Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 3581

Received 14th March 2014,
Accepted 17th April 2014

DOI: 10.1039/c4ob00565a

www.rsc.org/obc

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

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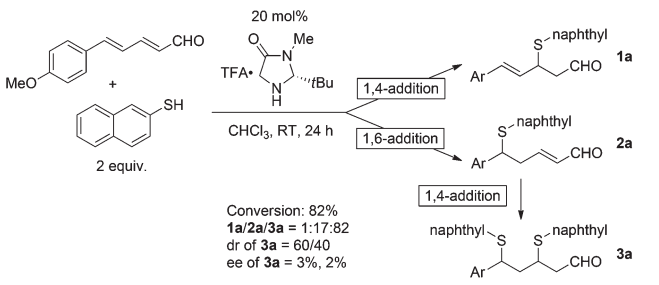
Regio- and enantioselective addition of thiols to α,β,γ,δ-unsaturated aldehydes was performed with a resin-supported peptide catalyst. It was shown that a 1,4-adduct was generated mainly at the initial stage of the reaction, and this was eventually converted to a thermodynamically stable 1,6- and 1,4-diadduct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

The 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 reactions which 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 a substrate promotes the nucleophilic addition by lowering the LUMO energy level of the π-conjugated system, which simultaneously controls the 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 range of reactions with π-extended substrates.

The 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 the 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



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

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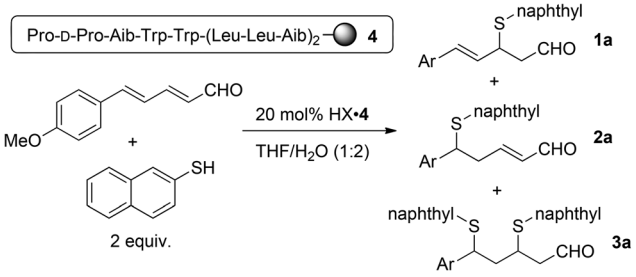
†Electronic supplementary information (ESI) available: Experimental details, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra and HPLC traces. See DOI: 10.1039/c4ob00565a

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

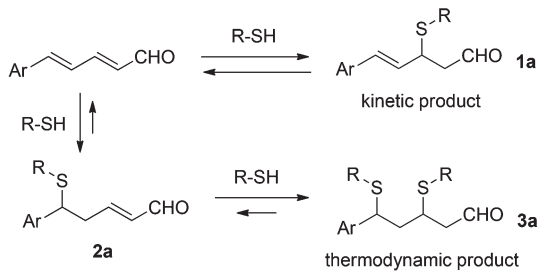


Entry	HX	T (°C)	t (h)	Conversion (%)	**1a : 2a : 3a**	dr of **3a**	ee (%) of **3a**
1	TFA	RT	24	83	2 : 22 : 76	57/43	29, −14
2	TFA	RT	3	67	50 : 7 : 43	57/43	52, 25
3	TFA	0	3	34	53 : 13 : 34	60/40	76, 66
4[a]	TFA	0	3	40	57 : 14 : 29	60/40	70, 59
5	TFA	0	10	70	29 : 39 : 32	63/37	72, 53
6	$PhCO_2H$	0	3	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

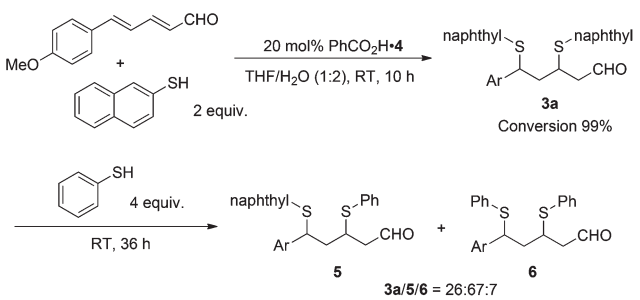
[a] The non-supported peptide with a C-terminal amide was used. [b] Reaction was performed with 4 equiv. of 2-naphthalenethiol in MeOH–H_2O (1 : 2). [c] The yield of the corresponding alcohol of **3a** was 54%.

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.

Because of the high applicability for various enantioselective reactions, the 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 the 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 the enantioselectivity of the diadduct **3a** dramatically changed (Table 1, entry 2). In particular, the ratio of the 1,4-adduct **1a** was considerably higher. This indicates that the 1,4-addition predominates at the initial stage of the reaction as reported earlier;[6] however, the 1,4-adduct **1a** is eventually converted to the 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 the product **3a** suggests the occurrence of the retro-Michael reaction from the diadduct **3a**. To confirm the retro-Michael/Michael addition process, the following experiment was conducted. After converting all reactants into the 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 both the 1,4- and 1,6-additions are reversible as



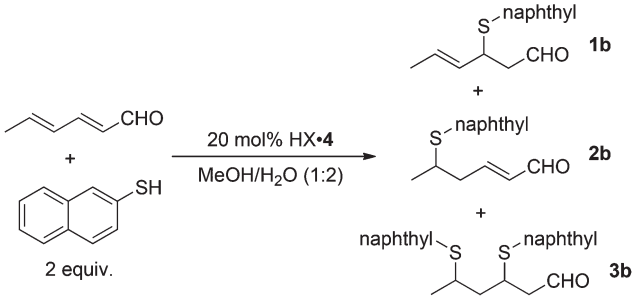
Scheme 2 Proposed reaction pathway for generation of **3a**.



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

depicted in Scheme 2. To obtain the product **3a** in a regio- and enantioselective manner, it is essential to promote dissociation of the 1,4-adduct **1a** while suppressing the retro-Michael addition from the 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

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



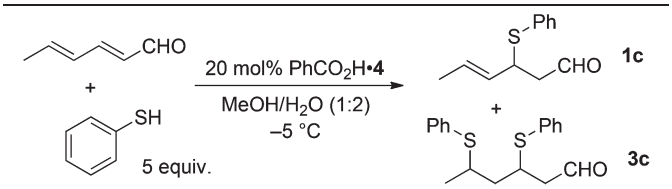
Entry	HX	T (°C)	t (h)	Conversion (%)	**1b : 2b : 3b**	dr of **3b**	ee (%) of **3b**
1[a]	TFA	RT	6	99	0 : 10 : 90	57/43	18, −6
2	TFA	−10	12	12	28 : 0 : 82	55/45	84, 55
3	$PhCO_2H$	−15	12	75	55 : 0 : 45	57/43	75, 38
4[b]	$PhCO_2H$	−15	20	76	22 : 0 : 78[c]	56/44	75, 44

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

catalyst, the use of benzoic acid instead of TFA mainly provided the 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 the major product with good regio- and enantioselectivity (Table 1, entry 8).

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 the diadduct **3b** as the 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 with 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 the product **3c** occurred after 24 h while 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 activity (Table 3, entries 3 to 5).

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] The 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 were 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 in the reaction with π-extended systems can be expected.

Acknowledgements

This work was partially supported by JSPS KAKENHI (grant number 23550116), and by MEXT KAKENHI (grant number 24105506).

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