Pure Appl. Chem., Vol. 78, No. 2, pp. 409–414, 2006. doi:10.1351/pac200678020409 © 2006 IUPAC

Dual Lewis acid–Lewis base activation in enantioselective additions to aldehydes*

Erica Wingstrand, Stina Lundgren, Maël Penhoat, and Christina Moberg[‡]

Department of Chemistry, Organic Chemistry, Royal Institute of Technology, SE 100 44 Stockholm, Sweden

Abstract: Reaction of benzaldehyde with ethyl cyanoformate in the presence of Lewis acidic Ti(IV) complexes of bispyridylamide or salen ligands and Lewis basic amines affords the *O*-alkoxycarbonylated cyanohydrin. In the presence of the salen-based catalytic system, acetyl cyanide can also be added to benzaldehyde, providing a highly enantioselective direct route to the *O*-acetylated cyanohydrin.

Keywords: Lewis base; Lewis acid; cyanohydrin; titanium; salen; bispyridylamide.

INTRODUCTION

Enantioselective cyanations of carbonyl compounds have been the subject of intensive recent investigations due to the synthetic usefulness of the products obtained [1]. Although versatile synthetic routes to cyanohydrins have been known for more than 100 years [2] and the first asymmetric addition of HCN was already achieved by Rosenthaler in 1908 [3], it is only recently that efficient enantioselective processes have been developed. The asymmetry in the products has been introduced using enzymes, organocatalysts, or metal catalysts. Among these, a variety of chiral metal catalysts have proven to be particularly successful, providing highly enantioenriched products from aldehydes as well as ketones.

Trimethylsilyl cyanide (TMSCN) has most commonly been used as the source of cyanide ions. In contrast to reactions using potassium or sodium cyanide, additions of TMSCN afford direct access to *O*-silylated cyanohydrins and are therefore irreversible, thus permitting higher ee values to be achieved. Direct access to other *O*-functionalized derivatives is also desirable for the preparation of a variety of natural and synthetic products. Therefore, cyanoformates [4] and cyanophosphonates [5], providing enantioenriched cyanohydrin-*O*-carbonates and phosphonates, respectively, have been used in combination with chiral Lewis acid catalysts. While nonracemic *O*-acetylated derivatives have been obtained by reaction of aldehydes with potassium cyanide in the presence of an anhydride in reactions catalyzed by Ti(IV) and V(V) salen complexes [6], no enantioselective direct additions of acetyl cyanide or other acyl cyanides [7] to aldehydes were known when we started our studies.

We have previously investigated silylcyanations of aldehydes catalyzed by bispyridylamides [8] complexed to Ti(IV) and Zr(IV) [9]. Although reactions using TMSCN gave high yields of *O*-silyl protected cyanohydrins with moderate enantioselectivity (up to 70 % ee at room temperature), no reaction was observed when TMSCN was replaced by ethyl cyanoformate. We therefore decided to attempt to

^{*}Pure Appl. Chem. **78**, 197–523. An issue of reviews and research papers based on lectures presented at the 13th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-13), Geneva, Switzerland, 17–21 July 2005.

[‡]Corresponding author

modify the catalytic system by the addition of Lewis bases, which were assumed to be able to activate the cyanoformate.

LEWIS ACID-LEWIS BASE ACTIVATION

Cyanation of carbonyl compounds can be catalyzed by Lewis acids and Lewis bases [10] alone, although dual Lewis acid–Lewis base activation has proven to often result in more efficient formation of products [11]. Thus, Corey demonstrated that a mixture of a bisoxazoline and its magnesium complex catalyzed the addition by dual activation [12]. Highly enantioselective additions were later achieved in the presence of achiral phosphine oxides, which activate the silyl cyanide, and chiral aluminum binol complexes, which activate the carbonyl compound [13]. The Lewis basic and Lewis acidic sites were also successfully incorporated into the same molecule [13]. The phosphine oxide function could be replaced by an amino group [14], and the binol group by carbohydrate-derived diol functions [15] to afford enantioselective bifunctional catalysts. Dual activation has also been observed in additions of cyanoformates [16] and cyanophosphonates [5] to carbonyl groups.

Ti-bispyridylamide complexes

The addition of ethyl cyanoformate (2) to benzaldehyde (1) in the presence of Lewis acidic bispyridylamide (6) complexes and Lewis bases was thus studied (Scheme 1). We were pleased to find that the addition of ethyl cyanoformate occurred smoothly in the presence of 4 mol % $Ti(OiPr)_4/6$ and 2 mol % of dimethylaminopyridine (DMAP) to provide the product with 70 % conversion and 58 % ee at room temperature [17].



Scheme 1

Ti-salen complexes

Encouraged by these results, we decided to study the effect of Lewis base activation on the addition of ethyl cyanoformate using Ti-salen dimer 7, which has been demonstrated to catalyze highly enantio-selective additions of TMSCN [18] as well as cyanoformate [4] to several aldehydes. In the presence of 10 mol % of DMAP, the reaction of benzaldehyde with 2 equiv of 2 catalyzed by 5 mol % of dimer 7, occurred within 4 h as compared to 18 h at $-42 \,^{\circ}C$ [4] without DMAP, with only a minor loss in selectivity (from 95 to 93 % ee). By lowering the amount of 2, the selectivity was increased without any larger change in activity (Table 1, entry 1). The use of different achiral and chiral Lewis bases was studied (entries 2–4). Et₃N and diisopropylethylamine (DIEA) gave essentially quantitative conversions within 3 h. The chiral bases did not offer any advantages, and replacing 7 with *ent*-7 had only a minor effect on the reaction outcome (entries 5–8) [19].



 Table 1 Cyanation of benzaldehyde with 1.2 equiv of 2

 catalyzed by 5 mol % of 7 in the presence of Lewis bases.^a

Entry	Lewis base (10 %)	Time (h)	% Conv. ^b	% ee (<i>S</i>) ^c
1	DMAP	8	95	94
2	DABCO	7	90	90
3	Et ₃ N	3	97	92
4	DIEA	3	96	89
5	Cinchonidine	4	98	94
6	Quinine	4	93	93
7 ^d	Cinchonidine	7	93	-94
8 ^d	Quinine	7	97	-94

^aAll reactions were run at -40 °C. ^bDetermined by GC-MS. ^cDetermined by chiral GC. ^d*ent*-7 was used.

Acetyl cyanide

Acetyl cyanide (**3**) did not add to benzaldehyde in the presence of only 7 at -40 °C, although at higher temperatures a slow nonselective reaction took place (Table 2, entries 1 and 2). By adding DMAP, the reaction occurred smoothly at -40 °C (entry 3). Activation by DABCO, Et₃N, and DIEA was effective, but the use of DIEA led to decreased selectivity (entries 5–7). Use of chiral bases had little effect on the enantioselectivity, and, consequently, replacement of 7 with *ent*-7 had no larger influence on the reaction outcome (entries 8–11) [19].

Entry	Lewis base (10 %)	T (°C)	Time (h)	% Conv. ^a	% ee (<i>S</i>) ^b
1	-	-40	24	0	n.d.
2	_	25	24	30	53
3	DMAP	-40	6	57	94
4	DMAP	25	4	97	67
5	DABCO	-40	9	67	92
6	Et ₃ N	-40	8	96	94
7	DIEA	-40	8	97	81
8	Cinchonidine	-40	9	78	96
9	Quinine	-40	9	80	92
10 ^c	Cinchonidine	-40	9	75	-92
11 ^c	Quinine	-40	9	73	-95

Table 2 Cyanation of benzaldehyde with 2 equiv of **3** catalyzed by 5 mol % of **7** in the presence of Lewis bases.

^aDetermined by GC-MS.

^bDetermined by chiral GC.

cent-7 was used.

In the presence of only Lewis base, a slow reaction occurred and low enantioselectivity was achieved with chiral Lewis bases (Table 3). This demonstrates that a dual Lewis acid–Lewis base activation is necessary for the reaction to take place efficiently [19].

Table 3 Cyanation of benzaldehyde with 3 catalyzed by Lewis bases.^a

Entry	Lewis base (10 %)	Time (h)	% Conv. ^b	% ee (S) ^c
1	DMAP	8	<1	_
2	DABCO	8	<1	_
3	Et ₃ N	8	13	-
4	DIEA	8	16	_
5	Cinchonidine	8	9	40
6	Quinine	8	2	15

^aAll reactions were run at -40 °C.

^bDetermined by GC-MS.

^cDetermined by chiral GC.

Variation in enantiomeric excess

During our studies of TMSCN additions to benzaldehyde catalyzed by Ti(IV)-bispyridylamide complexes, we found that the enantiomeric excess (ee) increased over time [9]. Addition of enantioenriched product to the reaction mixture had no effect on this decreased enantioselectivity in the initial part of the reaction, nor did it slow addition of benzaldehyde. A reasonable explanation seemed to be that formation of a catalyst exhibiting higher enantioselectivity took place slowly during the catalytic process. Indeed, we found that when benzaldehyde was reacted with TMSCN with a catalyst that previously had been employed for the silylcyanation of valeraldehyde, only a minor variation of ee with time was observed and higher selectivity was obtained (79 % ee as compared to 70 % under normal conditions) [20]. A similar variation in ee has been reported by Belokon, North, and coworkers in cyanations employing a monomeric Ti-salen complex [18] and as well with a dimeric Ti-salen complex [21]. An increase in enantioselectivity with time was also observed using 2 or 3 in cyanations of benzaldehyde mediated by 7 and DMAP (Fig. 1) [22]. Reactions with 2 as cyanide source resulted in a smaller change in ee with time than those with 3 as the cyanide source. From this observation, we conclude that also with our bifunctional Lewis acid–Lewis base system the selective catalyst is formed slowly during the reaction.



Fig. 1 Variation of ee with time in cyanations of benzaldehyde with 2 or 3 catalyzed by 5 mol % 7 in the presence of DMAP.

CONCLUSIONS

Highly enantioselective additions of ethyl cyanoformate and acetyl cyanide were achieved employing dual Lewis acid–Lewis base activation, providing direct access to *O*-alkoxycarbonylated and *O*-acetyl-ated cyanohydrins. Optimization of reaction conditions was achieved by varying the nature of the Lewis base, making the reactions suitable for efficient high-throughput screening using normal laboratory equipment or microreactors, thereby minimizing the consumption of reagents and consumables [23].

ACKNOWLEDGMENTS

This work was financed by the Swedish Foundation for Strategic Research.

REFERENCES

- 1. (a) J.-M. Brunel and I. P. Holmes. Angew. Chem., Int. Ed. 43, 2752 (2004); (b) M. North. Tetrahedron: Asymmetry 14, 147 (2003).
- 2. D. T. Mowry. Chem. Rev. 42, 189 (1948).
- 3. L. Rosenthaler. Biochem. Z. 14, 238 (1908).
- 4. Y. N. Belokon, A. J. Blacker, L. A. Clutterbuck, M. North. Org. Lett. 5, 4505 (2003).
- (a) A. Baeza, J. Casas, C. Nájera, J. M. Sansano, J. M. Saá. *Angew. Chem., Int. Ed.* 42, 3143 (2003); (b) Y. Abiko, N. Yamagiwa, M. Sugita, J. Tian, S. Matsunaga, M. Shibasaki. *Synlett* 2434 (2004).
- (a) Y. N. Belokon, A. V. Gutnov, M. A. Moskalenko, L. V. Yashkina, D. E. Lesovoy, N. S. Ikonnikov, V. S. Larichev, M. North. *Chem. Commun.* 244 (2002); (b) Y. N. Belokon, P. Carta, A. V. Gutnov, V. Maleev, M. A. Moskalenko, L. V. Yashkina, N. S. Ikonnikov, N. V. Voskoboev, V. N. Khrustalev, M. North. *Helv. Chim. Acta* 85, 3301 (2002).

© 2006 IUPAC, Pure and Applied Chemistry 78, 409–414

- 7. Enantioselective additions of benzoyl cyanide to aldehydes were recently presented: A. Baeza, C. Nájera, J. M. Sansano, J. M. Sáa. *Tetrahedron: Asymmetry* **16**, 2385 (2005).
- 8. O. Belda and C. Moberg. Coord. Chem. Rev. 249, 727 (2005).
- 9. O. Belda, S. Duquesne, A. Fischer, C. Moberg. J. Organometal. Chem. 689, 3750 (2004).
- 10. S.-K. Tian and L. Deng. J. Am. Chem. Soc. 123, 6195 (2001).
- (a) J.-A. Ma and D. Cahard. Angew. Chem., Int. Ed. 43, 4566 (2004); (b) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki. Synlett 1491 (2005).
- 12. E. J. Corey and Z. Wang. Tetrahedron Lett. 34, 4001 (1993).
- (a) Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki. J. Am. Chem. Soc. 121, 2641 (1999); (b)
 Y. Hamashima, D. Sawada, H. Nogami, M. Kanai, M. Shibasaki. Tetrahedron 57, 805 (2001).
- 14. J. Casas, C. Nájera, J. M. Sansano, J. M. Saá. Org. Lett. 4, 2589 (2002).
- (a) Y. Hamashima, M. Kanai, M. Shibasaki. J. Am. Chem. Soc. 122, 7412 (2000); (b) K. Yabu, S. Masumoto, S. Yamasaki, Y. Hamashima, M. Kanai, W. Du, D. P. Curran, M. Shibasaki. J. Am. Chem. Soc. 123, 9908 (2001).
- (a) J. Casas, A. Baeza, J. M. Sansano, C. Nájera, J. M. Saá. *Tetrahedron: Asymmetry* 14, 197 (2003);
 (b) N. Yamagiwa, J. Tian, S. Matsunaga, M. Shibasaki. *J. Am. Chem. Soc.* 127, 3413 (2005).
- 17. E. Wingstrand and C. Moberg. Unpublished results.
- Y. N. Belokon, S. Caveda-Cepas, B. Green, N. S. Ikonnikov, V. N. Khrustalev, V. S. Larichev, M. A. Moscalenko, M. North, C. Orizu, V. I. Tararov, M. Tasinazzo, G. I. Timofeeva, L. V. Yashkina. J. Am. Chem. Soc. 121, 3968 (1999).
- 19. S. Lundgren, E. Wingstrand, M. Penhoat, C. Moberg. J. Am. Chem. Soc. 127, 11592 (2005).
- 20. E. Wingstrand, O. Belda, C. Moberg. Unpublished results.
- 21. Y. N. Belokon, A. J. Blacker, P. Carta, L. A. Clutterbuck, M. North. *Tetrahedron* 60, 10433 (2004).
- 22. S. Lundgren, E. Wingstrand, C. Moberg. Unpublished results.
- 23. C. Jönsson, S. Lundgren, S. J. Haswell, C. Moberg. Tetrahedron 60, 10515 (2004).