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# Diastereodivergent Catalytic Asymmetric Michael Addition of 2-Oxindoles to α,β-Unsaturated Ketones by Chiral Diamine Catalysts

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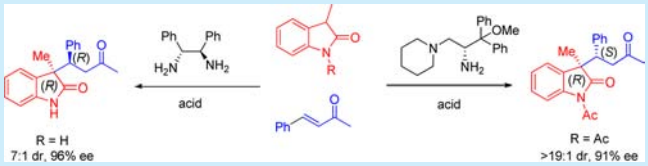
Supporting Information

**ABSTRACT:** A diastereodivergent catalytic asymmetric Michael addition of 2-oxindoles to α,β-unsaturated ketones has been successfully developed with two complementary chiral diamine catalysts, affording chiral 3,3-disubstituted oxindoles with two adjacent chiral centers. Diastereodivergence has been realized through modifying substrates and utilizing different catalysts. Either *anti*-or *syn*-configured products possessing vicinal quaternary and tertiary stereogenic centers were produced with high enantioselectivities.




Asymmetric catalysis has experienced rapid development over the past three decades,[1] opening up various methods to control enantio- and diastereoselectivity of the reactions. However, when two or more stereocenters are asymmetrically created in a single chemical transformation, how to afford a complementary sense of diastereoselectivity and enantioselectivity is still a great challenge. Perfectly diastereoselective asymmetric reactions have already been established, but these are normally limited to the selective synthesis of one of the possible relative configurations.[2] Only a few pioneers such as MacMillan,[3] Deng,[4] Melchiorre,[5] Maulide,[6] Chen,[7] Carreira,[8] and Ye[9] have engaged in the development of catalytic concepts and systems to generate every possible product diastereomers. Considering the synthetic importance of each possible diasteromers in drug discovery and application for macromolecular biological targets with specific spatial relationships, the development of efficient catalytic asymmetric methodologies is particularly appealing and useful. Here, we focused our attention on the development of diastereodivergence-oriented enantioselective synthesis of 3,3-disubstituted oxindoles through the Michael addition of α,β-unsaturated ketones with oxindoles.

3,3-Disubstituted oxindoles are valuable building blocks which can be utilized as frameworks incorporated in substructures of natural products and synthetic intermediates of bioactive molecules.[10] Many efforts have been devoted to versatile and powerful methods for the synthesis of functionalized and complex 3,3-disubstituted oxindole based on carbon−carbon bond formation.[11] 2-Oxindoles as suitable carbon nucleophiles[12] with prochiral centers are widely involved in the synthesis of natural products and biologically active molecules through a catalytic reaction with high enantioselectivity. The stereocontrolled additions of prochiral 3-alkyl/aryl-substituted 2-oxindoles to α,β-unsaturated aldehydes,[13] nitroolefins,[14] azodicarboxylate,[15] and aldimines[16] have been drastically promoted by both metal[17] and organic catalysts.[18] By employing organocatalysis with a catalyst derived from cinchona alkaloids, an enantioselective conjugate addition of prochiral 2-oxindoles with enones was achieved.[19] Subsequently, Melchiorre[20] and Tsogoeva[21] reported the asymmetric Michael addition of 2-oxindoles to cyclic enones under the chiral amine catalysts. Recently, Zhao[22] developed a novel phosphonium phase-transfer catalyst in the reaction between 2-oxindole and methyl vinyl ketone. Although a number of successful methods realized the construction of the quaternary carbon with high enantioselectivity, highly diastereodivergent synthesis of such chiral 2-oxindole compounds has never been reported in the literature. Herein, we present the first example of a highly diastereodivergent catalytic asymmetric Michael reaction of 2-oxindoles to α,β-unsaturated ketones.

Based on these considerations, we began our optimization studies on the Michael addition of 3-methyl-2-oxindole with benzalacetone in $CH_2Cl_2$ at room temperature. Trials with $C_2$-symmetric diamine (1*R*,2*R*)-1,2-diamino-cyclohexane and (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine, poor diastereoselectivity was achieved (Table 1, entries 1 and 2). Subsequently, the asymmetric additions of **2a** with **3a** under the catalysis of chiral 9-amino(9-deoxy)epiquinine smoothly converted to the adduct in good conversion and enantioselectivity, albeit with low diastereoselectivity (Table 1, entry 3). A chiral thiourea catalyst with the (1*R*,2*R*)-1,2-diaminocyclohexane and 9-amino(9-deoxy)epiquinine motif, which was one of the best catalysts in asymmetric Michael addition of enones with malonates and nitroalkanes,[14] unfortunately exhibited relatively lower reactivity and provided the product **4a** with poor diastereo- and enantioselectivity (67% ee, 4:1 *anti*/*syn*, Table 1, entry 4). It is noteworthy that the diastereoselectivity of the products was reversed under the different catalysts. We observed that *anti*/*syn*

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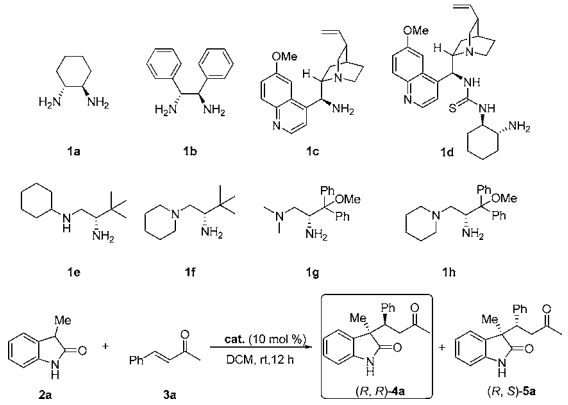
**Table 1. Optimization Studies of *Anti*-Selective Michael Addition of 2a and 3a**




| entry[a] | catalyst | additive (mol %) | conv (%)[b] | 4a/5a[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | **1a** | $PhCO_2H$ (20) | 95 | 2:1 | 87 |
| 2 | **1b** | $PhCO_2H$ (20) | 96 | 1.5:1 | 84 |
| 3 | **1c** | $PhCO_2H$ (20) | 70 | 1.2:1 | 79 |
| 4 | **1d** | $PhCO_2H$ (20) | 32 | 4.3:1 | 67 |
| 5[e] | **1e** | $PhCO_2H$ (20) | 98 | 1:3 | 30 |
| 6[e] | **1f** | $PhCO_2H$ (20) | 98 | 1:1.5 | 95 |
| 7[e] | **1g** | $PhCO_2H$ (20) | 23 | 1:10 | 0 |
| 8[e] | **1h** | $PhCO_2H$ (20) | 34 | 1:10 | 16 |
| 9[e] | **1b** | *N*-Boc-*D*-Phg(40) | 87 | 7:1 | 96 |

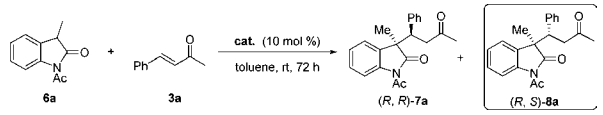
[a]Reaction conditions: a mixture of **2a** (0.1 mmol), **3a** (0.2 mmol), and the catalyst (10 mol %) in solvent (0.2 mL) was stirred at room temperature for 12 h. [b]Conversion was determined by GC. [c]Determined by $^1$H NMR of the crude reaction mixture. [d]Determined by HPLC analysis on chiral stationary phase.. [e]The solvent is toluene.

selectivities switch employed chiral primary amine catalysts **1e**−**h** with poor results (Table 1, entries 5−8).

Subsequently, the impact of a Brønsted acid was investigated,[23] leading to different stereoselectivity and reactivity. We eventually found that a combination of catalyst **1b** loading with 10 mol % and *N*-Boc-D-Phg loading with 40 mol % was optimal for this reaction.[23] A solvent screening indicated that the reaction was able to tolerate a series of solvents. After consideration of all these factors, including solubility, toluene was thus chosen as the best solvent.

Having implemented an efficient sythesis of *anti*-3,3-disubstituted oxindoles, we began to develop desired methods to access the complementary *syn*-products. As demonstrated by previous screening, we envisaged that chiral primary−tertiary amine catalysts could achieve the stereodivergence. Initially, a series of chiral primary amine catalysts were applied in the conjugate addition of 3-methyloxindole **2a** to benzalacetone **3a** after a lot of screening. To our delight, these catalysts provided the anticipated *syn*-products, but the results were not satisfying.[23] We then made some modifications on the substrate 3-methyloxindole, and ultimately *N*-Ac-protected 3-methyl oxindole and benzalacetone were selected for the template reaction.[23] The results were summarized in Table 2. Cyclohexyl amine derived catalyst **1e** gave poor diastereoselectivity results (Table 2, entry 1),[24] while piperidine-derived catalyst **1f** revealed excellent ability in the diastereocontrol, affording <1:19 *anti*/*syn* but the low enantioselectivity (Table 2, entry 2). When the steric hindrance around the primary amine group increased, the enantioselectivity of the reaction was greatly influenced (Table 2,

**Table 2. Optimization Studies of *Syn*-Selective Michael Addition of 6a and 3a**




| entry[a] | catalyst | additive (mol %) | conv (%)[b] | 7a/8a[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | **1e** | $CH_3CO_2H$(20) | 75 | 1:1 | 83 |
| 2 | **1f** | $CH_3CO_2H$(20) | 82 | <1:19 | 67 |
| 3 | **1g** | $CH_3CO_2H$(20) | 78 | <1:19 | 60 |
| 4 | **1h** | $CH_3CO_2H$(20) | 58 | <1:19 | 89 |
| 5[e,f] | **1h** | *L*-TA(20) | 80 | <1:19 | 91 |

[a]Reaction conditions: a mixture of **6a** (0.10 mmol), **3a** (0.15 mmol), and the catalyst (10 mol %) in solvent (0.2 mL) was stirred at room temperature for 72 h. [b]Conversion was determined by chiral GC. [c]Determined by $^1$H NMR of the crude reaction mixture. [d]Determined by HPLC analysis on chiral stationary phase. [e]20 mol % catalyst. [f]Reaction performed at 0 °C. TA = tartaric acid.

entries 3 and 4, from 60% to 89%).[25] On the basis of these results, a 20 mol % loading of catalyst **1h** was selected for further screening. The diastereoselectivity and yield were improved through acid screening. Satisfactory results (80% yield, 91% ee and <1:19 *anti*/*syn*) were obtained when the combination of 20 mol % of catalyst **1h** with 20 mol % of L-tartaric acid (TA) was employed, and the reaction was performed in toluene at 0 °C for 3 days.

With the optimal reaction conditions in hand, the scope of the anti-Michael reaction with respect to both the nucleophile and electrophile was investigated. Good to excellent diastereo- and enantioselectivities of the products were obtained. Aryl *α*,*β*-unsaturated ketones substituted with either electron-withdrawing or electron-donating groups on the benzene and linear *α*,*β*-unsaturated ketones were found to be well tolerated in this transformation (Table 3, entries 2−12). Regardless of the sterically hindered substituent on the benzene rings, the transformation could consistently give good yields (up to quantitative) and high enantioselectivities and good diastereoselectivities, and especially for 2-naphthyl substituents, the best sterocontrol was observed (ee up to 99%). To our great delight, 2-oxindole bearing a benzyl group also showed good reactivities, and good yields could be obtained with excellent diastereo- and enantioselectivities. On the other hand, variously substituted 3-benzyl-2-oxindoles were explored with a significant improvement in *anti*/*syn* selectivity (up to 19:1).

The scope of the Michael addition between *N*-Ac-protected 2-oxindoles **6** and various *α*,*β*-unsaturated ketones **3** under the optimized conditions was studied. As indicated in Table 4, a broad generality of enones covering aromatic, aliphatic, and linear substituents were tolerated, and excellent stereoselectivities were obtained (<1:19 *anti*/*syn*, >90% ee). With the variation of the electronic effect at the phenyl ring, the stereoselectivities remained excellent (Table 4, entries 1−11 and 14−23). The yields decreased slightly for aliphatic *α*,*β*-unsaturated ketones, but the stereoselectivities remained good (up to 96% ee) (Table 4, entries 12, 13, 24, and 25). The substituents in *N*-Ac-protected oxindoles such as benzyl and electron-withdrawing or electron-donating substituents on the benzyl had little influence on the stereoselectivity (Table 4, entries 14 and 23−26).

The sense of stereoselection with *anti*-adducts was confirmed by single-crystal X-ray crystallography of product **12**, which was derived from **4m** and chiral (*S*)-1-phenylethanamine, and the



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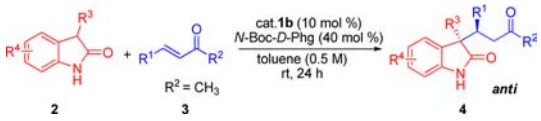
**Table 3. Scope of the Michael Addition for the *Anti*-Diastereoisomers 4**




2 3 4

| entry[a] | $R^1$ | $R^3$ | $R^4$ | yield (%)[b] | *anti*/*syn*[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | Ph | Me | H | 94(**4a**) | 7:1 | 96 |
| 2 | 3-$MeC_6H_4$ | Me | H | 95(**4b**) | 5:1 | 96 |
| 3 | 4-$MeC_6H_4$ | Me | H | 95(**4c**) | 6:1 | 97 |
| 4 | 3-$ClC_6H_4$ | Me | H | 94(**4d**) | 5:1 | 96 |
| 5 | 4-$ClC_6H_4$ | Me | H | 80(**4e**) | 6:1 | 97 |
| 6 | 2-$MeOC_6H_4$ | Me | H | 87(**4f**) | 4:1 | 90 |
| 7 | 4-$MeOC_6H_4$ | Me | H | 72(**4g**) | 4:1 | 96 |
| 8 | 3-$FC_6H_4$ | Me | H | 88(**4h**) | 4:1 | 95 |
| 9 | 4-$FC_6H_4$ | Me | H | 85(**4i**) | 5:1 | 96 |
| 10 | 3-$BrC_6H_4$ | Me | H | 97(**4j**) | 5:1 | 96 |
| 11 | 2-naphthyl | Me | H | 90(**4k**) | 6:1 | 99 |
| 12 | Me | Me | H | 96(**4l**) | 9:1 | 97 |
| 13 | Ph | Bn | H | 95(**4m**) | >19:1 | 93 |
| 14 | 4-$MeC_6H_4$ | Bn | H | 80(**4n**) | >19:1 | 96 |
| 15 | 2-$ClC_6H_4$ | Bn | H | 91(**4o**) | 6:1 | 90 |
| 16 | 2-$MeOC_6H_4$ | Bn | H | 97(**4p**) | 3:1 | 90 |
| 17 | 3-$MeOC_6H_4$ | Bn | H | 94(**4q**) | 7:1 | 99 |
| 18 | 4-$MeOC_6H_4$ | Bn | H | 95(**4r**) | 6:1 | 95 |
| 19 | 2-$FC_6H_4$ | Bn | H | 97(**4s**) | 6:1 | 94 |
| 20 | 3-$FC_6H_4$ | Bn | H | 91(**4t**) | 9:1 | 96 |
| 21 | 4-$FC_6H_4$ | Bn | H | 86(**4u**) | 19:1 | 96 |
| 22 | 3-$BrC_6H_4$ | Bn | H | 81(**4v**) | 9:1 | 96 |
| 23 | Ph | 2-$FC_6H_4CH_2$ | H | 50(**4w**) | 10:1 | 96 |
| 24 | Ph | 4-$FC_6H_4CH_2$ | H | 97(**4x**) | 12:1 | 97 |
| 25 | Ph | 4-$BrC_6H_4CH_2$ | H | 91(**4y**) | >19:1 | 96 |
| 26 | Ph | 4-$OHC_6H_4CH_2$ | H | 52(**4z**) | 7:1 | 91 |
| 27 | Ph | 4-$CNC_6H_4CH_2$ | H | 61(**4aa**) | 5:1 | 94 |
| 28 | Ph | *n*-Bu | H | 70(**4ab**) | 7:1 | 96 |
| 29 | Ph | Bn | 6-Cl | 98(**4ac**) | 6:1 | 90 |

[a]Unless otherwise noted, all reactions were carried out under 0.2 mmol of **2** and 0.4 mmol of **3** (2.0 equiv) in tolutene (0.4 mL) at room temperature for the given time in the presence of 10 mol % of catalyst and 40 mol % of *N*-Boc-D-Phg. [b]Yields of the isolated products. [c]Determined by $^1$H NMR of the crude reaction mixture. [d]Determined by HPLC analysis on chiral stationary phase.

**Table 4. Scope of the Michael Addition for the *Syn*-Diastereoisomers 7**


6 3 8

| entry[a] | $R^1$ | $R^2$ | $R^3$ | yield (%)[b] | *anti*/*syn*[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | Ph | $CH_3$ | $CH_3$ | 80(**8a**) | <1:19 | 91 |
| 2[e] | 3-$CH_3C_6H_4$ | $CH_3$ | $CH_3$ | 95(**8b**) | 1:15 | 91 |
| 3[e] | 4-$CH_3C_6H_4$ | $CH_3$ | $CH_3$ | 90(**8c**) | 1:10 | 91 |
| 4 | 2-Naphthyl | $CH_3$ | $CH_3$ | 94(**8d**) | 1:9 | 89 |
| 5[e] | 4-$MeOC_6H_4$ | $CH_3$ | $CH_3$ | 82(**8e**) | <1:19 | 90 |
| 6 | 4-$CNC_6H_4$ | $CH_3$ | $CH_3$ | 87(**8f**) | <1:19 | 81 |
| 7 | 4-$ClC_6H_4$ | $CH_3$ | $CH_3$ | 96(**8g**) | <1:19 | 92 |
| 8 | 4-$FC_6H_4$ | $CH_3$ | $CH_3$ | 97(**8h**) | <1:19 | 91 |
| 9 | 3-$FC_6H_4$ | $CH_3$ | $CH_3$ | 96(**8i**) | <1:19 | 90 |
| 10 | 4-$BrC_6H_4$ | $CH_3$ | $CH_3$ | 97(**8j**) | <1:19 | 90 |
| 11 | 3-$BrC_6H_4$ | $CH_3$ | $CH_3$ | 99(**8k**) | <1:19 | 90 |
| 12[e] | $CH_3(CH_2)_2$ | $CH_2CH_3$ | $CH_3$ | 65(**8l**) | <1:19 | 95 |
| 13[e] | $CH_3(CH_2)_3$ | $CH_3$ | $CH_3$ | 65(**8m**) | <1:19 | 91 |
| 14 | Ph | $CH_3$ | Bn | 94(**8n**) | <1:19 | 89 |
| 15 | 3-$MeOC_6H_4$ | $CH_3$ | Bn | 94(**8o**) | <1:19 | 87 |
| 16 | 4-$MeOC_6H_4$ | $CH_3$ | Bn | 98(**8p**) | 1:8 | 90 |
| 17 | 2-Naphthyl | $CH_3$ | Bn | 98(**8q**) | 1:17 | 87 |
| 18 | 4-$ClC_6H_4$ | $CH_3$ | Bn | 95(**8r**) | <1:19 | 90 |
| 19 | 4-$BrC_6H_4$ | $CH_3$ | Bn | 98(**8s**) | <1:19 | 90 |
| 20 | 3-$BrC_6H_4$ | $CH_3$ | Bn | 70(**8t**) | <1:19 | 90 |
| 21[f] | $CH_3(CH_2)_2$ | $CH_2CH_3$ | Bn | 61(**8u**) | <1:19 | 96 |
| 22[f] | $(CH_3)_2(CH_2)_3$ | $CH_3$ | Bn | 58(**8v**) | <1:19 | 81 |
| 23 | Ph | $CH_3$ | 4-$FC_6H_4CH_2$ | 70(**8w**) | 1:19 | 86 |
| 24 | Ph | $CH_3$ | 3-$BrC_6H_4CH_2$ | 76(**8x**) | <1:19 | 92 |
| 25[f] | Ph | $CH_3$ | 4-$CNC_6H_4CH_2$ | 60(**8y**) | <1:19 | 95 |
| 26[f] | Ph | $CH_3$ | 4-$AcOC_6H_4CH_2$ | 70(**8z**) | <1:19 | 86 |

[a]Unless otherwise noted, all reactions were carried out under 0.2 mmol of **6** and 0.3 mmol of **3** (1.5 equiv) in toluene (0.4 mL) at 0 °C for the given time in the presence of 20 mol % of catalyst and 20 mol % of L-TA. [b]Yields of the isolated products. [c]Determined by $^1$H NMR of the crude reaction mixture. [d]Determined by HPLC analysis on chiral stationary phase. [e]4 days. [f]5 days.

absolute configuration of *syn*-adducts was confirmed by single-crystal X-ray crystallography of **8x**, as shown in the Supporting Information. Further studies focusing on mechanism are currently in progress by our laboratory.

In conclusion, we have developed a novel method to achieve diastereodivergent and enantioselective direct Michael addition of 2-oxindoles to $\alpha,\beta$-unsaturated ketones. The reactions proceed very well with significantly broad substrate scope and excellent stereoselectivity by modifying substrates and utilizing two complementary diamine catalysts. The two catalytic systems could access the corresponding *anti*- or *syn*-diastereoisomers as the major product with high enantiocontrol.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, analytical data, and NMR. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01149.

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### Notes

The authors declare no competing financial interest.



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