Asymmetric Catalysis

DOI: 10.1002/ange.200704315

Catalytic Enantioselective Passerini Three-Component Reaction**

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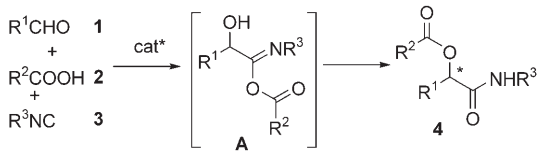
The Passerini three-component reaction (P-3CR) involves the condensation of a carbonyl compound **1**, a carboxylic acid **2**, and an isocyanide **3** with the concurrent generation of a stereogenic center to afford an α-acyloxyamide **4** (Scheme 1).[1] Together with the Ugi four-component reaction



Scheme 1. Passerini three-component reaction.

(U-4CR),[2] the P-3CR has been investigated intensively during the past two decades. Many innovative variations have been uncovered and have led to the facile synthesis of a large collection of diverse heterocyclic scaffolds in a step- and atom-economic manner.[3] Although a number of diastereoselective P-3CRs[4] and U-4CRs[5] are known, only limited success has been attained in the development of enantioselective P-3CRs[6–11] and U-4CRs.[12] Denmark and Fan developed an asymmetric α-addition of isocyanides to aldehydes catalyzed by a chiral Lewis base with good to excellent enantioselectivity.[7] The protocol is applicable to nonchelating aldehydes, but it is a bimolecular transformation without a carboxylic acid substrate. Dömling and co-workers screened a large number of metal–ligand combinations in a parallel fashion and found that a stoichiometric amount of a Ti–taddol complex (taddol = 1,1,4,4-tetraphenyl-2,3-*O*-isopropylidene-D-threitol) promoted the P-3CR to afford α-acyloxyamides with low to moderate enantioselectivity.[8] Schreiber and co-workers demonstrated that an indan-pybox–Cu^{II} complex (pybox = pyridinebis(oxazoline)) could catalyze the P-3CR.[9] Nevertheless, the enantiomerically enriched Passerini adduct was obtained only when a chelating aldehyde was used.

The development of a truly catalytic enantioselective three-component Passerini reaction of wide application scope remains a significant challenge, in sharp contrast to the formidable progress made in the field of asymmetric synthesis in general. Several pitfalls exist that make this task particularly challenging: 1) the complexity of the reaction mechanism, 2) the competitiveness of the uncatalyzed background reaction, 3) the potential of the three components, all of which are Lewis bases, to coordinate to or deactivate the catalyst, and 4) the problem of catalyst turnover as a result of product inhibition. Indeed, when a nonchelating aldehyde is used, the reaction produces an imidate intermediate **A** that is bidentate in nature. Furthermore, the P-3CR adduct itself is also a bidentate ligand and can therefore compete with the substrate to coordinate to the catalyst (Scheme 1). We proposed recently to use a chiral catalyst with a single coordination site for the enantioselective α-addition of isocyanides to aldehydes. As a proof of concept, we described an enantioselective synthesis of 2-(1-hydroxyalkyl) 5-aminooxazoles by the Lewis acid catalyzed condensation of an aldehyde with an α-isocyanoacetamide.[10b] As a continuation of this research, we report herein that the presence of a carboxylic acid is tolerated well in the [(salen)Al^{III}Cl]-catalyzed α-addition of isocyanides to aldehydes and document an efficient catalytic enantioselective three-component Passerini reaction that is applicable to a wide range of nonchelating aliphatic aldehydes.

The P-3CR of 2-methylpropanal (**1a**), benzoic acid (**2a**), and benzyl isocyanide (**3a**) in toluene was used as a standard reaction for the screening of possible chiral Lewis acid catalysts (catalyst loading: 0.1 equiv). In a control experiment, the reaction proceeded even at −40 °C in the absence of a catalyst to afford the racemic adduct **4a** in 37% yield (Table 1, entry 1). As the carboxylic acid itself catalyzed the P-3CR, we designed a protocol involving the slow addition over 1 h of the carboxylic acid to the solution of the catalyst, **1a**, and **3a** to minimize or suppress the undesired background reaction. Representative results obtained by varying the ligand structure, the metal source, the temperature, and the concentration of the reaction mixture are summarized in Table 1. When *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-(*R*,*R*)-cyclohexane-1,2-diamine (**5a**) was used as the supporting ligand[13] in association with Et_2AlCl,[14] the adduct **4a** was produced with 63% *ee* (Table 1, entry 2). The enantioselectivity dropped significantly when Et_3Al was used instead of Et_2AlCl (Table 1, entry 3). Other salts, such as $MnCl_3$, $CrCl_3$,

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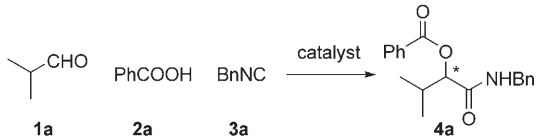
[**] We gratefully acknowledge the National Science Foundation of China (NSFC), the Chinese Academy of Sciences, and the CNRS (France) for financial support.

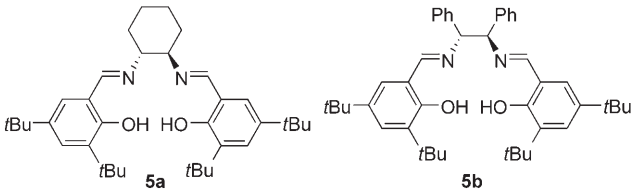
Supporting information for this article, including experimental procedures, product characterization, and the ^{1}H NMR spectra and HPLC traces (chiral phase) of **4a**–**p**, is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Survey of reaction conditions for the enantioselective P-3CR of **1a**–**3a**.[a]



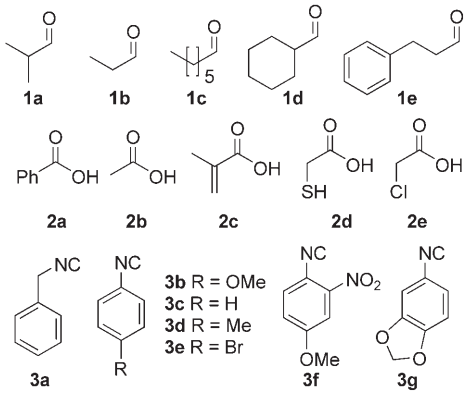
Entry	Catalyst	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	none	−40	37	rac.
2	**5a** + Et_2AlCl	−40	70	63
3	**5a** + Et_3Al	−40	32	8
4	**5a** + $MnCl_3$	−40	36	19
5	**5a** + $CrCl_3$	−40	54	24
6	**5a** + $Ti(OiPr)_4$	−40	trace	n.d.[d]
7	**5a** + Et_2Zn	−40	35	0
8	**5a** + Et_2AlCl	−20	51	53
9	**5a** + Et_2AlCl	−60	26	80
10[e]	**5a** + Et_2AlCl	−40	50	59
11[f]	**5a** + Et_2AlCl	−20	71	47
12	**5b** + Et_2AlCl	−40	66	51

[a] General conditions: **1a**/**2a**/**3a** 1:1:1, 48 h, $c = 0.33$ M, toluene. [b] Yield of the analytically pure product. [c] Determined by HPLC analysis on a chiral phase. [d] Not determined. [e] The reaction was performed at a concentration of 0.1 M. [f] The reaction was performed in CH_2Cl_2. Bn = benzyl.



$Ti(OiPr)_4$, and Et_2Zn, were found to be inefficient (Table 1, entries 4–7). When the reaction was carried out at the higher temperature of −20 °C, the *ee* value of the product decreased, probably as a result of a more pronounced background reaction (Table 1, entry 8). At −60 °C, the reaction afforded the adduct **4a** with 80 % *ee*, albeit in lower yield (Table 1, entry 9). A decrease in the concentration of the reaction mixture led to a decrease in both the reaction rate and the *ee* value of the product (Table 1, compare entries 2 and 10). The reaction proceeded well in CH_2Cl_2 but with slightly decreased enantioselectivity (Table 1, entry 11). Finally, the salen compound **5b** derived from 1*R*,2*R*-diphenylethylenediamine was less efficient as a ligand than **5a** (Table 1, compare entries 2 and 12).

Under the optimized conditions (that is, with presynthesized [**5a**–$Al^{III}Cl$] (0.1 equiv) at a reagent concentration of 0.33 M in toluene, with a reaction time of 48 h at −40 °C, and with slow addition of the acid), good to excellent enantioselectivity was generally observed with representative aliphatic aldehydes, carboxylic acids, and isocyanides (Scheme 2 and Table 2). As might be



Scheme 2. Starting materials used in the enantioselective P-3CR.

expected, the enantioselectivity depended on the structures of the isocyanide and the aldehyde. The selectivity of the reaction increased when the aliphatic isocyanide substrate was exchanged for a less-reactive aromatic isocyanide (Table 2, entries 1 and 2 versus 3 and 4), presumably owing to the suppression of the uncatalyzed background reaction.[15] However, no clear-cut tendency was discernable with respect to the electronic effect of substituents on the aromatic ring (Table 2, entries 7 and 11–16). 4-Methoxy-2-nitrophenyl isocyanide (**3f**), which was developed by Martens and co-

Table 2: Generality of the [(salen)$Al^{III}Cl$]-catalyzed enantioselective Passerini reaction.[a]

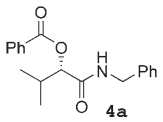
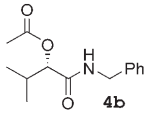
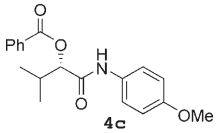
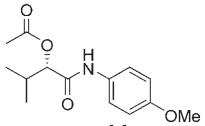
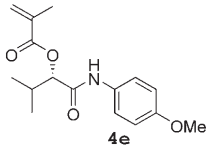
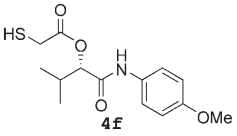
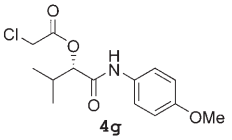
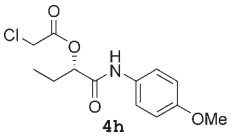
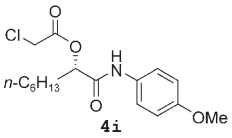
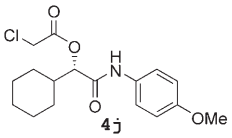
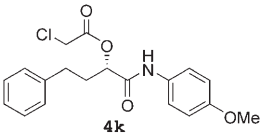
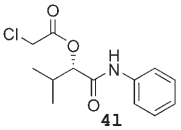
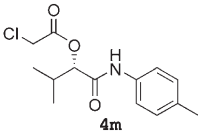
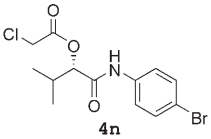
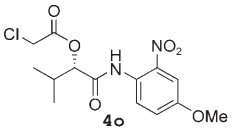
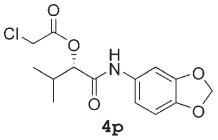
Entry	Aldehyde	Acid	Isocyanide	Product	Yield [%]	*ee* [%]
1	**1a**	**2a**	**3a**	 **4a**	70	63
2	**1a**	**2b**	**3a**	 **4b**	59	63
3	**1a**	**2a**	**3b**	 **4c**	63	84
4	**1a**	**2b**	**3b**	 **4d**	60	84
5	**1a**	**2c**	**3b**	 **4e**	62	80

Table 2: (Continued)

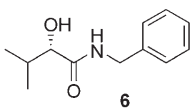
Entry	Aldehyde	Acid	Isocyanide	Product	Yield [%]	*ee* [%]
6	**1a**	**2d**	**3b**	 **4f**	51	75
7	**1a**	**2e**	**3b**	 **4g**	64	>99
8	**1b**	**2e**	**3b**	 **4h**	66	87
9[b]	**1c**	**2e**	**3b**	 **4i**	67	73
10	**1d**	**2e**	**3b**	 **4j**	59	87
11[b]	**1e**	**2e**	**3b**	 **4k**	68	71
12[b]	**1a**	**2e**	**3c**	 **4l**	68	93
13	**1a**	**2e**	**3d**	 **4m**	61	81
14[b]	**1a**	**2e**	**3e**	 **4n**	52	88
15[c]	**1a**	**2e**	**3f**	 **4o**	66	75
16	**1a**	**2e**	**3g**	 **4p**	64	68

[a] General conditions: 0.33 M solution in toluene, **1**/**2**/**3**/catalyst 1:1:1:0.1, slow addition of **2** to the premixed solution of the catalyst, **1**, and **3**. [b] Catalyst loading: 20%. [c] The reaction was performed in toluene/dichloromethane (3:1) owing to the low solubility of **3f** in toluene.

workers[16] as a convertible isocyanide, also participated in this reaction to afford **4o** with 75% *ee* (Table 2, entry 15). Compound **4o** can be hydrolyzed readily to the corresponding α-hydroxy acid under basic conditions.[16] The use of both linear and α-branched aliphatic aldehydes provided the corresponding adducts with excellent enantioselectivity. The reaction of 2-methylpropanal (**1a**) with **2e** and **3b** afforded the corresponding adduct **4g** in 64% yield with an exceptional 99% *ee* (Table 2, entry 7). However, the reaction of pivalaldehyde with **2e** and **3b** afforded the racemic adduct in 74% yield, and aromatic aldehydes failed to participate in this condensation reaction.[17] The aromatic acid **2a**, the α,β-unsaturated acid **2c**, and aliphatic acids, such as acetic acid (**2b**) and the functionalized substrates α-thioacetic acid (**2d**) and α-chloroacetic acid (**2e**), participated in the reaction to afford the corresponding α-acyloxyamides with good to excellent enantioselectivity (75–99% *ee*; Table 2, entries 3–7). The presence of a chloroacetyl functionality in **4g–p** provides an interesting handle for subsequent functionalization. The observation that the structure of the acid influenced the enantioselectivity of the reaction may indicate that this component is involved directly in the key C–C bond-forming process even in the presence of a Lewis acid catalyst.

Comparison of the sign of optical rotation of the α-hydroxyamides **6** and **7** obtained by saponification of the corresponding esters **4a** and **4c** with that of the authentic samples derived from (*S*)-2-hydroxy-3-methylbutyric acid enabled us to assign the *S* configuration to **4a** and **4c**. The observed *S* enantioselectivity indicates that the isocyanide attacks predominantly the *Re* face of the aldehyde.

In summary, we have described an efficient enantioselective Passerini three-component reaction catalyzed by a readily available and stable Lewis acid catalyst. Good to excellent enantioselectivity was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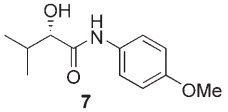
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observed with a variety of nonchelating aldehydes, carboxylic acids, and isocyanides. We hypothesize that a chiral Lewis acid catalyst with one coordination site is essential for the development of enantioselective Passerini- and Ugi-type reactions.

Experimental Section

General procedure: The [(salen)$Al^{III}Cl$] complex (30.3 mg, 0.05 mmol) derived from *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-(*R*,*R*)-cyclohexane-1,2-diamine (**5a**) was added with dry toluene (0.3 mL) to a 25-mL flame-dried round-bottomed flask equipped with a stir bar under argon. The mixture was stirred until the catalyst had dissolved completely. The aldehyde (0.5 mmol) was then added as a solution in toluene (0.1 mL), and the resulting mixture was stirred at room temperature for 0.5 h. The mixture was then cooled to −40 °C, a solution of the isocyanide (0.5 mmol) in toluene (0.1 mL) was added, and the mixture was stirred for a further 10 min. A solution of the acid (0.5 mmol) in toluene (1 mL) was then added slowly with a syringe pump (addition time: 1 h). The reaction mixture was stirred at −40 °C for 48 h, then quenched with saturated aqueous $NaHCO_3$ solution, stirred at room temperature for 0.5 h, and extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to give the corresponding α-acyloxyamide **4**.

Received: September 18, 2007
Published online: November 15, 2007

Keywords: aluminum · asymmetric catalysis · isocyanides · multicomponent reactions · salen ligands

[1] a) L. Banfi, R. Riva in *Org. React.*, *Vol. 65* (Ed.: A. B. Charette), Wiley, New York, **2005**, pp. 1–140; b) for an oxidative P-3CR, see: T. Ngouansavanh, J. Zhu, *Angew. Chem.* **2006**, *118*, 3575–3577; *Angew. Chem. Int. Ed.* **2006**, *45*, 3495–3497.

[2] a) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300–3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; b) for an oxidative Ugi-type reaction, see: T. Ngouansavanh, J. Zhu, *Angew. Chem.* **2007**, *119*, 5877–5880; *Angew. Chem. Int. Ed.* **2007**, *46*, 5775–5778.

[3] a) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51–80; b) R. V. A. Orru, M. De Greef, *Synthesis* **2003**, 1471–1499; c) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem. Res.* **2003**, *36*, 899–907; d) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144; e) P. Tempest, *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 776–788; f) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89.

[4] a) S. Marcaccini, D. Miguel, T. Torroba, M. Garcia-Valverde, *J. Org. Chem.* **2003**, *68*, 3315–3318; b) R. Frey, S. G. Galbraith, S. Guelfi, C. Lamberth, M. Zeller, *Synlett* **2003**, 1536–1538; c) G. Cuny, R. Gamez-Montano, J. Zhu, *Tetrahedron* **2004**, *60*, 4879–4885; d) P. R. Krishna, G. Dayaker, P. V. N. Reddy, *Tetrahedron Lett.* **2006**, *47*, 5977–5980.

[5] a) H. Kunz, W. Pfrengle, *J. Am. Chem. Soc.* **1988**, *110*, 651–652; b) R. J. Linderman, S. Binet, S. R. Petrich, *J. Org. Chem.* **1999**, *64*, 336–337; c) G. F. Ross, E. Herdtweck, I. Ugi, *Tetrahedron* **2002**, *58*, 6127–6133; d) A. Basso, L. Banfi, R. Riva, G. Guanti, *J. Org. Chem.* **2005**, *70*, 575–580.

[6] D. Seebach, G. Adam, T. Gees, M. Schiess, W. Weigand, *Chem. Ber.* **1988**, *121*, 507–517.

[7] a) S. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2003**, *125*, 7824–7825; b) S. Denmark, Y. Fan, *J. Org. Chem.* **2005**, *70*, 9667–9676.

[8] U. Kusebauch, B. Beck, K. Messer, E. Herdtweck, A. Dömling, *Org. Lett.* **2003**, *5*, 4021–4024.

[9] P. R. Andreana, C. C. Liu, S. L. Schreiber, *Org. Lett.* **2004**, *6*, 4231–4233.

[10] a) S. X. Wang, M. X. Wang, D. X. Wang, J. Zhu, *Eur. J. Org. Chem.* **2007**, 4076–4080; b) S. X. Wang, M. X. Wang, D. X. Wang, J. Zhu, *Org. Lett.* **2007**, *9*, 3615–3618.

[11] For reviews, see: a) "Catalytic Asymmetric Multicomponent Reactions": J. Seayad, B. List in *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**, pp. 227–299; b) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628–1661; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634; c) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581.

[12] To date, no enantioselective U-4CR has been reported.

[13] a) J. F. Larrow, E. N. Jacobsen, *Top. Organomet Chem.* **2004**, *6*, 123–152; b) T. Katsuki, *Chem. Soc. Rev.* **2004**, *33*, 437–444.

[14] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315–5316; b) J. K. Myers, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 8959–8960; c) G. M. Sammis, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 4442–4443; d) D. A. Evans, J. M. Janey, N. Magomedov, J. S. Tedrow, *Angew. Chem.* **2001**, *113*, 1936–1940; *Angew. Chem. Int. Ed.* **2001**, *40*, 1884–1888; e) B. Saito, H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2007**, *129*, 1978–1986; f) for the structure of compounds of Group 13 metals with salen ligands, see: D. A. Atwood, M. J. Harvey, *Chem. Rev.* **2001**, *101*, 37–52.

[15] The reaction of *tert*-butylisocyanide with **1a** and **2a** afforded the P-3CR adduct in 53% yield. However, to date we have been unable to determine the *ee* value of this adduct.

[16] W. Maison, I. Schlemminger, O. Westerhoff, J. Martens, *Bioorg. Med. Chem.* **2000**, *8*, 1343–1360.

[17] We have no clear-cut explanation for these observations, although aromatic aldehydes are known to be less reactive in the Passerini reaction. Note that aromatic aldehydes are better substrates than aliphatic aldehydes in the procedure of Denmark and Fan.[7]

