Organocatalysis

Asymmetric Synthesis of Fully Substituted Cyclopentane-Oxindoles through an Organocatalytic Triple Michael Domino Reaction

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Dedicated to Professor Wilhelm Keim on the occasion of his 80th birthday

Abstract: An efficient, highly stereoselective asymmetric synthesis of fully functionalized cyclopentanes bearing an oxindole moiety and several other functional groups in one pot has been developed. Key step is an organocatalytic triple Michael domino reaction forming three C–C bonds and six stereocenters, including a quaternary one. Starting from equimolar amounts of simple substrates, a high molecular complexity can be reached after a Wittig olefination in one pot. The new protocol can easily be scaled up to gram amounts.

Significant effort has been devoted to the development of synthetic strategies that rapidly construct diverse and complex molecular structures, not only for the total synthesis of natural products but also to provide practical and sustainable methods for the preparation of bioactive compounds, such as pharmaceuticals and agrochemicals.[1] In this regard, asymmetric organocatalytic domino/cascade reactions have been intensively investigated in recent years owing to their well-known intrinsic advantages over classical approaches.[2] In 2006, our group reported the first multicomponent organocatalytic triple domino reaction, which opened an efficient access to functionalized cyclohexene derivatives.[3] While the majority of newly developed organocatalytic cascade reactions focuses on six-membered ring systems,[4] polysubstituted cyclopentanes[5] as common motifs in natural products and pharmaceuticals (Figure 1) are of equal importance. Thus, several efficient organocatalytic procedures for the asymmetric synthesis of cyclopentane derivatives have recently been reported.[6] We envisaged to develop a new organocatalytic approach to fully substituted cyclopentanes bearing multiple stereocenters by employing a triple domino reaction.

Oxindoles[7] have been intensively investigated owing to their broad biological and pharmacological activities.[8] In 2010, Björklund and co-workers reported that cyclopentane-containing oxindoles possess antitumor activity.[9] The racemic compounds were synthesized by a traditional stepwise procedure, and it was shown that the absolute configuration plays an important role for the antitumor activity.[10] Therefore, it is highly desirable to develop enantioselective catalytic procedures for the synthesis of such core structures. We envisaged that a triple domino reaction involving a Michael addition of an oxindole to a strong electron-withdrawing unsaturated conjugated diene and subsequent double Michael additions with cinnamaldehyde could provide an efficient and straightforward route for the asymmetric synthesis of fully substituted cyclopentane core structures bearing an oxindole unit.

Herein, we report such a novel asymmetric Michael/Michael/Michael sequence to construct a variety of potentially bioactive products containing a cyclopentane ring through the formation of three C–C bonds and six stereocenters (Scheme 1).

For the initial screening, we performed the reaction of oxindole 1a, unsaturated conjugated diene 2, and (E)-cinnamaldehyde (3a) by using diphenyl prolinol trimethylsilyl ether A as catalyst in CHCl₃ at room temperature, followed by a one-pot Wittig reaction (Table 1). To our delight, the reaction using 0.3 equivalents of catalyst A proceeded well, affording product 4a in a good domino yield (40%) with very good diastereoselectivity and enantioselectivity (15:1 d.r. and 89% ee; entry 1). When lowering the catalyst loading to 0.1 equivalents, the yield re-

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mained the same and the diastereoselectivity decreased to 5.5:1; however, the enantioselectivity increased to 94% (entry 2). The addition of benzoic acid as additive increased the yield and diastereoselectivity slightly, but had a negative effect on the enantioselectivity (entry 3). Furthermore, no improvement was obtained when the reaction was performed at a lower temperature (entry 4). Increasing the catalyst loading to 0.5 equivalents led to product 4a in a good yield of 52% with excellent diastereo- and enantioselectivity (15:1 d.r. and 98% ee; entry 5). When the starting materials 1a, 2, and 3a were added in portions, a better result was obtained (63% yield, 15:1 d.r., and 99% ee; entry 6). Using CH₂Cl₂ instead of CHCl₃ as solvent resulted in an improved yield of 70% and excellent enantioselectivity (98%), albeit with a lower diastereoselectivity (7:1 d.r.; entry 7). A subsequent solvent screening revealed that CHCl₃ was the best choice (entries 7–10). Several structurally similar proline-derived catalysts B, C, D, E, and F were tested, but no better results were obtained (entries 11–15). In addition, (S)-proline (G) was ineffective for this reaction (entry 16).

With the optimized conditions in hand (Table 1, entry 6), the substrate scope and limitations were explored. As shown in Scheme 2, substrates with various substituents at the 3- or 5-position of the oxindole were tolerated. Oxindoles 1a–c bearing a phenyl group at the 3-position reacted well with cinnamaldehyde 3a, providing the corresponding products 4a–c in yields ranging from 63–72% with good diastereo- (7:1–15:1) and excellent enantioselectivities (97–99%). Under the condi-

Table 1. Screening of the reaction conditions.[a]

| Entry | Catalyst | Solvent | Yield [%][b] | d.r.[c] | ee [%][d] |
|-------|----------|---------|--------------|--------|----------|
| 1[a]  | A        | CHCl₃   | 40           | 15:1   | 89       |
| 2[b]  | A        | CHCl₃   | 40           | 5:1    | 94       |
| 3[c]  | A        | CHCl₃   | 49           | 8:1    | 86       |
| 4[d,e] | A        | CHCl₃   | 48           | 3:1    | 87       |
| 5      | A        | CHCl₃   | 52           | 15:1   | 98       |
| 6[f]  | A        | CHCl₃   | 63           | 15:1   | 99       |
| 7      | A        | CHCl₃   | 70           | 7:1    | 98       |
| 8      | A        | toluene | 52           | 6:1    | 96       |
| 9      | A        | ether   | 13           | 15:1   | 98       |
| 10     | A        | dioxane | 21           | –      | 98       |
| 11     | B        | CHCl₃   | 40           | 10:1   | 98       |
| 12     | C        | CHCl₃   | 31           | 7:1    | 95       |
| 13     | D        | CHCl₃   | 25           | 8:1    | n.d.[g] |
| 14     | E        | CHCl₃   | 32           | n.d.   | n.d.     |
| 15     | F        | CHCl₃   | 26           | n.d.   | n.d.     |
| 16     | G        | CHCl₃   | 0            | –      | –        |

[a] Reaction conditions (method A): all reactions were performed by using 1a (0.25 mmol, 77.3 mg), 2 (0.25 mmol, 43.0 mg), 3a (0.25 mmol, 33 mg), and catalyst (0.5 equiv) in CHCl₃ (2 mL) for 22 h at room temperature followed by a one-pot olefination reaction for 5 h (Wittig reagent 5: 0.375 mmol, 125 mg), unless otherwise stated. [b] Yield of isolated product 4a as a mixture of diastereomers after column chromatography. [c] Determined by ‘H NMR spectroscopy. [d] Determined by chiral HPLC analysis for the major diastereomer. [e] Using 0.3 equiv catalyst. [f] Using 0.1 equiv catalyst. [g] Addition of 0.2 equiv PhCO₂H. [h] Performed at –20°C. [i] Method B: 1a, 2, and 3a were added in three portions at 0, 3, and 6 h. Wittig reagent 5 (0.5 mmol, 167.0 mg) was added in two portions at 22 and 25 h (stirring for 6 h in total). [j] 0.5 mmol scale. [k] Mixture of diastereomers. [l] Not determined.

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See Scheme 2 for the substrate scope of oxindoles 1. Yield refers to isolated product 4 as a mixture of diastereomers after column chromatography. The d.r. value was determined by ‘H NMR spectroscopy and the ee value by HPLC analysis for the major diastereomer. [a] Method A: all the reactions were performed by using 1a (0.5 mmol), 2 (0.5 mmol), 3a (0.5 mmol), and catalyst A (0.25 mmol) in CHCl₃ (4 mL) for 22 h at room temperature followed by a one-pot Wittig reaction for 5 h (reagent 5: 0.75 mmol), unless otherwise stated. [b] Method B (see Table 1).

Scheme 1. Asymmetric synthesis of fully substituted cyclopentanes bearing an oxindole moiety through a triple Michael addition (retrosynthetic analysis).

Scheme 2. The substrate scope of oxindoles 1. Yield refers to isolated product 4 as a mixture of diastereomers after column chromatography. The d.r. value was determined by ‘H NMR spectroscopy and the ee value by HPLC analysis for the major diastereomer. [a] Method A: all the reactions were performed by using 1a (0.5 mmol), 2 (0.5 mmol), 3a (0.5 mmol), and catalyst A (0.25 mmol) in CHCl₃ (4 mL) for 22 h at room temperature followed by a one-pot Wittig reaction for 5 h (reagent 5: 0.75 mmol), unless otherwise stated. [b] Method B (see Table 1).
tions of method A, product 4d was also formed in good results as well (57 % yield, 11:1 d.r., and 99 % ee). Reactions with oxindoles containing a benzyl or methyl group at the 3-position afforded products 4e or 4f with excellent enantioselectivities, albeit with diminished yields and diastereoselectivities (4e: 30 % yield, 3:1 d.r.; 4f: 44 % yield, 2:1 d.r.).

Next, we applied this protocol to a broad range of aldehydes 3b-f bearing various electron-rich or electron-deficient aromatic groups (Scheme 3). For example, methoxy, chloro, and nitro groups were well tolerated in the reaction of cinnamaldehydes 3b-d with oxindole 2a, providing the corresponding products 4g-i in yields ranging from 61–65 % with excellent diastereo- and enantioselectivities (9:1–15:1 d.r. and 97–99 % ee). No significant difference in the outcome for product 4h was observed when employing either method A or B. The domino reaction also worked well when using a lower catalyst loading of 0.3 equivalents to obtain the desired product 4h (49 % yield, 7:1 d.r., and 98 % ee). For substrate 3e with a nitro group at the ortho-position, the reaction also proceeded well, affording product 4j in 61 % yield with 15:1 d.r. and 97 % ee. To further extend the substrate scope, a heterocyclic 2-furyl α,β-unsaturated aldehyde 3f was tested under the conditions and product 4k was obtained in a good yield of 47 % with excellent enantioselectivity (99 % ee), albeit with a low diastereoselectivity (3:1 d.r.). To our delight, substrate 1e with a benzyl group at the 3-position reacted well with cinnamaldehydes 3b and 3g, providing products 4l and 4m in good yields with good diastereoselectivities (47 % yield, 8:1 d.r. and 63 % yield, 10:1 d.r., respectively), as well as excellent enantioselectivities (99 % ee).

To test the scalability of the new protocol, we performed the reaction on a gram scale under the optimized conditions (method B); product 4a was obtained in a good yield of 68% (2.3 g) with good diastereo- and excellent enantioselectivity (8:1 d.r. and 99 % ee). Furthermore, the tert-butoxycarbonyl (Boc) protecting group could be easily removed in the presence of trifluoroacetic acid (TFA) at room temperature from oxindole 4a to get the deprotected compound 6 in 94 % yield with 95 % ee (Scheme 4). The absolute configuration of the stereocenters in compound 4a was unambiguously determined by X-ray crystallography (Figure 2).[11]

A possible mechanism is proposed in Scheme 5. The first Michael addition of oxindole 1a to (E,E)-5-nitro-2,4-pentadienoic acid ethyl ester (2) is initiated by the diarylprolinol silyl ether catalyst, which acts as a Brønsted base in the process, providing an active intermediate I that was observed by mass spectrometry. The active intermediate I reacts quickly with cinnamylaldehyde 3a through a second Michael reaction via iminium activation, providing an intermediate II, which is further transformed to the product aldehyde 4a by a third Michael reaction via enamine activation. The final product 4a is then obtained by olefination of 4a’ using the Wittig reagent 5.

In conclusion, a novel organocatalytic domino protocol was developed to construct a series of potentially bioactive, fully
substituted cyclopentanes bearing different functional groups including an oxindole moiety in good yields, very good diastereo-, and excellent enantioselectivities. It is worth noting that the one-pot triple Michael sequence creates three bonds and six stereocenters, including one quaternary center, by using equimolar amounts of reactants under mild reaction conditions. Although a high catalyst loading (0.5 equiv) was required for most substrates to obtain high diastereoselectivities, the protocol was also successfully applied to some substrates using a lower amount of catalyst (0.3 equiv). The scalability of the new protocol to grams was demonstrated without loss in efficiency.

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Scheme 5. A proposed pathway for the asymmetric synthesis of fully substituted cyclopentanes. Im = imininium activation; En = enamine activation.

Experimental Section

General procedure for the organocatalytic domino reaction (described for the synthesis of 4a as a typical example)

Method A: A glass vial (10 mL) equipped with a magnetic stirring bar was charged with 1a (154.6 mg, 0.5 mmol), 2 (86 mg, 0.5 mmol), 3a (66 mg, 0.5 mmol), and catalyst A (81.5 mg, 0.25 mmol). After adding CHCl₃ (4 mL), the reaction tube was purged by using an argon flow for 1 min. After that, the second portion of 1a (51.5 mg, 0.17 mmol), 2 (28.7 mg, 0.17 mmol), and 3a (22 mg, 0.17 mmol) was added to the reaction tube. After purging by using an argon flow for 1 min, the mixture was stirred for another 3 h. After that, the third portion of 1a (51.5 mg, 0.17 mmol), 2 (28.7 mg, 0.17 mmol), and 3a (22 mg, 0.17 mmol) was added to the reaction mixture, which was stirred for another 16 h after purging by using an argon flow for 1 min. Then, the first portion of Wittig reagent 5 (83.5 mg, 0.25 mmol) was added to the reaction tube. The mixture was stirred for 3 h after purging by using an argon flow for 1 min. After that, the second portion of Wittig reagent 5 (83.5 mg, 0.25 mmol) was added to the reaction mixture. The mixture was stirred for another 3 h after purging by using an argon flow for 1 min. The resulting solution was then directly applied to flash chromatography (at first using pentane/ethyl acetate = 10:1, then pentane/ethyl acetate = 5:1 as eluent) to afford product 4a as a yellow solid (209 mg, 0.31 mmol, 63 % yield, 15:1 d.r., 99 % ee).

For both cases, the major diastereoisomer could be isolated as a colorless solid by using a preparative TLC plate (hexane/isopropanol = 15:1 as eluent).

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[10] According to the Bjørklung group, some S-configured oxindole derivatives possess potential antitumor activity, while the racemic compounds show complete tumor regression. The enantiomers were separated by chiral stationary-phase chromatography.

[11] The absolute configuration of 4a was determined by X-ray crystallographic analysis. CCDC 1028110 (4a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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