Organocatalysis

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Rationalization of an Unusual Solvent-Induced Inversion of Enantiomeric Excess in Organocatalytic Selenylation of Aldehydes**

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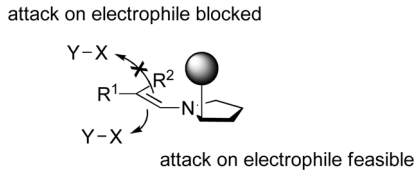
Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

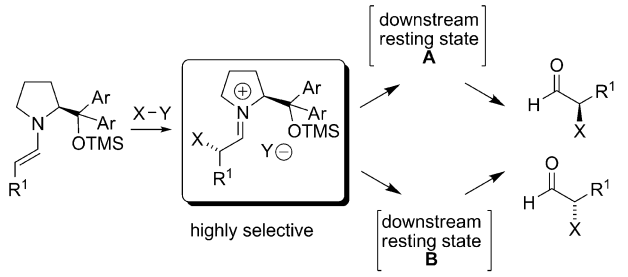
Abstract: *An unusual solvent-induced inversion of the sense of enantioselectivity observed in the α-selenylation of aldehydes catalyzed by a diphenylprolinol silyl ether catalyst is correlated to the presence of intermediates formed subsequent to the highly selective C–Se bond-forming step in the catalytic cycle. This work provides support for a mechanistic concept for enamine catalysis and includes a general role for "downstream intermediates" in selectivity outcomes in organocatalysis.*

The diarylprolinol silyl ether system has been termed a "general organocatalyst"[1] because of its highly selective mediation of reactions with enamine, dienamine, and conjugated iminium ion intermediates.[2] The sense of the stereochemical outcome in enamine catalysis is typically rationalized by the steric model shown in Scheme 1,[3–5] where the preferred *E* isomer of the enamine reacts in its s-*trans* conformation. Attack from one face is hindered by the bulky side chain of the pyrrolidine ring.

We recently revealed a number of cases in which identification of stable intermediates formed downstream from this step in the catalytic cycle led to the suggestion that the electrophile addition shown in Scheme 1 may not control the stereochemical outcome in all cases.[3] Scheme 2 shows how a bifurcation of the pathway after this step introduces the possibility of subsequent alteration of the stereoselectivity imparted in that step.



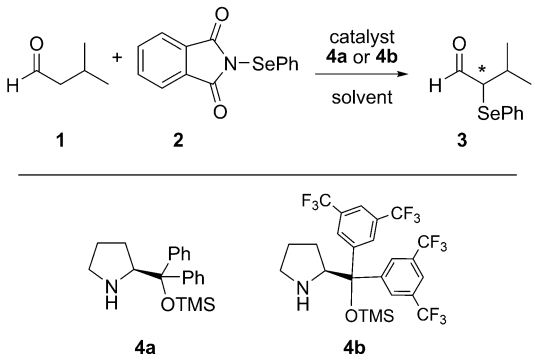
Scheme 1. Steric transition-state model for enamine catalysis.



Scheme 2. Role of downstream intermediates.[3b]

Herein we report that downstream intermediates are further implicated in an intriguing and heretofore unexplained reversal of the sense of enantioselectivity as a function of solvent in the α-selenylation of aldehydes catalyzed by **4a** (see Scheme 3),[6] an effect that is difficult to rationalize by the model of Scheme 1. The current work extends our recent studies of other enamine–electrophile reactions[3] and suggests generality for this refined model which may inform further reaction optimization in organocatalysis.

The α-selenylation reaction was reported previously by Melchiorre and co-workers[7] and by Cordova and co-workers, with excellent enantioselectivities in accordance with the steric model shown in Scheme 1.[6] In one example, however,



Scheme 3. α-Selenylation of aldehydes catalyzed by diarylprolinol ethers.

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the latter group observed an inversion in the sense of product enantioselectivity for a reaction carried out in CH_3CN compared to that in toluene or $CHCl_3$. More recently, an inversion of enantioselectivity with a change of solvent was also reported in this reaction using a polymer-supported version of a MacMillan imidazolidinone catalyst.[8] Observations of a solvent-induced inversion in enantioselectivity are relatively rare in organocatalysis. In one of the few other cases reported, MacMillan and co-workers observed an inversion in enantioselectivity in the construction of pyrrolo-indolines by imimium activation with imidazolidinone catalysts, and the inversion was broadly correlated with solvent dielectric constant.[9]

Table 1 shows results for the reaction of Scheme 3 screening different solvents and catalysts.[10] These studies confirm the inversion in the sense of enantioselectivity in CH_3CN

Table 1: Catalyst and solvent screening in the reaction of Scheme 3.[a]

Entry	Catalyst	Solvent	Dielectric constant	*ee* [%]
1	**4a**	hexanes	1.89	97 (*S*)
2	**4a**	toluene	2.38	93 (*S*)
3	**4a**	$CHCl_3$	4.81	6 (*R*)
4	**4a**	THF	7.58	25 (*R*)
5	**4a**	CH_2Cl_2	8.93	39 (*R*)
6	**4a**	CH_3CN	37.5	44 (*R*)
7	**4b**	hexanes	1.89	99 (*S*)
8	**4b**	toluene	2.38	98 (*S*)
9	**4b**	THF	7.58	99 (*S*)
10	**4b**	CH_2Cl_2	8.93	51 (*S*)

[a] Reaction conditions: 0.225 M **1a**, 0.025 M **2**, 0.0025 M catalyst, ambient temperature. All reactions gave quantitative conversion of the limiting reactant **2**.[10] THF = tetrahydrofuran.

observed by Cordova and demonstrate that catalyst **4a** shows a shift from high *S*-(**3**) selectivity in *n*-hexane and toluene to moderate selectivity for *R*-(**3**) in CH_2Cl_2 and THF as well as CH_3CN. A rough correlation with dielectric constant is found, similar to that observed by MacMillan and co-workers.[9] The catalyst **4b** does not exhibit reversal of the sense of enantioselectivity but the lower *ee* value for *S*-(**3**) observed in CH_2Cl_2 compared to that in toluene indicates a similar trend of increased selectivity for the *R*-(**3**) product observed for catalyst **4a**.

Kinetic studies of the reaction of Scheme 3 in CH_2Cl_2, carried out using reaction calorimetry, revealed a linear temporal profile exemplifying a constant reaction rate (Figure 1). Along with the observed overlay in kinetic profiles for reactions carried out at different concentrations, zero-order kinetics is demonstrated in both substrates [**1**] and [**2**]. First-order kinetics in [catalyst] and lack of catalyst deactivation over the course of the reaction were also confirmed. The reaction rate was enhanced in the presence of both water and acid (Figure 2). The enantioselectivity was constant over the course of the reaction and was not influenced by acid.

The form of these kinetic profiles mirrors those observed previously when using **4** in both the conjugate addition of aldehydes to nitrostyrene and in the α-chlorination of

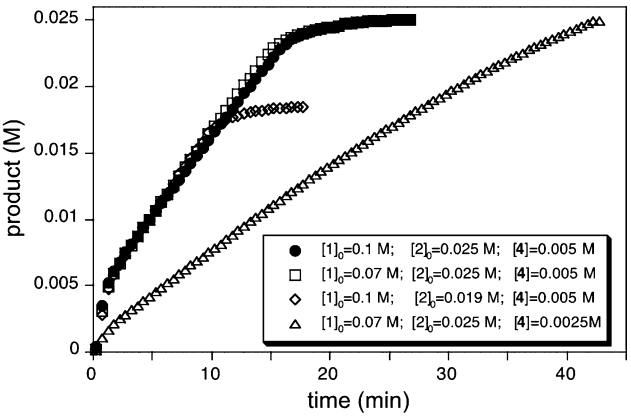
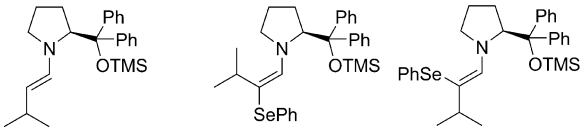


Figure 1. Calorimetric monitoring of the reaction shown in Scheme 1. Reaction carried out in CH_2Cl_2 by varying initial concentrations of the substrates **1** and **2** and the catalyst **4a** as shown. Added 0.005 M acetic acid, and run at ambient temperature.[10]

isovaleraldehyde,[3] behavior demonstrated to be a kinetic marker for a catalyst resting state containing both substrates and therefore one that lies downstream in the cycle from the electrophile addition step.

Interaction between the aldehyde **1** and catalyst **4a** produced the *E*-enamine **5**, as revealed by NMR NOESY/



s-*trans*-**5** (*E*)-**6** (*Z*)-**6**

conformational analysis,[10,11] to be predominantly the *s-trans* conformer in all solvents.[10] The species **5** was observed in the presence or absence of catalytic amounts of acid, with larger concentrations of acid or water shifting the resting state back to the free catalyst. Upon addition of the electrophile **2**, the

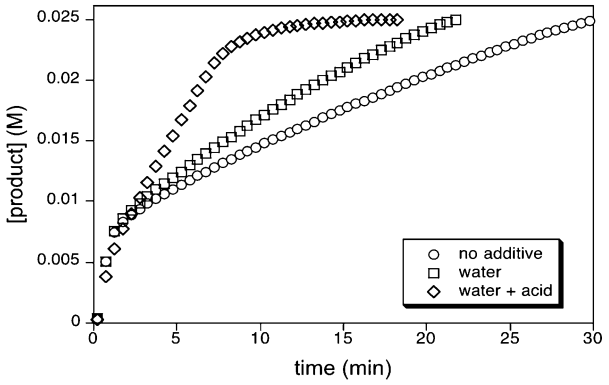


Figure 2. Reaction calorimetric monitoring of the reaction shown in Scheme 1. Reaction carried out in CH_2Cl_2 in the absence and presence of water and acid additives as shown. $[\mathbf{1}]_0 = 0.1$ M; $[\mathbf{2}]_0 = 0.025$ M; $[\mathbf{4a}]_0 = 0.005$ M; ambient temperature.[10]

species **5** was no longer observed, and the resting state was revealed to be product enamine species **6**. While (*E*)-**6** and (*Z*)-**6** are present in nearly equal concentrations in both CD_2Cl_2 and CD_3CN, *E*-(**6**) is the sole catalytic species observed in [D_8]toluene.[10]

NMR spectroscopic monitoring under the reaction conditions (Figure 3) confirmed both the zero-order kinetics observed by reaction calorimetry and the catalyst resting state

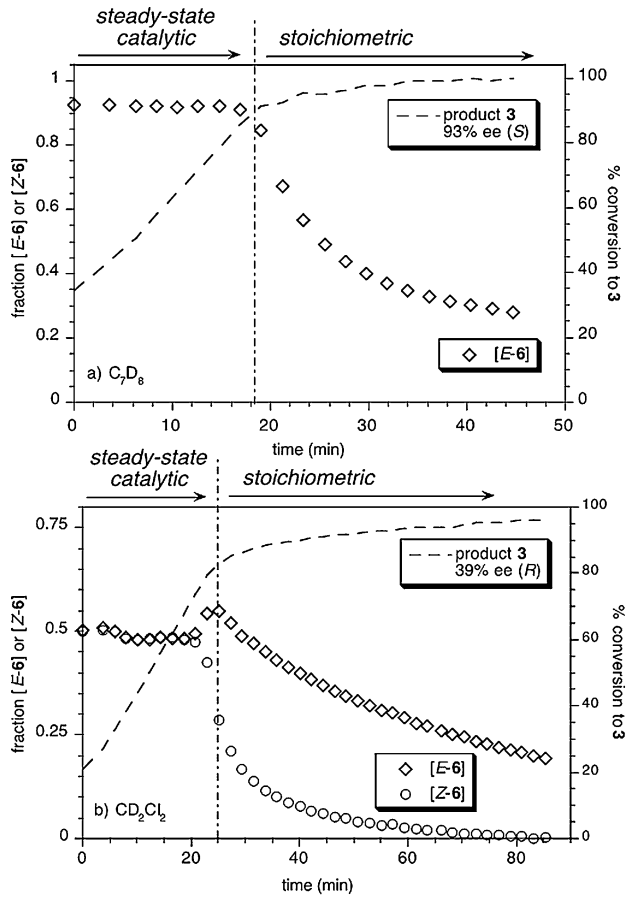


Figure 3. NMR monitoring of the reaction of Scheme 3 with $[\mathbf{1}]_0 = 0.25$ M, $[\mathbf{2}]_0 = 0.03$ M, and [**4a**] = 5 mM[10] in C_7D_8 (a) and CD_2Cl_2 (b). Left axis: fraction of catalytic species. Right axis: fraction conversion into **3**.

as the product enamine **6**, as (*E*)-**6** in [D_8]toluene and as a nearly equimolar mixture of (*E*)-**6** and (*Z*)-**6** in CD_2Cl_2. The species **6** maintains constant concentration until the reaction approaches nearly full conversion of the limiting substrate **2**, at which point the concentration of **6** begins to decay. In CD_2Cl_2, where both *E*- and *Z*-product enamines are present, species (*Z*)-**6** decays more rapidly than (*E*)-**6**. From these observations we assign the zero-order kinetic regime associated with constant concentration of **6** to the period of steady-state catalytic turnover, where the catalyst resting state **6** is replenished as quickly as it is turned over to product. Following this regime, the final reaction turnovers correspond to the stoichiometric reaction of the catalyst resting state, when it can no longer maintain its steady-state concentration after the limiting substrate has been depleted.

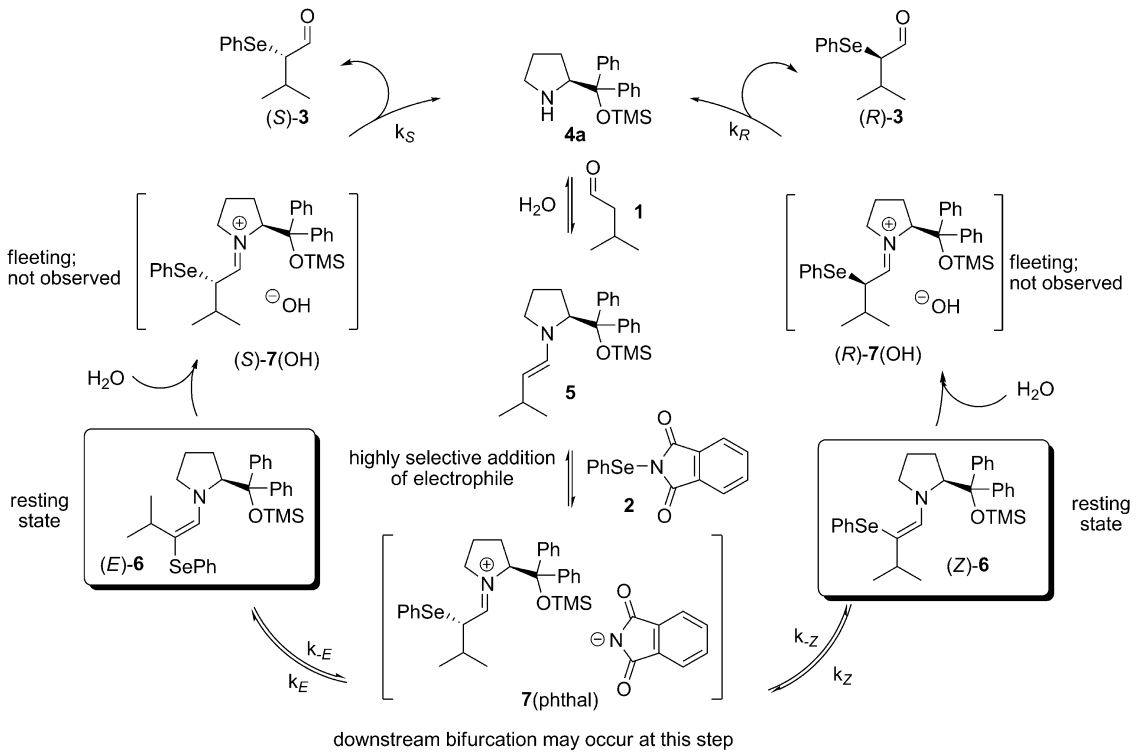
Scheme 4 helps to rationalize the observed inversion of enantiomeric excess in CD_2Cl_2 compared to that in [D_8]toluene by implicating (*E*)-**6** and (*Z*)-**6** as active intermediates in the pathways toward the opposite enantiomers of product **3**. As the sole intermediate observed in toluene, (*E*)-**6** leads to highly selective production of (*S*)-**3**. In CD_2Cl_2, (*Z*)-**6** is implicated as the species producing (*R*)-**3** by its faster decay compared to that of (*E*)-**6** and the concomitant reversal towards (*R*)-**3** as the major product. The enantiomeric ratio is given by the relative rates of the rate-determining reaction of the product enamines, as shown in Equation (1). This

$$\text{e.r.} = \frac{1+ee}{1-ee} = \frac{\text{rate}(R-(\mathbf{3}))}{\text{rate}(S-(\mathbf{3}))} = \frac{k_R}{k_S}\cdot\frac{[Z-(\mathbf{6})]}{[E-(\mathbf{6})]} \quad (1)$$

equation shows why the observed constant [(*E*)-**6**] and [(*Z*)-**6**] results in constant enantiomeric excess over the course of the reaction until the very last turnovers. For the reaction in CD_2Cl_2, the ratio of product enamine concentrations is approximately unity and k_R/k_S is given by the ratio of [(*Z*)-**6**]/[(*E*)-**6**] decay, which as shown in Figure 3b gives $k_R > k_S$. Thus the observed shift in *ee* value toward (*R*)-**3** in CD_2Cl_2 is rationalized by the relative concentrations and reactivities of the product enamines in the rate-determining step.

A mechanistic concept involving product enamines in the stereodetermining step requires the reactions of the enamines (*E*)-**6** and (*Z*)-**6** to lead selectively and irreversibly to (*S*)-**3** and (*R*)-**3**, respectively.[12] This concept of kinetic stereospecificity in enamine-based catalysis was proposed by us[3b,d] as part of our studies of the conjugate addition of aldehydes to nitro olefins using catalysts such as **4a**, based on NMR evidence of the stereospecific hydrolysis of product enamines. Analogous species were invoked in a further example, although not observed experimentally, in our mechanistic rationale of the α-chlorination of aldehydes. The current selenylation case further supports this reaction pathway and provides the first direct experimental observation of the role of product enamines in the steady-state catalytic cycle. The irreversibility of product formation from **6** is supported by the fact that neither racemization of **3** nor formation of (*E*)-**6** or (*Z*)-**6** is observed even when the product mixture is left in contact with the catalyst for extended periods after the reaction is finished.[10]

Calculations reveal that (*Z*)-**6** is intrinsically more stable than (*E*)-**6** by 1.43 kcal mol^{-1} in the gas phase [M062X/6-311 + G(2df,p)//B3LYP/6-311G(d,p)].[10] This energy difference was found to change with inclusion of solvent (by CPCM), to 0.51 kcal mol^{-1} in toluene and 0.07 kcal mol^{-1} in CH_2Cl_2. The observation of (*E*)-**6** as the sole intermediate in toluene, despite the computed greater thermodynamic stability of (*Z*)-**6**, and the high enantioselectivity to product (*S*)-**3** suggest that the iminium **7**(phthal) with a phthalimide counterion may exhibit an intrinsic kinetic preference to form (*E*)-**6**. NMR-EXSY data indicate that interconversion occurs between (*E*)-**6** and (*Z*)-**6** in CD_2Cl_2, although at a rate slower than that of the reaction so that (*E*)-**6** and (*Z*)-**6** are not fully equilibrated during the reaction, in accordance with the observed change in their relative concentrations during the final stoichiometric portion of the reaction.



Scheme 4. Proposed reaction network illustrating selectivity control by intermediates formed downstream from addition of electrophile.

The fact that (*Z*)-**6** is not observed in toluene suggests that the (*E*)-**6**/(*Z*)-**6** interconversion may be suppressed in nonpolar compared to polar solvents. Increased solvent polarity may stabilize the transition state leading back to the charged iminium ion intermediate **7**(phthal), essentially making the reverse pathway from **6** to **7**(phthal) more accessible. This reversibility facilitates the bifurcation in the reaction pathway shown in Scheme 4 which leads to erosion of the kinetic enantioselectivity toward (*S*)-**3** via (*E*)-**6**. Hydrolysis of the product enamines proceeds through an iminium ion, (*S*)-**7**(OH) or (*R*)-**7**(OH), which is distinct from **7**(phthal) by being counterbalanced by a hydroxy group instead of the original phthalimide, and is present in fleeting concentration post rate-determining step. In this scenario, low (and inverted) product enantioselectivity in polar solvents would be attributed not to low (or inverted) facial selectivity in the stereogenic bond-forming step shown in the steric model of Scheme 1, which is indeed highly stereoselective, but instead to the downstream interchange of intermediates which react to give opposite products. Thus the prediction of the initial enamine–electrophile encounter based on catalyst bulk as shown in Scheme 1 is accurate but does not account for the downstream partitioning of the pathway, partitioning which can lead to erosion, and indeed inversion, of enantioselectivity, as highlighted in this example.[13]

This rationale suggests that proper choice of reaction conditions can improve ultimate product selectivity by suppressing the driving force towards equilibration between downstream intermediates on opposing pathways. High enantioselectivity was achieved here by employing a nonpolar solvent, but the choice in the electrophile counterion may also play a role in enhancing the reversibility of the reactions of the iminium cation, which leads to the downstream bifurcation of pathways. The choice of counterion has been demonstrated to affect stability in stoichiometric studies by Seebach and co-workers.[14] The nature of the counterion may also be a factor in the difference in efficacy of electrophiles observed in MacMillan's imidazoldinone-catalyzed α-chlorination of aldehydes, where enantioselectivity was dramatically increased when *N*-chlorosuccinimide was replaced with 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one.[15] We have identified stable downstream species which form with the former but not with the latter.[10] Enhanced enantioselectivity using the quinone chlorinating agent in that case may be attributed not to a difference in selectivity in the Cl addition step but rather to a lack of formation of stable intermediates downstream from this step.

In summary, identification of active catalytic intermediates along with in situ monitoring of their reaction progress by NMR spectroscopy permits the rationalization of an unusual solvent-induced inversion of enantiomeric excess in the organocatalytic α-selenylation of aldehydes. The initial high selectivity at the enamine electrophile reaction step may be eroded by competition between two intermediates, formed downstream from this step, which react at different rates to form opposite enantiomeric products. This work provides further insights into the mechanism of enamine catalysis in cases where the generally accepted transition-state model of Scheme 1 proves to be necessary but not sufficient in rationalizing the observed stereochemical outcome. Reaction design and optimization might be accelerated by consideration of the kinetics and thermodynamics of the formation

and reaction of stable intermediates formed subsequent to the stereogenic bond-forming step.

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