ORGANIC LETTERS

2007
Vol. 9, No. 6
1149−1151

Catalytic Asymmetric Three-Component Acyl-Strecker Reaction

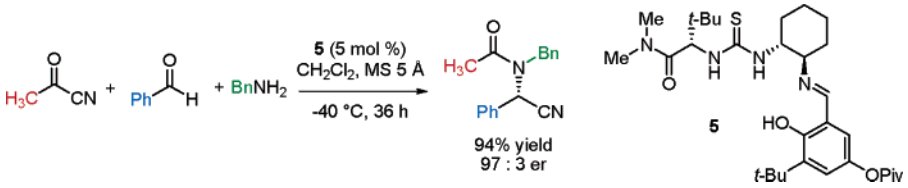
Subhas Chandra Pan and Benjamin List*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany

list@mpi-muelheim.mpg.de

Received February 2, 2007

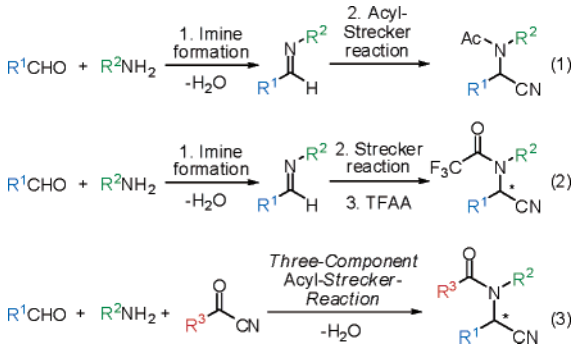
ABSTRACT



The first organocatalytic asymmetric three-component Strecker reaction, the urea-catalyzed acylcyanation of in situ generated imines, has been developed. Different α-amido nitriles are formed in excellent yields and enantioslectivities from aldehydes, amines, and acyl cyanides in the presence of Jacobsen's thiourea catalyst 5. Despite its obvious use for the synthesis of α-amino acids and their derivatives, our reaction may find use in diversity oriented synthesis and medicinal chemistry.

Catalytic asymmetric Strecker reactions are highly useful for the preparation of chiral α-amino acid derivatives.[1] Although there are already a number of versatile indirect variants of this transformation,[2,3] only a single direct catalytic asymmetric *three-component* Strecker reaction of aldehydes, aromatic amines, and HCN has been described by Kobayashi et al.[4] Replacing the highly toxic and volatile HCN in such catalytic asymmetric Strecker reactions with a more convenient cyanide source and expanding the scope of the amine component would clearly be desirable. We have recently developed a novel variant of the Strecker reaction, the Brønsted acid catalyzed acylcyanation of imines (acyl-Strecker reaction) with commercially available acetyl cyanide as an HCN equivalent (Scheme 1, eq 1).[5,6] Previously, acetyl cyanide and other cyanoformates have only been used in catalytic enantioselective acylcyantions of carbonyl com-

Scheme 1. Discussed Strecker Variants



(1) For reviews, see: (a) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795−2827. (b) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875−877. (c) Spino, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1764−1766. (d) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359−373.

(2) (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901−4902. (b) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315−5316. (c) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279−1281. (d) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867−870. (e) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012−10014. (f) Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, 1919−1922.

(3) (a) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3186−3188. (b) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160. (c) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284−4285. (d) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650−1652. (e) Nakamura, S.; Sato, N.; Sugimoto, M.; Toru, T. *Tetrahedron*: *Asymmetry* **2004**, *15*, 1513−1516. (f) Banphavichit, V.; Mansawat, W.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron* **2004**, *60*, 10559−10568. (g) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548−2549. (h) Berkessel, A.; Mukherjee, S.; Lex, J. *Synlett* **2006**, 41−44. (i) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617−2619. (j) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Fini, F.; Pettersen, D.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 9869−9872.

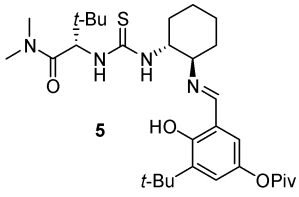
10.1021/ol0702674 CCC: $37.00
Published on Web 02/24/2007

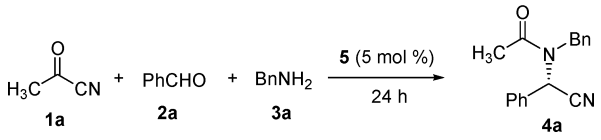
pounds.[7] After investigating several chiral phosphoric acid and thiourea catalysts,[8,9] we identified Jacobsen thiourea **5** to be an effective and highly enantioselective catalyst of this reaction.[10] Our two-step protocol (imine formation, acetylcyanation) may be considered a simplification of the Jacobsen−Strecker reaction where three operations—imine formation, Strecker reaction, and amide formation—are required to isolate a stable α-amido nitrile product (eq 2).[2] We reasoned that a further refinement of the reaction might be possible by developing an attractive one-pot three-component catalytic asymmetric acyl-Strecker reaction (eq 3).

Such a process would constitute the first organocatalytic asymmetric three-component Strecker-type reaction. Moreover, as a three-component reaction, this methodology may benefit diversity oriented synthesis. Here we report the successful realization of this concept.

Initially we found that stirring benzaldehyde (**2a**), benzyl amine (**3a**), $MgSO_4$, catalyst **5**, and acetyl cyanide (**1a**) at 0 °C for 24 h in toluene resulted in poor yield of the desired product **4a** and side product formation. Not unexpectedly, a considerable amount of *N*-benzyl acetamide was formed resulting from the direct reaction of benzyl amine with acetyl cyanide. We hypothesized that to suppress this side reaction, the order of reagent mixing may be crucial. Indeed, when acetyl cyanide was added last, significant conversion to the desired product could be realized (Table 1, entry 1).

Table 1. Optimizing the Reaction Conditions





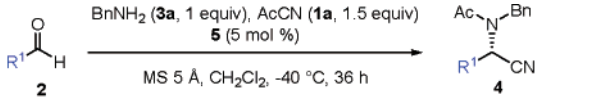
entry[a]	solvent	additive	temp (°C)	yield (%)	er
1	toluene	$MgSO_4$	0	84	57:43
2	toluene	MS 5 Å	0	10	80:20
3	CH_2Cl_2	none	0	63	74:26
4	CH_2Cl_2	$MgSO_4$	0	68	78:22
5	CH_2Cl_2	MS 5 Å	0	66	87:13
6	CH_2Cl_2	MS 5 Å	−40	83	94:6
7[b]	CH_2Cl_2	MS 5 Å	−40	85	97:3
8[c]	CH_2Cl_2	MS 5 Å	−40	98	97:3

[a] Aldehyde, amine, additive, and catalyst were stirred for 2 h at 0 °C before acetyl cyanide was added. [b] Aldehyde, amine, and additive were stirred for 2 h at 0 °C before the catalyst and acetyl cyanide (at −40 °C) were added. [c] Aldehyde, amine, and additive were stirred for 2 h at rt before the catalyst and acetyl cyanide (at −40 °C) were added.

However, the product was formed with poor enantioselectivity. Switching the drying reagent to 5 Å molecular sieves and the solvent to dichloromethane significantly improved the enantioselectivity (entries 2−5). Even higher enantioselectivity was observed after lowering the temperature to −40 °C (entry 6). Finally, we realized that the best result (98% yield, 97:3 er) was obtained if the aldehyde was first mixed with the amine and MS 5 Å for 2 h at rt before the catalyst and acetyl cyanide were added subsequently at −40 °C (entries 7 and 8). Decreasing the catalyst loading to 1 mol % resulted in considerably lower yield and enantioselectivity.

With optimal reaction conditions established we initiated a study to explore the scope of this new catalytic asymmetric three-component reaction.[11] First, the reaction of a variety of different aldehydes **2** with benzyl amine (**3a**) as the amine component and acetyl cyanide (**1a**) was examined (Table 2).[12] Noteworthy, the reactions took place efficiently in good

Table 2. Catalytic Asymmetric Acylcyanation of Different Aldehydes with Acetyl Cyanide and Benzyl Amine



entry[a]	R^1	product	yield (%)	er[b]
1	Ph	**4a**	94	97 : 3
2	4-$MeOC_6H_4$	**4b**	88	96 : 4
3	4-ClC_6H_4	**4c**	78	96 : 4
4	2-naphthyl	**4d**	92	97 : 3
5		**4e**	82	96 : 4
6	^{i}Pr	**4f**	92	96 : 4
7	^{t}Bu	**4g**	46	97 : 3
8	^{n}Bu	**4h**	75	94 : 6
9[c]	^{t}BuCH$_2$	**4i**	97	96 : 4

[a] Aldehyde **2** (0.5 mmol), benzyl amine (**3a**, 0.5 mmol), and molecular sieves 5 Å (150 mg) were stirred at rt for 2 h in CH_2Cl_2 (2 mL). Catalyst **5** (0.025 mmol) and after cooling to −40 °C acetyl cyanide **1a** (0.75 mmol) were added and the mixture was stirred for 36 h before the usual workup. [b] Determined by chiral HPLC. [c] With 10 mol % of catalyst **5**.

to excellent yields with a high level of enantioselectivity for all studied aldehydes. Particularly high enantioselectivities were observed with aromatic aldehydes (entries 1−4) and an α,β-unsaturated aldehyde (entry 5). But even an aliphatic branched and an α-trisubstituted aldehyde gave excellent enantioselectivities (entries 6 and 7). In the case of the most challenging α-unbranched aldehydes (entries 8 and 9), slightly lower er values were obtained. However, at least in the case of 3,3-dimethylbutanal, the er could be significantly increased (96:4) when we used 10 mol % of catalyst **5**.

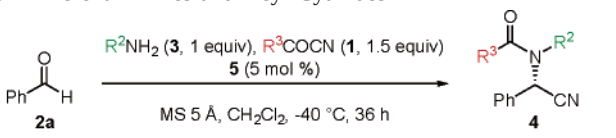
(4) (a) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762−766. (b) Kobayashi, S.; Ishitani, H. *Chirality* **2000**, *12*, 540−543.

(5) Pan, S. C.; Zhou, J.; List, B. *Synlett* **2006**, 3275−3276.

(6) For alternative non-enantioselective variants, see: (a) Dornow, A.; Lüpfert, S. *Chem. Ber.* **1956**, *89*, 2718−2722. (b) Dornow, A.; Lüpfert, S. *Chem. Ber.* **1957**, *90*, 1780−1786. (c) Dornow, A.; Lüpfert, S. U.S. patent 2849477, 1958. (d) Gardent, M. J.; Delépine, M. M. *C. R. Acad. Sci.* **1958**, *247*, 2153−2156. (e) Rai, M.; Krishan, K.; Singh, A. *Indian J. Chem., Sect. B* **1978**, *16*, 834−835. (f) Sakamoto, M.; Akiyama, Y.; Furumi, N.; Ishii, K.; Tomimatsu, Y.; Date, T. *Chem. Pharm. Bull.* **1983**, *31*, 2623−2631.

A variety of amines were probed next with benzaldehyde (**2a**) as the aldehyde component (Table 3). It turned out that three different benzyl amines can be used to give the products in high yields and excellent enantioselectivities (entries 1−3). The electronic properties of the aromatic system of the amine component do not seem to influence the yield and enantioselectivity of the reaction. Furfuryl amine having an heteroaromatic moiety can also be employed (entry 4). Allyl amine has also been used and still gave the desired product in good results (entry 5). Moreover, the reaction also affords the product with a simple alkyl amine although in slightly lower enantioselectivity (entry 6). Apparently, the third component of our reaction can be varied equally well. In preliminary experiments we found that heptanoyl cyanide reacts with benzaldehyde and benzyl amine to provide product **4p** in 84% yield and 94:6 er (entry 7).[13] That the reaction products (i.e., **4g**) can readily be converted into α-amino acids and their salts without racemization and in high yields via acid-mediated hydrolysis and hydrogenolysis has previously been established in our laboratories.[10]

Table 3. Catalytic Asymmetric Acylcyanation of Benzaldehyde with Different Amines and Acyl Cyanides



entry[a]	R^2	R^3	product	yield (%)	er[b]
1	4-$MeOC_6H_4CH_2$	Me	**4j**	95	97 : 3
2	4-$ClC_6H_4CH_2$	Me	**4k**	93	97 : 3
3	1-naphCH_2	Me	**4l**	92	97 : 3
4	2-furCH_2	Me	**4m**	83	90 : 10
5	Allyl	Me	**4n**	88	94 : 6
6	^{n}Pent	Me	**4o**	76	87 : 13
7	Bn	^{n}Hex	**4p**	84	94 : 6

[a] Reaction conditions as described in Table 2 were used. [b] Determined by chiral HPLC.

In summary, we have developed the first organocatalytic asymmetric variant of the classical three-component Strecker reaction. The operational simplicity, practicability, and mild reaction condition render it an attractive approach for the generation of different α-amido nitriles. In comparison to the Jacobsen−Strecker reaction, which uses the same catalysts, the newly developed variant avoids highly toxic HCN, does not require preformation of the imine intermediate, and avoids derivatization with TFAA. Despite its obvious use for the synthesis of α-amino acids and their derivatives, our reaction may find use in diversity oriented synthesis and medicinal chemistry.

Acknowledgment. This work was funded in part by the DFG (Priority program "Organocatalysis" SPP1179). Generous support by the Max-Planck-Society and by Novartis (Young Investigator Award to B.L.) is gratefully acknowledged. We also thank BASF, Degussa, Merck, Saltigo, and Wacker for general support and for donating chemicals.

Supporting Information Available: Experimental and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0702674

(7) (a) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636−3638. (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021−3024. (c) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413−3422. (d) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6295−6196. (e) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron*: *Asymmetry* **2003**, *14*, 197−200. (f) Baeza, A.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Tetrahedron: Asymmetry* **2005**, *16*, 2385−2389. (g) Belokon, Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.* **2003**, *5*, 4505−4507. (h) Belokon, Y. N.; Ishibashi, E.; Nombra, H.; North, M. *Chem. Commun.* **2006**, *16*, 1775−1777. (i) Gou, S.; Wang, J.; Liu, X.; Wang, W.; Chen, F.-X.; Feng, X. *Adv. Synth. Catal.* **2007**, *349*, 343−349. For the first use of acetyl cyanide in an acylcyanation of aldehydes, see: (j) Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592−11593. (k) Lundgren, S.; Wingstrand, E.; Moberg, C. *Adv. Synth. Catal.* **2007**, *349*, 364−372.

(8) For reviews, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999−1010. (b) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909−3912.

(9) For reviews, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289−296. (b) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299−4306. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−1543. (d) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418−5427. (e) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062−2064.

(10) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 612−614.

(11) For a review on catalytic asymmetric multicomponent reactions, see: Seayad, J.; List, B. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; WILEY-VCH: Weinheim, Germany, 2005; pp 277−298.

(12) If HCN was used rather than acetyl cyanide, under the same reaction conditions, following standard in situ derivatization with trifluoroacetic acid anhydride, the obtained product was essentially racemic.

(13) No conversion was obtained when cyanoformate esters or benzoylcyanide were used as the cyanide source.