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Enantioselective Synthesis of Chiral 5-Carbamoyl-3-pyridyl Alcohols by Asymmetric Autocatalytic Reaction

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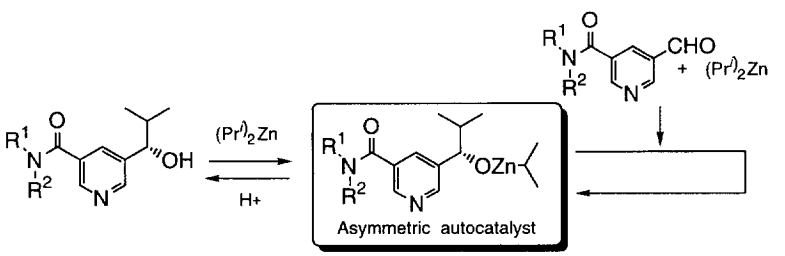
Abstract: A catalytic amount of a chiral zinc alkoxide of 5-carbamoyl-3-pyridyl alkyl alcohol catalyzes an enantioselective alkylation of 5-carbamoylpyridine-3-carbaldehyde by diisopropylzinc to afford itself in up to 86% e.e. with the same configuration as the catalyst. Enantioselectivity is dependent on the structure of substituents on the nitrogen atom of the amide.

Recently, catalytic asymmetric synthesis has been appreciated as an important method for preparing optically active compounds. This is due to the rapid development of highly enantioselective reactions using catalytic amounts of chiral organometallic reagents. However, when reuse, deterioration of the chiral catalysts and complexity of purification of the product from the chiral catalyst are taken into account, there are only a few practical reactions reported.

On the other hand, an asymmetric autocatalytic reaction,[1] where a chiral catalyst and the product have the same structure and configuration, intrinsically exclude the above problems, *i. e.*, a trace amount of a chiral source produces itself without using any other chiral auxiliary and the separation process of the product from the catalyst is not required.[1] Asymmetric autocatalytic reactions so far reported are limited to those of simple compounds, for example, 3-pyridyl alkyl alcohols catalyzes enantioselective alkylation of pyridine-3-carbaldehyde by dialkylzincs to give themselves with the same configuration as the catalysts;[2] however, the e.e.s of the newly-formed alcohols were low (up to 35% e.e.). It is a challenging theme to find a highly enantioselective asymmetric autocatalytic reaction of a more functionalized compound.

We here report the utilization of zinc alkoxides of chiral 5-carbamoyl-3-pyridyl alkanols as asymmetric



Scheme 1. Asymmetric autocatalytic reaction of 5-carbamoyl-3-pyridyl alkanols

autocatalysts to realize such a reaction. As shown in Scheme 1, chiral zinc alkoxides, generated from chiral 5-carbamoyl-3-pyridyl alcohols and diisopropylzinc, were self-replicated by the addition of 5-carbamoylpyridine-3-carbaldehydes and diisopropylzinc, and the 5-carbamoyl-3-pyridyl alcohols were obtained after quenching with acid.

Firstly, optically active 5-carbamoyl-3-pyridyl alkyl alcohols **2a-d** were prepared by the enantioselective alkylation of 5-carbamoylpyridine-3-carbaldehydes **1a-d**[3] using 20 mol% of (1*S*, 2*R*)-*N*,*N*-dipropylnorephedrine (DPNE).[4,5]

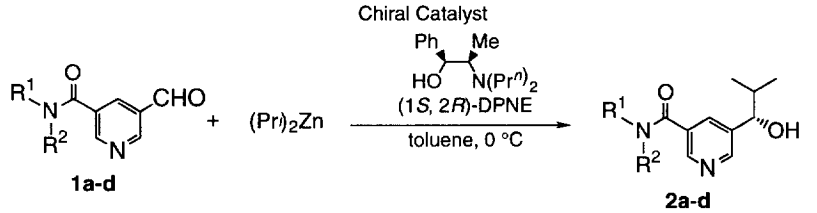


Table 1. Enantioselective alkylation of **1a-d** using (1*S*, 2*R*)-DPNE as a chiral catalyst

Entry[a]	R^1	R^2		Yield (%)	E.e. (%)[b,c]
1	MeO	Me	**2a**	56	90
2	Pr^i	Pr^i	**2b**	56	94
3	Bu^i	Bu^i	**2c**	82	88
4	Bu^n	Bu^n	**2d**	70	89

[a] Molar ratio. (1*S*, 2*R*)-DPNE : **1**: (Pr^i)$_2$Zn = 0.2 : 1.0 : 3.0. [b] Determined by HPLC analysis using a chiral column (Daicel Chiralpak AS by 5% 2-propanol in hexane for **2a**, **d**; Daicel Chiralcel OD, 3% 2-propanol in hexane for **2b**, **c**). [c] Absolute configurations are tentatively assigned to be *S* based on the results that (1*S*, 2*R*)-DPNE catalyzes the addition of (Pr^i)$_2$Zn to benzaldehyde to afford (*S*)-alcohol (ref. 6).

As a result, 5-carbaomoylpyridine-3-carbaldehyde **1a**, possessing Weinreb's amide at the 5-position, and compounds **1b-d**, possessing dialkyl substituents on the nitrogen atom of the amides, were enantioselectively isopropylated by diisopropylzinc[6] to give the corresponding pyridyl alkyl alcohols **2a-d** in high optical yields (88-94% e.e.) (Table 1).

Next, asymmetric autocatalytic reactions were examined between 5-carbamoylpyridine-3-carbaldehydes **1a-d** and diisopropylzinc using a catalytic amount of the chiral 5-carbamoyl-3-pyridyl alkyl alcohols **2a-d** as asymmetric autocatalysts.

It was found that 5-carbamoyl-3-pyridyl alkyl alcohols **2a-c** with the same configuration as the catalysts were newly formed in the asymmetric autocatalytic reaction (Table 2). Chiral catalyst **2a**, possessing Weinreb's amide, automultiplied with good e.e. (Entry 1).[7] Moreover, the branched alkyl groups on the nitrogen atom of the amide, especially the isopropyl group, enhanced the enantioselectivity as an asymmetric autocatalysis and asymmetric autocatalyst **2b** produced itself with high e.e. (86% e.e.) (Entry 3). On the other hand, pyridyl alcohol **2d**, possessing the straight chain substituents (*n*-Bu) on the nitrogen atom automultiplied with low e.e. (30% e.e.). These results indicate that the methoxy group of Weinreb's amide or branched bulky groups such as isopropyl and isobutyl groups on the nitrogen atom are essential for the highly enantioselective asymmetric autocatalyst.

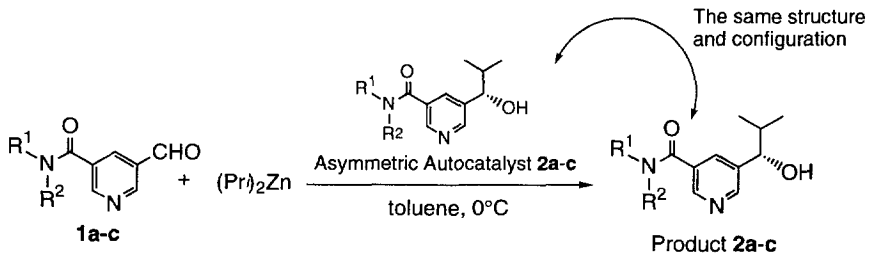


Table 2. Asymmetric autocatalytic reaction using 5-carbamoyl-3-pyridyl alcohols **2a-c** as chiral catalysts

Entry[a]	R^1	R^2		Cat	Time	Catalyst & Product		Product	
				(% e.e.)	(h)	Yield(%)	E.e.(%)[b]	Yield(%)	E.e.(%)
1	MeO	Me	**2a**	90	47	96	73	76	68
2	Pr^i	Pr^i	**2b**	94	48	94	81	74	78
3[c]	Pr^i	Pr^i	**2b**	94	60	77	88	57	86
4	Bu^i	Bu^i	**2c**	88	49	119	74	99	71

[a] Molar ratio. **2** (catalyst) : **1**: $(Pr^i)_2Zn$ = 0.2 : 1.0 : 2.2. [b] Determined by HPLC analysis using a chiral column. [c] Molar ratio. **2b** (catalyst) : **1b** : $(Pr^i)_2Zn$ = 0.2 : 1.0 : 1.2.

For these past several years, we[8] and others[9] have studied asymmetric autocatalytic reactions. This paper reports the first example of asymmetric autocatalysis of functionalized alcohols and discloses that the introduction of a carbamoyl group at the 5-position of pyridine-3-carbaldehyde improves the asymmetric autocatalytic activity. It is thought that the influence of bulkiness of the amide group on the optical yield is a clue to elucidate the mechanism of asymmetric autocatalytic reaction.

Acknowledgment

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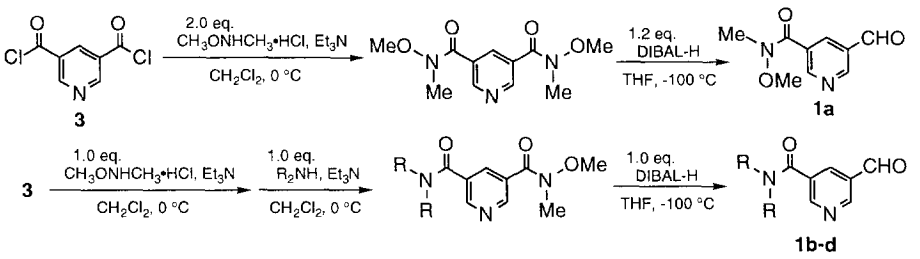
3 Synthesis of 5-carbamoylpyridine-3-carbaldehyde **1a-d**. Compound **1a** was prepared by symmetrical amidation[10] of pyridine-3,5-dicarbonylchloride **3** with *N,O*-dimethylhydroxylamine following a reduction of one of the amides[11] using 1.2 equivalents of DIBAL-H at -100 °C. Compounds **1b-d** were prepared by asymmetrical amidation of **3** with *N,O*-dimethylhydroxylamine and the corresponding dialkylamine, following a reduction of Weinreb's amide[11] using 1.0 equivalent of DIBAL-H at -100 °C.



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7 Typical experimental procedure and calculation of newly-formed alcohol **2** (Table 2, Entry 1) were as follows: After a mixture of 3-pyridyl alcohol (*S*)-**2a** [27.4 mg (0.10 mmol), 90.3% e.e., containing (*S*)-isomer (26.1 mg), (*R*)-isomer (1.3 mg)] in toluene (4.0 ml) and $(Pr^i)_2Zn$ (1.1 ml of 1 M toluene solution, 1.1 mmol) was stirred for 20 min at 0 °C, a toluene solution (5.0 ml) of aldehyde **1a** (97.1 mg, 0.50 mmol) was added at 0 °C. The reaction mixture was stirred for 45 h at 0 °C, and then quenched by the addition of 1 mol dm^{-3} hydrochloric acid (5 ml) and satd. aq. $NaHCO_3$ (15 ml) at 0 °C. The mixture was filtered using celite and the filtrate was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the crude products on silica gel TLC (thin-layer chromatography) gave **2a** (82.9 mg), which is a mixture of the newly formed alcohol **2a** and the catalyst alcohol (27.4 mg). HPLC analysis of the mixture using a chiral column (DAICEL CIRALPAK AS, eluent: 5% 2-propanol in hexane; flow rate: 1.0 ml/min; 254 nm UV detector) showed that it had an enantiomeric purity of 75.4% e.e. Therefore, the mixture contained (*S*)-isomer (72.7 mg) and (*R*)-isomer (10.2 mg). The amount of newly-formed alcohol **2a** was 82.9-27.4=55.5 mg (0.38 mmol, 76% yield), consisting of the major (*S*)- isomer (72.7-26.1=46.6 mg) and the minor (*R*)- isomer (10.2-1.3=8.9 mg). Therefore, the newly-formed (*S*)-enriched alcohol **2a** had an enantiomeric purity of 67.9% e.e.

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