

Remote Ester Groups Switch Selectivity: Diastereodivergent Synthesis of Tetracyclic Spiroindolines

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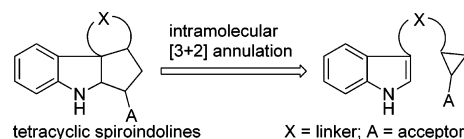
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S Supporting Information

ABSTRACT: Stereocontrol in the synthesis of structurally complex molecules, especially those with all-carbon quaternary stereocenters, remains a challenge. Here, we reported the preparation of a class of tetracyclic cyclopenta-fused spiroindoline skeletons through Cu(II)-catalyzed intramolecular [3 + 2] annulation reactions of donor–acceptor cyclopropanes with indoles. Both *cis*- and *trans*-diastereomers of tetracyclic spiroindolines are accessed with high selectivities by altering the remote ester groups of cyclopropanes. The origins of this stereocontrol are identified using DFT calculations: attractive interactions between the ester group and arene favor the generation of the *trans* isomer, while the formation of the *cis* isomer is preferred when steric repulsions become predominant.

Polycyclic spiroindolines are constituents of many alkaloid natural products¹ as well as some biologically active molecules.² Considerable efforts have been devoted to the synthesis of this motif.³ Of those synthetic methods developed, indole based cycloaddition^{3b,g} and cascade reactions^{3e,f,h,i} have shown extraordinary elegance and efficiency. As chemical transformations of donor–acceptor (D–A) cyclopropanes were elucidated to be useful in organic synthesis,^{4–7} we conceived that an intramolecular reaction might offer a new strategy to prepare a class of tetracyclic cyclopenta-fused spiroindoline skeletons by joining the indole and cyclopropane with a linker (Scheme 1). Here, we describe the development of

Scheme 1. Newly-Designed Intramolecular [3+2] Annulation Approach to Tetracyclic Spiroindolines

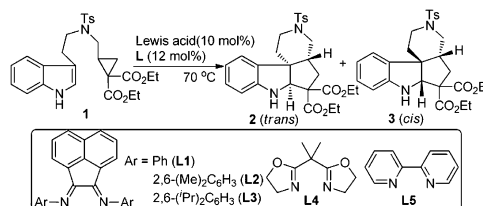


this approach to tetracyclic spiroindolines with three continuous stereocenters including an all-carbon quaternary stereocenters in a five-membered ring. In particular, we observed that the diastereoselectivity of this new reaction can be switched by changing the remote ester groups of cyclopropanes: the isopropyl ester is highly favorable for the *trans* diastereomer, while the 2-adamantyl ester is the best for the *cis* one. The origins

of this stereochemical control are also determined by density functional theory (DFT) calculations.

Initial attempts began with the intramolecular [3 + 2] annulation of newly designed cyclopropane **1**. In the presence of 10 mol % of Sc(OTf)₃, the reaction proceeded very well at 70 °C in 1,2-dichloroethane (DCE), giving the tetracyclic spiroindoline in 80% yield as shown in Table 1 (entry 1).

Table 1. Reaction Optimization



entry ^a	Lewis acid	L	solvent	yield (%) ^b	dr (2/3) ^{c,d}
1	Sc(OTf) ₃	–	DCE	80	50/50
2	Cu(SbF ₆) ₂	L1	DCE	57	66/34
3	Cu(SbF ₆) ₂	L2	DCE	55	75/25
4	Cu(SbF ₆) ₂	L3	DCE	61	83/17
5	Cu(SbF ₆) ₂	L4	DCE	87	55/45
6	Cu(SbF ₆) ₂	L5	DCE	26	54/46
7 ^e	Cu(SbF ₆) ₂	L3	DCE	83	83/17
8 ^e	Cu(SbF ₆) ₂	L3	toluene	73	81/19
9 ^e	Cu(SbF ₆) ₂	L3	THF	trace	76/24
10 ^e	Cu(SbF ₆) ₂	L3	CH ₃ CN	NR	–
11 ^e	Cu(SbF ₆) ₂	L3	DMSO	NR	–

^aConducted on 0.25 mmol scale, solvent (4 mL), reaction time: 4–48 h. ^bIsolated yields of products **2** and **3**. ^cDetermined by ¹H NMR spectroscopy of the crude products. ^dThe *cis* isomer is defined by H-atoms on the tertiary carbon which are on the same side of the cyclopentyl ring. The *trans* is defined by H-atoms on the tertiary carbon which are on opposite sides of the cyclopentyl ring. ^eAt 30 °C.

Unfortunately, the diastereoselectivity is very poor. Then we explored the common strategies⁸ such as by optimizing the Lewis acids,^{8a} reaction conditions,^{8b–f} and ligands^{8g} to improve the stereoselectivity. When In(OTf)₃ and Cu(ClO₄)₂·6H₂O were employed, poor diastereoselectivities were obtained (see Supporting Information (SI), Table S1, entries 2 and 11). By using Zn(OTf)₂, the annulation was sluggish (Table S1, entry 8).

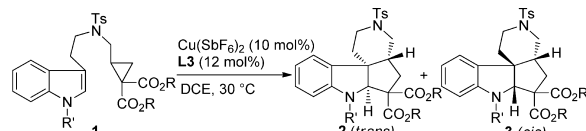
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When the reaction was catalyzed by $\text{Cu}(\text{SbF}_6)_2$ (10 mol %) in the presence of diimine ligand **L1**, we were pleased to find that the reaction speeded up significantly and finished in 4 h with 66/34 dr in 57% yield (entry 2). More hindered diimine ligands provide better stereoselectivities (entries 2–4). To our delight, when *N*-2,6-diisopropylphenyl diimine **L3** was employed as the ligand, the yield and diastereoselectivity increased to 61% and 83/17, respectively (entry 4). Other ligands such as bisoxazoline **L4** and bipyridine **L5** were also examined, but resulted in poor diastereoselectivities (55/45 and 54/46 dr, entries 5 and 6). Lowering the reaction temperature to 30 °C afforded an 83% yield without erosion of diastereoselectivity (entry 7). Solvent screening showed that toluene could lead to a 73% yield and 81/19 dr, but THF, acetonitrile, and DMSO proved to be unsuitable in this reaction (entries 8–11).

After hundreds of trials failed to improve the diastereoselectivity to a satisfactory result (for details, see SI), we focused on changing the ester R group of the cyclopropane. As shown in Table 2, when the R group of the ester was changed from ethyl to

Table 2. Effect of Ester Groups



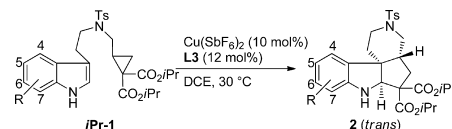
entry ^a	R'	R	yield (%) ^b	dr (2/3) ^c
1	H	Et	83	83/17
2	H	Me	87	74/26
3	H	<i>n</i> Hex	77	78/22
4	H	<i>i</i> Pr	77	90/10
5	H	<i>c</i> Hex	83	88/12
6	H	3-Pent	45	89/11
7	H	<i>t</i> Bu	trace	–
8	H	1-Ad	trace	–
9	H	CH ₂ <i>t</i> Bu	64	15/85
10	H	CH ₂ -1-Ad	52	9/91
11	H	2-Ad	61	6/94
12	CH ₃	<i>i</i> Pr	85	84/16
13	CH ₃	2-Ad	79	5/95

^aConducted on 0.25 mmol scale, DCE (4 mL). ^bIsolated yields of products 2 and 3. ^cDetermined by ¹H NMR spectroscopy of the crude products. Pent = pentyl; Ad = adamantyl.

methyl, the diastereomeric ratio was decreased to 74/26 (entry 2), suggesting that the ester groups on the cyclopropane ring may have a significant influence on the selectivity. Therefore, a variety of substrates **1** with different ester groups were examined in this intramolecular [3 + 2] annulation. It was found that changing the ester R group from a primary to secondary alkyl group can improve the diastereoselectivity greatly (entries 2–6).⁹ The isopropyl group proved to be optimal with respect to the selective synthesis of *trans* diastereomer **2** (2/3: 90/10, entry 4). Continuing to increase the size of esters by introducing tertiary alkyl groups, such as *tert*-butyl and 1-adamantyl, destroyed the reactivity (entries 7–8). To our surprise, a sudden inversion of selectivity to *cis* diastereomer **3** (2/3: 15/85, entry 9) was observed when *neo*-pentyl ester was used, and the *cis/trans* ratio can be further elevated to 94/6 by employing the 2-adamantyl group (entry 11). This diastereo-divergence switched by the ester group was also observed in the reactions using the corresponding *N*-methylindole substrates (entries 12–13).

To investigate the generality of this reaction, we synthesized a variety of cyclopropanes **1** with 2-propyl and 2-adamantyl ester groups. Under the optimal conditions, we first evaluated with isopropyl esters (*i*Pr-**1**) for the synthesis of *trans* product **2**. As shown in Table 3, substituents such as F, Cl, Br, and alkyl on the

Table 3. Reaction Scope with Isopropyl Esters

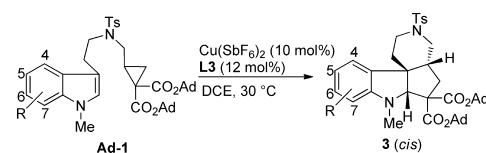


entry ^a	R	product	yield (%) ^b	dr (<i>trans/cis</i>) ^c
1	H	2a ^d	77	90/10
2	5-Me	2b	71	94/6
3	5-F	2c	77	93/7
4	5-Cl	2d	84	93/7
5	5-Br	2e	83	93/7
6	6-F	2f	60	88/12
7	6-Cl	2g	73	89/11
8	7-Me	2h	80	91/9
9	7-Br	2i	84	94/6
10	4-Me	2j	50	>99/1
11	4-F	2k	71	95/5
12	4-Cl	2l	68	>99/1
13	4-Br	2m	81	>99/1

^aConducted on 0.25 mmol scale, DCE (4 mL). ^bIsolated yields. ^cDetermined by ¹H NMR spectroscopy of the crude products. ^dConfirmed by X-ray diffraction analysis.

indole, as well as different substitution patterns (4, 5, 6, 7-), are well tolerated in the reaction, giving the desired products in good yields with high diastereoselectivities (from 88/12 to >99/1 dr, entries 2–11). With electron-donating and -withdrawing groups at different positions of the aromatic ring of indole, in cases of 2-adamantyl ester substrates (**Ad-1**), the reactions showed good reactivity and excellent diastereoselectivities affording *cis* tetracyclic spiroindolines **3** (72–95% yield, 93/7–96/4 dr; Table 4, entries 2–10). In addition, the reactions in Tables 3 and

Table 4. Reaction Scope with 2-Adamantyl Esters



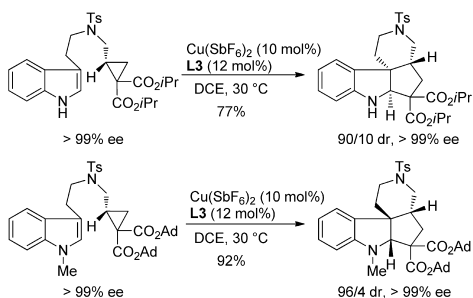
entry ^a	R	product	yield (%) ^b	dr (<i>cis/trans</i>) ^c
1	H	3a ^d	79	95/5
2 ^e	5-OMe	3b	95	95/5
3	5-Me	3c	90	96/4
4	5-F	3d	92	95/5
5	5-Cl	3e	93	94/6
6	5-Br	3f	84	95/5
7	6-F	3g	93	93/7
8	6-Cl	3h	91	94/6
9	7-Me	3i	92	96/4
10 ^e	4-OMe	3j	72	95/5

^aConducted on 0.25 mmol scale, DCE (4 mL). ^bIsolated yields. ^cDetermined by ¹H NMR spectroscopy of the crude products. ^dConfirmed by X-ray diffraction analysis. ^eWith 20 mol % catalyst. Ad = 2-adamantyl.

4 were carried out under very mild conditions and finished within 24 h. The stereochemistries of **2a** and **3a** were identified by X-ray analysis.¹⁰

The current method is suitable to prepare chiral tetracyclic spiroindolines. As shown in Scheme 2, when the optically pure

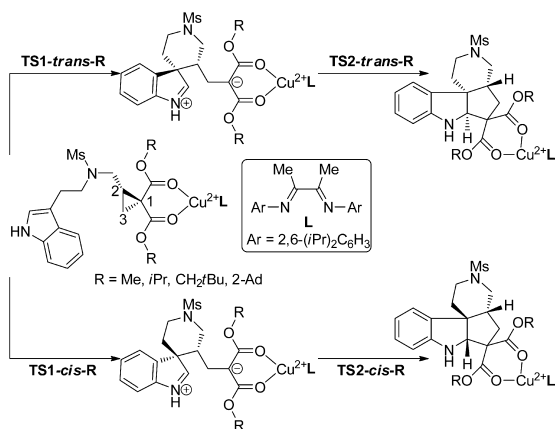
Scheme 2. Synthesis of Chiral Tetracyclic Spiroindolines from Optically Pure Substrates



isopropyl or 2-adamantyl substrate was employed, the chirality from the cyclopropane is completely transferred to the product, similar to the cycloaddition¹¹ of aldehydes and D–A cyclopropanes.

The aforementioned results showed excellent generality of the current reaction and that 2-propyl esters **iPr-1** gave *trans*-isomers **2** while 2-adamantyl esters **Ad-1** afforded *cis*-isomers **3**. As the 2-propyl and 2-adamantyl groups are remote to the first reactive site and both are secondary alkyl groups, it is hard to explain the effect of the ester group on the stereochemistry by only its steric hindrance and electronic properties. To further understand the mechanism of the intramolecular annulation of indole with a D–A cyclopropane, especially the origins of the unique diastereoselectivity control by the remote ester groups, DFT calculations were performed on four reactions with different R groups shown in Scheme 3.¹² Once cyclopropane-1,1-dicarbonyl

Scheme 3. DFT Study on Intramolecular [3 + 2] Reactions Involving Different Ester Groups



ylate is activated by a Cu(II) catalyst, the intramolecular indole C3-nucleophilic attack to the cyclopropane C2 carbon generates two diastereomeric intermediates through transition states **TS1-trans-R** and **TS1-cis-R**, respectively (Figure 1). Computational results show that regardless of the size of the R group, this step is irreversible (for details, see the SI), determining the stereochemistry of final products. The subsequent ring-closure process leads to the cycloadduct with two methine hydrogen atoms in a

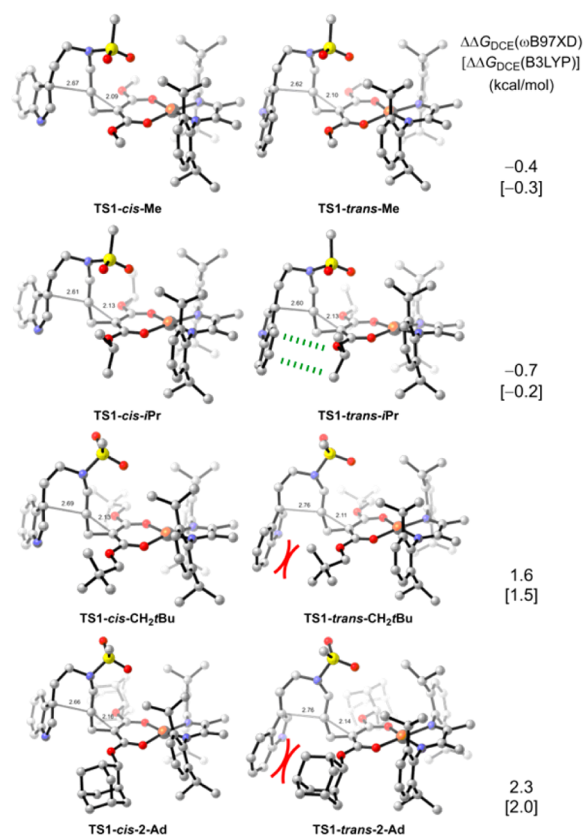


Figure 1. DFT-optimized structures of transition states **TS1-trans-R** and **TS1-cis-R** and DFT-computed relative activation Gibbs free energies (R = Me, *iPr*, CH₂tBu, 2-Ad; carbon, gray; nitrogen, blue; oxygen, red; sulfur, yellow; copper, brown; H-atoms are not shown for clarity; distances are given in angstroms).

trans configuration via **TS2-trans-R** or the *cis* one via **TS2-cis-R** (Scheme 3).

As shown in Figure 1, for the reaction with the methyl ester, DFT calculations using the ω B97XD¹³ and B3LYP¹⁴ methods indicate that formation of the *trans* product via **TS1-trans-Me** is slightly favored, in agreement with the experimental result (Table 2, entry 2). In the case of the isopropyl ester, a better *trans* selectivity is obtained experimentally (Table 2, entry 4). This trend is only reproduced by the ω B97XD method, which yields better results when describing medium- to long-range electron correlation and dispersion effects than those from the traditional B3LYP method.^{13,15} As the size of the R group from methyl to isopropyl increases, there is no significant steric repulsion generated between the ester and arene in the transition state **TS1-trans-iPr**, but the attractive interactions,¹⁶ which include dispersion forces,¹⁷ become stronger. In the Wilcox molecular torsion balance experiment, it was reported that the noncovalent interactions between isopropyl and arene are ~ 0.5 kcal mol⁻¹ larger than the methyl-arene interactions in the organic solvent.¹⁸ This value is very close to the ω B97XD energy difference for the enhanced *trans* selectivity (Me: -0.4 kcal mol⁻¹, *iPr*: -0.7 kcal mol⁻¹, Figure 1). When the R group becomes much bulkier (R = CH₂tBu, 2-Ad), the steric repulsions increase dramatically in the transition state **TS1-trans-R** as evidenced by the elongated forming C–C bond (2.76 vs 2.60–2.62 Å, to avoid steric clashes, Figure 1). Therefore, the formation of *cis* products via **TS1-cis-CH₂tBu(2-Ad)** is preferred.

In summary, we have succeeded in developing a simple, efficient method for the highly diastereoselective construction of tetracyclic spiroindoline skeletons through Cu(II)-catalyzed intramolecular [3 + 2] reactions of cyclopropane-1,1-dicarboxylates with indoles. Unprecedentedly, the diastereoselectivities of the present reaction could be readily switched by altering the remote ester groups of cyclopropanes: the isopropyl ester is highly favorable for the *trans* diastereomer, while the 2-adamantyl ester is the best for the *cis* one. Thus, it provides not only a new approach for the remote control of diastereoselection but also a one-step and facile access to both *cis*- and *trans*-diastereomers of tetracyclic spiroindolines under the same reaction conditions. DFT calculations show that attractive interactions between the isopropyl ester and arene enhance the *trans* selectivity, and that the steric repulsions caused by the bulky 2-adamantyl group make the *cis* product predominant.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental procedures, characterizations and analytical data of products, spectra of NMR and HPLC, and computational details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (10) CCDC 981305 (2a) and 981312 (3a) contain 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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