Asymmetric one-pot sequential Friedel–Crafts-type alkylation and α-oxyamination catalyzed by a peptide and an enzyme

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Abstract

In the presence of a peptide catalyst and the oxidative enzyme laccase, a one-pot sequential reaction including a Friedel–Crafts-type alkylation of α,β-unsaturated aldehydes followed by an α-oxyamination was realized. The reaction in aqueous solvent to promote the enzymatic oxidation, and the use of a peptide catalyst compatible with such conditions, were essential. The present sequential reaction afforded oxygen-functionalized indole or pyrrole derivatives in a highly enantioselective manner.

Findings

Indole derivatives represent a class of biologically active compounds [1-3], and they often have chiral carbon chains attached to indole rings. A Friedel–Crafts-type asymmetric alkylation (FCAA) to indoles is a versatile method for synthesizing such chiral indole derivatives. To date, a number of FCAA reactions by either metal catalysts or organocatalysts have been reported [4-11]. Especially because organocatalysts have been demonstrated to possess a high feasibility for sequential reactions [12-16], it is expected that a sequential reaction including an organocatalytic FCAA step could provide highly functionalized indole compounds [17-20].

Indoles with an oxygenated stereogenic carbon at the β-position of the ring, such as indolmycin [21,22] and diolmycin [23], are known as antibiotics (Figure 1). The framework of these compounds could be constructed through the conjugate addition of an indole to α,β-unsaturated aldehydes followed by oxygenation at the α-position of the carbonyl group. If such a sequence can be realized in a one-pot reaction, it would be a powerful method for the synthesis of oxy-functionalized indole derivatives with operational simplicity. To date, there has been no report on the FCAA reaction combined with an α-oxygenation of aldehydes [24-29] in a one-pot sequential reaction.
Table 1: One-pot sequential Friedel–Crafts-type alkylation/α-oxyamination.

| entry | solvent   | 2:3:4a | syn/anti of 4a | ee [%]b of syn-isomer (anti-isomer) |
|-------|-----------|--------|----------------|-----------------------------------|
| 1     | H2O       | 67:14:19 | 75:25          | 96 (64)                           |
| 2     | H2O/THF 9:1 | 32:17:51 | 73:27          | 96 (62)                           |
| 3     | H2O/THF 5:1 | 44:10:46 | 76:24          | 97 (57)                           |
| 4     | H2O/THF 2:1 | 17:5:78  | 75:25          | 98 (56)                           |
| 5     | H2O/THF 1:1 | 15:85:0  | –              | –                                 |

aDetermined by 1H NMR spectroscopy of crude mixture. bDetermined by HPLC analysis after being reduced to the corresponding alcohol.
such as in the case of H$_2$O/THF 1:1, the peptide/laccase-catalyzed oxidation did not proceed at all, due to inactivation of laccase (Table 1, entry 5). This indicates the importance of water as a solvent for realization of the present sequential reaction.

To elucidate the origin of the stereocontrol in the present sequential reaction, the following control experiment was conducted. After the first FCAA reaction, peptide catalyst 1 was removed by filtration and another peptide catalyst 5, which is the enantiomer of 1, was added to promote the α-oxyamination (Scheme 1). In this case, the anti-isomer was obtained as a major diastereomer, and the ee value of the anti-product was high. The reversal of the diastereoselectivity along with the high ee of the major diastereomer demonstrates that the stereochemical course of the second-step α-oxyamination was determined mainly by the stereostructure of the peptide catalyst rather than by the chirality of the intermediate 3.

Finally, other substrates were tested in the present one-pot sequential reaction system (Table 2). Several substituted indoles gave the products with high enantioselectivity (Table 2, entries 1 to 3). As an α,β-unsaturated aldehyde, 3-nitrocinnamaldehyde was also applicable (Table 2, entry 4). Other than indoles, a pyrrole compound could be employed as a starting nucleophile in the sequential FCAA/α-oxyamination (Table 2, entry 5).

In conclusion, the FCAA followed by the asymmetric α-oxyamination was realized in a one-pot reaction, by using a peptide catalyst and laccase. This sequential reaction afforded the

\[ \text{Scheme 1: Effect of the stereostructure of the peptide catalyst.} \]

\[ \text{Table 2: Examples of the one-pot synthesis of oxygenated heteroaromatic compounds.} \]

| entry | product | time (h) of first step | yield [%]$^a$ | syn/anti$^b$ | ee [%]$^c$ of syn-isomer (anti-isomer) |
|-------|---------|------------------------|---------------|-------------|-------------------------------------|
| 1     | ![Image](image1.png) | 24                     | 59            | 75:25       | 98 (56)                             |
| 2     | ![Image](image2.png) | 24                     | 70            | 79:21       | 98 (73)                             |
Table 2: Examples of the one-pot synthesis of oxygenated heteroaromatic compounds. (continued)

|   | Structure | Yield | Isolated yield | Determined by | HPLC analysis after being reduced to the corresponding alcohol. |
|---|-----------|-------|----------------|---------------|---------------------------------------------------------------|
| 3 | ![Structure](image) | 72    | 57             | 75:25         | 98 (55)                                                       |
| 4 | ![Structure](image) | 36    | 55             | 72:28         | 98 (61)                                                       |
| 5 | ![Structure](image) | 48    | 51             | 70:30         | 91 (30)                                                       |

aIsolated yield. bDetermined by 1H NMR spectroscopy. cDetermined by HPLC analysis after being reduced to the corresponding alcohol.

oxygen-functionalized indole derivatives with high optical purity. By utilizing the wide applicability of peptide catalysts in aqueous media, and mild reaction conditions for enzymatic reactions, various types of new sequential reactions can be expected for producing highly functionalized compounds.

Supporting Information
Supporting Information File 1
Typical experimental procedure, spectroscopic data for products, determination of stereochemistry, 1H and 13C NMR spectra and HPLC charts. [http://www.beilstein-journals.org/bjoc/content/ supplementary/1860-5397-8-152-S1.pdf]

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References
1. Sene, M.; Yamada, F. Nat. Prod. Rep. 2004, 21, 278–311. doi:10.1039/b212257
2. Ruiz-Sanchis, P.; Savina, S. A.; Albérico, F.; Álvarez, M. Chem.–Eur. J. 2011, 17, 1386–1408. doi:10.1002/chem.201001451
3. Saxton, J. E. Nat. Prod. Rep. 1997, 14, 559–590. doi:10.1039/np971400559
4. Jørgensen, K. A. Synthesis 2003, 1117–1125. doi:10.1055/s-2003-39176
5. Bandini, M.; Melloni, A.; Umami-Ronchi, A. Angew. Chem., Int. Ed. 2004, 43, 550–556. doi:10.1002/anie.200301679
6. Bandini, M.; Melloni, A.; Tommasi, S.; Umami-Ronchi, A. Synlett 2005, 1199–1222. doi:10.1055/s-2005-865210
7. Bandini, M.; Eichholzer, A. Angew. Chem., Int. Ed. 2009, 48, 9608–9644. doi:10.1002/anie.200901843
8. You, S.-L.; Cai, Q.; Zeng, M. Chem. Soc. Rev. 2009, 38, 2190–2201. doi:10.1039/b817310a
9. Bartoli, G.; Benicivni, G.; Dalpozzo, R. Chem. Soc. Rev. 2010, 39, 4449–4465. doi:10.1039/b923063g
10. Terrasson, V.; de Figueiredo, R. M.; Campagne, J. M. Eur. J. Org. Chem. 2010, 2635–2655. doi:10.1002/ejoc.200901492
11. Zeng, M.; You, S.-L. Synlett 2010, 1289–1301. doi:10.1055/s-0029-1219929
12. Enders, D.; Grondal, C.; Hüttl, M. R. M. Angew. Chem., Int. Ed. 2007, 46, 1570–1581. doi:10.1002/anie.200603129
13. Walji, A. M.; MacMillan, D. W. C. Synlett 2007, 1477–1489. doi:10.1055/s-2007-980382
14. Yu, X.; Wang, W. Org. Biomol. Chem. 2008, 6, 2037–2046. doi:10.1039/b800245m
15. Grondal, C.; Jeanly, M.; Enders, D. Nat. Chem. 2010, 2, 167–178. doi:10.1038/nchem.539
16. Ramachary, D. B.; Jain, S. Org. Biomol. Chem. 2011, 9, 1277–1300. doi:10.1039/c0ob00611d
17. Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. J. Am. Chem. Soc. 2005, 127, 15051–15053. doi:10.1021/ja055545d
18. Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. Angew. Chem., Int. Ed. 2008, 47, 5661–5665. doi:10.1002/anie.200801354
19. Chi, Y.; Scroggins, T.; Fréchet, J. M. J. Am. Chem. Soc. 2008, 130, 6322–6323. doi:10.1021/ja8013456
20. Simmons, B.; Walji, A. M.; MacMillan, D. W. C. Angew. Chem., Int. Ed. 2009, 48, 4349–4353. doi:10.1002/anie.200900220
21. Routien, J. B. J. Bacteriol. 1966, 91, 1663.
22. Werner, R. G.; Thorpe, L. F.; Reuler, W.; Nierhaus, K. H. Eur. J. Biochem. 1976, 68, 1–3. doi:10.1110/j.1432-1033.1976.tb10758.x
23. Tabata, N.; Tomoda, H.; Takahashi, Y.; Haneda, K.; Iwai, Y.; Woodruff, H. B.; Ōmura, S. J. Antibiot. 1993, 46, 756–761. doi:10.7164/antibiotics.46.756
24. Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. J. Am. Chem. Soc. 2003, 125, 10888–10889. doi:10.1021/ja037096s
25. Zhong, G. Angew. Chem., Int. Ed. 2003, 42, 4247–4250. doi:10.1002/anie.200352097
26. Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. Tetrahedron Lett. 2003, 44, 8293–8296. doi:10.1016/j.tetlet.2003.09.057
27. Sibi, M. P.; Hasegawa, M. J. Am. Chem. Soc. 2007, 129, 4124–4125. doi:10.1021/ja069245n
28. Kano, T.; Mil, H.; Maruoka, K. Angew. Chem., Int. Ed. 2010, 49, 6641–6644. doi:10.1002/anie.201002965
29. Simonovich, S. P.; Van Humbeck, J. F.; MacMillan, D. W. C. Chem. Sci. 2012, 3, 58–61. doi:10.1039/c1sc00556a
30. Akagawa, K.; Akabane, H.; Sakamoto, S.; Kudo, K. Org. Lett. 2008, 10, 2035–2037. doi:10.1021/ol800031p
31. Akagawa, K.; Akabane, H.; Sakamoto, S.; Kudo, K. Tetrahedron: Asymmetry 2009, 20, 461–466. doi:10.1016/j.tetasy.2009.02.036
32. Akagawa, K.; Yamashita, T.; Sakamoto, S.; Kudo, K. Tetrahedron Lett. 2009, 50, 5602–5604. doi:10.1016/j.tetlet.2009.07.071
33. Akagawa, K.; Fujiwara, T.; Sakamoto, S.; Kudo, K. Org. Lett. 2010, 12, 1804–1807. doi:10.1021/ol100415h
34. Akagawa, K.; Fujiwara, T.; Sakamoto, S.; Kudo, K. Chem. Commun. 2010, 46, 8040–8042. doi:10.1039/c0cc02301a
35. Akagawa, K.; Kudo, K. Adv. Synth. Catal. 2011, 353, 843–847. doi:10.1002/adsc.201000805
36. Akagawa, K.; Kudo, K. Org. Lett. 2011, 13, 3498–3501. doi:10.1021/ol2012956
37. Akagawa, K.; Suzuki, R.; Kudo, K. Adv. Synth. Catal. 2012, 354, 1280–1286. doi:10.1002/adsc.201100950
38. Witayakran, S.; Ragauskas, A. J. Adv. Synth. Catal. 2009, 351, 1187–1209. doi:10.1002/adsc.200800775
39. Kolundzic, F.; Noshi, M. N.; Tjandra, M.; Movassaghi, M.; Miller, S. J. J. Am. Chem. Soc. 2011, 133, 9104–9111. doi:10.1021/ja202708g
40. Ganachaud, C.; Garfagnoli, V.; Tron, T.; Isaczio, G. Tetrahedron Lett. 2008, 49, 2476–2478. doi:10.1016/j.tetlet.2008.02.021
41. Appayee, C.; Brenner-Moyer, S. E. Org. Lett. 2010, 12, 3356–3359. doi:10.1021/ol101167z