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A Novel Rate Enhancement in Titanium and Zirconium Alkoxide Mediated Cyano Group Transfers by the Addition of a Salycylal Type Schiff Base, *dl*-3-(2-Hydroxy-1-naphthylidene)-imino-ε-caprolactam. A Neighboring Amide Effect

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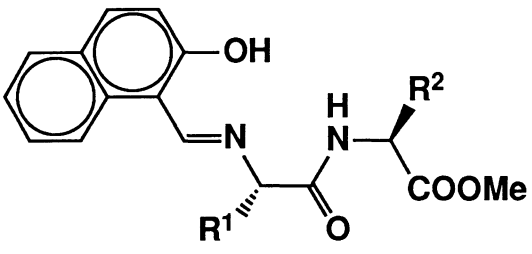
The addition of a salycylal type Schiff base containing amide, *dl*-3-(2-hydroxy-1-naphthylidene)-imino-ε-caprolactam (Nap-ACL) to titanium (IV) 2-propoxide or zirconium (IV) 1-propoxide accelerates cyano group transfers of acetone cyanohydrin with various carbonyl and imino compounds to give the corresponding cyanated products.

The role of ligands on metals in inorganic and organometallic chemistry is of great importance and in some cases unexpected reactivities and selectivities are found in reactions on metallic compounds due to the effect of ligands.[1)] Salycylal Schiff bases have been recognized as ligands of various metals and their complexes have been widely used for selective synthetic organic reactions especially asymmetric syntheses.[2)] On the other hand, we have recently reported a transhydrocyanation of acetone cyanohydrin with several aldehydes mediated by titanium (IV) 2-propoxide or aluminum alkyls. Although the reactions by the titanium reagent afforded corresponding aldehyde cyanohydrins in good yield, the rate was shown to be slow and the reaction required long period at room temperature for the complete conversion.[3)] Thus, we have examined the effect of additives as ligands of the titanium reagent for the purpose of rate enhancement. Various additives including phenols, diols, and salycylal Schiff bases resulted in giving little satisfactory conversions. However, the addition of a Schiff base composed of a salycylaldehyde derivative and acyclic dipeptide esters (**1**) [4, 5)] as a ligand of titanium (IV) 2-



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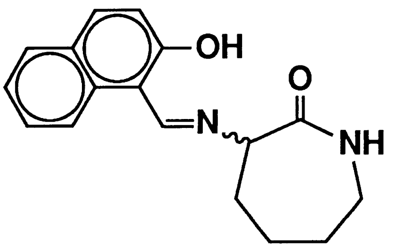
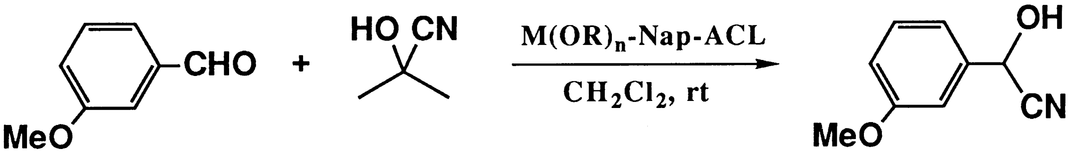


Nap-ACL (2)

propoxide was surprisingly found to induce a dramatic rate enhancement in the transhydrocyanation. The result suggests that the structure of the additive requires to possess following functional groups; (a) phenolic hydroxyl group, (b) carbon nitrogen double bond, and (c) amide group at an appropriate position to satisfy the favorable rate enhancement. Thus, above structural requirements were represented by the employment of *dl*-3-(2-hydroxy-1-naphthylidene)-imino-ε-caprolactam (Nap-ACL: **2**), a simple compound which is readily available by the reaction of 2-hydroxy-1-naphthaldehyde and *dl*-3-amino-ε-caprolactam.[6)] We herein describe the novel rate enhancement by the addition of Nap-ACL (**2**) in the titanium alkoxide mediated transhydrocyanation of acetone cyanohydrin with aldehydes.

The transhydrocyanation of an aldehyde (**3a**) and acetone cyanohydrin was carried out by using 1.0: 1.0: 1.0: 3.0 mixture of **3a**, $Ti(OPr^i)_4$, **2**, and acetone cyanohydrin to give the corresponding cyanohydrin (**4a**) in 87% yield after stirring for 3 h at room temperature, apparently demonstrating that a significant rate enhancement was observed compared with the reaction in the absence of Nap-ACL (**2**) (99% yield, 19 h). It should be noted that the reaction was also successful even with a catalytic amount of the titanium alkoxide and **2** (5 mol% each). On the other hand, no reaction occurred with a catalytic amount of $Ti(OPr^i)_4$ (5 mol%) without **2**. Moreover, a similar rate enhancement was observed in the employment of zirconium (IV) 1-propoxide. Indeed, the reaction by the zirconium reagent and Nap-ACL (**2**) (5 mol% each) afforded the cyanohydrin **4a** in 72% yield at room temperature for 24 h; however, a

Table 1. Transhydrocyanation of acetone cyanohydrin and **3a** in the presence of $M(OR)_n$ and Nap-ACL **2** [a)]



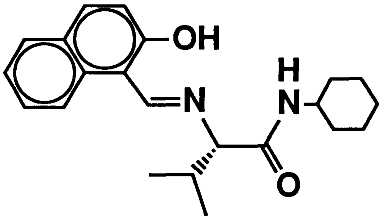
3a **4a**

$M(OR)_n$ (mol%)[b)]	Nap-ACL[c)]	Time / h	Yield /%[d)]
$Ti(OPr^i)_4$ (100)	-	19	99
$Ti(OPr^i)_4$ (100)	+	3	87
$Ti(OPr^i)_4$ (5)	+	24	63
$Ti(OPr^i)_4$ (5)	-	48	0
$Zr(OPr)_4$ (100)	-	42	89
$Zr(OPr)_4$ (5)	+	24	72

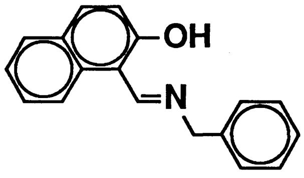
a) The reactions were carried out by using 1:3 of **3a** and acetone cyanohydrin under N_2. b) Based on the amount of aldehyde. c) The ratio of Nap-ACL and $M(OR)_n$ was 1 : 1 when Nap-ACL was used. d) Based on ^1H NMR measurement of the crude product after acidic workup.

stoichiometric amount of the zirconium without **2** required 42 h to yield 89% of the product to the contrary. Results are summarized in Table 1.

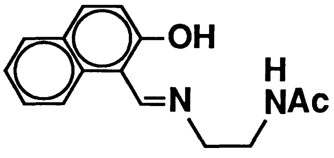
It is important that the structure of the ligand must be a Schiff base of α-amino amide with a salycylaldehyde derivative. Indeed, the Schiff base of (S)-valine cyclohexylamide and 2-hydroxynaphthaldehyde (Nap-Val-NHCy, **5a**) exhibited a similar reactivity to Nap-ACL (**2**). However, **5b** derived from benzylamine (no amide group) as an additive resulted in no reaction. Moreover, **5c** synthesized from N-acetylethylenediamine was less effective than **1**, **2**, and **5a** (35% yield, 70 h) showing that the position of the amide group is considerably significant for the efficient rate enhancement.



5a

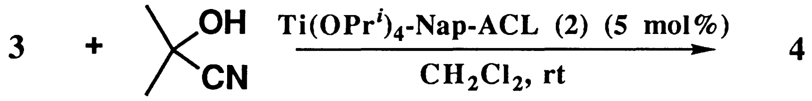


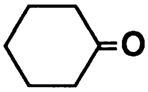
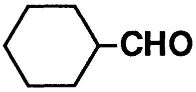
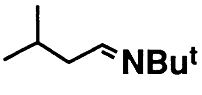
5b



5c

Table 2. Cyano group transfer of acetone cyanohydrin toward **3** catalyzed by $Ti(OPr^i)_4$ -**2** (5 mol%) [a)]



3	Time h	Yield %	3	Time h	Yield %
PhCHO 3b	27	75	 3d	3	>99
 3c	2.5	>99	 3e	2	$63^{b)}$

a) The amounts of $Ti(OPr^i)_4$ and **2** were based on **3**. The ratio of **3** and acetone cyanohydrin was 1.0: 3.0. b) The reactions were not successful with stoichiometric $Ti(OPr^i)_4$ or without catalyst.

The cyano group transfers of acetone cyanohydrin to several aldehydes and related compounds were examined similarly. As shown in Table 2, successful cyano group transfers were observed. Aliphatic aldehydes reacted much faster than aromatic ones. In addition, the reactions with a ketone (**3d**) and an imine (**3e**) afforded the corresponding cyanated products (**4d**, **4e**) in good to excellent yield.

In conclusion, rate enhancement in titanium and zirconium alkoxide mediated transhydrocyanation by the addition of Nap-ACL (**2**) is demonstrated. The amide group in the ligand is considered to play an important role for the enhanced reactivity of the metallic species.7) Further studies concerning the mechanism and extension to other titanium and zirconium mediated reactions are under way.

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4) The 2-hydroxynaphthylidene imino group has been utilized as a protective group in peptide synthesis: J. C. Seehan and J. V. Grenda, *J. Am. Chem. Soc.*, **84**, 2417 (1962), F. C. McIntire, *ibid.*, **69**, 1377 (1949).

5) Schiff base (**1**) is used as a chiral auxiliary of organoaluminum reagent for catalytic asymmetric reactions in our separate research: H. Nitta, A. Mori, and S. Inoue, unpublished results.

6) The mixture of 2-hydroxynaphthaldehyde and 3-amino-ε-caprolactam in ethanol was stirred at room temperature for 12 h to give a yellow precipitate, which was filtered and dried *in vacuo* (88%).

7) A similar neighboring amide effect was reported: P. Beak and R. A. Brown., *J. Org. Chem.*, **47**, 34 (1982), P. Beak and A. I. Meyers, *Acc. Chem.Res.*, **19**, 356 (1986), and references cited therein.

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