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Facile and Racemization-Free Conversion of Chiral Nitriles into Pyridine Derivatives†

Barbara Heller,*,‡ Bernd Sundermann,§ Christine Fischer,‡ Jingsong You,‡ Waiqiang Chen,‡ Hans-Joachim Drexler,‡ Paul Knochel,|| Werner Bonrath,⊥ and Andrey Gutnov‡

Leibniz-Institut für Organische Katalyse an der Universität Rostock e.V., Buchbinderstr. 5-6, 18055 Rostock, Germany, Grünenthal GmbH, Center of Research, 52099 Aachen, Germany, LMU München, Institut für Organische Chemie, Butenandtstr. 5-13, 81377 München, Germany, and Roche Vitamins Ltd., Reseach and Development, 4070 Basel, Switzerland

barbara.heller@ifok.uni-rostock.de

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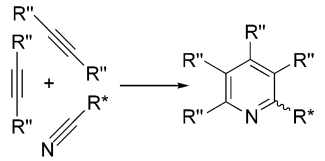
The results described herein demonstrate how the very mild reaction conditions of the Co(I)-catalyzed photochemical [2 + 2 + 2] cyclocotrimerization are suited to prepare chiral compounds containing unsubstituted and polysubstituted 2-pyridyl moieties starting from chiral nitriles without any detectable loss of enantiomerical purity. This further increases the already very broad synthetic scope of this particular reaction.

Introduction

The notable successes in the application of phosphine-free, nitrogen-containing ligands to the area of asymmetric catalysis over the past decade has caused an exponential growth of interest in preparation, resolution, and utilization of pyridine-based chiral ligands.[1] Moreover, pyridyl-substituted optically pure compounds are of persistent importance for pharmaceutical drug research.[2] Thus, there is a general interest in a simple and selective synthetic access to optically active compounds containing a pyridyl moiety. Besides enzymatic syntheses,[3] which are of particular interest in the field of HIV research, transition-metal-catalyzed reactions leading to a variety of chiral compounds containing a pyridyl moiety have been described.[4−10]

SCHEME 1. [2 + 2 + 2] Cycloaddition



Through the construction of three new bonds in one reaction, the transition-metal-catalyzed [2 +2 + 2] cycloaddition of nitriles with a broad variety of alkynes (cyclocotrimerization; Scheme 1) is an atom-economical and extraordinarily effective method to prepare substituted pyridines.[11,12]

Substituted pyridines bearing a chirality are in principle accessible by this route when optically active nitriles are used. The thermally initiated variant of this reaction to 2-pyridines has been investigated in the groups of Botteghi[13,14] and Chelucci.[15−17] By employing ethyne

* To whom correspondence should be addressed. Fax: (0049)-381-466 93 24.
† Dedicated to Günther Oehme.
‡ Leibniz-Institut für Organische Katalyse an der Universität Rostock e.V.
§ Grünenthal GmbH.
|| LMU München.
⊥ Roche Vitamins Ltd.

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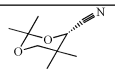
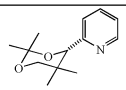
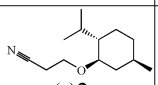
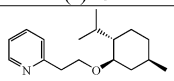
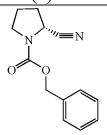
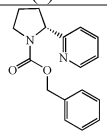
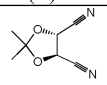
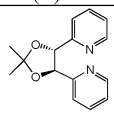
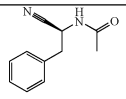
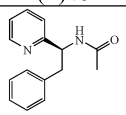
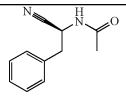
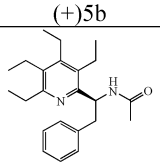
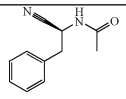
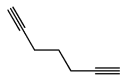
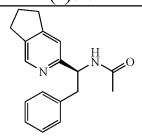
TABLE 1. Photocatalyzed [2 + 2 + 2] Cycloaddition to Optically Pure Compounds

Nr	nitrile	alkyne	corresponding pyridine	chem. yield	time	solvent
1	 (-)1a	2	 (-)1b	82%	5h	toluene
2	 (-)2a	2	 (-)2b	68%	6h	water
3	 (+)3a	2	 (+)3b	89%	5h	toluene
4	 4a	4	 (+)4b	82%	5h	hexane
5	 (-)5a	2	 (+)5b	64%	5h	toluene
5	 (-)5a	2	 (-)5c	83%	6h	toluene
5	 (-)5a		 (-)5d	64%	6h	toluene

pressures above 10 bar, reaction temperatures above 100 °C, long reaction times, and high catalyst concentrations acceptable yields were achieved. However, these rather drastic reaction conditions usually lead to a noticeable decrease of enantiomerical purity with respect to the starting material (nitrile). This is especially characteristic for primary and secondary α-aminonitriles.[18] In many cases, the enantiomeric excess of the final pyridine decreases by 2−10%, which is attributed to the high reaction temperatures (>100 °C) necessary to initiate the catalysis.[15−18] However, the Co(I)-catalyzed [2 + 2 + 2] cycloaddition of alkynes with nitriles can be carried out under very mild conditions (ambient temperature and pressure) if the required energy is supplied in the form of light.[19] This photochemical variant avoids the drastic reaction conditions of the thermally initiated method[20−22] and can be used to synthesize a broad variety of mono- to pentasubstituted pyridines.[11] Artificial light as well as sunlight can be used as sources of irradiation since the wavelength range between 350 and 500 nm was found to be optimal for promoting the catalysis.[23]

Besides improved operational safety with respect to the thermally initiated variant, the photochemical cyclocotrimerization bears the opportunity to improve chemoselectivity: byproducts arising from the homotrimerization of three alkyne molecules can be avoided.[24]

This manuscript aims to illustrate how the very simple and effective photochemical [2 + 2 + 2] cycloaddition of

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(15) Chelucci, G.; Falorni, M.; Giacomelli, G. *Synthesis* **1990**, 1121.
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(17) Chelucci, G. *Tetrahedron*: *Asymmetry* **1995**, *6*, 811.
(18) In one case, the synthezised pyridine was isolated with 44% yield and 15% ee[16] although the nitrile employed had an enantiomeric excess of 98% ee. For this reason, Falorni and co-workers have developed a "ring closure protection" protocol to prepare optically pure compounds containing a pyridyl moiety: Cossu, S.; Conti, S.; Giacomelli, G.; Falorni, M. *Synthesis* **1994**, 1429.
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(21) (a) Bönnemann, H.; Brinkmann, R.; Schenkluhn, H. *Synthesis* **1974**, 575−577. (b) For a review: Bönnemann, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 248; *Angew. Chem* **1985**, *97*, 264.
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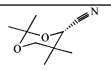
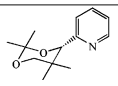
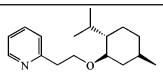
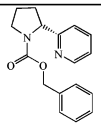
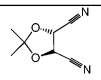
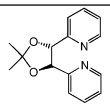
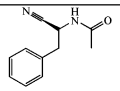
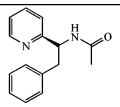
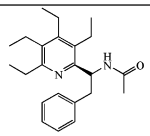
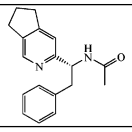
TABLE 2. GLC and HPLC Analysis of Optical Purity of Starting Nitriles and Pyridines Obtained

Nr	nitrile / pyridine	GLC/HPLC-column	eluent (HPLC)/ temperature (GLC)	α	% ee
(-)1a		Chirasil Dex CB (GLC)	70°C	1.05	>99
(-)1b		Chiralcel OD-H (HPLC)	hexane	1.20	>99
(-)2b		Chiralpak AD (HPLC)	hexane/2-propanol 99.6:0.4	1.36	>99
(+)3b		Whelk O1 (HPLC)	hexane/ethanol/ diisopropylamine 80:20:0.15	1.59	>99
(+)4a		Lipodex E (GLC)	130°C	1.15	>99.5
(+)4b		Chiralcel OD-H (HPLC)	hexane/ethanol 95:5	1.34	>99.5
(-)5a		Chiralcel OJ (HPLC)	hexane/ethanol 90:10	1.59	>99.5
(+)5b		Chiralcel OD-H (HPLC)	hexane/ethanol 98:2	1.33	>99.5
(-)5c		Chiralcel OD-H (HPLC)	hexane/2-propanol 98:2	1.22	>99.5
(+)5d		Chiralpak AD (HPLC)	hexane/ethanol 90:10	2.1	>99.5

2 equiv of an alkyne with 1 equiv of a nitrile can be used to prepare optically active compounds containing a pyridyl moiety.

Results and Discussion

Under irradiation with visible light (350−500 nm), the photochemical [2 + 2 + 2] cyclocotrimerization of optically active nitriles with alkynes catalyzed by [cpCo(cod)](η^5-cyclopentadienyl-η^4-cycloocta-1,5-dienecobalt(I)) can be used to prepare optically active compounds containing a pyridyl moiety. Good to excellent yields are achieved with reaction times between 4 and 6 h working in organic solvents (like toluene or hexane) or water as reaction medium. Table 1 illustrates the broad variety of functionalized chiral nitriles that can be employed successfully in this transformation.

2,2,5,5-Tetramethyl-1,3-dioxane-4-carbonitrile (**1a**)[25] has been converted into the corresponding pyridine as a racemate (*rac*-**1b**) as well as in the form of its (*S*)-enantiomer (−)-**1b** [(−)-(*S*)-2-(2,2,5,5-tetramethyl-1,3-dioxan-4-yl)pyridine]. Furthermore, through cyanethylation enantiomerically pure nitriles could be prepared from **(+)**- as well as **(−)**-3-(2-isopropyl-5-methylcyclohexyloxy)propionitrile **[**(+)- and (−)-**2a**] and were converted into the corresponding enantiomerically pure 2-[2-(2-isopropyl-5-methylcyclohexyloxy)ethyl]pyridine [(+)-

(25) Aquino, F.; Pauling, H.; Walther, W.; Plattner, D. A.; Bonrath, W. *Synthesis* **2000**, *5*, 731.

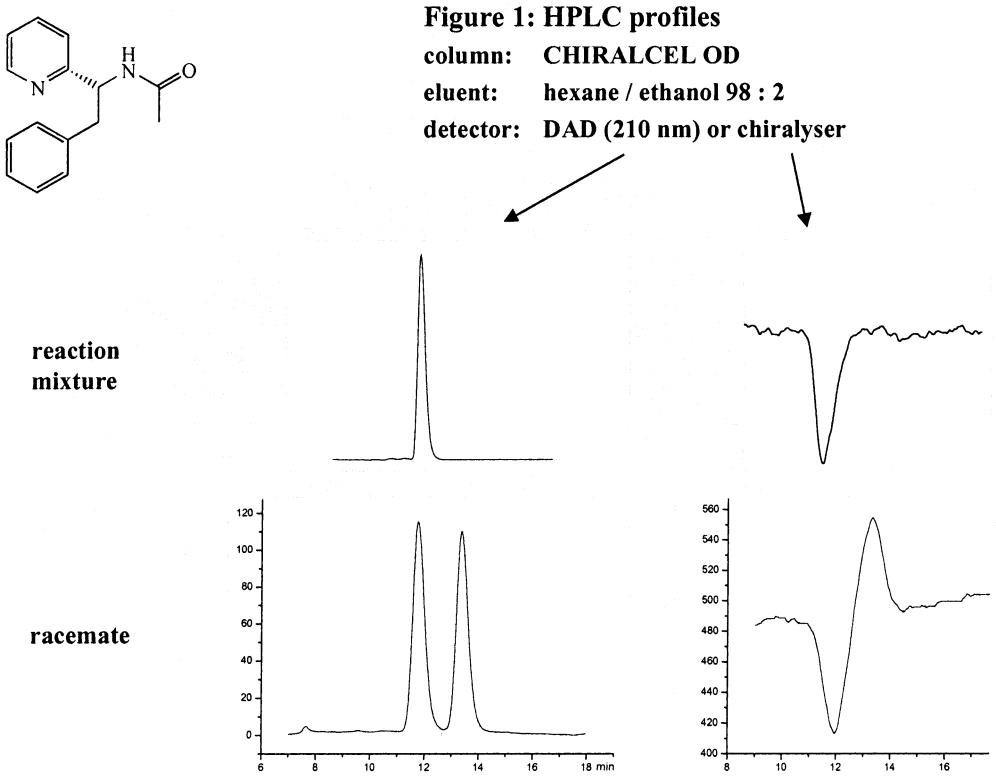


FIGURE 1. HPLC profiles.

and (−)-**2b**]. As further examples, the cbz-protected nitriles (+)- and (−)-**3a** (2-cyano-pyrrolidine-1-carboxycyclic acid benzyl ester) were derived from L- and D-proline[26] and photochemically converted into 2-pyridine-2-ylpyrrolidine-1-carboxycyclic acid benzyl ester [(+)- and (−)-**3b**]. (+)- and (−)-Tartaric acids were used to prepare the enantiomerically pure bisnitriles[27] [(+)- and (−)-**4a**] (2,2-dimethyl-1,3-dioxolane-4,5-dicarbonitrile) which were also converted to pyridine derivatives **4b** [(−)- and (+)-2,2-dimethyl-4,5-bis(2-pyridyl)-1,3-dioxolane, respectively]. Finally, the (+)- and (−)-enantiomers of an acetylated α-aminonitrile **5a** (*N*-(1-cyano-2-phenylethyl)acetamide[28]) have been used to prepare enantiomerically pure *N*-(2-phenyl-1-pyridin-2-ylethyl)acetamide [(+)- and (−)-**5b**], *N*-[2-phenyl-1-(3,4,5,6-tetraethylpyridin-2-yl)ethyl]acetamide [(+)- and (−)-**5c**], and *N*-[1-[6,7-dihydro-5*H*-[2]-pyridin-3-yl)-2-phenylethyl]acetamide [(+)- and (−)-**5d**]. In the case of the pyridines **5c** and **5d**, we have used a symmetrically disubstituted alkyne (3-hexyne for **5c**) and a bisalkyne (1,6-heptadiyne for **5d**), respectively, which were reacted with nitrile **5a** under photochemical conditions. Thus, it is shown that our method is also applicable for substituted alkynes and can be extended to the synthesis of polysubstituted pyridines bearing optically active moieties.

Contrary to findings reported for the thermally initiated variant of the [2 + 2 + 2] cyclocotrimerization, we have not observed any loss of optical purity. In our opinion, this can be attributed to our superior reaction conditions which are also more favorable in terms of yields and shorter reaction times. HPLC or GLC on chiral stationary phases were used for all examples to determine enantiomeric excesses (% ee) of the used nitriles and the final pyridines. The conditions employed and the obtained numerical values for these analyses are shown in Table 2.

Figure 1 depicts a routine HPLC analysis of the racemic pyridine **5b** and the reaction mixture containing the optically pure compound (−)-**5b**.

In conclusion, we have demonstrated that the racemization-free photochemical version of the Co(I)-catalyzed [2 + 2 + 2] cyclocotrimerization of alkynes and optically active nitriles can serve as an effective tool for the preparation of pyridine-containing chiral compounds, which are of considerable interest for asymmetric catalysis and pharmaceutical drug research.

Experimental Section

Analytical measurements were carried out using standard techniques unless indicated otherwise (see the Supporting Information for details).

General Procedure for [2 + 2 + 2] Cycloaddition of Ethyne and a Chiral Nitrile: (−)-(*S*)-2-(2,2,5,5-Tetramethyl-1,3-dioxan-4-yl)pyridine [(−)-1b]. A thermostated (25 °C) reaction vessel, equipped with a very effective quill

(26) After cbz-protection of proline and conversion into the amide (Sturm, K.; Geiger, R.; Siedel, W. *Chem. Ber.* **1963**, *96*, 609), the nitrile can be prepared by dehydration (Yamada, T.; Suegane, K.; Kuwata, S.; Watanabe, W. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1088).

(27) Knochel, P. Unpublished results.

(28) Heller, D.; You, J.; Drexler, H.-J. Unpublished results.

(29) (a) Bönnemann, H.; Bogdanović, B.; Brinkmann, R.; Spliethoff, B.; He, D. *J. Organomet. Chem.* **1993**, *451*, 23. (b) Jonas, K. *Angew. Chem.* **1985**, *97*, 292.

(30) Chelucci, G.; Falorni, M.; Giacomelli, G. *Gazz. Chim. Ital.* **1990**, *120*, 731.

spin bar, was loaded with 1 mL (5.9 mmol) of (−)-(*S*)-2,2,5,5-tetramethyl-1,3-dioxane-4-carbonitrile **(1a)** and 11.6 mg (0.05 mmol) of [cpCo(cod) = (η^5-cyclopentadienyl-η^4-cycloocta-1,5-diene-cobalt(I)]. Toluene (20 mL) was added to the mixture, and the vessel was connected to an ethyne delivering and measuring device providing a constant pressure of ethyne. Alternatively, ethyne may simply be bubbled through the solution. The mixture was irradiated by two 460 W Phillips HPM 12 lamps (∼420 nm) for 5 h. The reaction was quenched by switching off the lamps and simultaneously introducing air. The obtained reaction mixture was filtered and chromatographed on silica gel (5:1 toluene/ethyl acetate) to give 1.03 g (4.66 mmol) of pure (−)-(*S*)-2-(2,2,5,5-tetramethyl-1,3-dioxan-4-yl)pyridine (isolated yield 79%; GLC result from crude product: 82%). Chemical purity after workup: 99%. Optical purity: >99% ee. $[\alpha]^{21}_D$: −77.15 (*c* 1.0, C_2H_5OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.78 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.32 (d, 1H, J = 11.3 Hz, CH_2), 3.78 (d, 1H, J = 11.5 Hz, CH_2), 4.77 (s, 1H, CH), Py: 7.10 (t, 1H, J = 6.2 Hz), 7.39 (d, 1H, J = 8.0 Hz), 7.60 (t, 1H, J = 7.8 Hz), 8.43 (d, 1H, J = 4.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.7, 18.8, 21.9, 29.7, 33.8, 72.0, 80.4, 99.0, 122.2, 122.3, 136.0, 147.8, 159.0. MS *m*/*z*: 222 (M^+ + H, 1), 206 (7), 163 (12), 146 (14), 132 (10), 117 (9), 108 (100). Anal. Calcd for $C_{13}H_{19}NO_2$ (221.30): C, 70.56; H, 8.65; N, 6.33. Found: C, 70.45; H, 8.58; N, 6.25.

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Supporting Information Available: Analytical data for the prepared pyridine derivatives (structure, chemical name, yield, ^{1}H NMR, ^{13}C NMR, MS, C,H,N-analysis, and X-ray of the compounds **1b** and **5b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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