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Enantioselective Organocatalytic One-Pot Amination/aza-Michael/Aldol Condensation Reaction Sequence: Synthesis of 3-Pyrrolines with a Quaternary Stereocenter

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Abstract: Primary amine-catalyzed direct conversion of α,α-disubstituted aldehydes into 3-pyrrolines with a quaternary stereocenter is reported. The one-pot enantioselective sequence is based on a α-amination, an aza-Michael addition of hydrazine, an aldol condensation dehydratation and proceeds with good yields and excellent levels of enantioselectivity. Synthetically attractive applications including the formation of aziridinopyrrolidine or epoxypyrrolidine derivatives with good yields and selectivities are also described.

Keywords: hydrazine · one-pot reaction · organocatalysis · pyrrolines · synthetic methods

Introduction

3-Pyrrolines, also called 2,5-dihydropyrroles, present an important class of heterocycles due to their presence in natural and synthetic biologically active compounds.[1] These building blocks are also useful intermediates for direct access to other significant five-membered nitrogen-containing heterocycles, such as pyrrolidines and pyrroles. The synthetic value of such units has stimulated the development of various syntheses.[2] However, one-pot enantioselective methods for the construction of polysubstituted 3-pyrrolines are still limited.[3] To the best of our knowledge, no direct enantioselective syntheses of 3-pyrrolines with a quaternary stereocenter have been reported in the literature.[4] However, these building blocks are not rare in bioactive molecules (Figure 1). For example, *Erythrina* alkaloids exhibit a wide range of pharmacological effects.[5] (+)-Lapidilectine B was found to reverse multidrug resistance in vincristine resistant KB cells[6] and KSP inhibitor developed by Merck[7] contain this entity.

As part of our program to develop organocatalyzed C–N bond formation,[8] we report the first one-pot enantioselective synthesis of 2,2-disubstituted-3-pyrrolines through a new organocatalytic one-pot sequence amination/aza-Michael/aldol condensation from readily available substrates (Scheme 1).

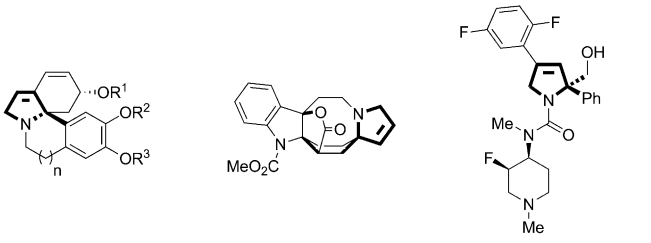
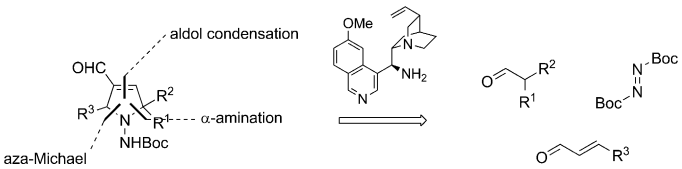


Figure 1. Biologically active compounds containing 2,2-disubstituted-3-pyrroline substructures.



Scheme 1. Organocatalytic strategy for the synthesis of 2,2-disubstituted-3-pyrrolines.

Results and Discussion

We have recently reported an enantioselective α-amination of α,α-disubstituted aldehydes.[8c] In connection with this work, we became interested in the implementation of this transformation into an organocatalytic sequence to synthesize nitrogen heterocycles. We reasoned that *tert*-butoxycarbonyl-protected hydrazine **1** ($R^1 = R^2 = t$Bu) could react with acrolein under an aza-Michael/aldol condensation by using the same catalytic conditions as those previously described for the α-amination, that is, 9-amino-(9-deoxy)-epi-quinine **2** (10 mol%) and TFA (30 mol%) in $CHCl_3$ (0.5 M).[9] Under these reaction conditions, the unexpected formation of a small amount of 3-pyrroline **3a** was detected, whereas cyclic

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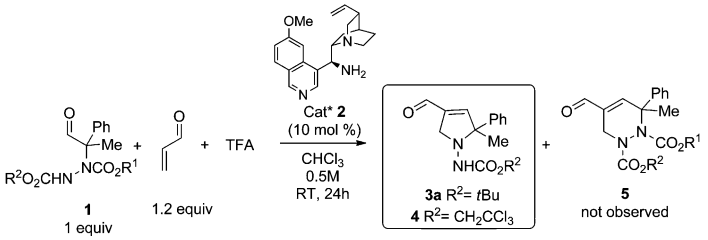
Table 1. Optimization of the aza-Michael/aldol condensation sequence.



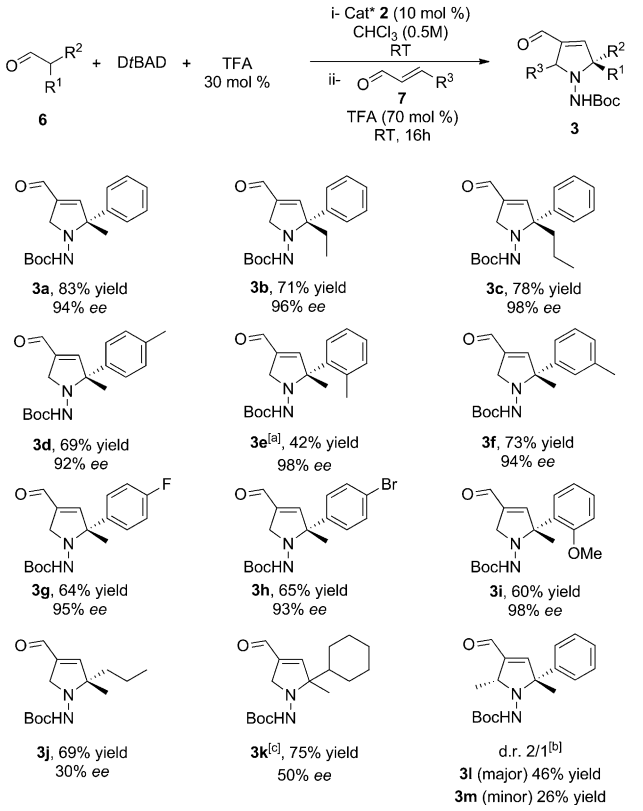
Entry	R^1	R^2	TFA [mol%]	Conversion [%][a]	Yield [%][b]
1	*t*Bu	*t*Bu	30	<5	<5
2	Bn	Bn	30	no reaction	
3	*i*Pr	*i*Pr	30	no reaction	
4	*t*Bu	*t*Bu	50	30	20[c]
5	*t*Bu	*t*Bu	75	65	37[d]
6	*t*Bu	*t*Bu	100	100	81
7[e]	*t*Bu	*t*Bu	100	100	11
8	*t*Bu	CH_2CCl_3	100	100	60

[a] Estimated by ^{1}H NMR analysis of the crude product. [b] Yield of the isolated product. [c] Starting material (50%) was recovered. [d] Starting material (10%) was recovered. [e] Reaction was carried out without catalyst.

hydrazine **5** was not observed (Table 1, entry 1). Considering the usefulness of structure **3a** and the lack of direct enantioselective access to these products, we decided to further investigate the organocatalyzed sequence. The essential deprotection of hydrazine **1** was confirmed by using stable carbamate-protecting groups under acidic conditions (Table 1, entries 2 and 3).

When isopropyloxycarbonyl- or benzyloxycarbonyl- protected hydrazines were engaged in the sequence, no reaction occurred, and the starting material was recovered. To promote the Boc cleavage, which seems to be required for the aza-Michael step, the amount of TFA was gradually increased (Table 1, entries 4–6). When the reaction was run in more acidic conditions (50 or 75 mol% TFA), the expected 3-pyrroline **3a** was obtained in better yields (20 and 37%, respectively). The best conditions were found when 100 mol% TFA was used, giving **3a** in 81% yield. To confirm the iminium activation of the acrolein by primary amine **2**, the reaction was run without a catalyst (Table 1, entry 7). In this case, extensive decomposition was observed, and **3a** was isolated in 11% yield. Finally, an orthogonally protected hydrazino aldehyde containing a Boc and a 2,2,2-trichloroethoxycarbonyl (Troc) group was synthesized to confirm the formation of the five-membered heterocycle instead of the six-membered one. When this compound was engaged in the sequence, 3-pyrroline **4** was obtained in 60% yield (Table 1, entry 8).[10]

With the optimized conditions of the aza-Michael/aldol condensation sequence in hand, the feasibility of a one-pot formation of 3-pyrrolines including the enantioselective α-amination to form the nitrogen-containing quaternary center was then examined (Scheme 2). First, this organocatalytic sequence was attempted with 2-phenylpropanal. The one-pot procedure consists of the reaction of 2-phenylpropanal **6a** (1.2 equiv) with di-*tert*-butylazodicarboxylate



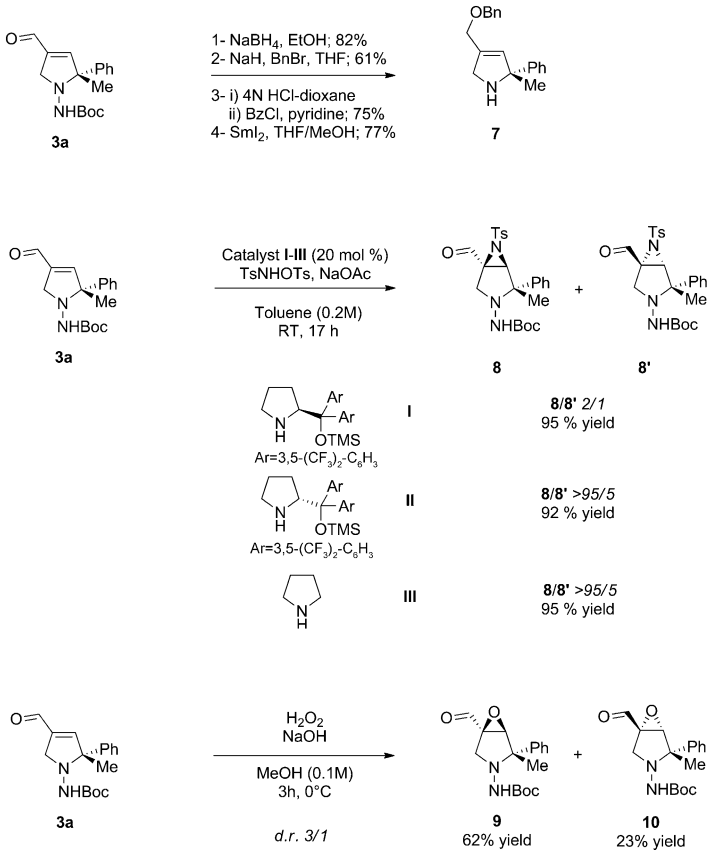
Scheme 2. Scope of the one-pot enantioselective synthesis of 3-pyrrolines (yield of the isolated product after purification by chromatography; the *ee* value was determined by HPLC). a) Monoprotected aldehyde was isolated (35%; see the Supporting Information for details); b) determined by ^{1}H NMR analysis of the crude product; c) absolute configuration has not been determined.

(D*t*BAD, 1 equiv) catalyzed by **2** (10 mol%) and TFA (30 mol%). The reaction mixture was stirred at room temperature until completion (typically, 2 h) at which point acrolein **7** (R^3=H; 1.2 equiv) and TFA (70 mol%) were added.[11] In this case, 3-pyrroline **3a** was obtained in good yield (83%) and excellent enantioselectivity (94%). The one-pot procedure was then extended to a variety of α,α-disubstituted aldehydes **6**. Different 2-phenyl substituted aldehydes could be engaged in this transformation giving 3-pyrrolines **3b** and **3c** in good yields and high levels of enantioselectivity. The influence of the aryl unit was next examined by using various 2-arylpropionaldehydes. Electron-withdrawing or electron-donating groups were well tolerated along with the substitution at *ortho*-, *meta*-, or *para*- position of the aryl moiety. 3-pyrrolines **3d–i** were isolated in good yields and stereoselectivities up to 98%. A lower yield was observed when R^2=*o*-MeC_6H_4 (**3e**, 42% yield) was used. In this case, the reaction was very slow and 35% of monoprotected aldehyde was also isolated.[12]

α,α-Dialkyl aldehyde (2-methylpentanal **6j**) was also tested in the cascade reaction, and the corresponding 3-pyrroline **3j** was obtained in 69% yield and 30% enantiomeric excess. More sterically hindered 2-cyclohexylpropionaldehyde **6k** gave better result in term of enantioselectivity and

pyrroline **3k** was synthesized in 75% yield and 50% *ee*. Finally, the use of crotonaldehyde **7** (R^3 = Me) instead of acrolein with 2-phenylpropionaldehyde afforded 2,2,5-trisubstituted-3-pyrrolines **3l** and **3m** as a separable mixture of diastereoisomers (diastereomeric ratio (d.r.) 2:1).

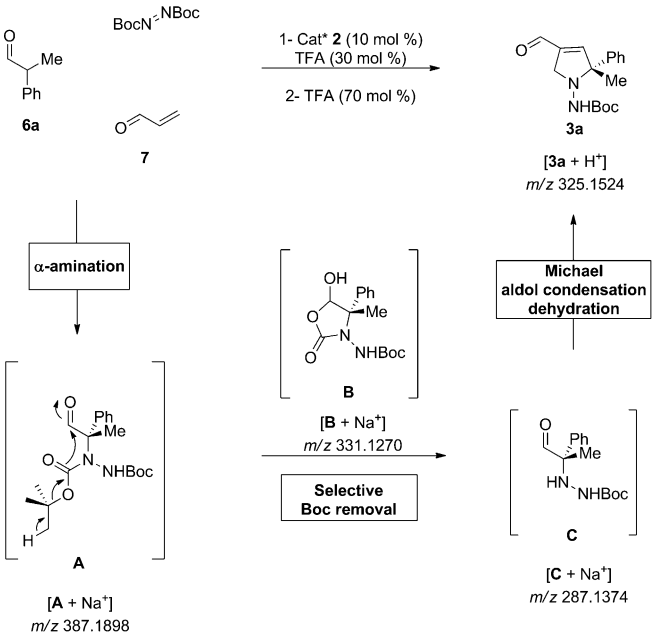
As illustrated in Scheme 3, synthetically attractive applications can arise from products **3**. Cleavage of the hydrazine



Scheme 3. Synthetic transformations of 3-pyrroline **3a**.

of 2-methyl-2-phenyl-3-pyrroline **3a** was envisaged. Reduction of the aldehyde, Bn-protection of the resulting alcohol and N–N bond cleavage with SmI_2 after hydrazine activation gave 3-pyrroline **7**. Highly functionalized pyrrolidine derivatives were synthesized. Product **3a** was applied in an organocatalyzed aziridination reaction developed previously in our group.[13] When catalyst **I** was used for the transformation, a diastereoisomeric mixture of nitrogen-containing bicyclic compound **8** and **8′** was obtained in 95% yield and moderate selectivity (d.r. 2:1). To uncover a possible match/mismatch effect between the chiral substrate and the catalyst, catalyst **II** was also tested. Indeed, a matched relationship between catalyst **II** and chiral pyrroline **3a** was observed and the aziridinopyrrolidine **8** was obtained in 92% yield as a single diastereoisomer. It is also worth noting that the quaternary stereocenter of **3a** plays a pivotal role in the stereochemical relay, because the use of pyrrolidine **III** as a catalyst led to compound **8** in 95% as a single diastereoisomer. This observation prompted us to investigate the parent epoxidation reaction. Moreover, epoxypyrrolidines are important intermediates in organic synthesis.[14] Enal **3a** was engaged in an epoxidation reaction under basic conditions (H_2O_2, NaOH) to afford the polysubstituted pyrrolidines **9** and **10** as a separable mixture of diastereoisomers (d.r. 3:1).

Based on the above discussed results, the reaction pathway described in Scheme 4 is proposed to explain the selective formation of **3**. Aldehyde **6** undergoes α-amination with D*t*BAD catalyzed by primary amine **2**. Under acidic conditions, the selective Boc cleavage of **A** could be explained by the formation of cyclic compound **B**, which might be subject to decarboxylation and leads to monoprotected aldehyde **C**. An organocatalyzed aza-Michael/aldol condensation sequence and a final dehydration allow the formation of 3-pyrroline **3**. Starting from 2-phenylpropionaldehyde **6a**, ESI-MS analyses were carried out to characterize the intermediates and to support the proposed mechanism. To a solution of 9-amino-(9-deoxy)-epi-quinine **2** (10 mol%) in $CHCl_3$, α,α-disubstituted aldehyde **6a**, di-*tert*-butyl azodicarboxylate, and TFA (30 mol%) were added successively at room temperature. The reaction mixture was stirred until the completion of the reaction. A first analytical sample was taken and injected. Intermediate **A** ([**A**+Na^+], *m*/*z* 387.1898) was detected. Acrolein **7** and TFA (70 mol%) were then added, and the resulting mixture was stirred for 15 min at room temperature. A second analytical sample was taken and injected. Intermediate **B** ([**B**+Na^+], *m*/*z* 331.1270) and **C** ([**C**+Na^+], *m*/*z* 287.1374) were detected. A third analytical



Scheme 4. Proposed pathway to 3-pyrrolines **3a** supported by ESI analyses.

sample was taken after 1 h of reaction and injected. Product **3a** ([**3a**+H^+] *m*/*z* 325.1524) was detected.

Conclusion

We have disclosed an efficient and highly enantioselective access to 2,2-disubstituted-3-pyrrolines through a new organocatalytic one-pot sequence amination/aza-Michael/aldol condensation from readily available substrates. These building blocks present in natural products or synthetic biologically active compounds can also be readily converted to different polysubstituted compounds, which should be useful in organic synthesis and medicinal chemistry. Current work within the group is directed to the incorporation of this methodology in total synthesis.

Experimental Section

General procedure for the formation of 3-pyrrolines 3a–m: To a solution of 9-amino-(9-deoxy)-epi-quinine **2** (0.05 mmol, 16 mg) in $CHCl_3$ (1 mL) were added successively at RT α,α-disubstituted aldehyde **6** (0.6 mmol), di-*tert*-butyl azodicarboxylate (0.5 mmol, 115 mg), and TFA (0.15 mmol, 12 μL). The reaction mixture was stirred until the completion of the reaction (typically 2 h, monitored by TLC). α,β-Unsaturated aldehyde (0.6 mmol) and TFA (0.35 mmol, 27 μL) were then added and the resulting mixture was stirred for 16 h at RT. The reaction was quenched with a saturated solution of $NaHCO_3$. The organic materials were extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and concentrated in vacuo after filtration. The residue was purified by flash chromatography (pentane/Et_2O) to give the desired product **3**.

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[1] For selected examples, see a) D. E. Beattie, G. M. Dover, T. J. Ward, *J. Med. Chem.* **1985**, *28*, 1617–1620; b) W. K. Anderson, A. S. Milowsky, *J. Med. Chem.* **1986**, *29*, 2241–2249; c) F. Bellina, R. Rossi, *Tetrahedron* **2006**, *62*, 7213–7256; d) H. Mack, D. Baucke, W. Hornberger, U. E. W. Lange, W. Seitz, H. W. Höffken, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2641–2647; e) U. E. W. Lange, D. Baucke, W. Hornberger, H. Mack, W. Seitz, H. W. Höffken, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2648–2653; f) S. Castellano, H. D. G. Fiji, S. S. Kinderman, M. Watanabe, P. de Leon, F. Tamanoi, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 5843–5845; g) Z. Wang, S. Castellano, S. S. Kinderman, C. E. Argueta, A. B. Beshir, G. Fenteany, O. Kwon, *Chem. Eur. J.* **2011**, *17*, 649–654.

[2] For a general review, see: M. Brichacek, J. T. Njardarson, *Org. Biomol. Chem.* **2009**, *7*, 1761–1770.

[3] For selected examples, see a) L. Jean, A. Marinetti, *Tetrahedron Lett.* **2006**, *47*, 2141–2145; b) A. Scherer, J. A. Gladysz, *Tetrahedron Lett.* **2006**, *47*, 6335–6337; c) Y.-Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660–5661; d) N. Pinto, N. Fleury-Brégeot, A. Marinetti, *Eur. J. Org. Chem.* **2009**, *1*, 146–151; e) W. Sun, G. Zhu, L. Hong, R. Wang, *Chem. Eur. J.* **2011**, *17*, 13958–13962; f) X. Han, F. Zhong, Y. Wang, Y. Lu, *Angew. Chem.* **2012**, *124*, 791–794; *Angew. Chem. Int. Ed.* **2012**, *51*, 767–770.

[4] For selected examples, see: a) M. P. Green, J. C. Prodger, A. E. Sherlock, C. J. Hayes, *Org. Lett.* **2001**, *3*, 3377–3379; b) T. J. Donohoe, D. House, *J. Org. Chem.* **2002**, *67*, 5015–5018; c) B. Mitasev, K. M. Brummond, *Synlett* **2006**, 3100–3104; d) L. Li, J. Zhang, *Org. Lett.* **2011**, *13*, 5940–5943.

[5] a) S. F. Dyke, S. N. Quessy in *The Alkaloids, Vol. 18* (Ed.: R. G. A. Rodrigo), Academic Press, New York, **1981**, pp. 1–98; b) M. E. Amer, M. Shamma, A. J. Freyer, *J. Nat. Prod.* **1991**, *54*, 329–363; c) T. Sano, Y. Tsuda in *The Alkaloids, Vol. 48* (Ed.: G. A. Cordell), Academic Press, New York, **1996**, pp. 249–337.

[6] a) K. Awang, T. Sévenet, M. Païs, A. H. A. Hadi, *J. Nat. Prod.* **1993**, *56*, 1134–1139; b) W.-S. Yap, C.-Y. Gan, Y.-Y. Low, Y.-M. Choo, T. Etoh, M. Hayashi, K. Komiyama, T.-S. Kam, *J. Nat. Prod.* **2011**, *74*, 1309–1312.

[7] a) C. D. Cox, M. J. Breslin, D. B. Whitman, P. J. Coleman, R. M. Garbaccio, M. E. Fraley, M. M. Zrada, C. A. Buser, E. S. Walsh, K. Hamilton, R. B. Lobell, W. Tao, M. T. Abrams, V. J. South, H. E. Huber, N. E. Kohl, G. D. Hartman, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2697–2702; b) C. D. Cox, P. J. Coleman, M. J. Breslin, D. B. Whitman, R. M. Garbaccio, M. E. Fraley, C. A. Buser, E. S. Walsh, K. Hamilton, M. D. Schaber, R. B. Lobell, W. Tao, J. P. Davide, R. E. Diehl, M. T. Abrams, V. J. South, H. E. Huber, M. Torrent, T. Prueksaritanont, C. Li, D. E. Slaughter, E. Mahan, C. Fernandez-Metzler, Y. Yan, L. C. Kuo, N. E. Kohl, G. D. Hartman, *J. Med. Chem.* **2008**, *51*, 4239–4252.

[8] a) R. Ait-Youcef, K. Sbargoud, X. Moreau, C. Greck, *Synlett* **2009**, 3007–3010; b) R. Ait-Youcef, X. Moreau, C. Greck, *J. Org. Chem.* **2010**, *75*, 5312–5315; c) A. Desmarchelier, H. Yalgin, V. Coeffard, X. Moreau, C. Greck, *Tetrahedron Lett.* **2011**, *52*, 4430–4432; d) A. Desmarchelier, J. Marrot, X. Moreau, C. Greck, *Org. Biomol. Chem.* **2011**, *9*, 994–997; e) V. Coeffard, A. Desmarchelier, B. Morel, X. Moreau, C. Greck, *Org. Lett.* **2011**, *13*, 5778–5781.

[9] For recent reports on organocatalytic aza-Michael by using hydrazides, see: a) O. Mahé, I. Dez, V. Levacher, J.-F. Brière, *Angew. Chem.* **2010**, *122*, 7226–7229; *Angew. Chem. Int. Ed.* **2010**, *49*, 7072–7075; b) N. R. Campbell, B. Sun, R. P. Singh, L. Deng, *Adv. Synth. Catal.* **2011**, *353*, 3123–3128; c) M. Fernández, E. Reyes, J. L. Vicario, D. Badía, L. Carrillo, *Adv. Synth. Catal.* **2012**, *354*, 371–376.

[10] a) A. J. Oelke, D. J. France, T. Hofmann, G. Wuitschik, S. V. Ley, *Angew. Chem.* **2010**, *122*, 6275–6278; *Angew. Chem. Int. Ed.* **2010**, *49*, 6139–6142; b) A. J. Oelke, F. Antonietti, L. Bertone, P. B. Cranwell, D. J. France, R. J. M. Goss, T. Hofmann, T. Knauer, S. J. Moss, P. C. Skelton, R. M. Turner, G. Wuitschik, S. V. Ley, *Chem. Eur. J.* **2011**, *17*, 4183–4194.

[11] When all the reagents were mixed together, extensive decomposition due to the incompatibility of D*t*BAD and acidic conditions was observed.

[12] For details, see the Supporting Information.

[13] A. Desmarchelier, D. Pereira de Sant'Ana, V. Terrasson, J.-M. Campagne, X. Moreau, C. Greck, R. M. de Figueiredo, *Eur. J. Org. Chem.* **2011**, 4046–4052.

[14] For selected examples in syntheses of natural products, see: a) J. Yamaguchi, H. Kakeya, T. Uno, M. Shijo, H. Osada, Y. Hayashi, *Angew. Chem.* **2005**, *117*, 3170–3175; *Angew. Chem. Int. Ed.* **2005**, *44*, 3110–3115; b) D. J. Wardrop, E. G. Bowen, *Chem. Commun.* **2005**, 5106–5108; c) T. Ling, B. C. Potts, V. R. Macherla, *J. Org. Chem.* **2010**, *75*, 3882–3885.

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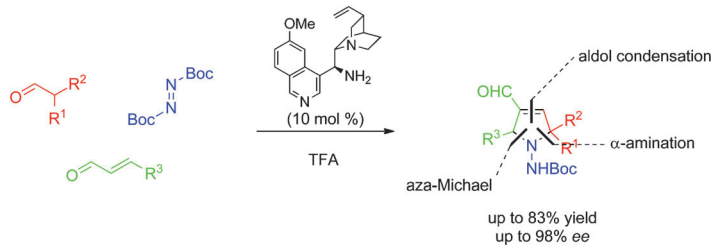

Expect the unexpected: Primary amine-catalyzed direct conversion of α,α-disubstituted aldehydes into 3-pyrrolines with a quaternary stereocenter is reported. The sequence involves an α-amination, an aza-Michael addition of hydrazine, an aldol condensation and proceeds with good yields and excellent levels of enantioselectivity (see scheme).

Organocatalysis

A. Desmarchelier, V. Coeffard, X. Moreau,* C. Greck* ..... ▮▮▮▮–▮▮▮▮

Enantioselective Organocatalytic One-Pot Amination/aza-Michael/Aldol Condensation Reaction Sequence: Synthesis of 3-Pyrrolines with a Quaternary Stereocenter