ORGANIC LETTERS

2010
Vol. 12, No. 2
264−267

Highly Enantioselective Titanium-Catalyzed Cyanation of Imines at Room Temperature

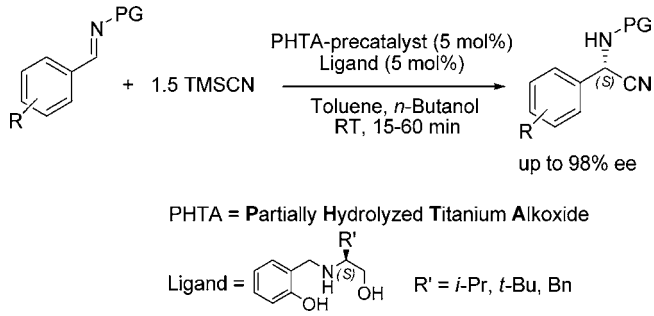
Abdul Majeed Seayad,*,† Balamurugan Ramalingam,† Kazuhiko Yoshinaga,‡ Takushi Nagata,‡ and Christina L. L. Chai*,†

Institute of Chemical and Engineering Sciences, 1 Pesek Road, Singapore 627833, and Mitsui Chemicals Asia Pacific Ltd., 1 Pesek Road, Singapore 627833

abdul_seayad@ices.a-star.edu.sg; christina_chai@ices.a-star.edu.sg

Received November 6, 2009

ABSTRACT



A highly active and enantioselective titanium-catalyzed cyanation of imines at room temperature is described. The catalyst used is a partially hydrolyzed titanium alkoxide (PHTA) precatalyst together with a readily available *N*-salicyl-*β*-aminoalcohol ligand. Up to 98% ee was obtained with quantitative yields in 15 min of reaction time using 5 mol % of the catalyst. Various N-protecting groups such as benzyl, benzhydryl, Boc, and PMP are tolerated.

The asymmetric Strecker reaction or the hydrocyanation of imines[1] followed by hydrolysis is the most common and effective method for the enantioselective synthesis of α-amino acids,[2] an important class of building blocks in synthesis. In the last two decades, several enantioselective methodologies for the synthesis of aminonitriles have been reported that use both metal[3,4] and organo[5,6] catalysts. However, the existing methodologies suffer from limitations such as the use of expensive catalysts and ligands as well as the requirement for very low temperatures (−75 to −40 °C) to achieve high enantioselectivities. Hoveyda et al.[3c] and Vilaivan et al.[7] have reported that higher enantioselectivities can be achieved at temperatures of 0−4 °C using Ti−peptide and Ti−salicyl-*β*-aminoalcohol based catalyst systems, respectively. However, longer reaction times such as 20−70 h are required to complete the reaction. In this study, we report a highly active and enantioselective catalyst system for the cyanation of imines at *ambient temperature*.[8]

† Institute of Chemical and Engineering Sciences.
‡ Mitsui Chemicals Asia Pacific Ltd.

(1) For reviews, see: (a) Larry, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 875. (b) Herald, G. *Chem. Rev.* **2003**, *103*, 2797. (c) Spino, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1764.

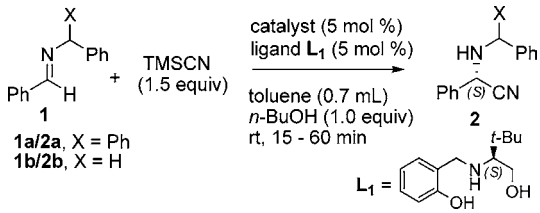
(2) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.

(3) For metal-catalyzed cyanation of aldimines see: (a) Sigman, M. S.; Jacobsen, N. E. *J. Am. Chem. Soc.* **1998**, *120*, 5315. (b) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3186. (c) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. W.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284. (d) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1650. (e) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Chem. Pharm. Bull.* **2000**, *48*, 1586. (f) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762. (g) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Valleé, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147. (h) Josephson, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594. (i) Hatano, M.; Hattori, Y.; Furuya, Y.; Ishihara, K. *Org. Lett.* **2009**, *11*, 2321. (j) Jarusiewicz, J.; Choe, Y.; Yoo, K. S.; Park, C. P.; Jung, K. W. *J. Org. Chem.* **2009**, *74*, 2873.

10.1021/ol902540h
Published on Web 12/21/2009

In our initial studies on the cyanation of benzhydryl imine **1a** using the easily accessible salicyl-β-aminoalcohol (**L_1**) ligand and Ti(OBu-*n*)$_4$ as a catalyst precursor, we observed a dramatic enhancement in catalytic activity when small amounts of water were present during the initial formation of the active chiral catalyst[9] (Table 1, entries 1−4). At very low water content of 10 ppm, the reaction was very slow and required >22 h for complete conversion (entry 1) at room temperature. At low conversions, the observed ee was only 68%, and the ee improved to 89% when 95% conversion to the product was achieved. To our surprise, the cyanation reaction was accelerated with an increased water content in the solvent, and nearly quantitative conversion was observed within 1 h of reaction time when toluene with a water content of 190 ppm was used.[10] Similarly, increased water content in the solvent also resulted in improved ee's. These observations may be due to the formation of multicentered chiral catalysts,[11] which are oligomeric in nature,[12] and are capable of activating both the imine and TMSCN thus resulting in higher catalytic activities and enantioselectivities.[13] The beneficial effect of oligomeric titanium alkoxide catalysts was recently reported for the cyanosilylation of aldehydes.[14]

Table 1. PHTA-Catalyzed Cyanation of Imine[a]



entry	catalyst	substrate	solvent water content, ppm	time (min)	yield[b] (%)	*ee*[c] (%)
1	Ti(OBu-*n*)$_4$ monomer	**1a**	10	60	9	68
				240	35	83
				1320	95	89
2	Ti(OBu-*n*)$_4$ monomer	**1a**	50	30	3	80
				60	23	90
				240	52	92
				360	70	92
3	Ti(OBu-*n*)$_4$ monomer	**1a**	100	15	38	91
				60	60	93
				180	87	94
				360	99	94
4	Ti(OBu-*n*)$_4$ monomer	**1a**	190	15	88	95
				60	99	95
5	PHTA	**1a**	190	15	99	96
6	Ti(OBu-*n*)$_4$ monomer	**1b**	10	15	25	36
				30	71	77
				60	93	78
7	Ti(OBu-*n*)$_4$ monomer	**1b**	190	15	99	86
8	PHTA	**1b**	190	15	99	87

[a] Imine, 0.2 mmol. [b] Yields were determined by ^{1}H NMR spectroscopy. [c] Analyzed by HPLC.

To further explore the potential of this concept, partially hydrolyzed titanium alkoxide (PHTA) was prepared by controlled hydrolysis and used as the catalyst precursor instead of the monomeric titanium alkoxide for the cyanation of imines. The purpose of the former is to improve on the preparation of the purported 'true' precatalyst system that was implied from the studies with the monomers.

The PHTA precatalyst was prepared by hydrolyzing Ti(OBu-*n*)$_4$ (0.5 mmol) using residual water (190 ppm)[15] in toluene (10 mL) by stirring for 18 h.[16] This 0.05 M solution was used as the PHTA precatalyst, and the chiral catalyst was prepared in situ by complexing with 1 equiv of the salicyl-β-aminoalcohol for 15−30 min of stirring at room

(4) For metal-catalyzed cyanation of ketoimines, see: (a) Byrne, J. J.; Chavarot, M.; Chavant, P.-Y.; Vallee', Y. *Tetrahedron Lett.* **2000**, *41*, 873. (b) Byrne, J. J.; Chavarot, M.; Chavant, P. Y.; Vallee, Y. *Tetrahedron: Lett.* **2000**, *41*, 873. (c) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634.

(5) For organo-catalyzed cyanation of aldimines see: (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (b) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. (c) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. (d) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. (e) Huang, J.; Corey, E. J. *Org. Lett.* **2004**, *6*, 5027. (f) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548. (g) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617. (h) Pan, S. C.; Zhou, J.; List, B. *Synlett* **2006**, 3275. (i) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 612. (j) Reingruber, R.; Baumann, T.; Dahmen, S.; Broese, S. *Adv. Synth. Catal.* **2009**, *351*, 1019. (k) Merino, P.; López, E. M.; Tejero, T.; Herrera, R. P. *Tetrahedron* **2009**, *65*, 1219.

(6)) For organo-catalyzed cyanation of ketoimines, see: (a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (b) Rueping, M.; Sugiono, E.; Moreth, S. A. *Adv. Synth. Catal.* **2007**, *349*, 759. (c) Huan, J.; Liu, X.; Wen, Y.; Qin, B.; Feng, X. *J. Org. Chem.* **2007**, *72*, 204. (d) Wang, J.; Hu, X.; Jiang, J.; Gou, S.; Huang, X.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 8468. (e) Hou, Z.; Wang, J.; Liu, X.; Feng, X. *Chem.—Eur. J.* **2008**, *14*, 4484. (f) Shen, K.; Liu, X.; Cai, Y.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2009**, *15*, 6008.

(7) (a) Mansawat, W.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron Lett.* **2003**, *44*, 3805. (b) Banphavichit, V.; Mansawat, W.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron.* **2004**, *60*, 10559. (c) Banphavichit, V.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron* **2007**, *63*, 8727. (d) Banphavichit, V.; Mansawat, W.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron* **2009**, *65*, 5849.

(8) (a) Part of the results were presented as a poster at the 227 ACS national meeting held at Salt Lake City, March 22−26, 2009. (b) Seayad, A. M.; Chai, C. L. L.; Ramalingam, B.; Nagata, T.; Yoshinaga, K. PCT Int. Appl. WO2008121074, 2008.

(9) The active chiral catalyst was prepared by complexing the titanium precursor with the ligand for 5−30 min with stirring in toluene.

(10) Further increase in water content gave inconsistent results. In general, catalytic performance decreases with an increase in water content beyond 300 ppm.

(11) For asymmetric catalysis involving more than one titanium center in the metal complex, see: (a) Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968. (b) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708. (c) Schetter, B.; Ziemer, B.; Schnakenburg, G.; Mahrwald, R. *J. Org. Chem.* **2008**, *73*, 813.

(12) For oligomeric metal oxo-alkoxide complexes, see: Bradley, D. C.; Mehrotra, I. P.; Rothwell, I. P.; Singh, A. *Alkoxo and Aryloxo Derivatives of Metals*: Academic Press: London, 2001; pp 405−411 and references therein.

(13) For similar dual activation of electrophiles and nucleophiles by adjacent metal centers, see the reviews: (a) Ma, J. A.; Cahard, D. *Angew. Chem. Int. Ed* **2004**, *43*, 4566. (b) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117.

(14) Yoshinaga, K.; Nagata, T. *Adv. Synth. Catal.* **2009**, *351*, 1495.

(15) The molar ratio of Ti:H_2O is 0.5:0.11.

(16) The calculated amount of water is 0.17 equiv to Ti(OBu-*n*)$_4$. The hydrolysis was confirmed by the formation of *n*-BuOH with concomitant decrease in the concentration of water as measured by in situ IR. The hydrolysis is generally faster, and a major part of hydrolysis takes place within 15 minutes. Hydrated inorganic salts can also be used for partial hydrolysis.

temperature. To this chiral catalyst solution, imine substrate **1a** or **1b**, TMSCN, and additive were added, and the cyanation reaction was carried out for 15 min. Gratifyingly, *up to 96% ee* with quantitative conversion was achieved in 15 min at room temperature using 5 mol % of the catalyst in the case of **1a** (Table 1, entry 5).

The effect of water and the enhanced catalytic performance of PHTA catalyst was also observed when *N*-benzyl imine **1b** was used as the substrate (Table 1, entries 6−8). The PHTA precatalyst obtained can be easily handled without following strict inert conditions, and the cyanation reactions need not be carried out under argon atmosphere as was necessary for the reactions carried out with the Ti−alkoxide monomer. The PHTA precatalyst is easy to prepare and is stable as no loss of catalytic activity was observed even after one month of storage. Further optimization studies were carried out using PHTA as the precatalyst. The effect of various catalyst and reaction parameters on the catalytic performance was evaluated using benzyl imine **1b** as a substrate for a short reaction time of 15 min at room temperature, and the results are presented in Table 2.

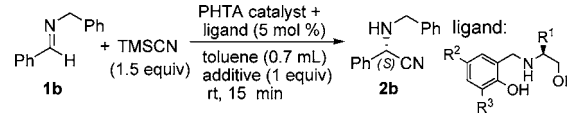
A proton source as an additive was found to be necessary for high catalytic activity, and to a certain extent, this also affects the enantioselectivities of the reactions.[17] Alcohols such as *n*-BuOH (Table 2, entry 1) and EtOH (Table 2, entry 3) as additives gave up to 87% ee and quantitative conversions in 15 min, while *i*-PrOH gave only 51% yield with 83% ee (Table 2, entry 2). Water can also be used as an additive, and only 0.5 equiv was required for optimal performance. Higher equivalents of water reduce the enantioselectivity of the reaction considerably (Table 2, entries 5 and 6).

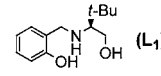
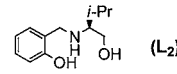
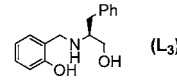
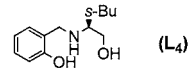
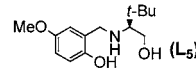
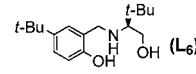
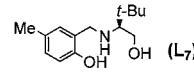
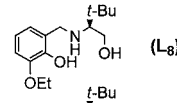
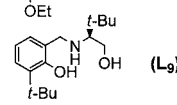
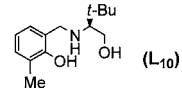
The tridentate salicyl-β-aminoalcohol ligand $\mathbf{L_1}$ with R^1 = *t*-Bu derived from salicylaldehyde and L-*tert*-Leucinol gave the highest enantioselectivity compared to those ligands with R^1 = *i*-Pr ($\mathbf{L_2}$), Bn ($\mathbf{L_3}$), or *s*-Bu ($\mathbf{L_4}$) as presented in Table 2. The effect of substituents R^2 and R^3 on the enantioselectivities of the reaction with imine **1b** was also examined. In general, no appreciable difference in enantioselectivity was observed when R^2 = OMe ($\mathbf{L_5}$) and Me ($\mathbf{L_7}$) or even when the sterically hindered *t*-Bu ($\mathbf{L_6}$) group was used. However, the ee was drastically decreased when $R^3 \neq$ H as observed with $\mathbf{L_8}$−$\mathbf{L_{10}}$. The effect was very much more pronounced with bulky alkyl substituents such as *t*-Bu as compared to the substituents with coordinating groups such as OEt. Nearly racemic product was obtained with $\mathbf{L_9}$ (R^3 = *t*-Bu) as compared to $\mathbf{L_{10}}$ (R^3 = Me), while up to 74% ee was observed when R^3 = OEt ($\mathbf{L_8}$). These results suggest that a larger steric bulk at the β-position of the aminoalcohol part of the ligand and smaller steric bulk at the salicylaldehyde part are required for optimum enantioselectivity. Hence, the simple ligand $\mathbf{L_1}$ was chosen for further studies.

With the above optimized reaction conditions, the effect of different N-protecting groups on enantioselectivity was investigated, and the results are presented in Table 3. Benzhydryl and *t*-butoxycarbonyl (Boc) protecting groups gave the highest enantioselectivities (96% and 98% ee, respectively). The results obtained for *N*-Boc imine (**1c**) are particularly remarkable since other catalyst systems that have been reported thus far gave lower enantioselectivity (up to 75%).[5a] Benzyl (**1b**) and allyl (**1f**) imines gave high enantioselectivities (87% and 85% ee, respectively), while *p*-methoxyphenyl (PMP, **1e**) and 9-fluorenyl (**1d**) protected imines gave moderate ee's (45% and 58%, respectively).

The substrate scope for this catalyst system was further examined with various substituted imines as presented in Scheme 1. Up to 98% and 97% ee were obtained for *o*-Cl (**4a**) and *o*-Br (**4b**) substituted aminonitriles when the

Table 2. Optimization Studies Using the PHTA Catalyst[a]



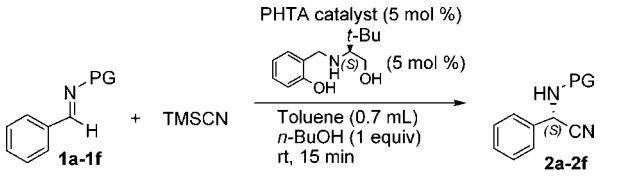
entry	ligand	additive	yield [b] (%)	ee [c] (%)
1		*n*-BuOH	99	87
2		*i*-PrOH	51	83
3	 ($\mathbf{L_1}$)	EtOH	99	87
4		MeOH	99	84
5		Water	99	77
6		Water [d]	99	85
7	 ($\mathbf{L_2}$)	*n*-BuOH	99	73
8	 ($\mathbf{L_3}$)	*n*-BuOH	99	69
9	 ($\mathbf{L_4}$)	*n*-BuOH	99	69
10	 ($\mathbf{L_5}$)	*n*-BuOH	99	85
11	 ($\mathbf{L_6}$)	*n*-BuOH	99	88
12	 ($\mathbf{L_7}$)	*n*-BuOH	99	87
13	 ($\mathbf{L_8}$)	*n*-BuOH	99	74
14	 ($\mathbf{L_9}$)	*n*-BuOH	99	3
15	 ($\mathbf{L_{10}}$)	*n*-BuOH	99	19

[a] Imine, 0.2 mmol. [b] NMR yield. [c] Analyzed by HPLC. [d] 0.5 equiv of water was used.

(17) The beneficial effect of alcohols as additives is well known in the literature, and generally *i*-PrOH is used.

(18) See Supporting Information for details.

Table 3. PHTA-Catalyzed Cyanation of Different N-Protected Imines[a]



entry	PG	yield, %[b]	ee, %
1	benzhydryl (a)	>99	96[d]
2	benzyl (b)	>99	87[d]
3	Boc (c)	>99	98[d]
4	9-fluorenyl (d)	93	58[d]
5	PMP (e)	98	45[e]
6	allyl (f)[c]	99	85[e]

[a] Imine, 0.2 mmol; TMSCN, 1.5 equiv. [b] Yields were determined by ^{1}H NMR spectroscopy. [c] The aminonitrile obtained was acylated using trifluoroacetic anhydride to obtain the amide for measuring yield and ee. [d] The configuration was assigned based on the specific rotation values reported for the aminonitrile or the corresponding amino acid.[18] [e] The stereochemistry of the aminonitrile is tentative.

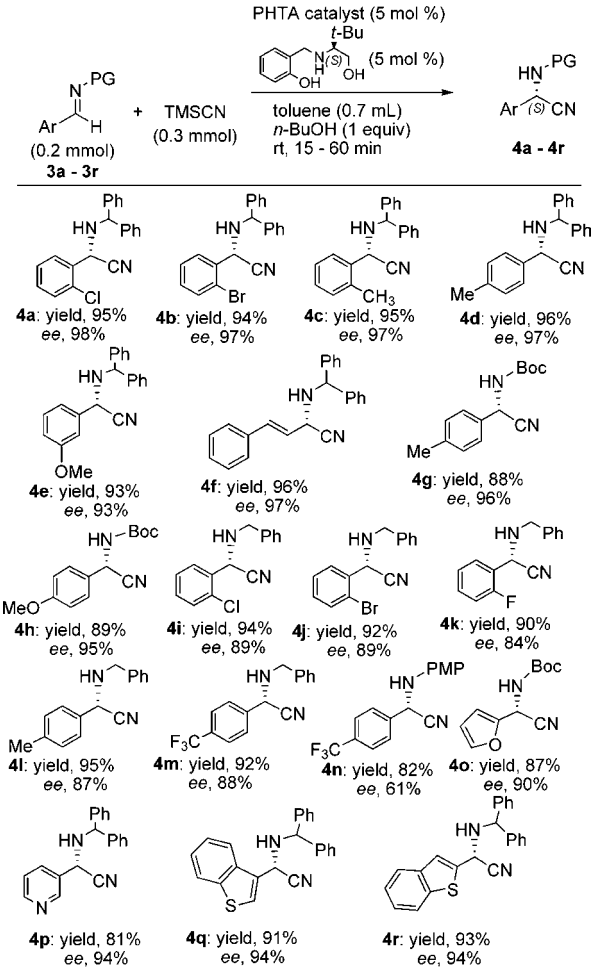
corresponding benzhydryl imines were used. Sterically hindered imines **3c** with the *o*-CH_3 substituent gave the product **4c** in very high ee (97%). The *meta*-substituted aminonitrile **4e** was also obtained in 93% ee. A noteworthy observation is that the cyanation of α,*β* unsaturated imine gave regioselective 1,2-addition product **4f** in 97% ee. In the case of benzyl imines, up to 90% ee was obtained for *o*-Cl (**4i**) and *o*-Br (**4j**) aminonitriles. Though unsubstituted PMP-protected imines gave only 45% ee (Table 3, entry 5), up to 61% ee was achieved when *p*-CF_3-substituted PMP-imine (**3n**) was used as the substrate.

Heterocyclic imines containing oxygen (**3o**), nitrogen (**3p**), and sulfur (**3q**, **3r**) were also found to give the corresponding cyanation products in very high enantioselectivities using the present catalyst system.

The aminonitriles **2a**, **2c**, **4g**, and **4j**−**4 m** were hydrolyzed as per the reported procedures[3c,5a,7d] to the corresponding amino acids and found to have the (*S*) configuration. Aminonitriles **2b**, **2d**, **4a**−**4d**, and **4f** were assigned the (*S*) configuration in comparison to the literature reports.[18]

In conclusion, partially hydrolyzed titanium alkoxide (PHTA) catalyst together with salicyl-*β*-aminoalcohol as the ligand provide very high catalytic activity and enantioselectivity for the cyanation of various imines at room temperature. *To the best of our knowledge this is the first report of a simple catalyst system that gives up to 98% ee for the cyanation of imines at room temperature in a short reaction time.* High enantioselectivities were obtained in the case of various benzhydryl, benzyl, and *N*-Boc imines. The unique

Scheme 1. Substrate Scope for the PHTA-Catalyzed Cyanation of Imines[a]



[a] The stereochemistries of the aminonitriles **4e**, **4h**, **4i**, and **4n**−**4r** are tentative.

nature of this catalyst system, its structure, and the mechanism as well as application to other reactions are currently under investigation.

Acknowledgment. This research work was supported by A*STAR Singapore and Mitsui Chemicals Asia Pacific Ltd. We thank Prof. Marc V. Garland and Dr. Li Chuanzhao, Institute of Chemical and Engineering Sciences, Singapore, for in situ IR measurements of PHTA catalyst.

Supporting Information Available: Experimental details and characterization of compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902540H