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Highly Diastereoselective Synthesis of Tetralin-Fused Spirooxindoles via Lewis Acid-Catalyzed C(sp^3)–H Bond Functionalization

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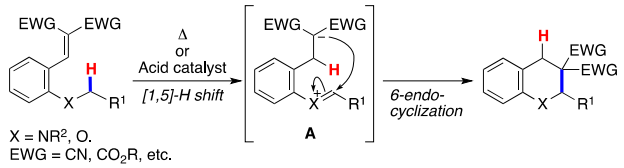
A highly diastereoselective synthesis of tetralin-fused spirooxindole derivatives was described. Treatment of benzylidene oxindoles with a catalytic amount of $Sc(OTf)_3$ in refluxing hexane afforded the target compounds in good chemical yields with excellent diastereoselectivities (up to >20:1). Detailed investigation of the reaction mechanism revealed that both interconversion of the two diastereomers and their solubility difference in reaction medium were the key to achieving excellent diastereoselectivities.

Keywords: C–H bond functionalization, tatralin, spirooxiindoles

Spirooxindoles with tetrasubstituted stereogenic centers at 3-position are of particular interest because they can be seen in many biologically active compounds and many synthetic chemists have devoted much time and effort to the development of efficient strategies for their synthesis.[1] Among the spirooxindole derivatives, there is keen interest in other useful structures, such as pyrrolidine, piperidine, and β-carboline-fused analogs. The fact that some of them have advanced into clinical trials has made them even more attractive synthetic targets than ever.[2]

Tetralins (tetrahydronaphthalenes) are found in many bioactive molecules[3] and the potent biological properties of compounds possessing a tetralin and an oxindole hybrid core are easy to imagine. However, to our surprise, very few synthetic methods have been reported for tetralin-fused spirooxindoles, especially for spirooxindole unit at 2-position of the tetralin core. Connon's group[4] and Peng and Huang's group[5] independently developed an effective method to synthesize the target structure by adopting Tamura cyclization and Michael/aldol sequence with 3-ylidene oxindole. It was notable that the highly diastereoselective syntheses of tetralin-fused spirooxindoles with three contiguous stereogenic centers were realized in both cases. Recently, Liu and Li's group reported a highly diastereoselective synthesis of the target molecule that involved a $FeCl_3$-mediated radical tandem reaction of 3-benzyl-2-oxindoles with styrenes.[6] Quite recently, Kesavan and co-workers reported that the Hauser-Craus annulation was also a reliable choice for synthesizing spirocarbocyclic oxindoles.[7]

Recently, hydride shift triggered internal redox reaction have been taken much interest because of its unique features (Scheme 1): (1) transformation of inert, C(sp^3)–H bond without external oxidants, and (2) construction of complex polycyclic frameworks from relatively simple starting materials.[8,9] The latter point stimulated many chemists to the construction of various complex polyheterocycles, including spirooxindoles and its analog (spiroindolenins), based on this methodology.



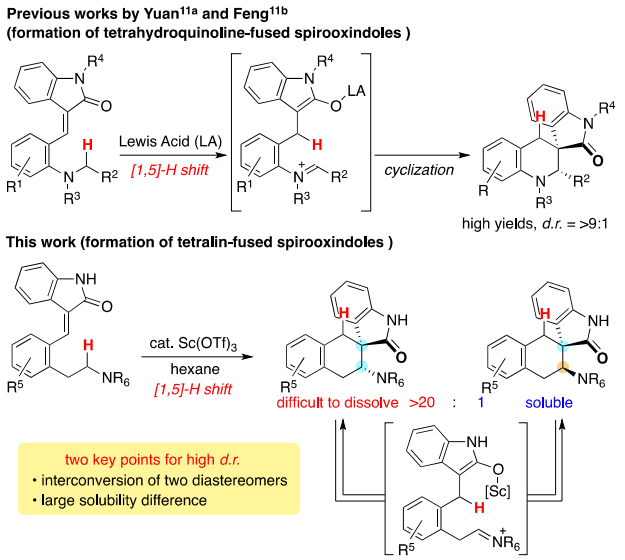
Scheme 1. C(sp^3)–H functionalization by the internal redox process.

The preliminary and important example for the synthesis of these class of skeleton by internal redox reaction was reported by Seidel and co-workers in 2011,[10a] in which conjugate iminium species derived from indoles (azafulvenium ions) were the key intermediate for promoting the [1,5]-hydride shift process. Stimulated by the results, Xu and Sun improved this reaction to the diastereoselective synthesis of spiroindolenins.[10b] Yuan and co-workers found that this methodology was effective tool for the highly diastereoselective synthesis of tetrahydroquinoline-fused spirooxindoles as shown in Scheme 2 (upper part).[11a] In 2015, asymmetric variant of Yuan's reaction was accomplished by Feng and co-workers with chiral scandium complex.[11b]

As part of our recent efforts to develop new catalytic C–H bond functionalization methodologies (internal redox reaction),[12] we have devised several effective methods for the preparation of various tetralin derivatives.[12c,d,i] In the early stage, this reaction system was limited to the construction of tetralins with a single stereogenic center.[12c,d] Quite recently, we found that highly diastereoselective synthesis of 1,3-disubstituted tetralins was achievable.[12i] Motivated by both our recent results and recent precedents for the synthesis of spirooxindoles via internal redox reaction, we turned our attention to the stereoselective construction of tetralin-fused spirooxindoles with contiguous stereogenic centers.

Herein we report a highly diastereoselective synthesis of tetralin-fused spirooxindoles via Lewis acid-catalyzed C(sp^3)–H bond functionalization. Two factors are essential to achieving excellent diastereoselectivity: (1) the interconversion of two diastereomers, and (2) a large solubility difference between the diastereomers in the reaction medium (hexane). The low to moderate diastereoselectivities after the initial product formation were significantly improved by the solubility difference induced diastereomer shift to afford various tetralin-fused

spirooxindoles in excellent diastereoselectivities (up to >20:1).



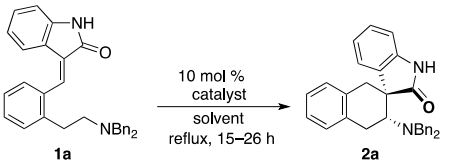
Scheme 2. Highly diastereoselective synthesis of tetralin-fused spirooxindoles by Lewis acid-catalyzed C(sp^3)–H bond functionalization.

Benzylidene oxindole derivative **1a** with an *N*,*N*-dibenzyl ethyl amine moiety at *ortho*-position was selected as the substrate because of its potentially high reactivity.[12f] Table 1 illustrates the results of examination of the reaction conditions. When a solution of **1a**[13] in $ClCH_2CH_2Cl$ was treated with 10 mol % of $Yb(OTf)_3$, which showed excellent catalytic performance in our previous study (1-aminoindane formation reaction from benzylamine derivatives),[12f] the desired reaction proceeded smoothly to afford adduct **2a** in excellent chemical yield with low diastereoselectivity (92%, *d.r.* = 2.0:1). $Gd(OTf)_3$ was also effective but the diastereoselectivity remained low (*d.r.* = 2.0:1, entry 2). Both $Hf(OTf)_4$ and $Mg(OTf)_2$ also afforded desired adduct **2a** in excellent chemical yields with low diastereoselectivities (entries 3 and 4, *d.r.* = 1.2–2.3:1). $Sc(OTf)_3$ resulted in a slightly improved diastereoselectivity of 2.9:1 while maintaining excellent chemical yield (95%, entry 5). Well-known and inexpensive strong Lewis acids, such as $TiCl_4$ and $SnCl_4$ afforded **2a** in good chemical yields with low diastereoselectivities (*d.r.* = 2.3–2.6:1, entries 6 and 7).

Next, the reaction solvent was examined with $Sc(OTf)_3$ as the catalyst, which offered quite interesting results. Diastereoselectivity was dramatically changed by the reaction solvent. Whereas diastereoselectivity was slightly decreased in toluene (*d.r.* = 1.5:1, entry 8), moderate selectivity was achieved in benzotrifluoride (*d.r.* = 4.6:1, entry 10). In particular, less polar solvents dramatically improved diastereoselectivity and hexane turned out to be the best. One diastereomer was obtained exclusively (*d.r.* = >20:1, entry 12).

The strong electron-donating ability of the amine moiety was indispensable to promote the desired hydride shift process, that is, both benzyl phenethyl ether derivative (*O*-analog) and *p*-methoxyphenethyl derivative (*C*-analog) did not afford the desired adducts completely.

Table 1. Examination of reaction conditions.

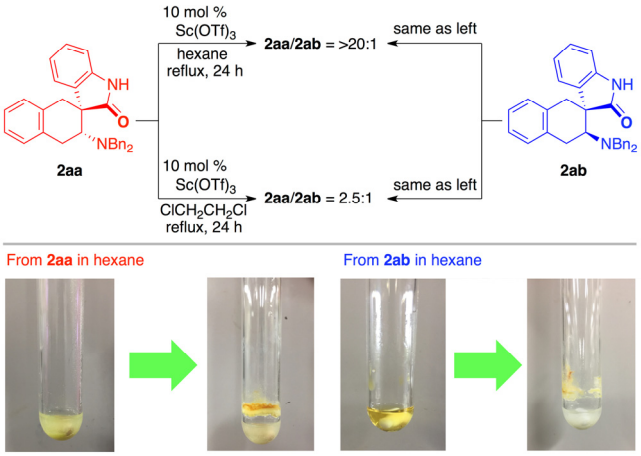


Run	Catalyst	Solvent	Yield (%)	D.r.[a]
1	$Yb(OTf)_3$	$ClCH_2CH_2Cl$	92	2.0:1
2	$Gd(OTf)_3$	$ClCH_2CH_2Cl$	99	2.0:1
3	$Hf(OTf)_4$	$ClCH_2CH_2Cl$	97	1.2:1
4	$Mg(OTf)_2$	$ClCH_2CH_2Cl$	86	2.3:1
5	$Sc(OTf)_3$	$ClCH_2CH_2Cl$	95	2.9:1
6	$TiCl_4$	$ClCH_2CH_2Cl$	95	2.6:1
7	$SnCl_4$	$ClCH_2CH_2Cl$	81	2.3:1
8	$Sc(OTf)_3$	toluene	98	1.5:1
9	$Sc(OTf)_3$	*p*-xylene	99	3.5:1
10	$Sc(OTf)_3$	benzotrifluoride	90	4.6:1
11	$Sc(OTf)_3$	cyclohexane	98	15:1
12	$Sc(OTf)_3$	hexane	96	>20:1

[a] Diastereomeric ratio was determined by comparing the integration value of the NH proton of oxindole moiety for each diastereomer in the ^1H NMR spectra.

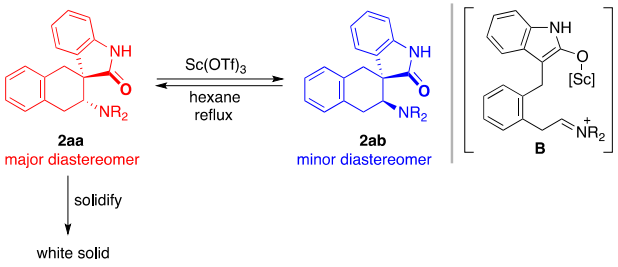
Fortunately, the two diastereomers were separable by silica-gel column chromatography and so we could examine the reversibility of the reaction by subjecting each diastereomer (**2aa** and **2ab**) to the optimized reaction conditions (entry 12, Table 1). These experiments gave two important pieces of information to understand the dramatic solvent effect of hexane (Scheme 3). First, the same diastereomeric ratio was obtained from both diastereomers and **2aa** was obtained exclusively (**2aa**:**2ab** = >20:1), which clearly indicated the reversibility of the reaction. Second, the solubility of **2aa** and **2ab** in hexane was completely different, that is, whereas minor diastereomer **2ab** was easily solubilized in refluxing hexane, major diastereomer **2aa** was not soluble at all. When **2ab** was subjected to the reaction conditions, the reaction mixture became a clear solution immediately (in less than 5 min) and a suspension 24 h later. In sharp contrast, the reaction mixture remained a suspension with **2aa** until the end of the reaction (24 h). It is worthy to note that the situation was markedly different in $ClCH_2CH_2Cl$, which exhibited low diastereoselectivity (*d.r.*= 2.9:1, entry 5, Table 1). The reaction mixture maintained a clear solution from the start to the end of the reaction for both diastereomers, and the same diastereomeric ratio was obtained (**2aa**:**2ab** = 2.5:1). These results suggest that the excellent diastereoselectivity in this

reaction might not be a result of thermodynamic control, in contrast to our recent report of the highly diastereoselective synthesis of 1,3-disubstituted tetralins.[12i]



Scheme 3. Examination of the reversibility of the reaction.

Based on the above results, the excellent diastereoselectivity of the reaction was rationalized as follows (Scheme 4): two diastereomers **2aa** and **2ab** interconverted easily under $Sc(OTf)_3$ catalysis through ring-opening and ring-closing processes via **B**, and there was only a small thermodynamic bias between these diastereomers according to the results with $ClCH_2CH_2Cl$ (*vide supra*). The key to achieving the excellent diastereoselectivity is the solubility difference between the diastereomers in hexane. The low solubility of **2aa** in hexane induced solidification, which led to the consumption of **2ab** by the redistribution of equilibrium. Repeating this process (solidification/redistribution of equilibrium) resulted in the accumulation of **2aa** in the solid form, and as a result, excellent diastereoselectivity was achieved.[14, 15, 16]



Scheme 4. Rationale for high diastereoselectivity.

The substrate scope of this reaction is summarized in Figure 1. Both excellent chemical yields and excellent diastereoselectivities were achieved in the case of oxindole derivatives **2b–d** possessing various substituents such as Me and Cl groups at 5 or 6-position of the oxindole unit (86–95%, *d.r.* = >20:1). The electronic nature of the aromatic ring of the tetralin core was almost negligible in this reaction. Substrates **1e–j** with electron-donating groups (Me and OMe) and an electron-withdrawing group (F) afforded corresponding adducts **2e–j** in excellent chemical yields with high to excellent diastereoselectivities (86–99%, *d.r.* = 7.1–>20:1). On the other hand, naphthyl-type product **2k** was obtained with moderate diastereoselectivity even in hexane (*d.r.* = 5.1:1), which was ascribed to the decreased solubility difference between the two diastereomers. In all cases, employment of hexane as the reaction solvent was the key to achieving excellent diastereoselectivities, and low diastereoselectivities were observed when the reactions were conducted in $ClCH_2CH_2Cl$.[17] The relative stereochemistries of major isomers were surmised as shown in Table 1, Schemes 1–3, and Figure 1 by analogy to **2aa** and **2c**, whose relative stereochemistries were unambiguously established by X-ray crystallographic analysis.[18]

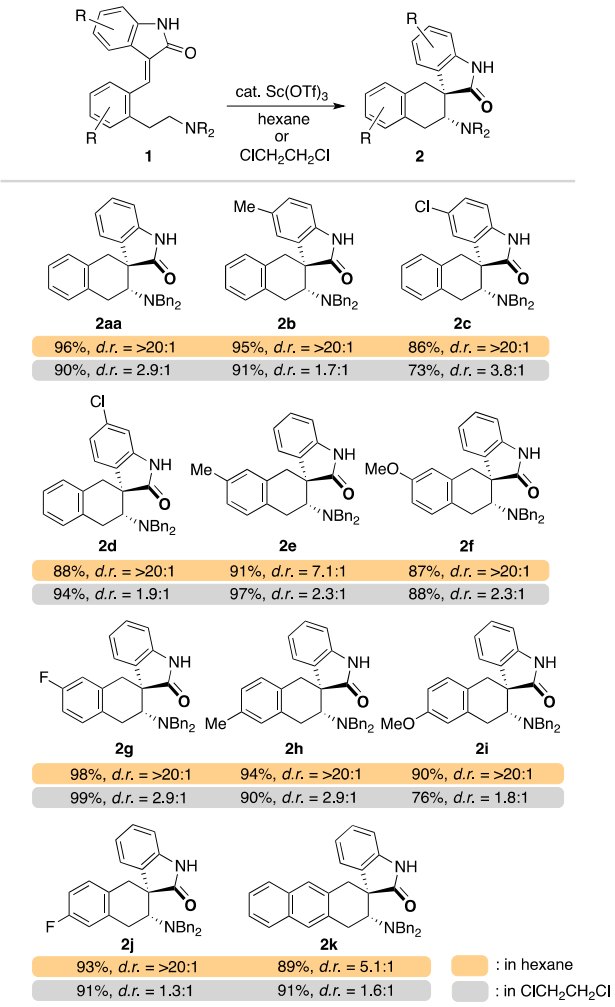


Figure 1. Substrate scope.

In summary, we have developed a highly diastereoselective synthesis of tetralin-fused spirooxindoles via Lewis acid-catalyzed C(sp^3)–H bond functionalization. Various substituents, such as electron-donating and electron-withdrawing groups on the aromatic ring, had an almost negligible effect on the reaction, and corresponding adducts **2a–j** were obtained in good to excellent chemical

yields with excellent diastereoselectivities (up to >20:1). Detailed investigation of the reaction mechanism revealed two key points for the excellent diastereoselectivity: (1) interconversion of the two diastereomers, and (2) a large solubility difference in hexane. Further investigations of the diastereoselective construction of polycycles by means of a hydride shift/cyclization system are underway in our laboratory and the results will be reported in due course.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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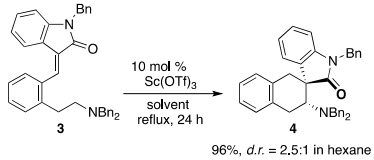
14 Employment of NH-free substrate **1**, which has low solubility in hexane, was important to achieve excellent diastereoselectivity. When the reaction was conducted with more lipophilic *N*-Bn analog **3**, the diastereomeric ratio remained low even with hexane (*d.r.* = 2.5:1).



96%, *d.r.* = 2.5:1 in hexane
98%, *d.r.* = 1.8:1 in $ClCH_2CH_2Cl$

15 Excellent diastereoselectivity was also achieved even with $Yb(OTf)_3$, $Gd(OTf)_3$, and $Hf(OTf)_4$ in hexane.

16 High electron donating ability of alkylamine moiety would be important for promoting the retro-aldol reaction

17 Attempts to extend the present reaction to the catalyzed, enantioselective reaction with chiral Sc-complex (with several Py-BOX ligands) were unsuccessful and **2aa** was obtained in the racemic form.

18 CCDC-1818264, 1818265, and 1818266 contains the supplementary crystallographic data of **1a**, **2aa**, and **2a** (See SI for details). This data can be obtained free of charge from The

Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request.