Asymmetric Catalysis

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Rationally Designed Multifunctional Supramolecular Iminium Catalysis: Direct Vinylogous Michael Addition of Unmodified Linear Dienol Substrates**

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Abstract: *The development of a direct vinylogous Michael addition of linear nucleophilic substrates is a long-standing challenge because of the poor reactivity and the considerable difficulty in controlling regioselectivity. By employing a rationally designed multifunctional supramolecular iminium catalysis strategy, the first direct vinylogous Michael addition of unmodified linear substrates to α,β-unsaturated aldehydes, to afford chiral 1,7-dioxo compounds with good yields and excellent regio- as well as enantioselectivity, has been developed.*

The field of vinylogous addition is one of the most dynamic and synthetically powerful areas in contemporary organic synthesis.[1] A broad range of organocatalytic, highly regioselective as well as stereoselective vinylogous Michael addition reactions have been successfully established.[2] Despite these significant advances, however, nearly all of these approaches are restricted to the use of cyclic vinylogous substrates which have good reactivity and a strong preference for the γ-selectivity (Figure 1 a).[2] For these substrates, at least one of the electron-rich double bonds needs to be incorporated in the ring systems. Owing to the poor reactivity and difficulty of controlling regioselectivity (γ versus α addition), the development of vinylogous Michael additions of linear substrates remains elusive. Recently, Schneider et al. elegantly developed the first Mukaiyama-type vinylogous Michael addition of rationally designed linear substrates to α,β-unsaturated aldehydes (Figure 1 b).[3] To date, however, a direct approach involving linear nucleophilic vinylogous substrates is unprecedented and further exploration in this direction is highly desired. In contrast to the indirect approach, the development of a direct approach will lead to different reaction mode, that is, a catalyst-controlled reaction as opposed to a substrate-controlled or substrate-influenced reactivity and regioselectivity (Figure 1 c).

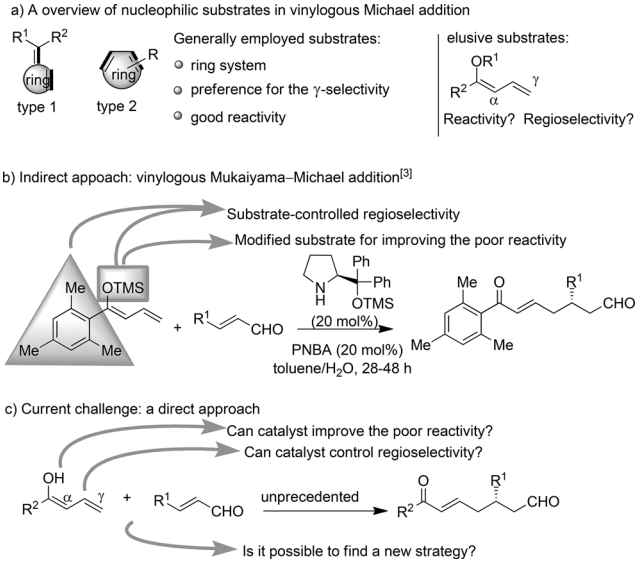

Figure 1. Different approaches for vinylogous Michael addition.

Initially, by employing a traditional strategy, we have investigated numerous different reaction conditions including catalysts, solvents, and additives etc. (for some typical reaction conditions, see Table 1). Disappointingly, only very low conversion and poor regioselectivity were obtained in all cases.

Recently, we established the concept of supramolecular iminium catalysis which can significantly activate iminium ions.[4] We envisioned that a rationally designed multifunctional supramolecular iminium catalysis strategy might be able to address the reactivity and regioselectivity issues in the direct vinylogous Michael addition of linear dienols to α,β-unsaturated aldehydes (Figure 2). By employing this triple-activation strategy, α,β-unsaturated aldehydes can be activated by the in situ generated iminium ion while vinylogous substrates can be activated and stabilized by anion-binding interactions. In taking a global view of the catalytic system, the supramolecular iminium ion will further activate the reaction by generating an ion-pair-separated, and more reactive iminum ion, in higher concentration. Meanwhile, the iminium catalyst could control enantioselectivity while the anion-binding catalyst could govern regioselectivity by shielding the α position of the vinylogous substrates.

Initially, the allylic ketone **1a** and cinnamaldehyde (**2a**) were used to test the feasibility of our hypothesis (Table 2). The addition of hydrogen-bonding catalysts such as **6a** and **6b** improved the conversion, albeit with no improvement in the

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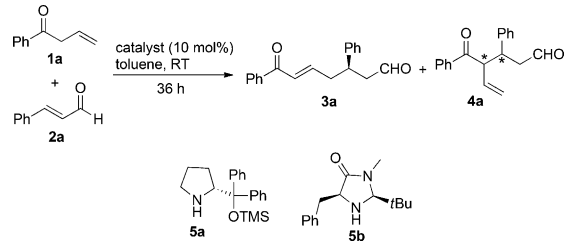
Table 1: Initial screening of reaction conditions.[a]



Entry	Cat.	Additive (10 mol%)	γ/α (**3a**/**4a**)[b]	Yield [%][c]	*ee* [%][d]
1	**5a**	–	2:1	15	98
2	**5a**	PhCOOH	2:1	18	98
3[e]	**5a**	CF_3COOH	–	trace	–
4	**5a**	TEA	1:1	<10	97
5	**5a**	DABCO	1:1	<10	98
6	**5b**	–	–	trace	–

[a] The reactions were carried out with **1a** (0.2 mmol), **2a** (0.2 mmol), **5** (10 mol%), and a cocatalyst (10 mol%) in 1.0 mL toluene at room temperature. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of isolated **3a**. [d] Determined by HPLC analysis, using a chiral stationary phase, by converting the product into an ester using $Ph_3PCHCOOMe$. [e] The addition of other acids such as CF_3SO_3H and HCl did not show reactivity. DABCO = 1,4-diazabicyclo[2.2.2]octane, TEA = triethylamine, TMS = trimethylsilyl.

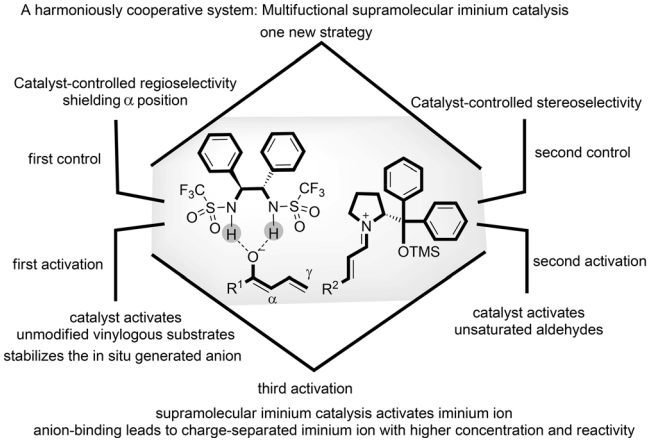
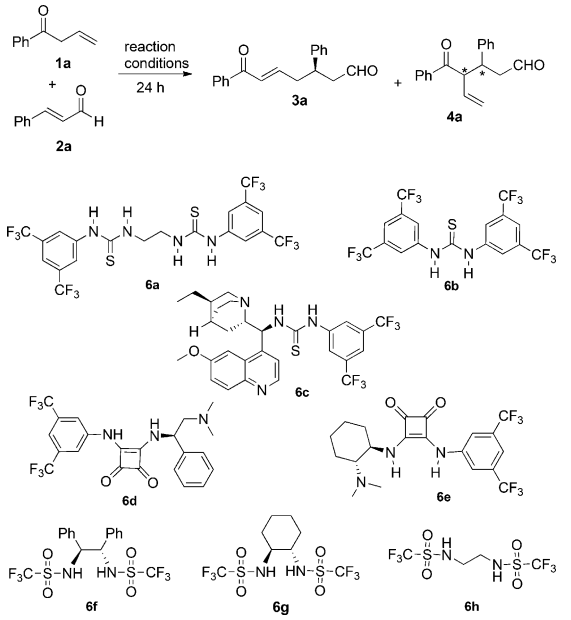


Figure 2. Strategy for the direct vinylogous Michael addition of linear dienol.

regioselectivity (entries 1 and 2). Bifunctional cocatalysts (**6c–e**) did not show good reactivity. To our delight, the use of the catalyst **6f** led to a very encouraging yield with good regioselectivity and excellent enantioselectivity (entry 6). However, using **6g** and **6h** resulted in lower yields and selectivities. The combination of the catalysts **5b** and **6f** did not show catalytic activity (entry 9). Next, different solvents were investigated and DCE was found to be an optimal one (entries 10–14). Further screening of the temperature showed 50 °C to be promising. When 1.5 equivalents of **2a** was used, a higher yield was obtained with the same excellent selectivity (entry 18). Furthermore, the reaction worked equally efficient upon reducing the loading of catalyst **6f** to 5 mol% (entry 19). However, employing 2 mol% of **6f** led to a drop in

Table 2: Screening of reaction conditions.[a]



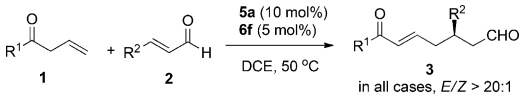
Entry[a]	Catalyst	*T* [°C]	Solvent	Yield [%][b]	γ/α[c] (**3a**/**4a**)	*ee* [%][d]
1	**5a**+**6a**	RT	toluene	27	1:1.7	95
2	**5a**+**6b**	RT	toluene	43	1.2:1	98
3	**5a**+**6c**	RT	toluene	30	1:1	99
4	**5a**+**6d**	RT	toluene	18	1.4:1	n.d.
5	**5a**+**6e**	RT	toluene	33	1.2:1	93
6	**5a**+**6f**	RT	toluene	63	5.4:1	97
7	**5a**+**6g**	RT	toluene	44	2:1	95
8	**5a**+**6h**	RT	toluene	33	2.2:1	93
9	**5b**+**6f**	RT	toluene	<10	–	–
10	**5a**+**6f**	RT	CH_2Cl_2	56	15:1	92
11	**5a**+**6f**	RT	DCE	72	>20:1	95
12	**5a**+**6f**	RT	hexane	trace	n.d.	–
13	**5a**+**6f**	RT	EtOH	12	n.d.	–
14	**5a**+**6f**	RT	xylene	60	4.6:1	97
15	**5a**+**6f**	40	DCE	78	>20:1	95
16	**5a**+**6f**	50	DCE	82	>20:1	95
17	**5a**+**6f**	60	DCE	80	>20:1	93
18[e]	**5a**+**6f**	50	DCE	87	>20:1	95
19[e,f]	**5a**+**6f**	50	DCE	88	>20:1	95
20[e,g]	**5a**+**6f**	50	DCE	72	>20:1	93
21[e]	**5a**	50	DCE	22	2:1	97

[a] Unless otherwise noted, all the reactions were carried out with **1a** (0.2 mmol), **2a** (0.2 mmol), **5** (10 mol%), and **6** (10 mol%) in 1.0 mL solvent as indicated at room temperature (about 18 °C) for 24 h. [b] Yield of the isolated γ-addition product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis using a chiral stationary phase. [e] 1.5 equiv **2a** was used. [f] 5 mol% **6f** was used. [g] 2 mol% **6f** was used. DCE = 1,2-dichloroethene, n.d. = not determined.

the yield and enantioselectivity (entry 20). In sharp contrast, in the absence of **6f**, only 22% yield and poor regioselectivity (γ/α 2:1, entry 21) were obtained.

With the optimized reaction conditions, substrate scope was investigated next. The allylic ketone **1** allowed incorporation of a wide range of substitutions into the desired products (Table 3). Aromatic substituents bearing both electron-withdrawing and electron-donating groups, as well as

Table 3: Substrate scope.[a]



Entry	R^1	R^2	*t* [h]	γ/α[b]	Yield [%][c]	*ee* [%][d]
1	Ph	Ph	20	>20:1	88 (**3a**)	95
2	2-ClC_6H_4	Ph	36	13:1	71 (**3b**)	87
3	3-ClC_6H_4	Ph	18	>20:1	86 (**3c**)	94
4	4-ClC_6H_4	Ph	20	>20:1	82 (**3d**)	93
5	2-FC_6H_4	Ph	15	>20:1	91 (**3e**)	94
6	2-BrC_6H_4	Ph	36	>20:1	66 (**3f**)	86
7	4-$MeOC_6H_4$	Ph	20	15:1	77 (**3g**)	96
8	2-MeC_6H_4	Ph	22	>20:1	75 (**3h**)	91
9	3-MeC_6H_4	Ph	17	>20:1	80 (**3i**)	96
10	4-MeC_6H_4	Ph	16	>20:1	87 (**3j**)	96
11	Piperonyl	Ph	22	>20:1	72 (**3k**)	97
12	3,4-$Me_2C_6H_3$	Ph	21	>20:1	70 (**3l**)	95
13	Ph	2-ClC_6H_4	16	>20:1	83 (**3m**)	96
14	Ph	3-BrC_6H_4	18	>20:1	90 (**3n**)	96
15	Ph	4-$NO_2C_6H_4$	18	>20:1	92 (**3o**)	94
16	Ph	4-CNC_6H_4	24	>20:1	78 (**3p**)	96
17	Ph	3,4-$Me_2C_6H_3$	17	>20:1	72 (**3q**)	94
18	Ph	3-MeC_6H_4	30	>20:1	77 (**3r**)	95
19	Ph	2-MeC_6H_4	20	>20:1	84 (**3s**)	97
20	Ph	furyl	24	5:1	80 (**3t**)	86
21	*c*-C_6H_{11}	Ph	24	4:1	53 (**3u**)	95
22	*n*-C_6H_{13}	Ph	18	4:1	45 (**3v**)	95
23[e]	Ph	Ph	24	>20:1	82 (**3a**)	96

[a] See the Supporting Information. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of the isolated γ-addition product. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Gram scale (**1a**, 10 mmol, 1.46 g; see the Supporting Information).

those with various substituents at the *ortho*, *meta*, and *para* positions, were all tolerated. The aliphatic substituents could also betolerated and the products were obtained with moderate yields and good selectivities (entries 21 and 22). The α,β-unsaturated aldehyde **2** could be varied and both electron-rich and electron-poor substrates with substituents at different positions worked effectively to provide products with good yields and excellent selectivities. However, aliphatic-group-substituted aldehydes did not work well under the optimized reaction conditions. A heteroaromatic group could also be employed and afforded the adduct **3t**, albeit with lower regio- and enantioselectivity. The absolute configuration was determined by comparing the optical rotation of the product with that of the reported compound (see the Supporting Information).[3] Furthermore, the reaction was amendable to gram-scale synthesis (entry 23).

In the absence of **6f**, only 22% yield and 2:1 γ/α selectivity were obtained. When using acids without anion-binding capabilities, poor yields and regioselectivities resulted (Table 1, entries 2 and 3). When the reaction was performed using racemic **5a** and **6f**, the adduct **3a** was obtained with dramatically improved yield (70%) and regioselectivity (>20:1; Figure 3). These control experiments demonstrated that cooperative catalysis gives rise to both of the reactivity and selectivity. When **5a** and the enantiomer of **6f** were employed, the desired product **3a** was obtained with much lower yield (Figure 3). This observation indicates that there is

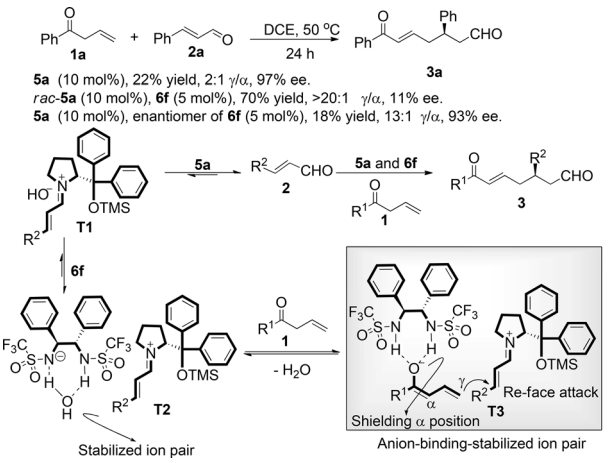


Figure 3. Proposed reaction pathway.

a matched and mismatched combination of the chiral catalyst pair. The very low concentration of **T1** made it difficult to observe this intermediate by ^{1}H NMR spectroscopy in C_6D_6. In sharp contrast, however, upon addition of **6f** to the mixture of **5a** and **2a**, the color of the reaction mixture changed immediately and a high concentration of the iminium ion was generated (see the Supporting Information). Anion binding has been heavily involved in enzyme catalysis and recently emerged as an attractive strategy in artificial catalysis.[5] Jacobsen et al. observed that the addition of a thiourea cocatalyst improves the reactivity and enantioselectivity for [5+2] cycloadditions of cationic oxidopyrilium ions.[6] Our previous study revealed that it is difficult to form a measurable concentration of iminium ion without the assistance of an anion-binding catalyst.[4] The deprotonation of **1a** will result in a reactive multifunctional supramolecular iminium **T3**. With the successful shielding of the α position of **1a** by **6f**, and the Si-face of the iminium ion by **5a**, a γ-selective, Re-face attack will afford **3.**

In summary, we have reported a new strategy for the direct vinylogous Michael addition of unmodified linear nucleophilic substrates. The desired 1,7-dioxo products were obtained with good yields and excellent selectivity. Conceptually, this is an attractive strategy for expanding the capability of supramolecular iminium catalysis, which has the potential to be a useful platform for studying how noncovalent interactions between ion pairs give rise to both of reactivity and selectivity.

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