screening of Other Lewis Acids: Cyanoamide **19** (100 mg, 0.39 mmol) was dissolved in dry THF (1 mL) in a dried flask under argon and DBU (0.116 mL, 0.78 mmol) was added. To the reaction was then added 2 equiv. of the Lewis acids [AgOTf (200 mg, 0.78 mmol); CuCl (77 mg, 0.78 mmol); $ZnCl_2$ (106 mg, 0.78 mmol)] and the reaction stirred at room temperature overnight. Reaction contents were then washed with a saturated solution of brine, dried with $MgSO_4$, concentrated, and analyzed by ^{1}H NMR spectroscopy (Table 5).

Table 5. Effect of added Lewis acid on the yield and conversion.

Lewis acid	SM remaining [%]	Product yield [%]
AgOTf	100	0
CuCl	100	0
$ZnCl_2$	100	0

Screening of Solvents: Cyanoamide **19** (256 mg, 1 mmol) was dissolved in dry solvent (1 mL) under argon and KO*t*Bu (1 M in THF, 2 mL, 2 mmol) was added. Silver sulfate (232 mg, 0.75 mmol) was then added and stirred at room temperature for about 48 h. The reaction contents were then washed with a saturated solution of brine, dried with $MgSO_4$, and concentrated and analyzed by ^{1}H NMR spectroscopy (Table 6).

Table 6. Effect of solvent on yield and conversion.

Solvent	KOtBu 1 M in	SM remaining [%]	Product yield [%]
THF	THF	59	41
THF	*t*BuOH	90	10
DMF	THF	100	0
Acetonitrile	THF	100	0

Screening of Bases: Cyanoamide **19** (100 mg, 0.39 mmol) was dissolved in dry THF under argon and 3 equiv. of base were added and stirred at room temperature. The reaction mixtures were left for about 48 h. Reactions were then washed with a saturated solution of brine, dried with $MgSO_4$, and concentrated and analyzed by ^{1}H NMR spectroscopy (Table 7).

Table 7. Effect of base on yield and conversion.

Base	pK_a	SM remaining [%]	Product yield [%]
*n*BuLi	51	decomp.	0
Schwesinger's base P4	42.7	100	0
*i*PrMgCl	≈ 40	decomp.	0
AgHMDS	–	decomp.	0
Schwesinger's base BEMP	27.6	100	0
KO*t*Bu	19	13	87
DBU	≈ 12	100	0

Screening of *tert*-Butoxide Counterions: Cyanoamide **19** (256 mg, 1 mmol) was dissolved under argon in enough dry THF to ensure that the concentration of substrate and base would be the same in all cases. Then, 3 equiv. of base [LiO*t*Bu (solid) (96 mg, 1.17 mmol); NaO*t*Bu (2 M in THF, 0.59 mL, 1.17 mmol); KO*t*Bu (1 M in THF, 1.17 mL, 1.17 mmol)] were added and stirred at room temperature overnight. Reactions were then washed with a saturated solution of brine, dried with $MgSO_4$, concentrated, and analyzed by ^{1}H NMR spectroscopy. The extents of reaction were determined by integrating the peaks identified in HPLC-MS analyses; peaks were not calibrated (Table 8, Figure 1).

Table 8. Effect of *tert*-butoxide counterion on yield and conversion.

Base	SM remaining [%]	Product yield [%]
LiO*t*Bu	80	20
NaO*t*Bu	13	87
KO*t*Bu	14	86

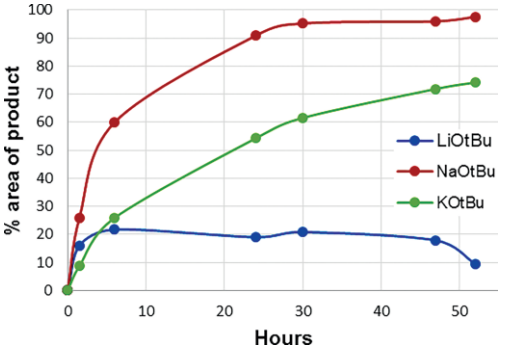


Figure 1. Effect of *tert*-butoxide counterion on reaction yield as a function of reaction time.

Amount of KOtBu: Cyanoamide **19** was treated in parallel reactions with various amounts of KO*t*Bu solution as described above. The reactions were followed by HPLC-MS. The peaks were not calibrated, so the results are given in peak areas, rather than mol. When using less than 3 equiv. of base, the reaction was slow or did not proceed at all. The results obtained for reactions using 3, 5 and 7 equiv. of base show a similar reaction profile (Figure 2).

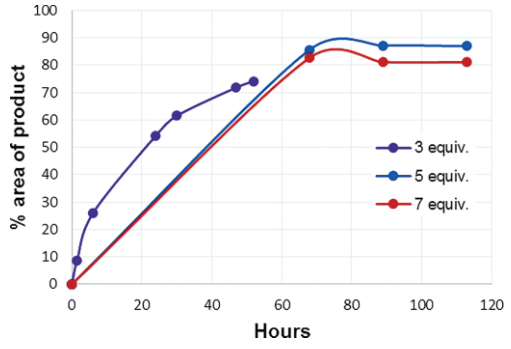
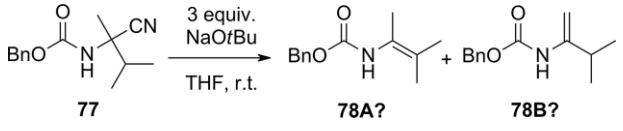


Figure 2. Results of varying equivalents of KO*t*Bu on the reaction as a function of time.

Screening of Workup Conditions: This screen was done with a crude mixture from the reaction of a benzylcarbamatonitrile **77**, which led to a mixture of products (see the discussion of **32**, Table 1 in the main text of the publication). The NMR of the crude reaction mixture showed peaks tentatively assigned to isomers of the desired product, so a systematic study was done to find mild workup conditions and purification conditions. Although the products were never obtained in pure form, it was possible to examine the spectra of the various fractions to evaluate decomposition, and the results are worth reporting here, because ketone-derived enamides are so sensitive that a guide to those working in the area is valuable (Scheme 9).



Scheme 9. Conversion of **77** to an enamide mixture used to evaluate workup and purification conditions.

78: NaO*t*Bu (2 M in THF, 3.9 mL, 7.8 mmol) was added to a solution of benzyl *N*-(1-cyano-1,2-dimethylpropyl)carbamate **77** (640 mg, 2.6 mmol) in dry THF (3 mL) under argon at room temperature and stirred for 25 h. The mixture was then diluted with *t*BuOMe (10 mL), split into five batches and each batch quenched in a different manner. Each quenched mixture was washed with saturated brine, and the organic layer dried with magnesium sulfate and concentrated. The quenching reagent had an influence on the stability of the crude reaction mixture. The NMR of a $CDCl_3$ solution of the crude product was measured immediately, and again after 3 d. The data depicting the impact of quenching conditions is summarized below (Table 9).

Table 9. Effects of quenching agents on the stability of crude enamide mixtures.

Quenching reagent	Equiv.	After workup decomposition	3 d in $CDCl_3$ decomposition
$NaHCO_3$ (s)	5	no	some
1 M $NaHCO_3$ (aq.)	excess	no	some
NH_4Cl (s)	5	no	yes
1 M NH_4Cl (aq.)	excess	some	yes
Acetic acid	5	no	yes

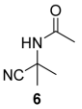
Screening of Purification Methods: 78: Benzyl *N*-(1-cyano-1,2-dimethylpropyl)carbamate (**77**) was treated with NaO*t*Bu as described above and worked up with a 1 M solution of $NaHCO_3$. ^1H NMR spectra were recorded on the crude product mixture, which was then split into 5 batches. Four batches were dissolved in DCM and adsorbed onto Isolute®. These were then poured on top of the column with the respective stationary phase shown in the Table and eluted with the solvent mixture shown. The remaining batch was distilled in a kugelrohr apparatus. The fractions in the eluent/distillate were examined by ^1H NMR spectroscopy, and compared with the spectrum of the crude product to evaluate the extent of decomposition during purification. There was, in all cases, some decomposition, and furthermore when the purification was repeated using the same method, the extent of decomposition varied from column to column, seemingly due to small changes in procedure we were unable to control. However, a column on silica deactivated by a small amount of Et_3N in the eluent, in general, gave the best results. Chromatography of other enamides on silica was more or less successful using these conditions (Table 10).

Table 10. Stability of enamide mixtures to various purification methods.

Purification	Solvent	Product purified decomposition
Silica	cyclohexane/EtOAc	some
Silica	cyclohexane/EtOAc/Et_3N (0.1 %)	some
Alumina	cyclohexane/EtOAc	some
Florasil®	cyclohexane/EtOAc	variable results
Reverse phase HPLC	water/MeCN	yes
Kugelrohr	–	some

Deuteration of the NH of Amides 79, 6, and 11: Using any of the three amides (**79**, **6**, or **11**), 0.36 mmol of substrate was dissolved in $CDCl_3$ (1 mL). CD_3OD (20 μL, 17.8 mg, 0.488 mmol, 1.35 equiv.) was added to each, and then either DBU (22 μL, 0.15 mmol, 0.4 equiv.), or K_2CO_3 (21 mg, 0.15 mmol, 0.4 equiv.) or no base was added and a measurement made about 30 min later. The NH peak was integrated against the other signals and the loss of the NH signal recorded. The NH signal in **79** did not exchange completely with either base, the corresponding signal for **6** exchanged with DBU but not with K_2CO_3. The NH signal of **11** exchanged completely with both bases (Table 11).

Table 11. Relative rates of NH deuteration under basic conditions.

Compounds	Base	NH/ND
 **79**	none	0.72
	DBU	0.84
	K_2CO_3	0.64
 **6**	none	0.91
	DBU	0
	K_2CO_3	0.84
 **11**	none	0.43
	DBU	0
	K_2CO_3	0

Reaction of NaO*t*Bu with Aldehyde-Derived Cyanoamides – Synthesis of Imidate 71: A solution of NaO*t*Bu in THF (2 M, 1.5 mL, 3 mmol) was added to a solution of 3,5-dichloro-*N*-(1-cyanopropyl)benzamide **70** (257 mg, 1 mmol) in THF (0.5 mL). After 2 h at

room temperature, TLC showed very little reaction so the mixture was heated to 60 °C for 3 h, then cooled and poured into $NaHCO_3$ (1 M)/ice/*t*BuOMe. The phases were separated, dried with $MgSO_4$, and evaporated to yield 266 mg of a mixture of products containing, according to the NMR of starting material, peaks that may be assigned to *E* and *Z* products and imidate **71**. This mixture was chromatographed over silica gel with a gradient of EtOAc/hexane to yield 58 mg of a fraction containing **71** as deemed by NMR spectroscopy. The spectral data consistent with **71** also showed peaks consistent with the *Z*-enamide. Trituration of this sample six times with cyclohexane ultimately gave 25 mg of pure **71**, m.p. 137–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (s, 2 H), 7.48 (s, 1 H), 6.32 (br. s, 1 H) 5.47 (m, 1 H), 1.65 (m, 2 H), 1.21 (s, 9 H), 0.94 (t, J = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 137.5 135.6, 131.5, 125.7, 76.5, 75.0, 30.7, 28.3, 9.3 ppm.

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Keywords: Synthetic methods · Regioselectivity · Elimination · Protecting groups · Cyanoamides · Enamides

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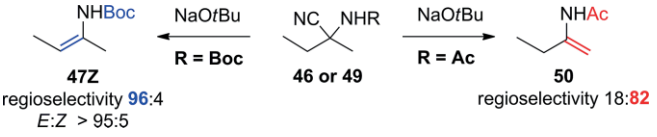

Treatment of ketone-derived cyanoamides with NaO*t*Bu leads to enamides in a simple, scalable, and inexpensive one-step operation in good yields. An E1cB mechanism, which fits all results and observations, is proposed. The *Z* geometry of the product enamide is highly favoured, and the regioselectivity can be directed by choice of the protecting group

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