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Cooperative Dual Catalysis: Application to the Highly Enantioselective Conjugate Cyanation of Unsaturated Imides

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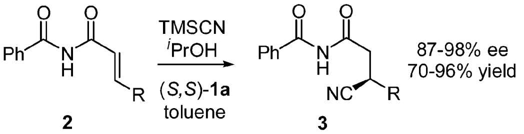
Catalysts for asymmetric additions of nucleophiles to electrophiles have traditionally been designed around the principle of Lewis acid activation of the electrophilic reacting partner (Figure 1, type 1).[1] By comparison, cooperative activation of both reacting partners can lead to enhanced reactivity and more specific control of the transition structure with respect to the catalyst's asymmetric environment, and this may serve to explain why two-metal ion catalysis is a common feature in enzyme-catalyzed reactions.[2] Dual activation with bimetallic systems has been established only recently in small-molecule-catalyzed asymmetric reactions, with the identification of two important classes of cooperative catalysts. Complexes of a single chiral ligand bearing two different metal ions have been developed and exploited extensively by Shibasaki and co-workers.[3,4] In these catalysts, one ion (usually a lanthanide or main group metal) serves as a Lewis acid activator of the electrophile, and the other (often an alkali metal) acts as a counterion to the nucleophile (type 2). Alternatively, several catalyst systems have been identified that promote addition reactions through dual activation of both substrates in nucleophile−electrophile additions by the same metal−ligand framework (type 3).[5] While catalyst oligomerization[6] strategies have provided a means to achieve type 3 systems with heightened reactivity, homobimetallic catalysis is intrinsically limited to systems in which the same metal−ligand complex is capable of activating both the electrophile and the nucleophile. We have been interested in developing a potentially more general design principle for cooperative catalysis, by engaging two different chiral catalysts tailored for their specific roles in substrate activation (type 4).[7] We describe here the successful illustration of this approach, wherein two distinct chiral metal complexes operate cooperatively in the highly enantioselective conjugate addition of cyanide to unsaturated imides.



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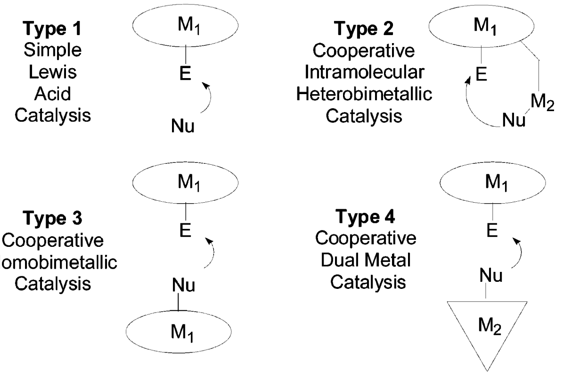

Figure 1. Different approaches to the catalysis of nucleophile (Nu)−electrophile (E) reactions. Geometric shapes (ovals, triangle) symbolize discrete chiral ligands.

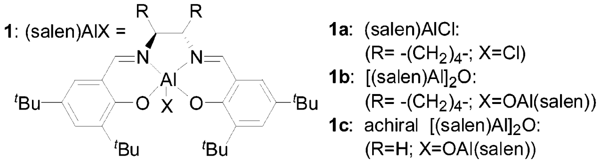

Figure 2. (Salen)Al complexes.

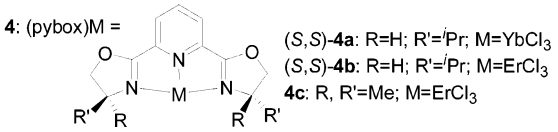

Figure 3. (Pybox)lanthanide complexes.

We reported recently that (salen)AlCl complex **1a** catalyzes the conjugate addition of hydrogen cyanide to unsaturated imides **2** (eq 1).[8] Highly enantioenriched cyanide adducts **3** were obtained, but high catalyst loadings, long reaction times, and in some cases elevated temperatures were required to induce acceptable substrate conversions. Mechanistic studies indicated that the reaction proceeds through a homobimetallic pathway, in which the catalyst activates both cyanide and the imide (i.e., type 3). Given that (salen)Al complexes have been shown to activate unsaturated imides (**2**) toward a variety of other nucleophilic addition reactions,[9] we hypothesized that the low reactivity in the cyanide additions may be due to inefficient activation of the nucleophile by the aluminum complex. To improve the rate and scope of the reaction, we explored the possibility of promoting a type 4 system by incorporating a second chiral catalyst capable of activating cyanide more effectively.

Chiral lanthanide complexes such as (pybox)YbCl$_3$ (**4a**) have been shown to promote the enantioselective addition of cyanide to meso epoxides with a second-order kinetic dependence on catalyst.[10,11] A cooperative (type 3) mechanism was proposed wherein one role of the catalyst is that of a cyanide activator. Similar lanthanide complexes displayed poor reactivity in the conjugate addition of cyanide to **2** (Table 1, entry 2), presumably as a result of inefficient activation of the imide. In contrast to the (salen)AlCl complex **1a**, the analogous μ-oxo dimer **1b** proved to be completely unreactive in the model reaction (entry 1), consistent with a complete absence of activation of the cyanide component. Remarkably, the combination of the two catalysts led to a highly reactive and enantioselective system (entry 3).

Under optimized conditions,[12] the dual-catalyst system afforded distinctly superior results relative to the (salen)AlCl complex **1a** reported previously (Table 2). Reaction times were reduced from 26−48 h to 8−14 h; the amount of TMSCN needed to achieve high conversions of imide could be lowered from 2.5 to 4.0 equiv to 2 equiv, while total catalyst loadings were decreased from 10−

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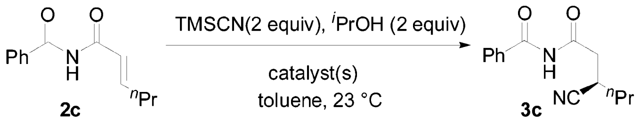
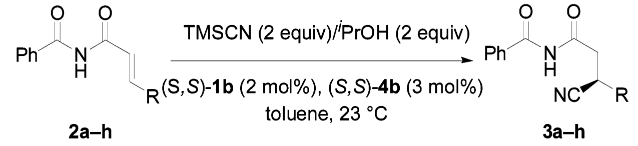
Table 1. Cyanide Conjugate Addition with Individual Catalysts vs the Dual-Catalyst System

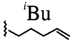


entry	Al complex	Er complex	conversion (%)^a	ee (%)^b
1	(*S*,*S*)-**1b**		<3	
2		(*S*,*S*)-**4b**	<3	
3^c	(*S*,*S*)-**1b**	(*S*,*S*)-**4b**	99	96

^{a} Determined by ^{1}H NMR. ^{b} Determined by HPLC using a Pirkle L-Leucine column. ^{c} (S,S)-**1b** (2 mol %), (S,S)-**4b** (3 mol %).

Table 2. Conjugate Addition of TMSCN to α,*β*-Unsaturated Imides Promoted by the Dual-Catalyst System **1b**/**4b**



Product	R	Time (h)	Isolated Yield (%)	ee (%)^a
3a	Me	14	85	96
3b	Et	8	87	94
3c	^{n}Pr	8	93	96
3d	^{i}Pr	8	84	94
3e	^{i}Bu	8	88	97
3f		14	94	93
3g	^{t}Bu	14	87	94
3h	CH_2OBn	48	80	93

^{a} Determined by HPLC using a Pirkle L-Leucine column.

Table 3. Effect of Ligand Stereochemistry on the Asymmetric Conjugate Addition of TMSCN/^{i}PrOH to **2c**^{a}

entry	Al complex	Er complex	conversion (%)^b	ee (%)
1	(*S*,*S*)-**1b**	(*S*,*S*)-**4b**	99 (87)	96
2	(*S*,*S*)-**1b**	(*R*,*R*)-**4b**	99 (20)	72
3	(*S*,*S*)-**1b**	**4c**	45	84
4		(*S*,*S*)-**4b**	<3	16^c
5	**1c**	(*S*,*S*)-**4b**	98	78

^{a} Reactions were carried out for 24 h at room temperature under the conditions shown in Table 2. ^{b} Determined by ^{1}H NMR. Numbers in parentheses correspond to conversions after 3.5 h. ^{c} Determined on product obtained after 17 days of reaction time.

15 mol % to 7 mol %.[13] All reactions were carried out successfully at room temperature, even in the case of less reactive imides. With certain substrates such as the functionalized imide **2h**, the dual-catalyst system also afforded increased enantioselectivity relative to catalyst **1a** alone (93 vs 89% ee).

Mechanistic studies of the dual-catalyst system were undertaken in order to glean insight into the nature of the cooperative effect and to assess the relative role of the two chiral complexes in the asymmetric induction. Kinetic analyses based on initial rates revealed a first-order dependence on both (salen)aluminum dimer **1b** concentration and (pybox)erbium **4b** concentration, indicating that both complexes are engaged in the rate-determining transition state. The relative role of the two chiral ligand environments was assessed by comparing diastereomeric ligand combinations as well as achiral ligand variants. Whereas one combination of catalyst enantiomers [e.g., (*S*,*S*)-**1b** + (*S*,*S*)-**4b**] afforded high enantioselectivity and rates (Table 3, entry 1), replacing the erbium complex with its enantiomer [i.e., (*S*,*S*)-**1b** + (*R*,*R*)-**4b**] led to substantially decreased ees and conversions (entry 2). When achiral (pybox)Er complex **4c** was combined with (*S*,*S*)-**1b** (entry 3), the conjugate addition proceeded with an intermediate level of enantioselectivity. Significantly, the combination of achiral (salen)Al complex **1c** and (pybox)erbium complex (*S*,*S*)-**4b** led to substantially higher enantioselectivity than that obtained with (*S*,*S*)-**4b** alone (entry 4 vs entry 5). Taken together, these results point to a mechanism of catalysis where both complexes not only are engaged in the rate-determining step but also function cooperatively in the asymmetric induction.

To our knowledge, this represents the first example of a system in which two distinct chiral metal complexes operate cooperatively to catalyze a highly enantioselective reaction. The dual-catalyst protocol also represents a significant practical improvement over the homobimetallic system for the conjugate addition of hydrogen cyanide to α,*β*-unsaturated imides, affording substantially increased rates and similar or better enantioselectivites. We are currently exploring the general applicability of the dual-chiral catalyst design concept.

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Supporting Information Available: Experimental procedures for the preparation of the catalysts and for the conjugated addition reactions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Optimized conditions: 2 equiv of TMSCN, 2 equiv of ^{i}PrOH, 2 mol % $[(salen)Al]_2O$ (**1b**), 3 mol % (pybox)$ErCl_3$ (**4b**), toluene, 23 °C. Pybox: $ErCl_3$ ratios of 1.2−2.0 were employed with no observable effect on ee or yield. Full experimental details and additional substrate entries are provided in Supporting Information.

(13) The concentration of $[(salen)Al]_2O$ complex **1b** is expressed here in terms of total metal concentration.

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