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Enantioselective Synthesis of SM-130686 Based on the Development of Asymmetric Cu(I)F Catalysis To Access 2-Oxindoles Containing a Tetrasubstituted Carbon

Daisuke Tomita, Kenzo Yamatsugu, Motomu Kanai,* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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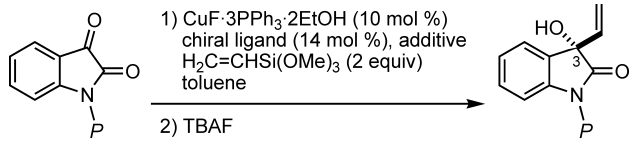
Oxindoles containing a chiral tetrasubstituted carbon at the benzylic position constitute a common structural motif in many biologically active compounds. A typical example is SM-130686 (**1**), a highly potent and orally active nonpeptidic growth hormone secretagogue.[1] The biologically significant enantiomer (*S*)-**1** was synthesized through resolution using chiral HPLC.[2] The catalytic asymmetric synthesis of molecules such as **1** that contain a tetrasubstituted carbon with significant structural complexity is among the most important current challenges in the field of asymmetric catalysis. Despite the existence of excellent catalytic asymmetric reactions to provide enantiomerically enriched 3-aryl-3-hydroxy-2-oxindoles,[3,4] none of them has been applied to the synthesis of **1**, likely because of the fact that the trifluoromethyl substituent at C4 position greatly hinders the construction of the C3 tetrasubstituted carbon (see below). In this communication, we describe the first enantioselective synthesis of **1** based on CuF-catalyzed arylation.

Previously, we developed a procedure for CuF-catalyzed enantioselective arylation and alkenylation of aldehydes and activated ketones (α-keto esters and trifluoromethyl ketones) using arylsilanes and alkenylsilanes as nucleophiles.[5] This procedure was extended to include enantioselective addition of arylboronates and alkenylboronates to aldehydes.[6] Mechanistically, reactive aryl- or alkenylcopper species were generated via transmetalation from the stoichiometric silicon- or boron-based reagents, and these organocopper species acted as the actual nucleophiles. Catalytic additive fluorides (such as TBAT or $PhBF_3K$) accelerated the reaction without affecting the enantioselectivity.[7]

To establish a basic methodology for the synthesis of **1**, we first optimized an intermolecular CuF-catalyzed enantioselective alkenylation and arylation of isatins using alkenyltrimethoxysilanes and aryltrimethoxysilanes as nucleophiles. Silicon-based nucleophiles were initially selected on the basis of previous findings: CuF-catalyzed reactions using silicon-based nucleophiles are generally more facile than those using boron-based nucleophiles, despite the identical enantioselectivity.[5a,6,8] This reactivity difference might be critical in targeting the synthesis of sterically hindered tetrasubstituted carbons.

We first studied the effects of chiral ligands in the reaction between PMB-*N*-protected isatin **2** and trimethoxyvinylsilane in the presence of CuF·$3PPh_3$·2EtOH[9] (10 mol %), chiral phosphines

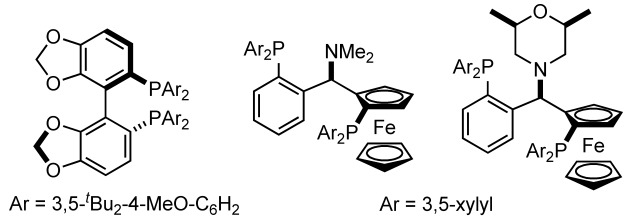
Table 1. Optimization of Cu-Catalyzed Enantioselective Vinylation of Isatins[a]



2: *P* = PMB
7a: *P* = DMTr

3: *P* = PMB
8aa: *P* = DMTr

entry	substrate	ligand	additive (mol %)	yield (%)[b]	ee (%)[c]
1[d]	**2**	**4**	TBAT (15)	92	45
2[d]	**2**	**5**	TBAT (15)	82	41
3[e]	**2**	**6**	TBAT (15)	46	75
4[f]	**2**	**6**	TBAT (30) + $Zn(OTf)_2$ (10)	>99	76
5[f]	**2**	**6**	ZnF_2 (30)	93	78
6[f]	**7a**	**6**	ZnF_2 (30)	90	88
7[g]	**7a**	**6**	ZnF_2 (15)	98	90



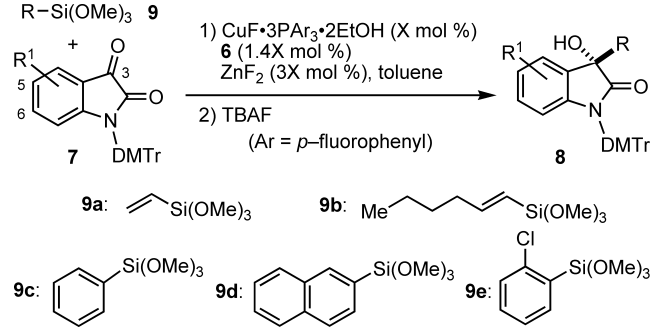
Ar = 3,5-^{t}Bu$_2$-4-MeO-C_6H_2
4: DTBM-SEGPHOS

5

Ar = 3,5-xylyl
6

[a] Standard conditions are shown in the scheme at the top of the table. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Using 20 mol % of the chiral ligand at 80 °C for 20 h. [e] At room temperature for 48 h. [f] At room temperature for 14 h. [g] Using 5 mol % of CuF·3P(C_6H_4-*p*-F)$_3$·2EtOH, 7 mol % **6**, and 15 mol % ZnF_2 at room temperature for 24 h.

Table 2. Cu-Catalyzed Enantioselective Alkenylation and Arylation of Isatins



entry	R^1		nuc.	X	time (h)	yield (%)[a]	ee (%)[b]
1[c]	H	(**7a**)	**9a**	5	24	98	90
2[c]	5-Cl	(**7b**)	**9a**	5	17	96	86
3[c]	5-OMe	(**7c**)	**9a**	5	22	95	81
4[c]	5-Me	(**7d**)	**9a**	5	22	99	84
5[c]	6-Cl	(**7e**)	**9a**	5	40	92	88
6[d]	5-Me	(**7d**)	**9b**	10	22	96	80
7[d]	H	(**7a**)	**9b**	10	18	98	90
8[d]	H	(**7a**)	**9c**	5	24	92	95[e]
9[d]	5-Me	(**7d**)	**9c**	10	24	90	96
10[d]	H	(**7a**)	**9d**	10	18	94	97
11[d]	H	(**7a**)	**9e**	10	18	91	96

[a] Isolated yield. [b] Determined by chiral HPLC. [c] At 25 °C. [d] At 35 °C. [e] The absolute configuration was determined to be (*S*).

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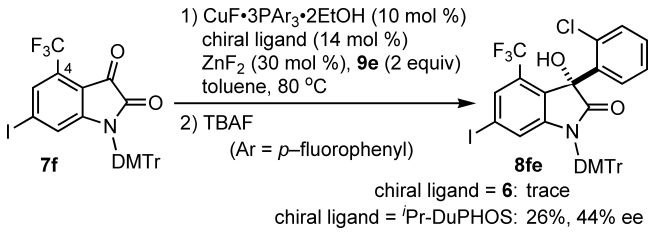
Scheme 1. Unsuccessful Attempts at Application of the CuF-Catalyzed Asymmetric Arylation to the Synthesis of SM-130686

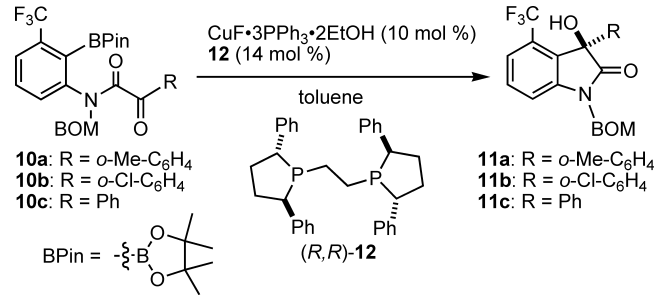


(20 mol %), and TBAT (15 mol %)[10] at 80 °C in toluene (Table 1, entries 1 and 2). Using DTBM-SEGPHOS (**4**), the optimum ligand in CuF-catalyzed enantioselective alkenylation and arylation of aldehydes,[5a] produced **3** in 92% yield, but the enantioselectivity was moderate (45% ee, entry 1). Screening of commercially available phosphines led to the identification of another promising candidate, Taniaphos (**5**),[11] which yielded **3** in 82% yield with 41% ee (entry 2). Because structural tuning of Taniaphos is easier than that of DTBM-SEGPHOS, **5** was selected as a lead chiral ligand for further optimization. On the basis of the hypothesis that a bulkier amine moiety in Taniaphos would fix the catalyst conformation more efficiently, the new Taniaphos derivative **6** was synthesized.[12] The enantioselectivity improved to 75% ee at room temperature using 14 mol % **6**, but the yield of **3** decreased to 46% (entry 3).

We then studied the effects of additive metal triflates to improve the reactivity. Combined addition of metal triflates (10 mol %) and TBAT (30 mol %) remarkably accelerated the reaction without affecting the enantioselectivity. $Zn(OTf)_2$ was the best additive, and the reaction reached completion in 14 h at room temperature (entry 4). No reaction proceeded when $Zn(OTf)_2$ was used as an additive in the absence of TBAT. We anticipated that in situ generation of ZnF_2 from $Zn(OTf)_2$ and TBAT was key to the acceleration. Therefore, a reaction using 30 mol % ZnF_2 without the addition of TBAT was conducted. As expected, product **3** was obtained in 93% yield with 78% ee (entry 5).

Finally, we investigated the effects of the substrate *N*-protecting group on the enantioselectivity. Although the enantioselectivity was constant irrespective of the substitution pattern on the aromatic ring

Table 3. Cu-Catalyzed Enantioselective Intramolecular Arylation



entry	substrate	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	**10a**	55	14	90	87
2	**10b**	65	24	70	77
3	**10c**	55	18	82	84

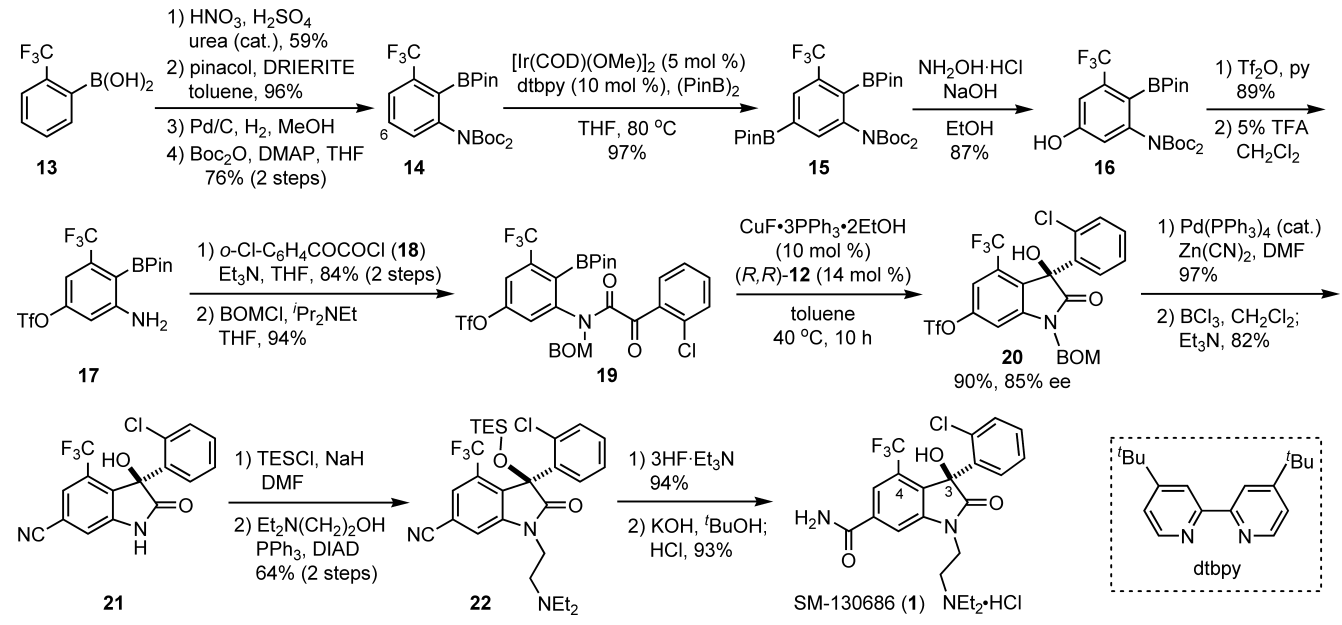
[a] Isolated yield. [b] Determined by chiral HPLC.

of benzyl-type *N*-protecting groups, triarylmethyl-*N*-protected substrates afforded significantly improved enantioselectivity. Specifically, product **8aa** with 88% ee was obtained in 90% yield when di(*p*-methoxyphenyl)phenylmethyl (DMTr)-*N*-protected isatin **7a** was used (entry 6). Catalyst loading could be reduced to 5 mol % while maintaining high enantioselectivity (90% ee, entry 7).[13]

Under the thus-optimized conditions, the substrate scope was studied (Table 2). Broad generality was observed with regard to the isatin substrates: both electron-withdrawing and -donating substituents at the C5 and C6 positions were tolerated (entries 2−5). Alkenylsilane **9b** with a longer alkyl chain, which was conveniently synthesized through olefin cross metathesis,[14] could be utilized as a nucleophile (entries 6 and 7). Catalytic enantioselective arylation of isatins also proceeded with excellent enantioselectivity (entries 8−11). The DMTr protecting group of **8** was removed by treatment with 10% TFA in CH_2Cl_2 in the presence of *p*-anisole in high yield without any racemization.[12] Therefore, this reaction is among the best methods for synthesizing enantiomerically enriched 3-hydroxy-2-oxindoles containing a tetrasubstituted carbon at the C3 position.

This CuF-catalyzed enantioselective arylation was applied to the reaction between isatin **7f** and arylsilane **9e**, targeting SM-130686 (Scheme 1). Unfortunately, **7f** was recovered almost completely,

Scheme 2. Catalytic Enantioselective Synthesis of SM-130686 (**1**)



and the desired product **8fe** was produced in only a trace amount. After a reexamination of chiral phosphine ligands, **8fe** was obtained in up to 26% yield with 44% ee using ^{i}Pr-DuPHOS as the chiral ligand. Obviously, the trifluoromethyl group at the C4 position dramatically hindered the reaction.

To overcome the unsatisfactory efficiency of the intermolecular arylation in the synthesis of SM-130686, we developed a catalytic enantioselective intramolecular arylation of α-keto amides as an alternative strategy.[15] Arylboronates instead of arylsilanes had to be used as substrates in this intramolecular version because of the robustness of arylboronates under various reaction and purification conditions in a multistep substrate synthesis. The feasibility of this new strategy was assessed using model substrates **10** (Table 3). Chiral ligand screening led us to identify Ph-BPE (**12**) as the optimum ligand in the intramolecular arylation.[16] Products **11** were obtained in both high yield and enantioselectivity in the absence of ZnF_2 (entries 1−3). Adding ZnF_2 produced detrimental effects on the enantioselectivity (77% ee for **11a** vs 87% ee in entry 1) in this intramolecular version.

Using this new methodology, we achieved the first catalytic asymmetric synthesis of SM-130686, as shown in Scheme 2. Nitration of **13** in the presence of a catalytic amount of urea[17] produced the *o*-nitroarylboronic acid containing the proper contiguous trisubstitution pattern, which was condensed with pinacol to afford the corresponding arylboronate. After reduction of the nitro group to an amino group, the resulting aniline was protected as diBoc **14**. Oxidation at C6 (oxindole numbering) was conducted with complete selectivity through Ir-catalyzed borylation[18] followed by monooxidation of the C6-boronate with hydroxylamine,[19] affording **16** in high two-step yield. The excellent selectivity in these two conversions is likely due to steric effects. *O*-Triflation and successive Boc cleavage afforded marginally stable aniline **17**, which was coupled with acyl chloride **18** (freshly prepared from the corresponding carboxylic acid and dichloromethyl methyl ether[20]) without purification. The resulting α-keto amide was treated with BOMCl (BOM = benzyloxymethyl) and Hünig's base, producing **19**, the substrate for the key catalytic enantioselective arylation.

The enantioselective intramolecular arylation of **19** proceeded in the presence of 10 mol % CuF−(*R*,*R*)-**12** catalyst, and product **20** was obtained in 90% yield with 85% ee. One-carbon homologation at the C6 position was conducted through Pd-catalyzed cyanation, and subsequent *N*-deprotection by treatment with BCl_3 afforded **21**. After the C3 tertiary hydroxy group was temporarily protected with a TES group, *N*-alkylation under Mitsunobu conditions produced **22** in 64% two-step yield. Synthesis of SM-130686 (**1**) was completed from **22** through desilylation followed by hydrolysis of the nitrile. This first catalytic asymmetric synthesis of **1** involved 17 steps with an overall yield of 10%. The efficiency was remarkably higher than that of the previous synthesis using chiral HPLC resolution (0.3% total yield).[1]

In conclusion, we achieved the first catalytic enantioselective synthesis of SM-130686 using CuF-catalyzed intramolecular arylation. This study demonstrates that asymmetric CuF catalysis can be applied to a critical C−C bond formation at a late stage in the synthesis of a complex molecule. Such "convergent asymmetric catalysis" will significantly improve synthetic efficiency. Studies targeting a more direct link between the development of asymmetric catalysis and more efficient complex-molecule synthesis are ongoing.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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