Aluminum-Catalyzed Asymmetric Addition of TMSCN to Aromatic and Aliphatic Ketones Promoted by an Easily Accessible and Recyclable Peptide Ligand**

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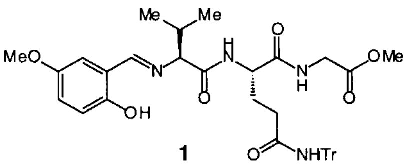
We have recently developed a number of catalytic asymmetric C–C bond-forming reactions that are promoted by chiral peptidic ligands in the presence of early or late transition metals.[1] Among these transformations are the Ti-catalyzed enantioselective additions of cyanide to epoxides[2] and imines.[3] Subsequent to the above studies, we set out to develop another important C–C bond-forming process: catalytic asymmetric synthesis of tertiary cyanohydrins by the addition of cyanide to a wide range of ketones, electrophiles for which only a few examples of catalytic asymmetric reactions involving carbon nucleophiles exist.[4] Such transformations would be of notable synthetic utility, since the resulting cyanohydrins can be converted into numerous optically pure or enriched synthons (e.g., tertiary α-hydroxy carbonyl compounds).[5]

Belokon has reported a Ti-catalyzed addition of TMSCN (TMS = trimethylsilyl) to aromatic ketones, in which a C_2-symmetric Schiff base is employed as the chiral ligand.[6] Shibasaki has disclosed enantioselective catalytic additions of TMSCN to aromatic and aliphatic ketones.[7] In the latter studies, a carbohydrate-derived bifunctional ligand and Ti(O*i*Pr)$_4$ promote the asymmetric additions. Most recently, Deng and Tian have outlined a method for cyanide addition to ketones with cyanoformate and catalytic amounts of cinchona alkaloids.[8] In spite of these important advances,[9–10] several pressing problems remain unresolved. Among these are the relatively low levels of enantioselectivity obtained with acyclic aliphatic ketones, especially in cases where there is little steric difference between the two substituents, and the long routes required for the synthesis of some of the more effective chiral ligands (up to thirteen linear steps).

Herein, we report a new approach to asymmetric cyanation of ketones that is Al-catalyzed, utilizes a peptidic chiral ligand, and delivers high enantioselectivity with both aromatic and aliphatic ketones. In addition, this method provides several practical advantages: it requires a recyclable chiral ligand **1** that is readily modifiable and can be easily synthesized in six simple steps and in 75% overall yield. In several cases, the method delivers higher levels of asymmetric induction than reported previously (particularly with aliphatic ketones).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To identify an effective chiral ligand and metal salt for the catalytic addition, we carried out systematic screening studies, taking advantage of the modularity of peptide-based chiral ligands and following protocols developed in our laboratories.[11] Acetophenone (**2**) was used as the substrate and TMSCN was selected as the nucleophile.[12] We were therefore able to establish that chiral peptide ligand **1** and Al(O*i*Pr)$_3$ effectively promote the enantioselective addition of TMSCN to **2**. These studies included an examination of various additives,[13] leading us to determine that the combined presence of MeOH and 3-Å molecular sieves are critical to reactivity as well as selectivity levels (see below for details).[12] Thus we find that treatment of acetophenone (**2**) with TMSCN in the presence of dipeptide Schiff base **1** (20 mol%), Al(O*i*Pr)$_3$ (20 mol%), MeOH (20 mol%), and 3-Å molecular sieves (2 equiv) leads to the efficient (>98% conversion) formation of cyanohydrin **3** in 88% *ee* and 93% yield (Table 1, entry 1).

The data illustrated in Table 1 demonstrate that a variety of aromatic ketones may be employed in the Al-catalyzed process. Reaction efficiencies and asymmetric inductions are not adversely influenced by electron-rich (Table 1, entry 3) or electron-deficient aryl substituents (Table 1, entries 4–7). Sterically hindered ketone **10** undergoes reaction to afford **11** efficiently (83% yield) and in 94% *ee*. Al-catalyzed asymmetric syntheses of **13** and **15** illustrate that this method is effective with cyclic substrates other than methyl aryl ketones (Table 1, entries 8, 9). Catalytic additions to **16** and **18** (Table 1, entries 10, 11) demonstrate that cyclic ketones are suitable substrates.

It is important to mention that ligand **1** can be easily recovered and used in subsequent asymmetric cyanide additions. As an example, **1** is recovered by silica-gel chromatography in >98% yield from the conversion of **2** into **3**. Subsequent use of the recovered ligand delivers similar levels of reactivity and selectivity. It must also be noted that either 10 or 20 mol% catalyst may be used. Although longer reaction times are required with reduced catalyst loading (10 mol% **1**, 72 h), the desired product is isolated without loss of enantioselectivity (Table 1, entries 2 and 5).

Acyclic aliphatic ketones can also be used in these Al-catalyzed additions; the corresponding cyanohydrins are isolated in >65% yield with high enantioselectivity. Both saturated (Table 2, entries 1, 2, and 4) and α,β-unsaturated alkenyl and alkynyl ketones (Table 2, entries 3 and 5–8) serve well as substrates. The unsaturated acyclic ketones, in particular, afford products of higher enantiopurity. Reactions may be effected in the presence of 10 mol% **1** and Al(O*i*Pr)$_3$ without diminution in enantioselectivity or yield (Table 2, entries 2, 6, and 8). The highly enantioselective addition to **28**

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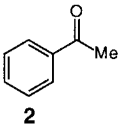
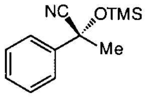
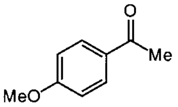
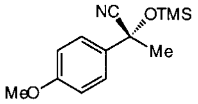
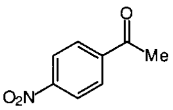
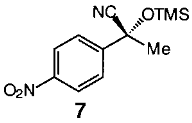
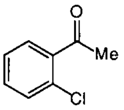
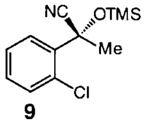
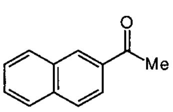
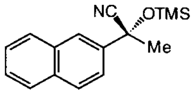
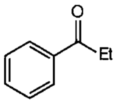
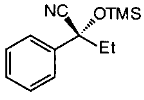
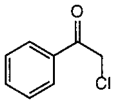
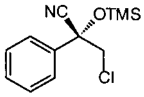
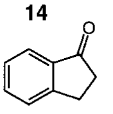
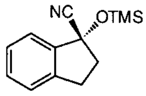
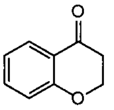
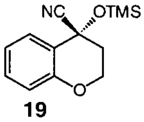
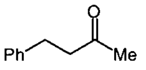
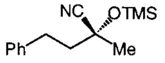
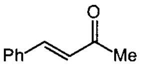
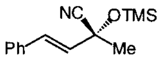
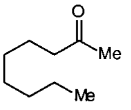
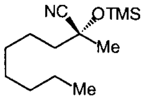
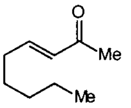
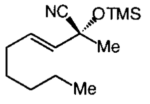
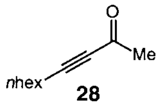
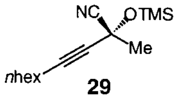
Table 1. Al-catalyzed enantioselective addition of TMSCN to aromatic ketones.[a]

Entry	Substrate	Product	mol% **1** and Al(O*i*Pr)$_3$	Yield [%][b]	*ee* [%][c]
2	 **2**	 **3**	10	84	91
1			20	93	88
3	 **4**	 **5**	20	67	91
4	 **6**	 **7**	20	>98	88
5			10	92	90
6	 **8**	 **9**	20	87	85
7	 **10**	 **11**	20	83	94
8	 **12**	 **13**	20	98	88
9	 **14**	 **15**	20	87	80
10	 **16**	 **17**	20	87	88
11	 **18**	 **19**	20	85	88

[a] Conditions: **1** and Al(O*i*Pr)$_3$ (indicated amounts), MeOH (20 mol%), TMSCN (2 equiv), molecular sieves (3 Å, 2 equiv by weight relative to substrate), toluene, −78 °C, 48 h (72 h for entries 2 and 5). [b] Conversions determined by GLC analysis (>98% in all cases). Yields after silica-gel chromatography. [c] All enantioselectivities determined by chiral GLC (CDGTA column); selectivity in entry 7 determined by chiral HPLC (Chiralpak OJ column).

Table 2. Al-catalyzed enantioselective addition of TMSCN to aliphatic ketones.[a]

Entry	Substrate	Product	mol% **1** and Al salt	Yield [%][b]	*ee* [%][c]
1	 **20**	 **21**	20	93	80
2			10	97	82
3	 **22**	 **23**	20	67	95
4	 **24**	 **25**	20	93	86
5	 **26**	 **27**	20	98	95
6			10	77	95
7	 **28**	 **29**	20	78	90
8			10	66	91

[a]–[c] See Table 1.

(Table 2, entries 7, 8) to afford cyanohydrin **29** is noteworthy (91% *ee*), as it illustrates that the present Al-catalyzed protocol may deliver high levels of enantioselectivity even when there is a modest steric difference between the two carbonyl substituents.

The particulars of the mechanism of the Al-catalyzed process must await the outcome of detailed kinetic and spectroscopic studies. Nevertheless, the following initial observations shed light on a few aspects of the asymmetric reaction:

1) The process is ligand accelerated;[14] <5% conversion is observed under identical conditions but in the absence of ligand **1**.
2) As illustrated in Scheme 1, the presence and the stereochemical identity of the AA2 moiety is pivotal to reaction efficiency and enantioselectivity. These findings suggest cooperative involvement of AA2 in delivering TMSCN or HCN to the Al-bound ketone. Such a scenario would be in agreement with the hypothesis put forth recently, based on extensive kinetic and other physical data, for the Ti-catalyzed cyanide additions to imines.[15]
3) In the absence of additives, reactions are significantly less efficient. For example, conversion of **2** into **3** proceeds to 30–60% conversion (vs >98%) when one or both additives are omitted from the reaction mixture.
4) When TMSCN addition to **2** is carried out in the presence of 20 mol% HCN (instead of MeOH), reaction proceeds to 71% conversion and **3** is formed in 81% *ee* (vs 64% conversion and 86% *ee* in the absence of HCN or MeOH). Thus, the positive effect of MeOH is likely not due to in situ HCN generation.[16]
5) When [D$_3$]-**2** (trideuteroacetophenone) is used, little or no variation in reaction efficiency or selectivity is observed. The effect of added MeOH is therefore not linked to regeneration of the ketone substrate by reaction with unreactive metal enolates that may be formed under the reaction conditions. Otherwise, due to the expected slower rate of enolate formation (primary isotope effect), the deuterated analogue would have reacted more readily and/or with higher levels of asymmetric induction.[4c]

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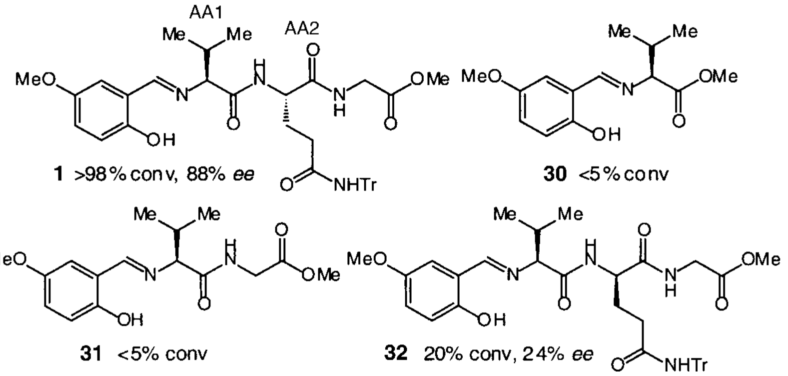

Scheme 1. Reactivity and enantioselectivity as a function of ligand structure; the presence and the relative stereochemistry (relative to AA1) of AA2 is critical to yield and *ee*. Data shown are for additions to ketone **2** under conditions indicated in Table 1 (20 mol% catalyst).

In summary, we have developed a new, efficient, and enantioselective method for the addition of TMSCN to aromatic (cyclic and acyclic) and aliphatic ketones (saturated and unsaturated). Substrates[17] and chiral ligands are prepared rapidly and efficiently (routine peptide coupling and Schiff base synthesis on a solid phase or in solution) and can be easily modified.[12] The levels of enantioselectivity observed are either competitive or higher than those reported previously (e.g., **19**, **25**, **29**). Asymmetric synthesis of **29** (Table 2, entries 7, 8) represents the first example of catalytic enantioselective cyanide addition to an alkynyl ketone. This Al-catalyzed C–C bond-forming method should thus prove to be a useful addition to the existing methods for the synthesis of nonracemic quaternary carbon centers.[18]

Experimental Section

3: Acetophenone (22.8 mg, 150.0 μmol), peptide Schiff base **1** (20.8 mg, 30.0 μmol), and powdered molecular sieves (3 Å, 40.0 mg) were suspended in toluene (300.0 μL). Aluminum isopropoxide (30.0 μL, 1.0 M in toluene, 30.0 μmol) and methanol (60.0 μL, 0.5 M in toluene, 30.0 μmol) were added successively. The mixture was allowed to stir for 5 min at 22 °C and then cooled to −78 °C. Trimethylsilyl cyanide (150.0 μL, 2.0 M in toluene, 300.0 μmol) was added dropwise into the reaction mixture and the resulting mixture was allowed to stir for 48 h at −78 °C. Pentane was added (500.0 μL) to quench the reaction and the resulting cold slurry was directly purified by silica-gel chromatography (pentane (10.0 mL) to remove toluene, followed by 100:1 pentane/Et_2O). The desired tertiary cyanohydrin **3** was collected as a clear, colorless oil (30.6 mg, 93%). IR (neat): $\tilde{\nu}$ = 3062 (w), 3024 (w), 2993 (w), 2967 (m), 2904 (w), 1495 (w), 1451 (m), 1369 (w), 1256 (s), 1230 (s), 1155 (s), 1123 (s), 1073 (m), 991 (s), 847 (s), 752 (s), 702 (s) cm^{-1}; ^1H NMR (400 MHz): $\delta = 7.56-7.53$ (m, 2H), 7.41–7.34 (m, 3H), 1.85 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz): $\delta = 142.2$, 128.9, 124.8, 121.9, 71.8, 33.8, 1.3; HR-MS: calcd for $C_{12}H_{17}NOSi$: 219.1079; found: 219.1082; elemental analysis: calcd for $C_{12}H_{17}NOSi$: C 65.71, H 7.81, N 6.39; found: C 65.78, H 7.84, N 6.59; $[\alpha]^{20}_D = +18.5°$ ($c = 1.25$, $CHCl_3$, 88% *ee*); GLC (CDGTA: column temperature = 80 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): t_r (major) = 46.2 min, t_r (minor) = 51.1 min. Absolute configuration was established to be *R* by comparison with optical rotation reported previously [lit. $[\alpha]^{24}_D = +21.9$ ($c = 1.18$, $CHCl_3$, 93% *ee*].[6a]

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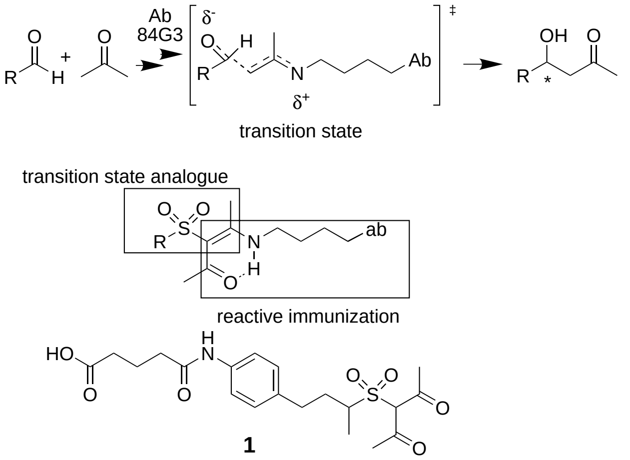
Unprecedented Regiocontrol Using An Aldolase I Antibody**

Virginie Maggiotti, Marina Resmini, and Véronique Gouverneur*

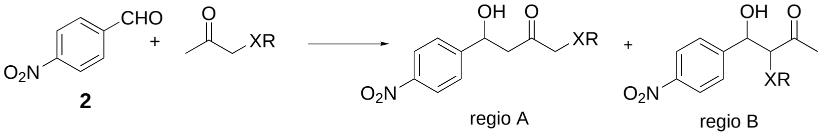
Dedicated to Professor Guy Ourisson

The aldol reaction is one of the most powerful methods for forming carbon–carbon bonds.[1] The value of the reaction relies upon the degree of regio-, diastereo-, and enantioselectivity that one could control. The two approaches towards catalytic asymmetric aldol reactions are biocatalysis and chemical catalysis with Lewis acids, Lewis bases, or small molecules.[2] Each has specific advantages and limitations and they should thus be regarded as complementary. By combining reactive immunization and transition state analogy into a single hapten, the groups of Lerner and Barbas developed a series of aldolase antibodies which use the enamine mechanism of natural occurring class I aldolases.[3] Here we report our findings that antibody 84G3 (ab84G3) raised against the β-diketo sulfone hapten **1**[4] (Scheme 1) is an effective asymmetric catalyst for the regio- and enantiocontrolled formation of a series of disfavored aldol products, therefore controlling reactivity in a unique way.



Scheme 1. Mechanism of the antibody-catalyzed aldol reaction (top) and reactive immunization with **1** for the generation of ab84G3 (bottom).

An inherent challenge to the use of unmodified unsymmetrical ketones in cross aldol reactions is the control of the regioselectivity. To study the regioselectivity of the cross aldol reaction in the presence of ab84G3, *para*-nitrobenzaldehyde **2** was chosen as the standard acceptor aldehyde [Eq. (1)]. As can be seen from Table 1, the unsymmetrical aliphatic ketones **3**–**6** undergo the aldol coupling in the presence of ab84G3. Analysis of the reaction mixtures by high-performance liquid chromatography (HPLC) indicated that in each case the antibody-catalyzed reaction occured exclusively at the less substituted carbon atom (products **7**, **9**, **11**, **13**), independently of the presence of heteroatoms in the donor ketones. This reactivity contrasts with the results obtained for the uncatalyzed reactions carried out under the same conditions (PBS, pH 7.4, Table 1). Indeed, the uncatalyzed reactions occurred preferentially at the more substituted carbon atom resulting in a mixture of *syn* and *anti* stereoisomers (products **8**, **10**, **12**, **14**). The other regioisomer is not observed or is formed only as a minor product.



(1)

3 X = CH_2, R = Me
4 X = CH_2, R = Et
5 X = O , R = Me
6 X = S , R = Me

7 X = CH_2, R = Me
9 X = CH_2, R = Et
11 X = O, R = Me
13 X = S, R = Me

8 X = CH_2, R = Me
10 X = CH_2, R = Et
12 X = O, R = Me
14 X = S, R = Me

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