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Dial-in selection of any of four stereochemical outcomes among two substrates by *in situ* stereo-reconfiguration of a single ambidextrous catalyst

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

ABSTRACT

We provide proof-of-principle that an ambidextrous catalyst is capable of independent, dial-in control of the absolute stereochemistry of two similar nitrostyrene Michael addition reactions by *in situ* oxidation and reduction of the catalyst. The catalyst is capable of both static and dynamic catalysis modes; in combination both modes allow access to all four possible stereochemical outcomes for the two nitroalkane products in a single process.

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Keywords:

Asymmetric catalysis

Ambidextrous

Dynamic

Helical inversion

Michael addition

Dynamic control of reactions in real time is rare in synthetic organic chemistry.^{1–12} Few examples exist of a catalyst or reagent able to change the outcome of a reaction *in situ*. Such control could open the doorway to new strategies for cascade reactions, polymer synthesis, materials chemistry, and other areas. The few existing examples of dynamic modulation of reactions tend to be on/off catalysts that catalyze the formation of a product in the “on” state and then lower the rate of product formation in the “off” state.^{1–12}

Figure 1. Ambidextrous catalyst in both Cu(II) (Δ -1) and Cu(I) (Δ -1) states

Real time control of reactions makes use of a dynamic catalyst that can be regulated by the user. For example, redox,

photochemical, and acid/base chemistry modulate the reactivity of dynamic catalysts. Some molecules are capable of acting as asymmetric catalysts that control the chirality of the product depending on the state of the catalyst.^{13–15} One such example was developed in our laboratory, using a redox reconfigurable scaffold that is capable of inverting helical chirality.^{16,17} After appending catalytic urea groups to the scaffold, the complex becomes a functional catalyst for the asymmetric conjugate addition of malonate esters to nitrostyrenes. The catalyst can be used in either copper oxidation state; the Cu(II) state produces the (S)-product and the Cu(I) state affords the (R)-product. It became apparent that some substituted nitrostyrenes reacted at significantly different rates than the unsubstituted *trans*- β -nitrostyrene when several different nitrostyrene substrates were tested against the same diethyl malonate reactant. Indeed, several groups have reported different rates of completion for the same asymmetric transformations carried out with metal- and thiourea-based catalysts.^{18–20}

With different nitrostyrenes reacting at different rates, we realized that an experiment could be devised in which two different nitrostyrene starting materials could be transformed into two similar Michael products, but with different preference in absolute stereochemistry. This unique outcome can be achieved if the ambidextrous catalyst is employed initially in one oxidation state and then switched *in situ* after the more electrophilic nitrostyrene is consumed.

With two nitrostyrene substrates, each forms a chiral center, and it can be reasoned that there are four possible stereochemical

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outcomes for the mixture of products. Table 1 is a truth table constructed to show all four of the possible stereochemical outcomes for a one-pot reaction with the ambidextrous catalyst using two different nitrostyrenes (ns-A and ns-B). Catalyst Δ/Λ -1 can essentially behave either in a dynamic or static fashion. When the catalyst is dynamic, it changes state during the course of the reaction. Static catalysis sees the catalyst remain in a single state throughout the reaction.

Table 1. Truth table for one pot reaction with two different nitrostyrene substrates (ns-A and ns-B). The catalyst state is switched after the consumption of one nitrostyrene resulting in different stereochemical outcomes for the two products.

Initial input	Second input		
	Cat. state	Δ -1	Λ -1
	Δ -1	ns-A: <i>S</i> ns-B: <i>S</i>	ns-A: <i>R</i> ns-B: <i>S</i>
	Λ -1	ns-A: <i>S</i> ns-B: <i>R</i>	ns-A: <i>R</i> ns-B: <i>R</i>

Before testing the *in situ* switching characteristics of the ambidextrous catalyst, we chose a pair of nitrostyrene candidates with a suitable difference in rate when reacting with diethyl malonate (**4**). We chose *trans*- β -nitrostyrene (**2**) as the first candidate due to the relatively high e.e. we obtained previously and its established reaction rate.^{16,17} Literature precedent and substrate screens led us to select a slower reacting nitrostyrene relative to *trans*- β -nitrostyrene for this experiment. A time course trial of *trans*-2,3-dimethoxy- β -nitrostyrene (**3**) was conducted to determine if the rate of reaction was slow enough compared to *trans*- β -nitrostyrene. The reaction conditions were optimized in an earlier study.

Scheme 1. Reaction conditions used to analyze the rate at which different nitrostyrenes react with diethyl malonate (**4**) and catalyst Δ -1.

Figure 2. Time course study on consumption of nitrostyrenes **2** (circles) and **3** (squares) using catalyst Δ -1 in acetonitrile

Nitrostyrene **2** was found to have a half-life of roughly $t_{1/2} \sim 110$ min. The electron donating methoxy groups of nitrostyrene **3** appear to greatly reduce the electrophilicity of the alkene leading to a much longer half-life at $t_{1/2} \sim 1440$ min. The catalyst itself switches immediately on oxidation/reduction as observed in CD experiments, and is expected to reconfigure in the milliseconds to seconds range based on previous rate studies completed on a closely related complex.²¹ Given the large difference in half-life between nitrostyrenes **2** and **3**, it is reasonable to suggest that enough time exists to switch the catalyst *in situ* and change the absolute stereochemistry of product **5** and **6**.

The first experiments performed were the static catalysis reactions in which the catalyst remains in a single oxidation state over the course of the reaction. This experiment validated that the catalyst is capable of producing both of the enantiomeric products of the two different nitrostyrenes simultaneously in the same reaction media. As previously mentioned, *trans*- β -nitrostyrene (**2**) was chosen as the faster-reacting substrate, with *trans*-2,3-dimethoxy nitrostyrene (**3**) as the slower-reacting nitrostyrene (Scheme 2). Acetonitrile was shown to give the best combination of stereoselectivity and yield as shown earlier. One equivalent of each nitrostyrene was added to the mixture to react with two equivalents of diethyl malonate (**4**). The catalyst was kept in the Δ -1 state in the first reaction to yield both products in the *S* absolute configuration.

Scheme 2. One-pot synthesis of both (*S*)-**5** and (*S*)-**6** using

Δ -1 in a static fashion

The results are similar to those found when each substrate is used alone with Δ -1. Both products are formed in the *S* absolute configuration with 69% e.e. of (*S*)-**5** and 30% e.e. of (*S*)-**6**. As expected, the static catalyst Δ -1 gives similar yields and e.e.'s when the reaction is performed with both nitrostyrene substrates in one pot as when the reactions are performed separately with a single nitrostyrene substrate. One-pot synthesis using Λ -1 yielded products with *R* absolute stereochemistry with 67% e.e. of (*R*)-**5** and 55% e.e. of (*R*)-**6**. These results confirm that two of the product combinations from the catalysis truth table (Table 1) can be obtained using one-pot conditions.

Scheme 3. Dynamic catalysis performed with the ambidextrous catalyst. The *in situ* reduction of the catalyst leads to chiral products with opposite absolute configurations [(*S*)-**5** and (*R*)-**6**].

After performing the static catalysis reactions and obtaining the expected products, we examined dynamic catalysis. The first dynamic reaction was performed using L-ascorbic acid to reduce Δ -1 to Λ -1 during the course of the reaction. L-ascorbic acid was chosen due to its lack of reactivity with the reagents and the breadth of studies on switching the catalyst scaffold with this reducing agent.^{22,23} Kinetic studies (Figure 2) indicate that nitrostyrene **2** was mostly consumed after three hours in the presence of Δ -1 and triethylamine. The reactants were added to the flask and allowed to react for three hours before 10 mol % of L-ascorbic acid was added to reduce the catalyst. The reduction was monitored qualitatively by a color change of the solution from green (Δ -1) to yellow (Λ -1). As hypothesized, the products were obtained in the opposite absolute stereochemistry, albeit with lower enantiomeric excess. Additional triethylamine was added to the reaction mixture to maintain the proper pH after the addition of L-ascorbic acid. The (*S*)-**5** product was obtained in 55% e.e., and the (*R*)-**6** product was obtained in 14% e.e. The lower e.e. obtained for each product when compared to the e.e. obtained with the static catalysts is likely to result from some amount of **3** reacting in the initial three hour period before catalyst switching and a small amount of remaining **2** reacting after catalyst switching. Unfortunately, **3** does not react so slowly that no product **5** is formed before complete consumption of the faster reacting nitrostyrene **2**.

Scheme 4. Dynamic catalysis oxidizing Δ -1 to obtain products of opposite absolute stereochemistry [(*R*)-**5** and (*S*)-**6**]

After proving the feasibility of dynamic catalysis, we sought to complete the truth table (Table 1) to see if all four product combinations could be obtained. The last sequence would require beginning the reaction with Δ -1 and then oxidizing the catalyst to the Λ -1 state. Previously, oxidation of the switching scaffold was carried out using ammonium persulfate.²⁴ This reagent was not amenable to oxidation *in situ* due to the lack of solubility of ammonium persulfate in acetonitrile. Other oxidizing agents such as TEMPO and DDQ were tested, but did not invert the chirality of the catalyst. With these initial tests we turned our attention to ceric ammonium nitrate (CAN) as the oxidizing agent for dynamic catalysis. CAN is relatively powerful reagent capable of oxidizing several different functional groups.²⁵ The reaction was initiated using Δ -1 and oxidized using CAN after three hours. Nitroalkane (*R*)-**5** was obtained in 64 % e.e. while the (*S*)-**6** product was attained with only 2% e.e. The yield of both addition products is lowered, possibly due to side reactions with CAN. It should be noted that although the enantiomeric excess of (*S*)-**6** was low, the change in enantiomeric excess was appreciable and confirmed a proof of principle.

With the results in hand it appears as though all four permutations of possible stereochemical products in the reaction can be obtained with some degree of selectivity. A graph (Figure 3) showing the magnitude of change for the products attained for all product combinations provides a picture of the ambidextrous catalyst's ability to manipulate stereochemical outcomes.

Figure 3. Graph showing the magnitude changes in enantiomeric excess using the ambidextrous catalyst Δ/Λ -1

The ambidextrous catalyst **1** has proven to be a highly versatile complex capable of modifying the stereochemical outcome of two different chiral products by *in situ* inversion. Depending on the oxidation state of the catalyst during the course of the reaction, all four possible stereochemical configurations with the two chiral products are accessible. The ability to determine the outcome relies on the oxidation state of the catalyst and also the electronic characteristics of the substrates. This form of real time control has rarely been achieved for organic reactions and has never been realized in asymmetric catalysis. This study begs the question of whether ambidextrous catalysts may control the stereochemistry of two different prochiral centers in one molecule or control tacticity in real time polymerization reactions.

Acknowledgments

We are grateful to the National Science Foundation (CHE-1412568) for financial support of this work.

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