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Peptide-catalyzed consecutive 1,6- and 1,4-additions of thiols to α,β,γ,δ-unsaturated aldehydes

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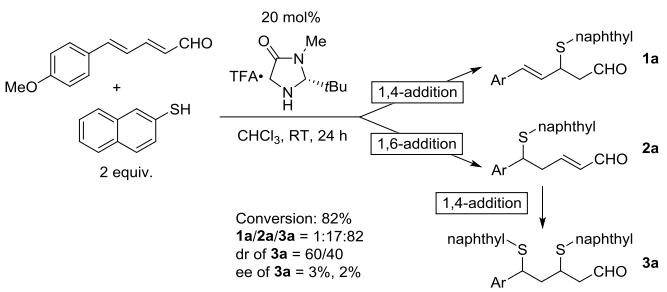
Regio- and enantioselective addition of thiols to α,β,γ,δ-unsaturated aldehydes was performed with a resin-supported peptide catalyst. It was shown that a 1,4-adduct was generated mainly at the initial stage of the reaction, and this was eventually converted to a thermodynamically stable 1,6- and 1,4-diadduct through retro-addition/addition reactions.

Asymmetric Michael addition of nucleophiles to α,β-unsaturated carbonyl compounds is one of the most powerful procedures for the synthesis of chiral molecules. Besides metal-catalyzed reactions,[1] a variety of asymmetric Michael additions by organocatalysts have been developed in recent years.[2,3] Among them, those proceed through the activation of carbonyl groups by chiral amine catalysts have been widely studied and offer a versatile method for utilizing various nucleophiles.[4] In such reactions, the formation of an iminium-ion intermediate between a catalyst and substrate promotes the nucleophilic addition by lowering the LUMO energy level of the π-conjugated system, which simultaneously controls enantioselectivity of the reaction.[5]

This type of organocatalytic addition has been applied to the substrates with extended π-systems, *e.g.* α,β,γ,δ-unsaturated carbonyl compounds. With such substrates, the conjugate addition generally takes place in a 1,4-selective manner, which has been rationalized by calculation; both the π-orbital coefficient of the LUMO and the partial positive charge at the β-position of the iminium-ion intermediate are larger than those at the δ-position.[6] Concerning this, some attempts have been made to overturn the 1,4-preference of conjugate additions.[7,8] Melchiorre and co-workers achieved the 1,6-selective addition by using 3-alkenylcyclohexenones or 2,4-dienals with a bulky substituent at the β-position to suppress the 1,4-addition.[9] Jørgensen and co-workers employed cycloalkenylidene-substituted acetaldehydes as Michael acceptors.[10] The same group also used finely designed nucleophiles for attaining the 1,6-addition to linear 2,4-dienals.[11] In those examples, however, regiochemistry is governed by the intrinsic reactivity of substrates, thus, the scope of organocatalyzed 1,6-selective reactions is still limited.[12,13] Recently, we have reported the reaction system aiming for catalyst-controlled 1,6-regioselectivity. With a resin-supported peptide catalyst consisting of specific secondary structures, regio- and enantioselective reduction of α,β,γ,δ-unsaturated aldehydes was realized.[14–16] Because of the larger size of peptides compared to low-molecular-weight catalysts, the peptide catalysts are expected to be applied to a wide scope of reactions with π-extended substrates.

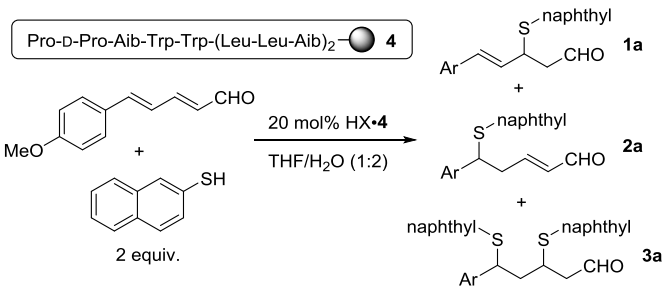


Scheme 1 Amine-catalyzed conjugate addition of a thiol to an α,β,γ,δ-unsaturated aldehyde.

Michael addition of thiols is useful for the synthesis of sulfur-containing biologically active compounds,[17] and some organocatalytic versions have appeared to date.[18] In 2005, Jørgensen and co-workers reported the asymmetric Michael addition of thiols to α,β-unsaturated aldehydes with a secondary amine catalyst.[19] When we tried this type of reaction using an α,β,γ,δ-unsaturated aldehyde in the presence of an imidazolidinone catalyst,[20] it was found that β,δ-diadduct **3a** was mainly obtained as a mixture of diastereomers (Scheme 1). As to the enantioselectivity, both diastereomers were nearly

racemic. Product **3a** is considered to be formed via consecutive 1,6- and 1,4-additions of two thiol molecules to the substrate aldehyde. This is interesting from the viewpoint that, in spite of using the linear 2,4-dienal, the 1,6-addition seemingly prevails over the intrinsic 1,4-preference of the addition to an iminium intermediate. To clarify the reaction mechanism and refine the reaction to an enantioselective version, we set out investigation for a peptide-catalyzed conjugate addition of thiols to α,β,γ,δ-unsaturated aldehydes.

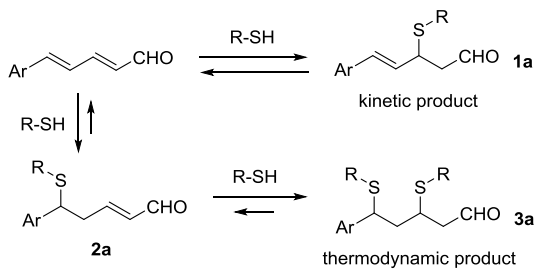
Table 1 Peptide-catalyzed thiol addition to an aromatic α,β,γ,δ-unsaturated aldehyde



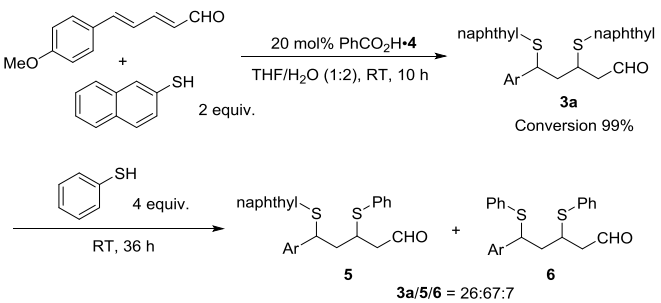
Entry	HX	*T* (°C)	*t* (h)	Conversion (%)	**1a**:**2a**:**3a**	dr of **3a**	ee (%) of **3a**
1	TFA	RT	24	83	2:22:76	57/43	29, –14
2	TFA	RT	3	67	50:7:43	57/43	52, 25
3	TFA	0	3	34	53:13:34	60/40	76, 66
4[a]	TFA	0	3	40	57:14:29	60/40	70, 59
5	TFA	0	10	70	29:39:32	63/37	72, 53
6	$PhCO_2H$	0	3	83	18:0:82	57/43	42, 15
7	TCA	0	3	29	30:4:66	58/42	62, 40
8[b]	TCA	0	24	76	6:3:91[c]	58/42	73, 58

[a] The non-supported peptide with a C-terminal amide was used. [b] Reaction was performed with 4 equiv. of 2-naphthylthiol in MeOH/H_2O (1:2). [c] Yield of the corresponding alcohol of **3a** was 54%.

Because of the high applicability for various enantioselective reactions, resin-supported peptide **4** was chosen as a catalyst.[21] With the trifluoroacetic acid (TFA) salt of this peptide, the reaction at room temperature for 24 h gave compound **3a** as a major product (Table 1, entry 1). Although the ee values were low, the reaction proceeded in a more enantioselective manner than the case with the low-molecular-weight organocatalyst. When the reaction time was shortened to 3 h under the same conditions, the distribution of the products and enantioselectivity of diadduct **3a** dramatically changed (Table 1, entry 2). Especially, the ratio of 1,4-adduct **1a** was considerably higher. This indicates that the 1,4-addition predominates at an initial stage of the reaction as reported earlier,[6] however, 1,4-adduct **1a** is eventually converted to thermodynamically most stable diadduct **3a** through repetition of retro-addition/addition reactions (Scheme 2).[19,22] The fact that elongating the reaction time decreased the enantioselectivity of product **3a** suggests the occurrence of retro-Michael reaction from diadduct **3a**. To confirm the retro-Michael/Michael addition process, the following experiment was conducted. After converting all reactants into diadduct **3a** in the presence of the peptide catalyst, a different thiol was added (Scheme 3). From the analysis of the resulting mixture after 36 h, it was revealed that thiol-exchanged products **5** and **6** were generated.[23] This demonstrates that the both 1,4- and 1,6-additions are reversible as depicted in Scheme 2. To obtain product **3a** in a regio- and enantioselective manner, it is essential to promote dissociation of 1,4-adduct **1a** while suppressing the retro-Michael addition from diadduct **3a**. When the reaction was conducted at 0 °C, higher enantioselectivity was attained despite low reaction rate and regioselectivity (Table 1, entry 3). At this temperature, prolonging the reaction could successfully increase the conversion without significant loss in enantioselectivity (Table 1, entry 5). As for the acid component of the catalyst, the use of benzoic acid instead of TFA mainly provided diadduct **3a**, however, the enantioselectivity was decreased (Table 1, entry 6). Moderate regioselectivity and enantioselectivity were observed with trichloroacetic acid (TCA) (Table 1, entry 7). Further optimization of reaction conditions such as the amount of the thiol, solvent, and time afforded compound **3a** as a major product with good regio- and enantioselectivity (Table1, entry 8).



Scheme 2 Proposed reaction pathway for generation of **3a**.

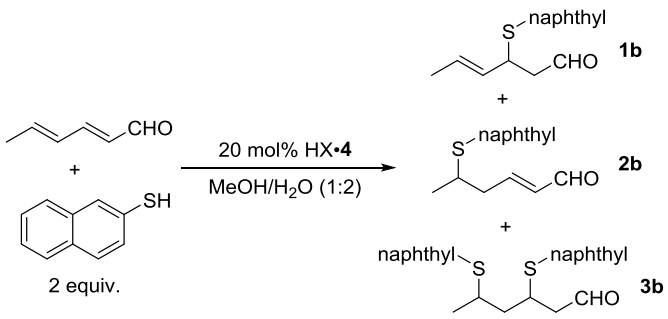


Scheme 3 Thiol-exchange reaction from diadduct **3a**.

Next, other combinations of substrates were tested for the peptide-catalyzed thiol addition to an α,β,γ,δ-unsaturated aldehyde. With an aliphatic 2,4-dienal instead of the aromatic one, the reaction proceeded smoothly to give diadduct **3b** as a major product in a poorly enantioselective manner (Table 2, entry 1). High regio- and enantioselectivity were attained at a low temperature, although the reaction was sluggish (Table 2,

entry 2). In this case, replacing TFA to benzoic acid was effective to enhance the reaction (Table 2, entry 3). Increasing the amount of the thiol and elongating the reaction time provided compound **3b** in good regio- and enantioselectivity (Table 2, entry 4). The similar tendency was observed with benzenethiol as a nucleophile. While the reaction with the benzoic acid salt of peptide **4** for 6 h was accompanied by a certain amount of 1,4-adduct **1c** (Table 3, entry 1), thermodynamic convergence into product **3c** occurred after 24 h with maintaining good enantioselectivity (Table 3, entry 2). The supported peptide catalyst recovered by filtration after the reaction could be reused at least three times without a significant loss in the catalytic ability (Table 3, entries 3 to 5).

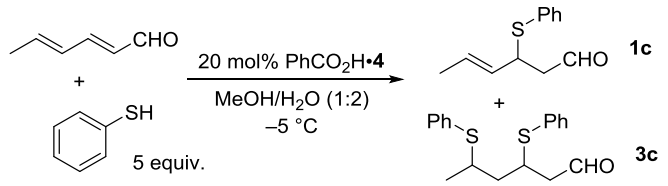
Table 2 Peptide-catalyzed thiol addition to an aliphatic α,β,γ,δ-unsaturated aldehyde



Entry	HX	*T* (°C)	*t* (h)	Conversion (%)	**1b**:**2b**:**3b**	dr of **3b**	ee (%) of **3b**
1[a]	TFA	RT	6	99	0:10:90	57/43	18, –6
2	TFA	–10	12	12	28:0:82	55/45	84, 55
3	$PhCO_2H$	–15	12	75	55:0:45	57/43	75, 38
4[b]	$PhCO_2H$	–15	20	76	22:0:78[c]	56/44	75, 44

[a] Reaction was performed in THF/H_2O (1:2). [b] Reaction was performed with 4 equiv. of 2-naphthylthiol. [c] Yield of the corresponding alcohol of **3b** was 28%.

Table 3 Convergence to a β,δ-diadduct by elongating the reaction time and reuse of the catalyst



Entry	reuse of peptide	*t* (h)	Conversion (%)	**1c**:**2c**:**3c**	dr of **3c**	ee (%) of **3c**
1	–	6	99	36:0:64	53/47	79, 42
2	–	24	99	2:0:98[a]	53/47	76, 54
3	1st reuse	24	99	0:0:100	53/47	74, 52
4	2nd reuse	24	99	0:0:100	53/47	78, 56
5	3rd reuse	24	99	2:0:98	52/48	79, 61

[a] Yield of the corresponding alcohol of **3c** was 65%.

Conclusions

Consecutive 1,6- and 1,4-additions of thiols to α,β,γ,δ-unsaturated aldehydes in an enantioselective way was realized with a resin-supported peptide catalyst. It was demonstrated that apparently good regioselectivity of the reaction was the result of the reversible nature of the thiol addition. To achieve high enantioselectivity, suppressing the racemization of the diadduct was essential, and the use of the peptide salt under optimum conditions was effective. Further application of the peptide catalyst for the reaction with π-extended systems can be expected.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra and HPLC traces. See DOI: 10.1039/c000000x/

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