ORGANIC LETTERS

2003
Vol. 5, No. 22
4021−4024

# Massive Parallel Catalyst Screening: Toward Asymmetric MCRs

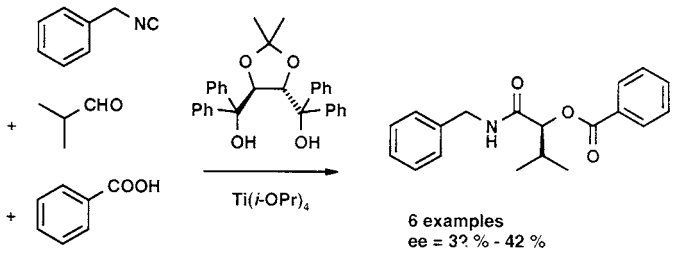
**Ulrike Kusebauch,[†] Barbara Beck,[†] Kim Messer,[†] Eberhardt Herdtweck,[‡] and Alexander Dömling*,[†]**

*Morphochem AG, Gmunderstr.37-37a, 81379 München, Germany, and Anorganisch Chemisches Institut der Technischen, Universität München, Lichtenbergstr.4, 85747 Garching, Germany*

*alexander.doemling@morphochem.de*

**Received June 5, 2003** *(Revised Manuscript Received September 2, 2003)*

## ABSTRACT




**Hundreds of Lewis acid/ligand combinations have been screened for stereochemical induction in the Passerini multicomponent reaction. The combination of titan tetraisopropylate and (4S,5S)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane was found to give enantiomeric excesses between 32% and 42% in several examples. The absolute stereo induction of one example was determined chemically and by means of X-ray crystallography. This comprises the first asymmetric Passerini reaction and the first example of a stereochemical induction in an isocyanide based multicomponent reaction by a chiral Lewis acid.**

Isocyanide-based MCRs belong to the most interesting diversity-generating reactions in organic chemistry.[1] Mostly in a one-pot manner, very many different scaffolds are accessible in a large number of examples from simple starting materials.[2] The most prominent of these isocyanide based MCRs are the Passerini reaction[3] (P-3CR) of isocyanides discovered in 1921, oxo components and carboxylic acids, and the Ugi reaction[4] (U-4CR) from 1959 of isocyanides, oxo components, primary amines, and carboxylic acids, respectively. During isocyanide-based MCRs, a new stereocenter is usually generated at the position of the former carbonyl carbon.[5] Unfortunately, no conclusive and general way to induce stereochemical information in the products of MCRs has been developed in the past. Ugi[6] early on recognized that the highest induction of the new stereocenter formed (Scheme 1) can be obtained from chiral amines in the case of U-4CR. In the first instance, chiral phenylethylamines have been utilized that could be cleaved hydrogenolytically or under acidic conditions.[7] Then chiral ferrocenylakylamines have been initially used as cleavable chiral ammonia equivalents.[8]

[†] Morphochem AG.
[‡] Universität München.

(1) (a) Ugi, I. *Proc. Estonian Acad. Sci. Chem.* **1995**, *44*, 237. (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.

(2) Recent examples include: (a) Brahmachary, E.; Ling, F. H.; Svec, F.; Frechet, J. M. J. *J. Comb. Chem.* **2003**, *5*, 441. (b) Marcaccini, S.; Miguel, D.; Torroba, T.; Garcia-Valverde, M. *J. Org. Chem.* **2003**, *68*, 3315. (c) Kim, Y. B.; Park, S. J.; Keum, G.; Janh, M. S.; Kang, S. B.; Lee, D. H.; Kim, Y. *Bull. Korean Chem. Soc.* **2002**, *23*, 1277. (d) Mironov, M. A.; Mokrushin, V. S.; Maltsev, S. S. *Synlett* **2003**, 943. (e) Beck, B.; Larbig, G.; Mejat, B.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003** *5*, 1047.

(3) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126.

(4) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.

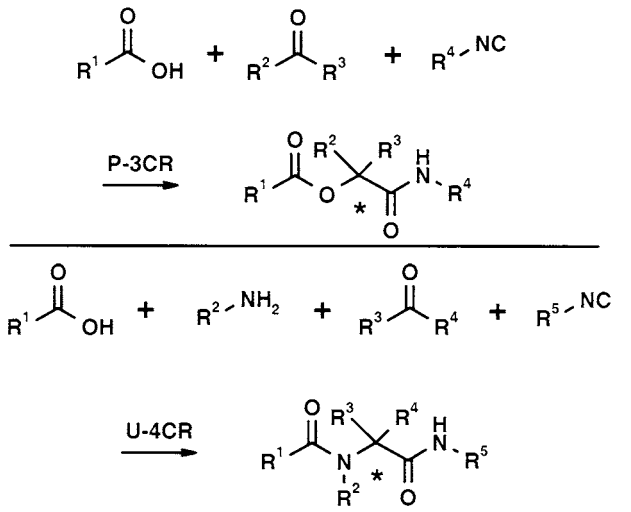
(5) During Ugi-4CR and Passerini-3CR symmetrical carbonyl compounds (e.g., formaldehyde, acetone, or cyclohexanone) do not result in a new stereocenter.

(6) Ugi, I. *Rec. Chem. Progr.* **1969**, *30*, 289.

(7) Ugi, I.; Offeremann, K.; Herlinger, H.; Marquarding, D. *Liebigs Ann. Chem.* **1967**, *709*, 1.

10.1021/ol035010u CCC: $25.00 
**Published on Web 10/03/2003**

**Scheme 1**

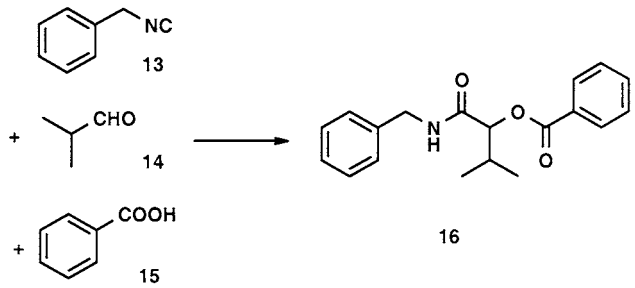



Later, Kunz et al.[9] and others[10] recognized that high induction could be obtained from glycosylamines. Thus, stereochemically pure α-amino acids have been synthesized. Unfortunately, none of these methods is generally applicable to the plethora of isocyanide-based MCRs. Moreover, the cleavage conditions are quite harsh and thus not compatible with a wide range of functional groups. Recently, Ugi et al. described a greatly improved stereoinduction using a thioglycosylamine with very mild cleavage condition.[11] For the P-3CR, no enantioselective procedure at all has been described in the past.[12] Moreover, chiral Lewis acids have never been used successfully in isocyanide-based MCRs to induce stereochemistry in the resulting products.[13]

Herein, we would like to present for the first time a chiral Lewis acid based approach toward the solution of the problem of stereoinduction in isocyanide-based MCRs.

To discover a way to induce stereoselectivity in the Passerini reaction, we chose to screen various Lewis acid/chiral ligand combinations.[14] We selected oxophilic Lewis acids[15] that have been reported to interact with the components of the P-3CR, aldehydes, carboxylic acids, and importantly isocyanides: Ti, Zr, Mg, Al, B, Cu, Zn, Sc, and Yb. As chiral ligands we used 12 different commercially available compounds with a known potential to induce other stereoselective reactions (Scheme 2).

**Scheme 2.** The Passerini Model Reaction




As a model and screening reaction we chose benzyl isocyanide **13**, isobutyric aldehyde **14**, and benzoic acid **15** as starting materials giving product **16** (Scheme 2). The reaction is high yielding (86%), does not show significant side products, and can be followed by HPLC using an UV detector. Baseline separation of the enantiomers with retention times of less than 30 min could be accomplished after some experimentation with Chiralcel-ODH (4.6 × 250 mm) as chiral stationary phase. This column performed better than a evaluation set of five short Pirkle-type Chirex columns (50 mm), although Chirex 3020 gave nearly separated peaks of the enantiomers. In contrast to the Ugi reaction, the Passerini reaction is preferably carried out in apolar aprotic solvents.[16] Therefore, as solvent we investigated ether, THF, DCM, toluene, and dioxane. In accordance with the experiments, the screening concentration of the educts was held at 0.5 M. Three ligand/Lewis acid ratios were used: 1/1, 1/2, and 2/1. The catalyst-to-educt ratio was either 1/1 or 0.5/1. The order of educt addition was aldehyde, isocyanide, and carboxylic acid. The reaction mixture was stirred overnight at room temperature and then quenched with aqueous $NaHCO_3$ and THF. The organic layer was separated and purified by a silica-based solid-phase extraction column. The enantiomeric excess was determined by HPLC, if necessary, after a further chromatographic separation.

Using 16 Lewis acids, 12 chiral ligands, and 5 solvents, an abundance of reactions was performed and screened (Figure 1). Many of the reactions gave a lot of side products as compared to the reaction without any additives. Often, the desired product was not found anymore. In some cases, the P-2CR product was formed instead, whereby water acts formally as acid component yielding the corresponding α-hydroxyamide. Several combinations especially including the Lewis acids **G** $Yb(OTf)_3$, **H** $Zn(OTf)_2$, **K** $MgBr_2$, **M** $MgBr_2{-}OEt_2$, and **N** $BF_3{-}OEt_2$ showed encouraging ee's. Unfortunately, several byproducts were formed. Therefore,

(8) Marquarding, D.; Hoffmann, P.; Heitzer, H.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 1969.

(9) (a) Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651. (b) Kunz, H.; Rück, K. *Angew. Chem.* **1993**, *105*, 355.

(10) (a) Goebel, M.; Ugi, I. *Synthesis* **1991**, 1095. (b) Linderman, R. J.; Binet, S.; Petrich, S. R. *J. Org. Chem.* **1999,** *64*, 336.

(11) Thiosugar amines, as chiral inductors, display the advantage of being easily cleavable ($Hg^{2+}$, 20 °C): Ross, G.; Ugi, I.; Herdtweck, E. *Tetrahedron* **2002**, *58*, 6127.

(12) A Camphor derived isocyanide has been described to induce diastereoselectivity in the P-3CR: Bock, H.; Ugi, I. *J. Prakt. Chem.* **1997**, *339*, 385.

(13) For the unsuccessful use of chiral Lewis acids in the P-2CR, see: Seebach, D.; Adam, G.; Gees, T.; Schiess, M.; Weigand, W. *Chem. Ber.* **1988**, *121*, 507.

(14) For a recent review on high-throughput methods for the development of new catalytic asymmetric reactions, see: Traverse, J. F.; Snapper, M. L. *DDT* **2002**, *7*, 1002.

(15) Yamamoto, H., Ed. *Lewis Acids in Organic Synthesis*,; Wiley: Weinheim, 2000; Vols. 1 and 2.

(16) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3168.

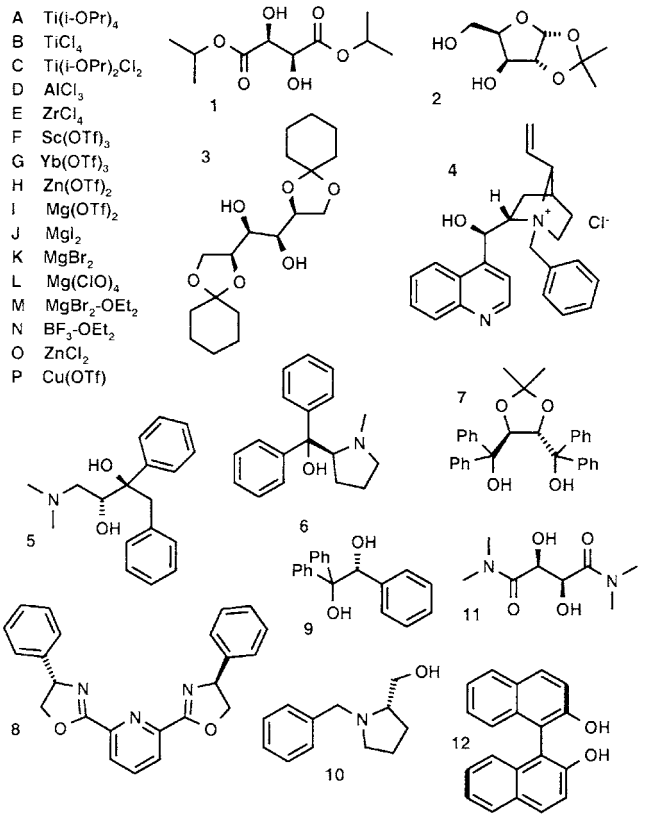


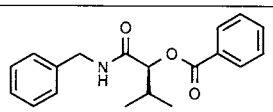
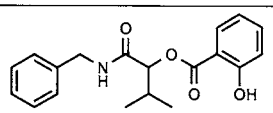
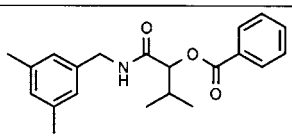
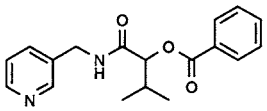
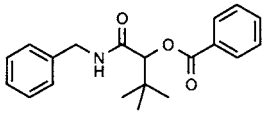
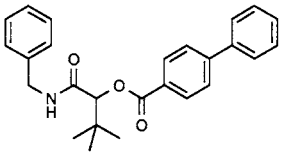

**Figure 1.**

these reactions were not investigated. Only the Lewis acid **A** Ti(*i*-OPr)$_4$ in combination with ligands **7**, **9**, and **12** showed significant ee's and clean reactions that allowed the isolation of the product at the same time. These reactions were repeated and examined more closely.

To get a first idea about scope and limitation of this catalyst **A7**, a couple of reactions varying the components (Table 1) were performed. Stereoinduction from 32% to 42% has been reached in these reactions. Generally, one observes that the reaction with additive suffers from poorer yields. During the hydrolysis of the reaction, considerable amounts of α-hydroxy methyl amides (P-2CR product) are formed.

The absolute stereoinduction was determined by performing the P-3CR between 2*S*-*N*-Boc-phenylalanine, isobutyraldehyde, and benzylisocyanide yielding the corresponding product **22** in a diastereomeric ratio of 1:1.27. The structure of the preferentially crystallizing isomer **22** was investigated by X-ray crystallography (Scheme 3) and the stereochemistry determined to be **2-*S*,5-*R***. This compound with known absolute stereochemistry was then subjected to saponification with aqueous sodium hydroxide solution, yielding the corresponding stereochemically pure, *R*-configured α-hydroxyamide **23**. The stereoisomeric mixture of the P-3CR with catalyst **A7** yielding compound **16** with an ee: 36% was also subject to saponification. The resulting mixture of the two alcohols (*R*- and *S*-23) as compared with the reference isomer *R*-23 obtained from the crystal **22**. This clearly indicates that the major stereoisomer is *S*-configured, proven by coelution of the isomer.

**Table 1.** Enantiomeric Excesses and Yields of Selected P-3CR

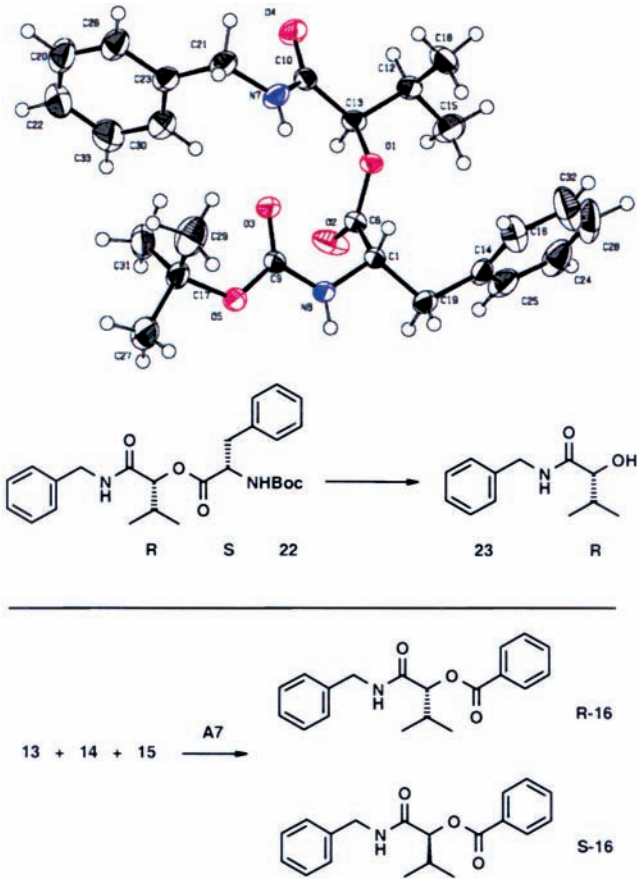
| Comp. no. | Structure | Yields (%) | ee (%) |
|---|---|---|---|
| 16 |  | 46[a] (86)[b] | 36[c] |
| 17 |  | 12 (93) | 32 |
| 18 |  | 31 (47) | 32 |
| 19 |  | 28 (76) | 42 |
| 20 |  | 48 (81) | 34 |
| 21 |  | 46 (95) | 36 |

[a] Isolated yield of the Passerini reaction performed on a 1 mmol scale with **A7**. [b] In brackets: isolated yield of the Passerini reaction performed on a 5 mmol scale without **A7**. [c] Enantiomeric excess of the Passerini reaction performed with **A7**.

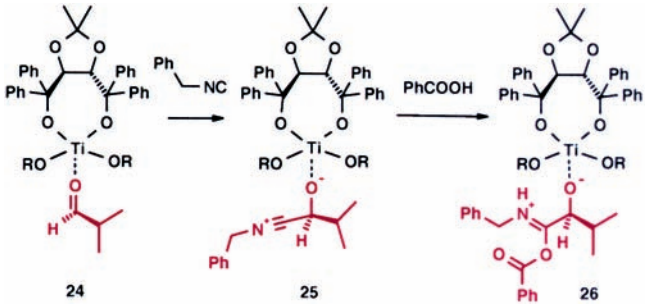
The reaction can be performed with sub-stoichiometric amounts of Ti and ligand, but a considerable loss of enantiomeric excess occurs. Clearly, in the stereochemistry-inducing step of the reaction the aldehyde has to be complexed by Ti (Scheme 4). Generally, titanium complexes are known to exist in complex mixtures of monomeric and oligomeric structures.[17] The configuration displayed in the rate-determining step causes the latter stereochemistry of the Passerini product. A possible complex **24** could account for the observed induction. The addition of the isocyanide onto the aldehyde carbon giving the imminium ion **25** could happen via a pre-coordination of the isocyanide on the titanium. Alternatively, the isocyanide inserts directly without precoordination with the titanium atom. Addition of the carboxylic acid yields the α-adduct **26**, which upon rearrangement forms the Passerini product.

(17) (a) Mahrwald, R.; Ziemer, B. *Tetrahedron Lett.* **2002**, *43*, 25, 4459. (b) Review: Weidman, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31.

**Scheme 3**




**Scheme 4**




In conclusion, we are reporting for the first time an enantioselective Passerini MCR using a chiral Lewis acid catalyst.[18] This catalyst system was found by screening of a multitude of different reactions. Although the observed ee's are not yet synthetically useful, chiral Lewis acids provide a promising and not yet explored tool toward chiral MCRs. The possibility to perform chiral MCRs would tremendously broaden the synthetic usefulness of these reactions. Further work is ongoing to improve the enantioselectivity of the P-3CR by modifying the ligands and reaction conditions and to investigate the reaction mechanism.

**Acknowledgment.** This work is dedicated to Lutz Weber on the occasion of his 45th birthday.

**Supporting Information Available:** General procedure for the Passerini reaction and $^{1}H$ and $^{13}C$ NMR, X-ray, and HPLC data are given. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035010U

(18) During the submission process, two more examples of stereoselective Passerini reaction where published: (a) Frey, R.; Galbraith, S. G.; Guelfi, S.; Lamberth, C.; Zeller, M. *Synlett* **2003**, 1536; (b) Denmark, S.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825.