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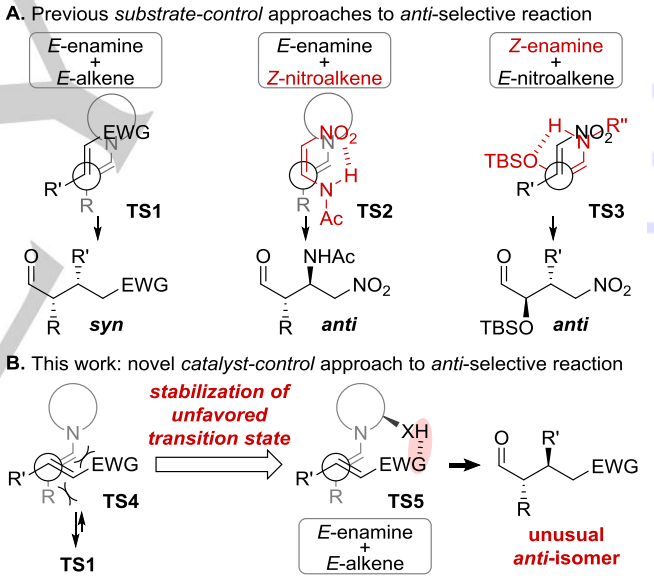
Catalyst-Controlled, Enantioselective and Diastereodivergent Conjugate Addition of Aldehydes to Electron-Deficient Olefins

S. B. Jennifer Kan[a], Hiroki Maruyama[a], Matsujiro Akakura[b], Taichi Kano*[a] and Keiji Maruoka*[a]

Abstract: A chiral amine-catalyzed, enantioselective and diastereodivergent method for aldehyde addition to electron deficient olefins is presented. Hydrogen bonding was used as a control element to achieve unusual *anti*-selectivity, which was further elucidated through mechanistic and computational studies.

Catalyst-controlled enantio- and diastereoselective reactions are valuable tools in asymmetric synthesis as chiral molecules possessing two or more stereocenters can be prepared in a single step. Ideally, given a set of reactants, access to any stereochemical permutations of the product could be achieved both predictably and selectively. While enantiomers can be synthesized by choosing the appropriate enantiomeric form of a chiral catalyst, preparing any diastereomer at will is substantially more difficult as the inherent diastereomeric bias of the substrate(s) need to be harnessed or overcome depending on the need.[1] This challenge has been addressed by changing the reaction solvents or additives, employing a combination of catalysts in tandem or cooperatively, or by using distinct catalysts that have complementary selectivity preferences.[1] On the other hand, chiral small-molecule catalysts have seldom been rationally engineered to switch diastereomeric specificities.[2] This is in contrast to how enzymes achieve complementary diastereocontrol in biocatalytic reactions, which can be attained through single amino acid mutations in the active site.[3]

We describe herein our studies on engineering chiral amine catalysts for diastereodivergent, asymmetric reactions; specifically, we present our findings in the context of conjugate addition of aldehydes to electron-deficient olefins. Catalytic asymmetric conjugate addition of carbon nucleophiles to electron-deficient alkenes is a fundamental carbon-carbon bond forming reaction in synthetic chemistry. The use of aldehydes as nucleophiles in this reaction is made possible through enamine formation in the presence of a chiral amine catalyst. The vast majority of these amine-catalyzed transformations involve reaction between an (*E*)-enamine intermediate and an (*E*)-olefin to give *syn*-conjugate adduct as the major diastereomer. The selectivity of this process is governed by an acyclic synclinal transition state, wherein minimal steric strain and close proximity between the enamine nitrogen and the electron-withdrawing group of the Michael acceptor are favored (**TS1**, Scheme 1A).[4] To reverse the stereochemical preference of this reaction to favor the *anti*-adduct, *substrate control* has previously been exploited, using either specific (*Z*)-olefins as acceptors (**TS2**),[5] or siloxyacetaldehydes as nucleophiles which form (*Z*)-enamines in the presence of a primary amine catalyst (**TS3**).[6] On the other hand, examples of *catalyst-controlled anti*-selective conjugate addition between simple aldehydes and (*E*)-alkenes are scarce and limited in scope.[7,8] We postulated that a conceptually different approach to achieving *anti*-selectivity could be through **TS5** (Scheme 1B), wherein a suitably positioned hydrogen bond donor is engineered to the amine catalyst to stabilize an otherwise high energy transition state **TS4**.[9] We were pleased that incorporating this logic into the design of axially chiral biaryl-based amine catalyst[10] transformed parent catalyst (*S*)-**1**, which preferentially give *syn*-products in the conjugate addition of aldehydes to enones,[11] into (*S*)-**2**,[12] a catalyst capable of delivering *anti*-product **4a** in 2.8/1 dr and excellent enantioselectivity (96% ee) (Scheme 2).



Scheme 1. Stereoselective conjugate addition of aldehydes to electron-deficient olefins *via* enamine catalysis.

With lead catalysts (*S*)-**1** and (*S*)-**2** in hand, we then set out to optimize the reactions (Scheme 3). Conjugate addition of propanal to enone **3a** under the influence of an appropriate amine catalyst gave the Michael-adduct, which underwent (*E*)-selective olefination to give **5a**. Modification of the *syn*-catalyst backbone led to the identification of (*S*)-**7** as the optimal catalyst, which performed best in toluene. Optimization of the *anti*-selective reaction revealed that catalyst (*S*)-**8**, which possessed hydroxydiphenylmethyl groups similar to (*S*)-**2** but owned a biaryl backbone that is more electron rich and smaller in dihedral angle, was more reactive and exhibited moderate *anti*-selectivities at low temperatures. The reaction catalyzed by (*S*)-**8** was *anti*-selective

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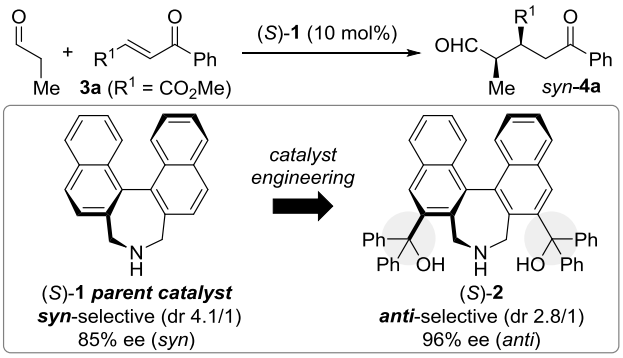
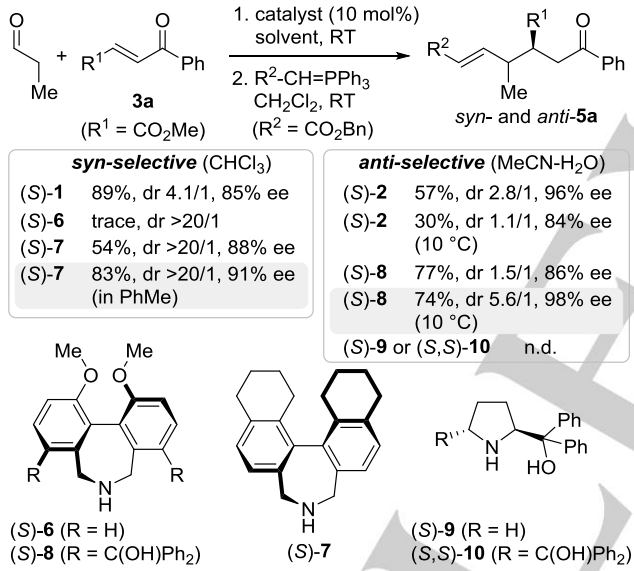


Scheme 2. Switching the diastereomeric specificity of axially chiral amine catalyst.

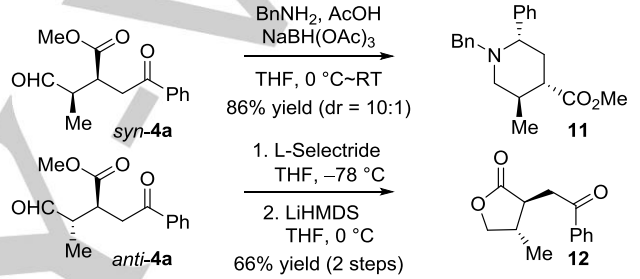
in all solvents examined, regardless of the polarity and hydrogen bonding ability of the solvents.[13] Other pyrrolidine-based catalysts gave either no desired product ((*S*)-**9** and (*S*,*S*)-**10)** or only trace amount of the *syn*-adduct (L-proline).



Scheme 3. Selected optimization studies of *syn*- and *anti*-selective conjugate addition.

With these procedures in hand, the reaction scope was investigated (Table 1). The *syn*-selective reaction catalyzed by (*S*)-**7** generally proceeded cleanly and competing self-aldol was not observed (condition A). The reaction accommodated a broad range of aldehydes (*syn*-**5a**−**5e**) and electron deficient olefins (*syn*-**5f**−**5m**). Unsymmetrical ketones preferentially react at the site β to the aromatic ketone as expected from the inherent kinetic regioselectivity of the substrate. Reaction with enal provided conjugate adduct (*syn*-**5n**) *exclusively* in 84% yield and 89% ee.[14] The current protocol is not compatible with less reactive acrylate and thio-acrylate (*syn*-**5o** and **5p**). The *anti*-selective reaction catalyzed by (*S*)-**8** was explored using some of the same set of reactants (condition B). In all cases, diastereoselectivity switch was observed despite moderate *anti*-selectivities and the enantioselectivities were uniformly excellent. The reaction with enal was chemoselective, yielding *anti*-**5n** in 72% yield and good selectivities. In both *syn*- and *anti*-selective reactions, reduced catalyst loading (5 mol%) was tolerated (*syn*- and *anti*-**5a**). Interestingly, (*Z*)-olefins could also be used for this chemistry as they undergo catalyst-mediated (*Z*) to (*E*) isomerisation *in situ*, yielding products of similar selectivities to those prepared from (*E*)-**3**.[13] The absolute configuration of the products was assigned by derivatization to known compounds.[13]

The *syn*- and *anti*-conjugate adducts are versatile building blocks for generating skeletal and stereochemical diversity. For example, reductive amination of *syn*-**4a** provided access for piperidine **11** bearing three non-contiguous stereocenters in 86% yield with good diastereoselectivity (Scheme 4). On the other hand, a reduction-lactonization sequence could be used to transform *anti*-**4a** to γ-lactone **12**.



Scheme 4. Synthesis of Piperidine **11** and γ-Lactone **12** from *syn* and *anti*-**4a**.

To account for the selectivities of the conjugate addition reaction, mechanistic and computational studies were carried out. Retro-conjugate addition was found not to be in operation under the reaction conditions, as crossover experiment did not yield any scrambled product (Scheme 5A). Epimerization studies suggested that while the *anti*-selective catalyst (*S*)-**8** could epimerize the aldehyde α-chiral center, this process could not shift the equilibrium to favor *anti*-**4a** as the major diastereomer (Scheme 5B). Taken together, these observations indicate that the *anti*-selectivity observed in conjugate addition most likely originated from the carbon-carbon bond formation step. Variants of catalyst (*S*)-**8** were next employed to probe the role of the hydroxydiarylmethyl groups in directing *anti*-selectivity. Interestingly, while des-hydroxy catalyst (*S*)-**14** and bis-*O*-methyl-protected catalyst (*S*)-**15** were both inactive, catalyst (*S*)-**16** with only one of the two alcohol moieties methylated was able to deliver the *anti*-product in 95% ee, albeit at a slower rate compared to its diol counterpart (Scheme 5C).[15]

DFT calculations for the (*S*)-**8** catalyzed reaction between propanal and enone **3a** was performed at the B3LYP/6-31G(d) level. This confirmed that the *anti*-selective reaction pathway is indeed more favorable than its *syn*-counterpart,[13] and that at least one hydrogen bonding interaction between the enone carbonyl oxygen and the alcohol moiety of catalyst (*S*)-**8** is present in the lowest lying *anti*-transition states (**TS6** and **TS7**, Figure 1).[13] This spatial arrangement dictates the facial selectivity of the electrophile, while at the same time renders the enamine *Re*-face

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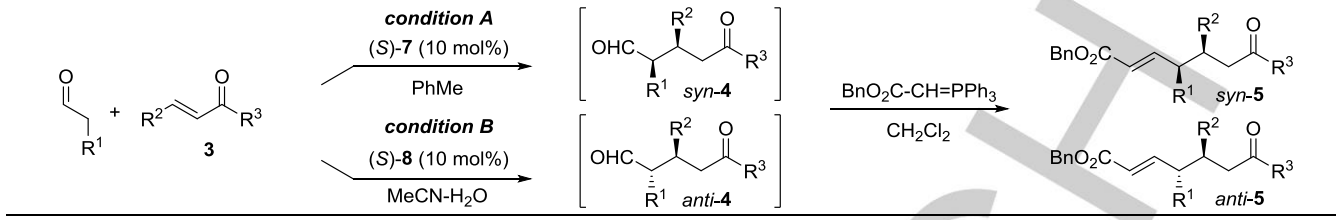
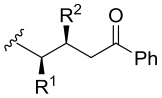
Table 1. Scope of *syn*- and *anti*-selective conjugate addition of aldehydes to electron deficient olefins.[a,b]

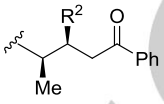


***syn*-selective (condition A)**



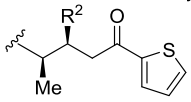
(R^2 = CO_2Me)

syn-**5a**	R^1 = Me	83%, dr >20/1, 91% ee (88%, dr 20/1, 91% ee)[c]
syn-**5b**	R^1 = Et	81%, dr >20/1, 91% ee
syn-**5c**	R^1 = Bu	89%, dr >20/1, 91% ee
syn-**5d**	R^1 = CH_2*i*-Pr	57%, dr 17/1, 85% ee
syn-**5e**[d]	R^1 = Bn	74%, dr >20/1, 91% ee

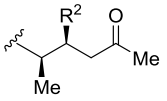


(R^2 = COR)

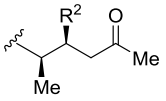
syn-**5f**	R = O*t*-Bu	74%, dr >20/1, 94% ee
syn-**5g**	R = SPr	59%, dr 14/1, 92% ee
syn-**5h**	R = Me	83%, dr 10/1, 90% ee
syn-**5i**	R = Et	53%, dr 13/1, 90% ee
syn-**5j**	R = Ph	80%, dr 13/1, 90% ee



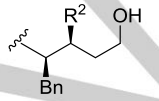
syn-**5k** (R^2 = CO_2Me)
83%, dr 14/1, 90% ee



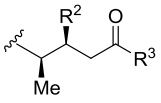
syn-**5l** (R^2 = CO_2Me)
55%, dr 11/1, 89% ee



syn-**5m** (R^2 = CO_2t-Bu)
61%, dr 16/1, 93% ee

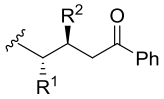


syn-**5n**[e] (R^2 = CO_2t-Bu)
84%, dr >20/1, 89% ee



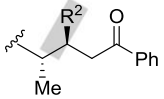
syn-**5o** (R^2 = CO_2Me, R^3 = OMe) n.d.
syn-**5p** (R^2 = CO_2Me, R^3 = SPr) n.d.

***anti*-selective (condition B)**

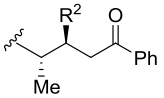


(R^2 = CO_2Me)

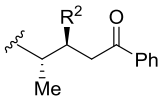
anti-**5a**[f]	R^1 = Me	74%, dr 5.6/1, 98% ee (83%, dr 4.2/1, >99% ee)[c]
anti-**5b**[g]	R^1 = Et	75%, dr 6.1/1, 98% ee
anti-**5c**[g]	R^1 = Bu	70%, dr 3.7/1, 97% ee
anti-**5e**[g]	R^1 = Bn	87%, dr 2.5/1, 98% ee



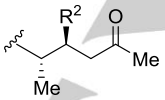
anti-**5f**[f] (R^2 = CO_2t-Bu)
84%, dr 3.1/1, 98% ee



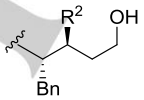
anti-**5i** (R^2 = COEt)
32%, dr 13/1, 95% ee



anti-**5j**[h] (R^2 = COPh)
78%, dr 3.2/1, 96% ee



anti-**5m** (R^2 = CO_2t-Bu)
53%, dr 2.4/1, 98% ee



anti-**5n**[e] (R^2 = CO_2t-Bu)
72%, dr 3.9/1, 97% ee

[a] Condition A: the reaction between aldehyde (2 equiv) and enone (1 equiv) was carried out in the presence of (*S*)-**7** (10 mol%) in toluene (0.5 M) for 4 to 72 h. Condition B: the reaction between aldehyde (2 equiv) and enone (1 equiv) was carried out in the presence of (*S*)-**8** (10 mol%) in MeCN-H_2O (1:1, 0.25 M) for 6 to 72 h. [b] Combined yield of *syn*- and *anti*-**5** over 2 steps. Dr determined by ^{1}H NMR. % Ee of the major diastereomer as determined by chiral HPLC. [c] The reaction was performed on 1 mmol scale using 5 mol% of catalyst. [d] Using 1.5 equiv of aldehyde. [e] Using 1 equiv of aldehyde and 2 equiv of enal. The conjugate addition adduct was reduced *in situ* ($NaBH_4$/MeOH) to give the corresponding diol. [f] Reaction performed at 10 °C. [g] Reaction performed at 0 °C. [h] Reaction concentration was 0.125 M.

more susceptible to react for proximity reason, consistent with the major (2*S*,3*S*)-isomer obtained experimentally. The transition state of the (*S*)-**7** catalyzed reaction was B3LYP/6-31G(d) optimized and found to be following a typical acyclic synclinal model (**TS8**). This is further stabilized by non-bonding interaction between the catalyst nitrogen atom and the α-carbon of the enone, as well as hydrogen bonding between the catalyst benzylic proton and the carbonyl oxygen atom of the electron withdrawing group at the β-position of the enone. The latter non-classical interaction is reminiscent of that found between ammonium salts and carbonyl compounds.[16]

We have identified two complementary catalysts suitable for the enantioselective and diastereodivergent conjugate addition of aldehydes to electron-deficient olefins. Hydrogen bonding was used as a control element to achieve unusual *anti*-selectivity, which was further elucidated through mechanistic and computational studies. Despite moderate *anti*-selectivity and limited substrate scope at this stage, the present approach showed potential for obtaining unusual stereoisomers.

Acknowledgements

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Keywords: stereodivergence • Michael addition • asymmetric catalysis • aldehydes • organocatalysis

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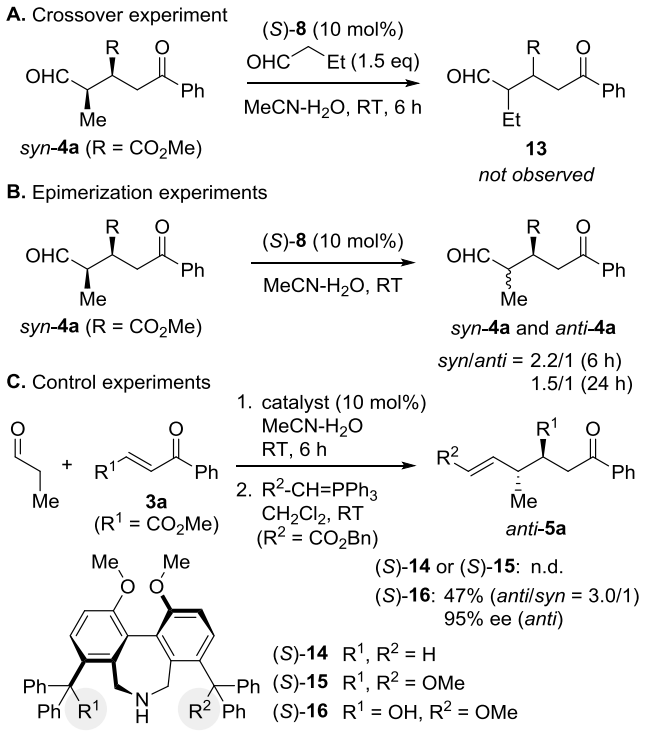

Scheme 5. Mechanistic studies.

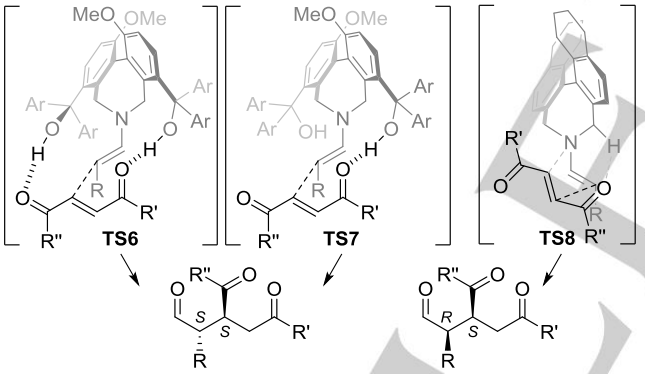

Figure 1. Proposed transition state models.

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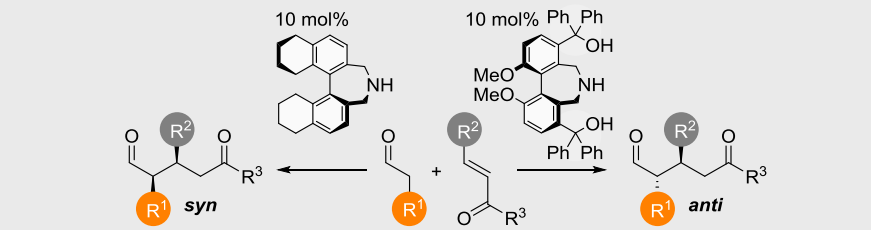

Diastereoswitch: A chiral amine-catalyzed, enantioselective and diastereodivergent method for aldehyde addition to electron deficient olefins is presented. Hydrogen bonding was used as a control element to achieve unusual *anti*-selectivity, which was further elucidated through mechanistic and computational studies.

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