Cyanation Catalysis

DOI: 10.1002/anie.200704461

Dinuclear {(salen)Al} Complexes Display Expanded Scope in the Conjugate Cyanation of α,β-Unsaturated Imides**

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The asymmetric conjugate addition of cyanide to α,β-unsaturated carbonyl derivatives provides access to broadly useful bifunctional chiral building blocks.[1,2] We reported [(salen)Al]Cl **1** (Figure 1) as the first effective catalyst for the enantioselective conjugate addition of cyanide to α,β-unsaturated carbonyl compounds.[1] Although highly enantioenriched adducts were obtained, high catalyst loadings and extended reaction times were required to induce acceptable conversions for a limited range of β-alkyl substituted imides. The observed second-order kinetic dependence on catalyst **1** provided preliminary evidence that the conjugate addition reaction proceeds through a cooperative bimetallic pathway in which the catalyst activates independently both the cyanide and the imide. This mechanistic model received strong support with the discovery of a heterobimetallic system that combines a {(salen)Al} and a {(pybox)Er} complex (pybox = 2,6-bis(2-oxazolinyl)pyridine, see Scheme 1) and displays significant rate accelerations and high enantioselectivities in reactions of β-alkyl derived imides.[3] Mechanistic studies revealed that the two catalysts operate cooperatively in both the rate and the enantiodetermining step.

A catalytic system employing a 2:1 ratio of a D-glucose-derived chiral ligand and Gd(iOPr)$_3$ was later developed by Shibasaki and co-workers for the cyanation of α,β-unsaturated *N*-acylpyrrole derivatives.[2] Remarkably, not only β-alkyl but also β-aryl substrates could be converted into the corresponding cyanation products in high yields and enantioselectivities. Nonetheless, this was again achieved at the cost of high catalyst loadings and prolonged reaction time.[4]

We sought to devise {(salen)Al}-based catalysts that enforce the cooperative mechanism through covalent linkage to appropriate cocatalysts. We investigated a series of a heterobimetallic dinuclear complexes that incorporate both pybox and salen frameworks, as typified by the structure depicted in Scheme 1. However, these proved to be not only challenging synthetic targets but also did not provide improved reactivity over the simple combination of mononuclear {(pybox)Er} and {(salen)Al} catalysts.

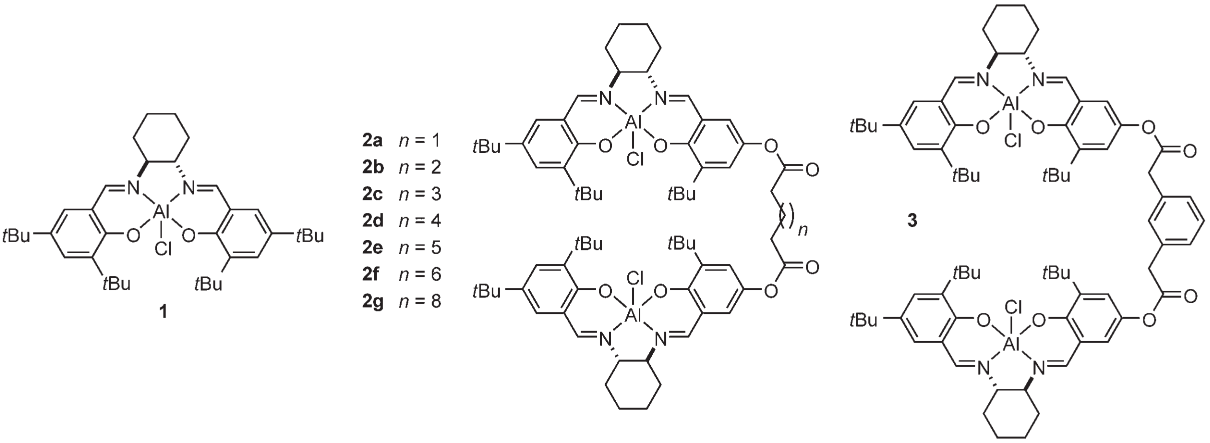

Figure 1. Mononuclear and linear dinuclear {(salen)Al} catalysts.

In contrast, we have found that readily accessible tethered dinuclear {(salen)Al} catalysts not only provide significant rate improvement with substrates studied previously, but also promote conjugate cyanation of important classes of imides that were unreactive with mononuclear catalysts or catalyst combinations. Kinetic data provide evidence for a mechanism involving intramolecular bimetallic catalysis. These results are described herein.

Increasing the effective molarity of {(salen)M} catalysts by linking salen units together has been shown to provide significant rate enhancements in epoxide ring-opening reac-

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[**] This work was supported by the NIH through Grant (GM-43214) and a Marie Curie postdoctoral fellowship (OIFP-6, 021364-AMEC) for C.M. We thank Dr. Eric R. Ashley and Qinghao Chen for helpful discussions. Herein, salen denotes 2,2′-[1,2-*trans*-cyclohexanediylbis(nitrilomethylidyne)]bis-3,5-di-*tert*-butylphenolate and derivatives thereof.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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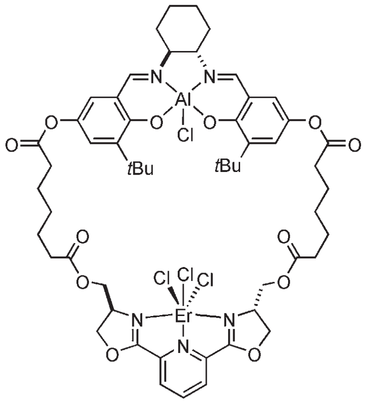


Scheme 1. A heterobimetallic dinuclear complex with the erbium center coordinated to the pybox moiety of the ligand and aluminum to salen.

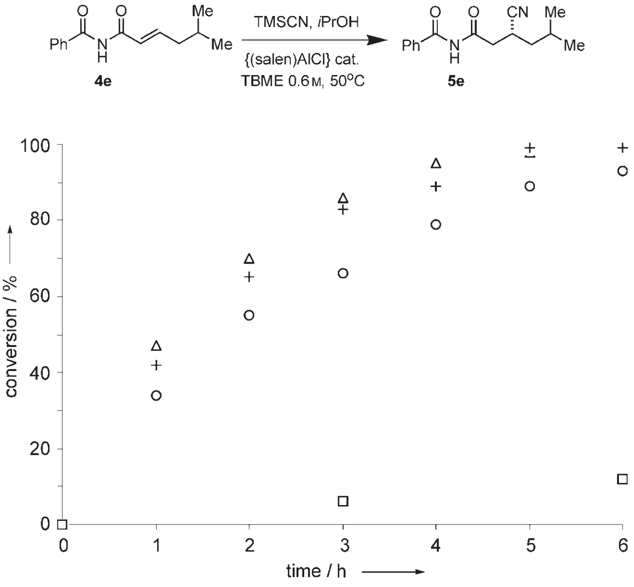


Figure 2. Comparative study on the reactivity of {(salen)Al} complexes **1** and **2c–g** in the catalytic conjugate cyanation of imide **4e**. □ **1** (90% *ee*), + **2c,d** (95% *ee*), △ **2e** (95% *ee*), ○ **2f,g** (93% *ee*). TMS = trimethylsilyl, TBME = *tert*-butyl methyl ether.

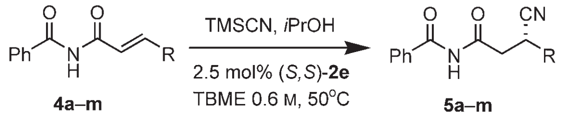
tions that proceed by cooperative, bimetallic mechanisms. This has been achieved by either preparation of dinuclear,[5] oligomeric,[6] dendrimeric,[7] or solid-supported[8] variants of the corresponding mononuclear catalysts. We pursued a similar approach for the {(salen)Al}-catalyzed conjugate addition of cyanide to α,β-unsaturated imides. To allow access to a range of transition-state geometries in the intramolecular reaction, we explored dinuclear {(salen)Al} complexes **2a–g** bearing linear and flexible tether units (Figure 1).

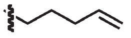
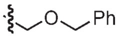
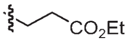
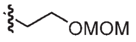
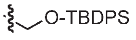
Preparation of the dinuclear catalysts was achieved in 6 steps from commercial materials in 22–34% overall yield. To assess the efficacy of these catalysts, we compared mononuclear complex **1** with dinuclear complexes **2a–g** in the conjugate cyanation of model substrate **4e** (see Table 1, R = *i*Bu) under optimal reaction conditions at catalyst concentrations of 5 mol% with respect to aluminum.[9] As reflected by the data on Figure 2, significant rate enhancement along with a measurable enantioselectivity increase were observed with the dinuclear catalysts. Thus, after 6 h, reaction of substrate **4e** proceeded only to 14% conversion into the corresponding cyanation product (90% *ee*) using **1**, whereas over 90% of cyanation product (93% *ee*) was obtained using dinuclear catalysts **2f** or **2g**. The rate enhancement is even more pronounced with catalysts **2c**, **2d**, and **2e**, which all exhibit very similar activity and enantioselectivity (> 99% conversion, 95% *ee* after 6 h).

Intrigued by the relative insensitivity of the linker length on the performance of dinuclear catalysts **2c–g**, a variety of alternative linkers were surveyed incorporating heteroatom, aryl, or alkyl substituents. None of these modifications led to improved catalysts for the reaction of model substrate **4e**, and instead erosion in enantioselectivity was generally observed. However, catalyst **3** (Figure 1), which incorporates a rigidifying element in the form of a 1,3-disubstituted aryl ring, exhibited comparable activity and enantioselectivity to the best dinuclear catalysts **2–e** (conversion > 99% after 5 h, 95% *ee*).

The improved reactivity between mononuclear {(salen)-Al} complex **1** and the related dinuclear analogues **2c–e** was extended to a variety of other substrates. Using 2.5 mol% of catalyst **2e**, standard β-alkyl substituted imides **4a–f** undergo complete conversion into the corresponding cyanation products **5a–f** within 6 to 8 h with high levels of enantioselectivity (91–95% *ee*; Table 1).

Table 1: Conjugate cyanation of α,β-unsaturated imides catalyzed by **2e**.[a]



Entry	Product	R	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**5a**	Me	8	98	91
2	**5b**	Et	6	96	91
3	**5c**	Pr	6	97	92
4	**5d**	*i*Pr	6	98	91
5	**5e**	*i*Bu	6	98	95
6	**5f**	Cy	6	97	95
7	**5g**	*t*Bu	14	99	91
8	**5h**		6	97	91
9	**5i**	 O Ph	8	> 99[d]	87
10	**5j**	 Ph	6	91	90
11	**5k**	 CO_2Et	6	> 99[d]	95
12	**5l**[e]	 OMOM	6	98[d]	96
13	**5m**[f]	 O-TBDPS	6	98[d]	84
14	**5n**[g]	 NH-Cbz	6	95[d]	87

[a] Reactions were carried out on 0.1–0.5 mmol scale using 6.5 equiv of TMSCN and *i*PrOH. [b] Yield of isolated product unless otherwise noted. [c] Determined by HPLC on a Pirkle L-leucine column (Regis). [d] Conversion determined by ^1H NMR using an internal standard. [e] MOM = methoxymethyl. [f] TBDPS = *tert*-butydiphenylsilyl. [g] Cbz = benzyl carbamate.

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Substrates **4g**–**i** required over 2 days reaction time and 10–15 mol % of **1** to attain high conversion, yet reached completion within 6-14 h with comparable levels of enantioselectivity using 2.5 mol % of **2e**. Imides bearing benzyl (**4i**),[10] MOM (methoxymethyl, **4l**), or TBDPS (*tert*-butyldiphenylsilyl, **4m**) ethers, ester (**4k**) as well as benzyl carbamate (**4n**) also afforded the corresponding cyanation products with high to very enantioselectivity within 6 to 8 h (Table 1).

More remarkably, conjugate cyanation of imides **6a**–**c**, which were completely unreactive with catalyst **1** or with the heterobimetallic combination, was effective with 5 mol % of either catalyst **2e** or **3**. Cinnamate derivative **6a** was thus converted into **7a** in 65 % yield and 95 % *ee* after 3 days' reaction time (Figure 3). Similarly, using 5 mol % of catalyst **3**, product **7b** was generated in 92 % *ee* with concomitant formation of a quaternary center, albeit in a modest 38 % yield.[11] The addition of cyanide to sorboyl imide **6c** catalyzed by **3** provided the 1,4-addition product **7c** exculsively in 47 % yield and 95 % *ee*. No trace of 1,6-addition product was observed.

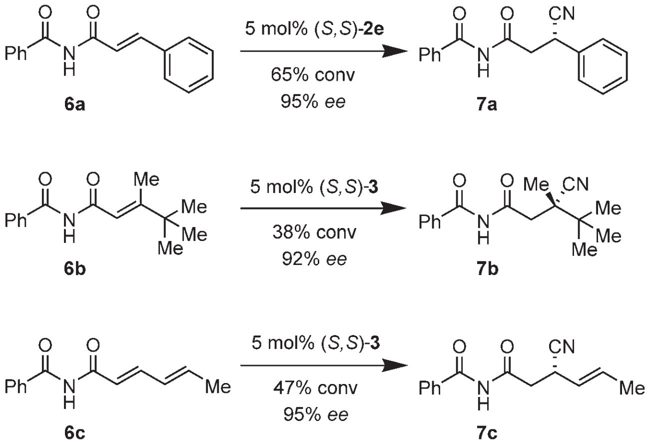

Figure 3. Conjugate cyanation of less reactive α,β-unsaturated imides catalyzed by **2e** or **3**. Reactions were carried out at 50 °C for 3 days on a 0.5 mmol scale using 6.5 equivalents of TMSCN and *i*PrOH, and 0.6 M *tert*-butyl methyl ether.

Kinetic studies of the 1,4-cyanation reaction of imide **4e** catalyzed by **2e** were carried out by monitoring initial rates of product formation by ^{1}H NMR spectroscopy. In contrast to the purely second-order dependence observed with mononuclear catalyst **1**,[1] a two-term rate law consistent with the participation of both intra- and intermolecular pathways was considered [Eq. (1)].

$$\text{rate} = k_{\text{intra}}\,[\text{cat.}] + k_{\text{inter}}\,[\text{cat.}]^2 \qquad (1)$$

Figure 4 shows a plot of rate/[cat.] versus [cat.] according to equation (2). The linear correlation with a positive slope

$$\text{rate}/[\text{cat.}] = k_{\text{intra}} + k_{\text{inter}}\,[\text{cat.}] \qquad (2)$$

and a nonzero intercept is consistent with a contribution of both inter- and intramolecular pathways (slope and *y* intercept, respectively) in the conjugate cyanation of imides. Remarkably, the second-order pathway with the dinuclear catalyst **2e** is two orders of magnitude greater than the second-order component of the reaction catalyzed by **1**.[12] A similar phenomenon was observed in epoxide ring-opening reactions catalyzed by dinuclear {(salen)Cr} complexes, and may be attributed to enhanced Lewis acidity of the dinuclear catalysts.[5]

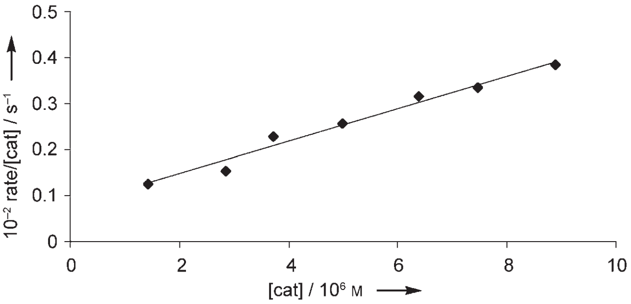

Figure 4. Plot of rate/[cat.] versus [cat.] for the conjugate cyanation of **4e** catalyzed by **2e**. k_{intra} = *y* intercept = 7.63 s^{-1}, k_{inter} = slope = 3.55×10^{-6} M, $R^2 = 0.9785$.

We have developed covalently linked dinuclear {(salen)Al} complexes that catalyze the conjugate cyanation of α,β-unsaturated imides with several orders of magnitude greater reactivity than the mononuclear analogue **1** and with comparable enantioselectivity. Addition products that were inaccessible with the original homobimetallic and heterobimetallic systems are now converted into the corresponding cyanation products with high level of enantioselectivity. Remarkably, the same dinuclear scaffolds have proven optimal for epoxide ring-opening and conjugate cyanation reactions, despite the use of different reactive metal centers and the fundamentally distinct geometrical characteristics of these transformations. We anticipate further applications of these linked salen–metal catalyst systems to other reaction classes.

Received: September 27, 2007
Revised: December 12, 2007
Published online: January 24, 2008

Keywords: aluminum · asymmetric catalysis · cyanation · dinuclear complexes · kinetics

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[9] See Supporting Information for a typical procedure. Data for catalysts **2a** and **2b** are not plotted because these catalysts were less enantioselective. After a reaction time of 20 h, catalyst **2a** furnished imide **5e** in 47 % yield and 86 % *ee*, and catalyst **2b** afforded the same product in 24 % yield and 68 % *ee*.

[10] This particular substrate requires 48 h reaction time with either the homobimetallic or the heterobimetallic systems described in references [1] and [2].

[11] At the end of the cyanation reactions using substrates **6a–c**, only starting material and product could be identified by ^{1}H NMR spectroscopy of the crude mixture.

[12] $k_{\text{mono}}(\mathbf{1}) = 3.77\times10^{-8}\,\text{M}^{-1}\,\text{s}^{-1}$, $k_{\text{inter}}\ (\mathbf{2e}) = 3.55\times10^{-6}\,\text{M}^{-1}\,\text{s}^{-1}$, $k_{\text{intra}}\ (\mathbf{2e}) = 7.63\ \text{s}^{-1}$. See Supporting Information for details. Similar results were obtained with catalyst **2c** and **2d**.

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