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Synergetic Tandem Enantiomeric Enrichment in Catalytic Asymmetric Multi-Component Reactions (AMCRs): Highly Enantioselective Construction of Tetracyclic Indolines with Four Continuous Stereocenters

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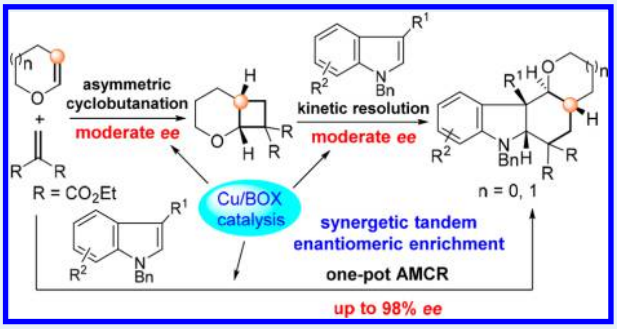
Supporting Information

ABSTRACT: Tetracyclic indolines are ubiquitous skeletons in bioactive natural products and pharmaceuticals, and efficient methods for their enantioselective synthesis are highly desired. Here, we report an efficient three-component formal [2 + 2 + 2] cycloaddition reaction between indoles, 2,3-dihydropyran, and methylene malonates for rapid construction of optically active tetracyclic indolines bearing four continuous stereocenters. Although the optimal catalyst Cu(II)/BOX displays only moderate enantioselectivities in either formal cyclobutanation or [4 + 2] cycloaddition reaction with donor−acceptor cyclobutanes bearing a nonracemizable stereocenter, the collaborative tandem enantiomeric enrichment in the one-pot asymmetric multicomponent reaction is highly effective, thereby affording a wide range of tetracyclic indoline derivatives with excellent diastereo- and enantioselectivities in high yields.



KEYWORDS: *copper catalysis, asymmetric multicomponent reaction, indolines, D−A cyclobutanes, cycloaddition*

INTRODUCTION

Formal [4 + *n*] cycloaddition reactions of donor−acceptor (D−A) cyclobutanes are highly efficient in rapid construction of densely substituted (poly)cyclic compounds and have attracted great attention in recent years.[1−4] In 2013, Matsuo et al. reported an elegant regioselective inter- and intramolecular [4 + 2] cycloaddition reaction of alkoxycyclobutanones and indoles in 31−98% yield with moderate to good diastereoselectivity.[5] Later, we developed an efficient three-component formal [2 + 2 + 2] protocol for rapid access to polycyclic spiroindolines from tryptamine-derived enamides and methylene malonates.[6] Very recently, we disclosed an intermolecular [4 + 2] annulation of D−A cyclobutanes **1** with substituted indoles **2**, which provides a facile construction of hydrocarbazoles **3** bearing three continuous stereocenters with good diastereoselectivities.[7] However, the enantioselection of this annulation is very sensitive to the donor substituents of the D−A cyclobutanes. For example, D−A cyclobutanes with sulfur-centered donating groups are remarkably better than the oxygenated ones (a, Figure 1).[7]

Given our continuous interest in asymmetric transformations of D−A cyclobutanes by using a side arm strategy,[2,8] the activated cyclobutanes **4** fused by oxygenated heterocycles are of great significance[4] because their enantioselective [4 + 2] annulation with 3-substituted indoles **2** readily affords the enantioenriched polycyclic indolines **5**, a key structural core

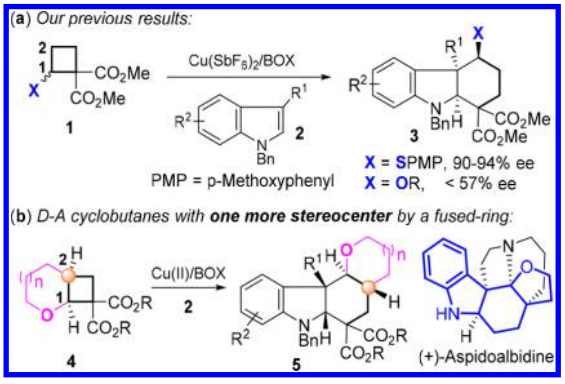


Figure 1. Catalytic asymmetric [4 + 2] annulation of indoles with D−A cyclobutanes bearing different numbers of stereocenters.

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embedded in the aspidoalbine family of alkaloids (b, Figure 1),[9] serving as an important alternative to the previous synthetic methodologies based on noble metal catalysis for tetracyclic indolines.[10] However, either kinetic resolution of the rigid fused cyclobutanes **4** with indoles or asymmetric cyclobutanation of cyclic electron-rich alkenes with methylene malonates to **4** are not highly enantioselective.[7,11] Gratifyingly, by using catalytic asymmetric multicomponent reactions (AMCRs)[12] that feature a synergetic tandem enantiomeric enrichment of both reactions relayed through the common ring-opening intermediate **M** of the cyclobutanes with a nonracemizable stereocenter C2 (Figure 2),[13] the highly efficient diastereo- and enantioselective

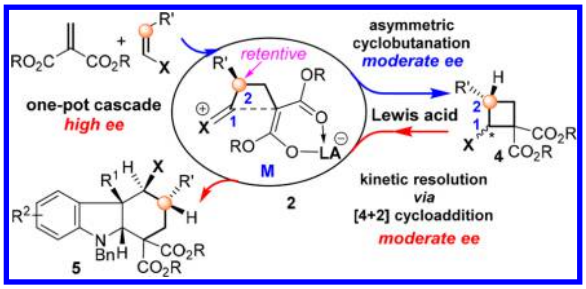

Figure 2. Synergetic tandem enantiomeric enrichment in catalytic AMCR relayed through a nonracemizable stereocenter.

2,3-fusion of indoles into such oxygenated bicyclic D−A cyclobutanes to form the desired indolines **5** is realized, which is reported herein.

RESULTS AND DISCUSSION

Initially, we attempted kinetic resolution of racemic cyclobutanes **4a** and **4b** with *N*-benzyl-3-methylindole **2a** by a formal [4 + 2] cycloaddition reaction catalyzed by Cu(II) salts in the presence of various chiral side arm modified BOX ligands, and the results were summarized in Figure S1.[14] The best kinetic resolution result showed only a moderate selectivity of 70% ee with a good diastereoselectivity catalyzed by $Cu(ClO_4)_2{\cdot}6H_2O$ and **L1** with a cyclohexyl-bisoxazoline framework (a, Figure 3), which was only slightly improved with respect to the oxygenated D−A cyclobutanes **1** in our previous studies.[7]

Generally, Lewis acid-promoted ring-opening of D−A cyclobutanes would afford a zwitterionic intermediate **M**, in which the stereocenter (C1) bound to the donor group is almost planarized while the stereocenter on the backbone such as C2 is nearly unaffected (Figure 2).[1e,11] Indeed, under racemic catalysis, reaction of the enantiomeric pure cyclobutane **4b** with **2a** afforded the corresponding indoline **5b** without any detectable loss of ee, whereas a similar reaction of the chiral cyclobutane **1a** lacking a stereogenic C2 with **2a** produced a racemic mixture of indoline **3a** (d and e, Figure 3). Furthermore, the divergence of the enantiopurity of both the recovered cyclobutanes also demonstrated the importance of the enantiogenic C2 in chiral retention of the D−A cyclobutanes during the reversible ring-opening process under Lewis acid catalysis (d and f, Figure 3).[11] Thus, we envisaged that retention of C2-configuration in **4** during the transformation to **5** may allow for a synergetic tandem enantiomeric enrichment between asymmetric cyclobutanation and catalytic kinetic resolution of **4** with **2**, thereby significantly enhancing the enantioselectivity of indolines **5** (Figure 2).

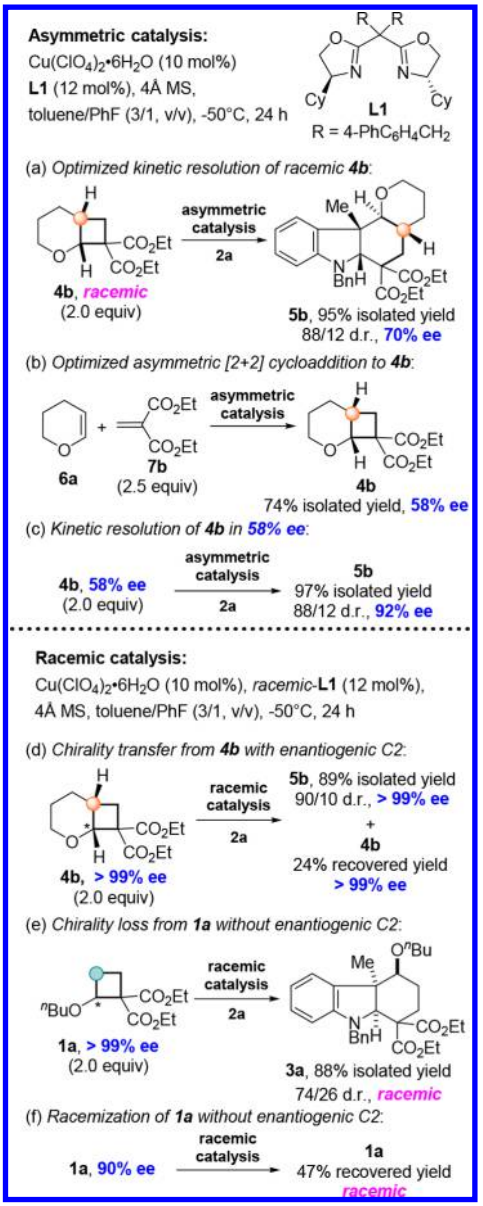

Figure 3. Elaboration of chirality transfer in Lewis acid-catalyzed annulation of D−A cyclobutanes.

Undoubtedly, the above results clearly revealed that a highly enantioselective synthesis of D−A cyclobutanes bearing a nonracemizable stereocenter like **4**, if available, could ideally lead to a facile access to the enantiomeric pure indolines **5**. Recently, we have disclosed a highly diastereo- and enantioselective Cu(II)/BOX-catalyzed [2 + 2] cycloaddition reaction of styrenes with methylidenemalonates to give the enantioenriched densely substituted cyclobutanes.[11] Unfortunately, under the reported reaction conditions, only a trace amount of cyclobutane **4b** was observed when the electron-rich alkene component was replaced by 2,3-dihydropyran.[14] However, **4b** could be isolated in 74% yield with a moderate enantioselectivity of 58% ee with **L1** (b, Figure 3). Gratifyingly, 2 equiv of **4b** in 58% ee enantiopurity reacted with **2a** smoothly produced indoline **5b** with 88:12 d.r. and 92% ee in 97% yield (c, Figure 3), showing the promising synergetic tandem enantiomeric enrichment relayed through the nonracemizable stereocenter in **4b**.

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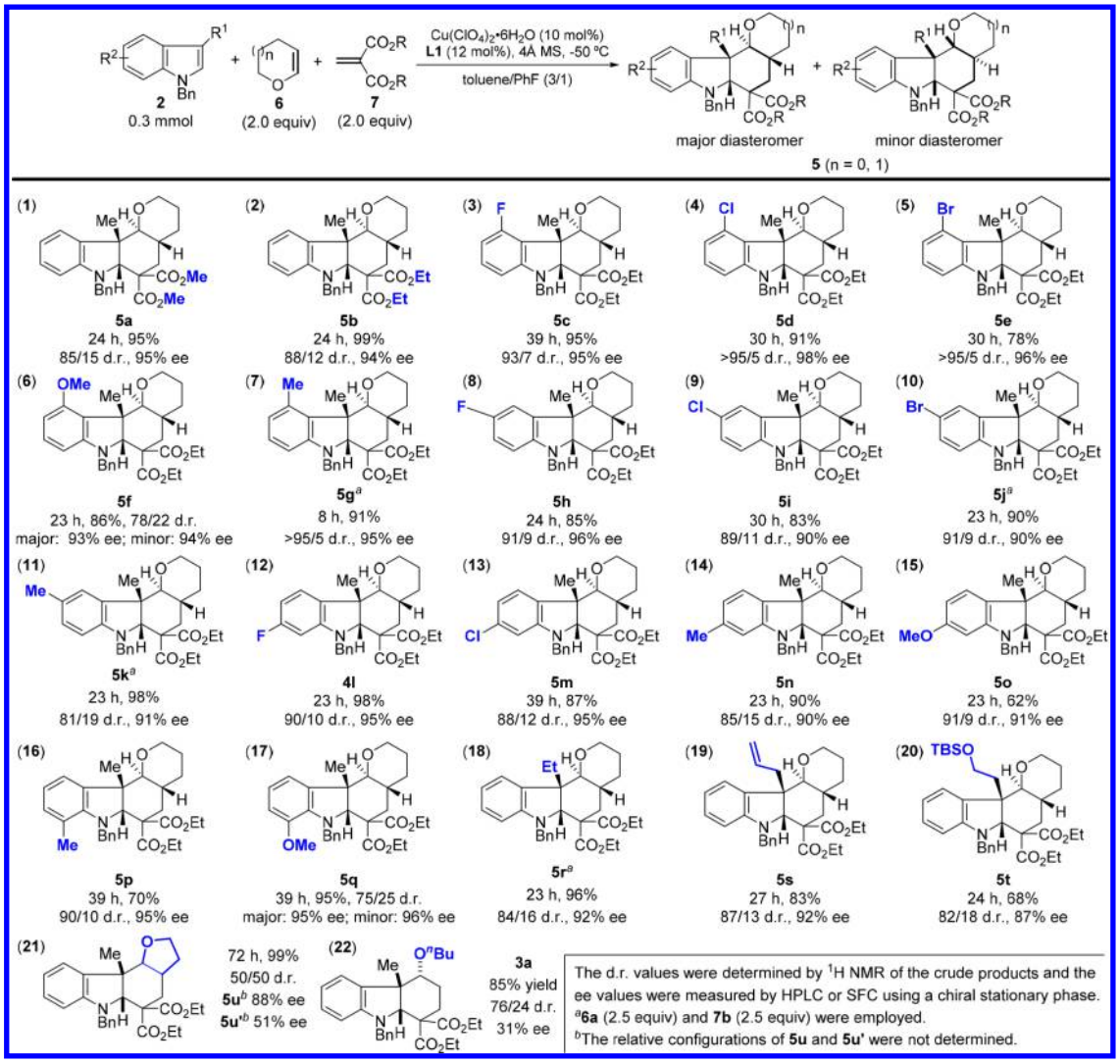

Figure 4. Substrate scope for copper-catalyzed AMCRs.

Encouraged by these results, we then began to investigate this enantiopurity upgradation in the catalytic AMCRs by a one-pot procedure. We also kept in mind that our recently reported tandem cyclization reaction of indoles with two molecules of methylidenemalonate might be problematic in terms of chemoselectivity.[15] The reaction condition optimization was carried out by employing indole **2a**, 2,3-dihydropyran **6a** and dimethyl methylidenemalonate **7a** as the model reactants, which were summarized in Figure S4 and Tables S1−S3.[14] In general, the combination of $Cu(ClO_4)_2{\cdot}6H_2O$ (10 mol %) and ligand **L1** (12 mol %) is the optimal catalyst, and a mixture of toluene and fluorobenzene (3/1 in volume) is the suitable solvent. The optimal reaction temperature was found to be −50 °C, at which excellent enantioselectivity was retained without significant decrease in reactivity and reaction rate. The concentration of the limiting substrate **2a** between 0.02 and 0.04 M was beneficial for the reaction.[14]

Generally, this copper-catalyzed AMCR works well with a wide range of indole derivatives. The results of the substrates were summarized in Figure 4. For dimethyl methylidenemalonate **7a**, indoline **5a** was isolated in 95% yield with 85/15 d.r. and 95% ee, and the diethyl **7b** is comparable (entries 1 and 2). Introduction of different substituents to the 4-position of the indole ring did not cause notable changes in the enantioselectivity, and tetracyclic indoles **5c−g** were obtained in good to excellent yields with excellent diastereoselectivities and 93−98% ee, while 4-methoxy one had a moderate d.r. of 78/22 (entries 3−7). Reactions of 5-substituted indoles with functional groups like halo and methyl afforded the annulation products **5h−k** in isolated yields up to 98% with up to 91/9 d.r. and up to 96% ee (entries 8−11). Furthermore, for indoles with electron-withdrawing groups at the 6-position, the annulation reaction proceeded smoothly to give indolines **5l** and **5m** in high yields with excellent diastereo- and enantioselectivities (entries 12−13). Meanwhile, the electron-donating groups at the 6-position of indoles are also tolerated, albeit with a slight decrease of ee (entries 14−15). In comparison to the electron-donating groups at the 4-, 5-, or 6-positions (entries 6, 7, 11, 14, and 15), reactions with 7-methyl (**2p**) and 7-methoxy (**2q**) indoles proceeded more slowly; however, the ee remained superior (entries 16 and 17). As observed for 4-methoxy indole, the reaction with 7-methoxy indole (**2q**) is also moderately diastereoselective.

It is noteworthy that 3-substituents other than methyl on the indole ring are compatible to the current reaction, such as ethyl, allyl, and $-CH_2CH_2OTBS$, which can readily furnish the enantioenriched indolines **5r−t** (entries 18−20, Figure 4). 2,3-Dihydrofuran (**6b**) is suitable for this annulation, giving a pair

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of diastereoisomers **5u** and **5u′** (50/50 d.r.) in a quantitative yield, and their enantiomeric ratios are 94/6 and 75/25, respectively (entry 21). As expected, because of the absence of a nonracemizable stereocenter in the cyclobutane intermediate **1a**, the reaction with *n*-butoxyethene gave the annulation product **3a** with only 31% ee in 85% yield (entry 22), showing no improvement with respect to the siloxy ones.[7]

Furthermore, this reaction worked well on gram-scale without decrease of yields and selectivities (Figure 5).[14] In addition, the *N*-benzyl group in **5a** was easily removed by hydrogenolysis to give compound **8** without detectable loss of enantioselection. Subsequent reduction of **8** with DIBAL-H and $NaBH_4$ selectively transformed one of the two ester groups to the primary alcohol **9**, which contains five continuous stereocenters with two chiral quaternary carbons.

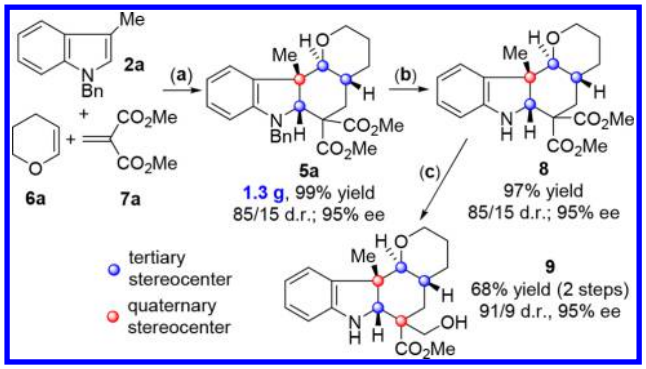

Figure 5. Gram-scale AMCR and chemical transformations of **5a**. Reaction conditions: (a) **2a** (3.0 mmol), **6a** (6.0 mmol), **7a** (6.0 mmol), $Cu(ClO_4)_2{\cdot}6H_2O$ (0.3 mmol), **L1** (0.36 mmol), 4 Å MS, fluorobenzene (35 mL), toluene (80 mL), −50 °C, 24 h. (b) **5a** (0.1 mmol), Pd/C 10 wt % (20.1 mg), H_2 (1 atm), MeOH (2.0 mL), RT, 24 h. (c) **8** (0.14 mmol), DIBAL-H (0.42 mL, 1.0 M in hexane), CH_2Cl_2 (3.0 mL), −78 °C, 24 h; then $NaBH_4$ (0.42 mmol), CH_2Cl_2 (3.0 mL), room temperature, 0.5 h.

The relative configurations of both **5a** and its minor diastereomer **5a′** as shown in the reaction equation in Figure 4 were confirmed by single-crystal X-ray diffraction analysis.[14] The absolute configuration of the major enantioisomer was assigned as (4a*R*, 6a*R*, 11b*S*, 11c*S*) as derived from single-crystal X-ray diffraction analysis of the chlorinated tetracyclic indoline **5d**.[14]

In summary, a highly regio-, diastereo-, and enantioselective Cu(II)/BOX-catalyzed asymmetric multicomponent reaction between indoles, 2,3-dihydropyran and methylene malonates to give highly enantioenriched tetracyclic indolines with four continuous stereocenters, including a chiral quaternary carbon, has been reported. Although the optimal Cu(II)/BOX catalyst displays only moderate enantioselection in either asymmetric cyclobutanation or formal [4 + 2] cycloaddition reaction with D−A cyclobutanes bearing a nonracemizable stereocenter, the synergetic tandem enantiomeric enrichment in this asymmetric multicomponent reaction is highly effective.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b00866.

Experimental procedures and spectral data for new compounds (PDF)

X-ray data of **5a** (CIF)

X-ray data of **5a′** (CIF)

X-ray data of **5d** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(14) For details, see the Supporting Information.

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