CHEMISTRY
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To be cited as: Chem. Asian J. 10.1002/asia.201601183

Link to VoR: http://dx.doi.org/10.1002/asia.201601183

A Journal of

ACES
Asian Chemical Editorial Society

A sister journal of Angewandte Chemie and Chemistry – A European Journal

WILEY-VCH

A Divergent Approach to the Diastereoselective Synthesis of 3,3-Disubstituted Oxindoles from Atropisomeric *N*-Aryl Oxindole Derivatives

Atsuo Nakazaki,*[a] Ayako Mori,[a] Susumu Kobayashi,[b] Toshio Nishikawa[a]

Keywords: asymmetric synthesis, C-N axial chirality, 3,3-disubstituted oxindole, isatin

Abstract: 3,3-Disubstituted oxindoles were divergently synthesized by diastereoselective transformations including nucleophilic addition, alkylation, and cycloaddition using common, axially chiral *N*-aryl oxindoles. Notably, high diastereoselectivities (up to >95:5) were observed with *ortho*-monosubstituted *N*-aryl oxindoles to give various oxindole scaffolds, and facile removal of the *p*-(benzyloxy)aryl moiety in axially twisted amides was achieved by a mild, two-step sequence.

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Supporting information for this article is available on the WWW under
http://dx.doi.org/10.1002/asia.xxxxxxxxx.

Introduction

Considerable attention has been given to 3,3-disubstituted oxindoles that incorporate a stereogenic center in the C3-position, since these particular scaffolds are widely embedded in indole alkaloids, drug candidates, and clinical pharmaceuticals (Figure 1).[1] For instance, PF1270A displays a high affinity for the histamine H3 receptor, whose ligands are potential therapeutic agents for diabetes, obesity, and central nervous system disorders.[2] SM-130686 possess potent growth hormone releasing activity and its dextro isomer is more potent than its enantiomer.[3] Therefore, a number of synthetic methods directed at 3,3-disubstituted oxindoles have been established based on enantioselective transformations.[4] Nevertheless diastereoselective approaches seem to be ideal for the divergent synthesis of stereochemically defined oxindoles, but this approach has remained relatively unexplored because the positions of the introduced chiral auxiliary is limited.[5] During the course of our studies aimed at the stereocontrolled synthesis of 3,3-disubstituted oxindoles,[6] we envisaged that a diastereoselective approach would allow for the divergent synthesis of 3,3-disubstituted oxindoles from a common, chiral non-racemic oxindole intermediate. Towards this end, we newly designed *N*-aryl oxindole **A** with axial chirality on the C-N bond (Scheme 1, a).[7,8] Thus, diastereoselective C-C bond-forming reactions of *N*-aryl oxindole, which is *N*-aryl isatin (**A**: X = O) or its carbon analogues (e.g., 3-alkylidene oxindole **A'**: X = CHR' or 3-alkyl oxindole **A"**: X = CH_2R') as the common intermediate, would take place from the less hindered diastereoface leading to 3,3-disubstituted oxindole **B**. Various diastereoselective reactions can be used to synthesize a wide variety of oxindole scaffolds from *N*-aryl oxindoles **A**-**A"** because of the versatility of these starting materials (Scheme 1, b).[9] Notably, stereochemically defined oxindole

10.1002/asia.201601183

C could be obtained after removal of the aryl moiety in **B** under mild oxidative conditions. Herein, we describe diastereoselective transformations including nucleophilic addition, alkylation, and cycloaddition using chiral racemic oxindoles, which are relatively easier to synthesize than their non-racemic counterparts; the facial selectivity is also discussed. The most striking features of this approach are the high diastereoselectivities (up to >95:5) using *ortho*-monosubstituted *N*-aryl oxindoles, and the high-yielded removal of the *p*-(benzyloxy)aryl moiety bearing a hindered *ortho*-substituent in the twisted amides by a two-step sequence under mild oxidation conditions [$PhI(OCOCF_3)_2$, MeCN-H_2O, 0 °C] after deprotection of the benzyl group.[8a] This two-step process allows for the divergent and stereoselective incorporation of various functionalities in the C3 position into oxindole scaffolds of considerable synthetic and medicinal interest.

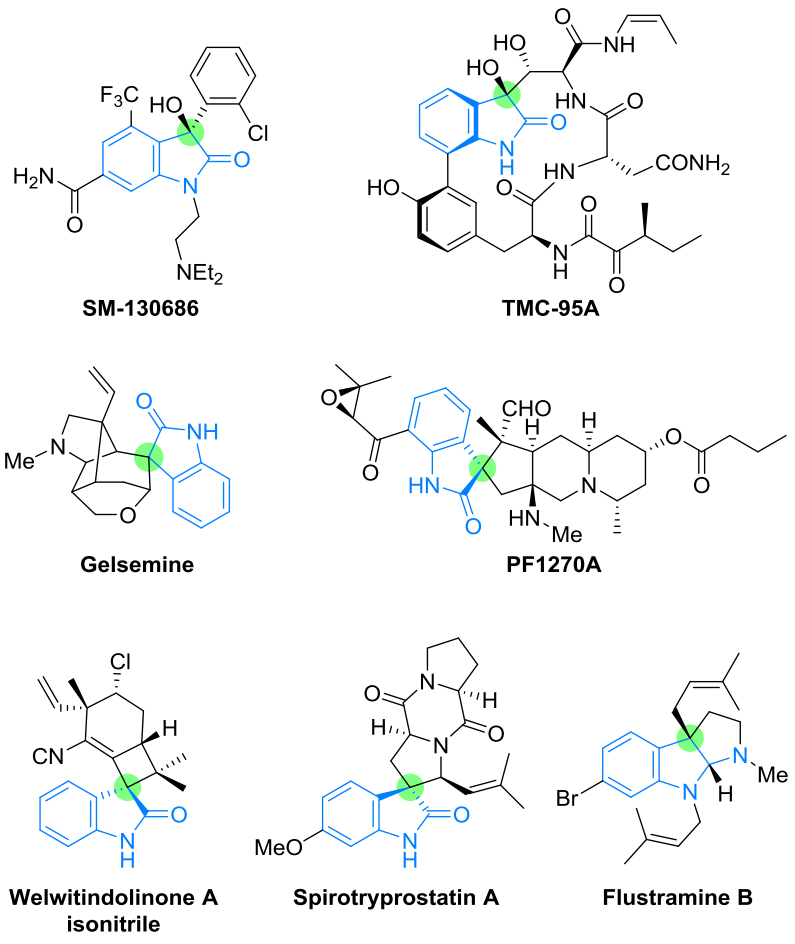
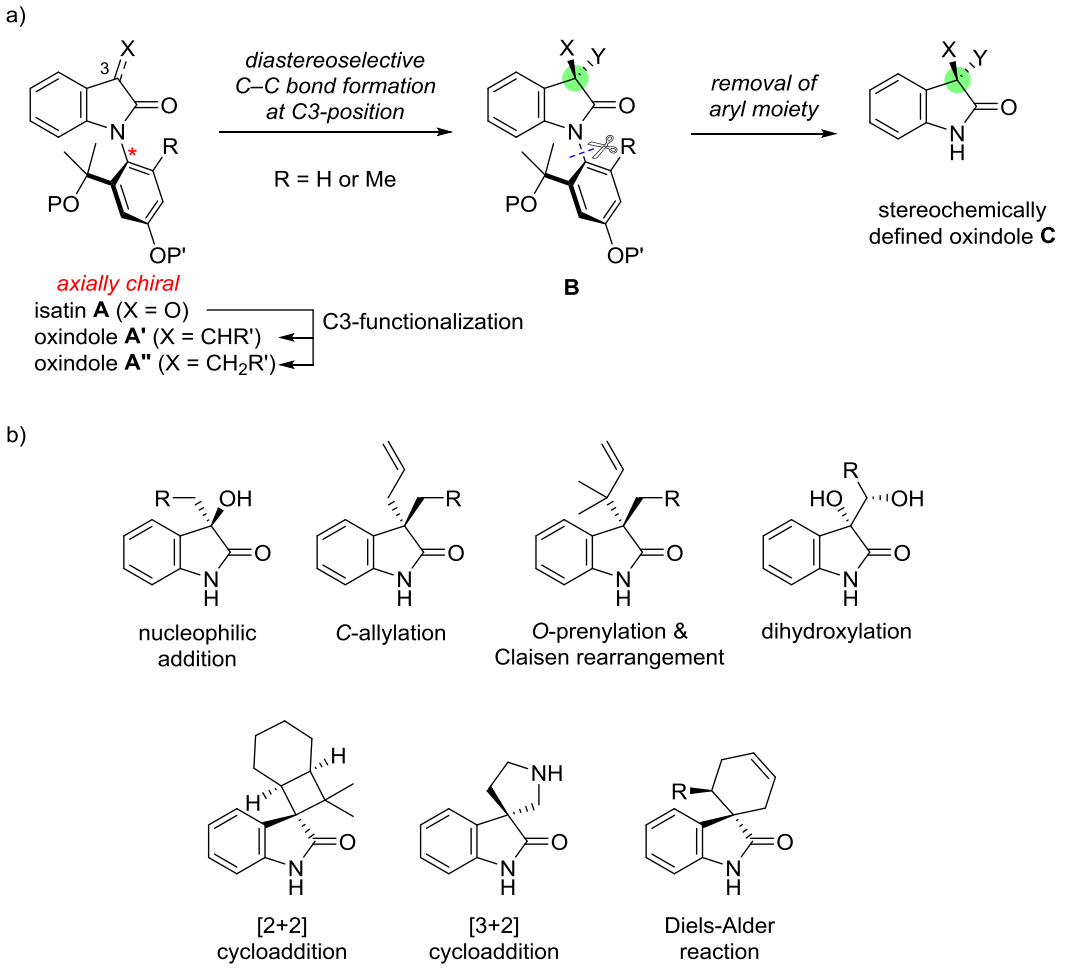


Figure 1. Oxindole alkaloids with a stereogenic center at C3-position.

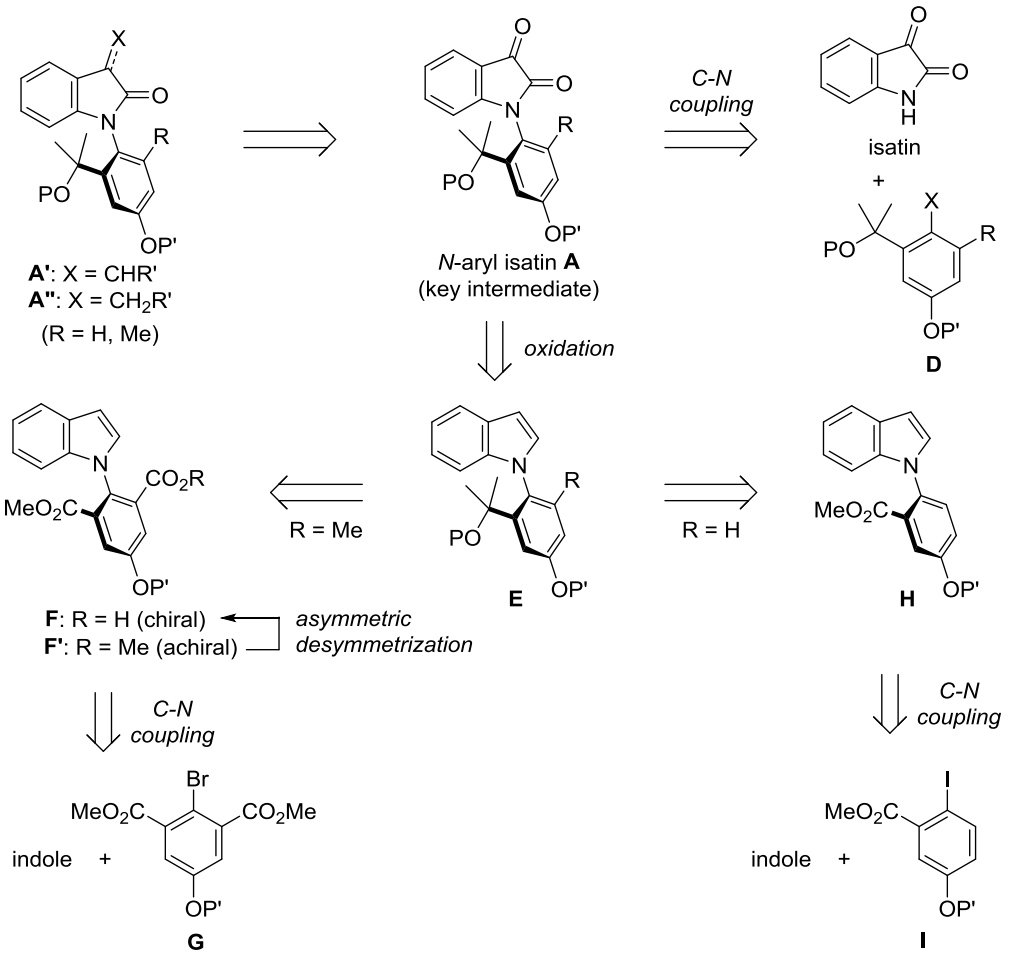


Scheme 1. a) General scheme for stereocontrol of the C3-stereogenic center of oxindoles with axial chirality. b) Potentially accessible scaffolds from axially chiral isatin **A**, oxindole **A'** or **A"**.

Results and Discussion

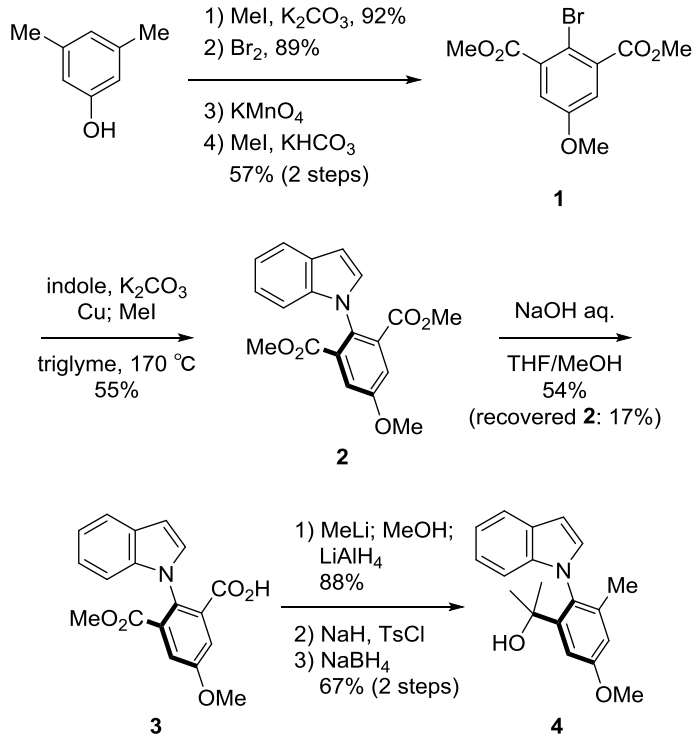
Synthetic plan for *N*-aryl oxindoles: Scheme 2 describes our initial synthetic plan in pursuit of chiral non-racemic isatin **A** and oxindoles **A'** and **A"** bearing an *ortho*-monosubstituted or *ortho*-disubstituted *N*-aryl group. We first expected that *N*-aryl isatin **A**, a versatile precursor for oxindoles **A'** and **A"**, could be synthesized through direct C-N coupling of isatin and bromoarene **D**. However, in our preliminary attempts, the transition metal-catalyzed C-N coupling of isatin and bromoarene **D** (e.g., R, P, and P' = Me) did not take place at all, and the related reaction using sterically less congested 2-bromo-5-methoxy-1,3-dimethylbenzene did not furnish the desired *N*-aryl isatin probably due to the severe steric hindrance.[10] Therefore we chose an alternative

stepwise approach via the oxidation of *N*-aryl indole **E**. In the synthesis of *ortho*-disubstituted *N*-aryl indole **E** (R = Me), asymmetric desymmetrization of achiral diester **F'** via enzymatic hydrolysis would be a viable approach to obtain chiral non-racemic *N*-aryl indole **F**. Needless to say, stable axial chirality in the synthetic intermediates involvong indoles **E** and **F** was essential for the transformation. Transition metal catalyzed C-N coupling of indole and bromoarene **G** with an *ortho*-diester would be a feasible approach to obtain achiral *N*-aryl indole **F**. Through a similar manner as the disubstituted system, *ortho*-monosubstituted *N*-aryl indole **E** (R = H) could be synthesized easily via *N*-aryl indole **H** derived from indole and sterically less congested iodoarene **I**. In order to clarify capability of its diastereofacial selectivity for each reaction, chiral racemic isatins were synthesized.



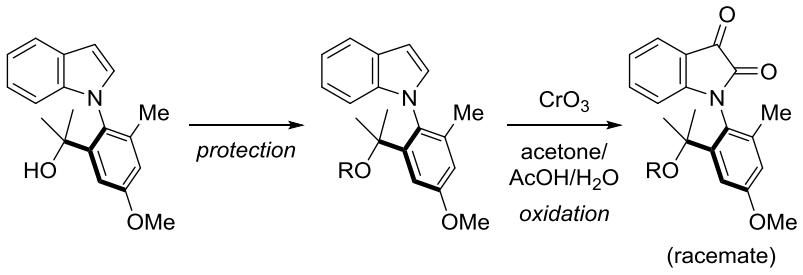
Scheme 2. Synthetic strategy for chiral non-racemic *N*-aryl isatin **A**, a key intermediate for related oxindole analogues **A'** and **A"**.

Synthesis of *ortho*-disubstituted *N*-aryl oxindoles: We first synthesized *ortho*-disubstituted *N*-aryl isatin **6** via the corresponding indole **4** (Scheme 4 and Table 1). Aryl bromide **1** (= **G**) was prepared from commercially available 3,5-dimethylphenol in four steps according to the literature.[11] C-N coupling of indole and bromoarene **1** was performed with Cu and K_2CO_3 in refluxing triglyme, followed by treatment with MeI to protect the partially formed carboxylate, leading to requisite diester **2**. To obtain the racemic *N*-aryl isatin, diester **2** was subjected to 0.7 equiv of NaOH aq. to afford the desired monocarboxylic acid **3** in moderate yield (54%) along with recovered starting material **2** in 17% yield. Monocarboxylic acid **3** is a chiral compound and a potentially useful precursor for the synthesis of chiral non-racemic isatins, if it possesses stable axial chrality. The stability of the axial chirality of **3** was determined by chiral HPLC analysis of chiral non-racemic **3**;[12] which revealed that **3** was easily racemized even at room temperature. Therefore, chiral non-racemic isatin should be synthesized by another strategy.[13] Methoxycarbonyl and carboxy groups in both *ortho*-positions in **3** were transformed into hydroxydimethylmethyl and methyl groups, respectively by the following sequence: treatment of **3** with MeLi and quenching the reaction by MeOH, followed by addition of excess $LiAlH_4$ in the same pot provided diol (not shown in Scheme 3). The resulting primary alcohol was converted into the corresponding chloride, which was then reduced with $NaBH_4$ to afford *N*-aryl indole **4** in good overall yield. Isatins **6a-e** bearing various protecting groups were synthesized as shown in Table 1. Protection of the *tert*-alcohol in **4** and subsequent oxidation of indole **5** using CrO_3 afforded the corresponding isatins **6**.[14]



Scheme 3. Synthesis of *N*-aryl indole **4**.

Table 1. Synthesis of *N*-aryl isatins **6a-e**. Nap = 2-naphthylmethyl. *m*-MPM = *m*-methoxyphenylmethyl.



4

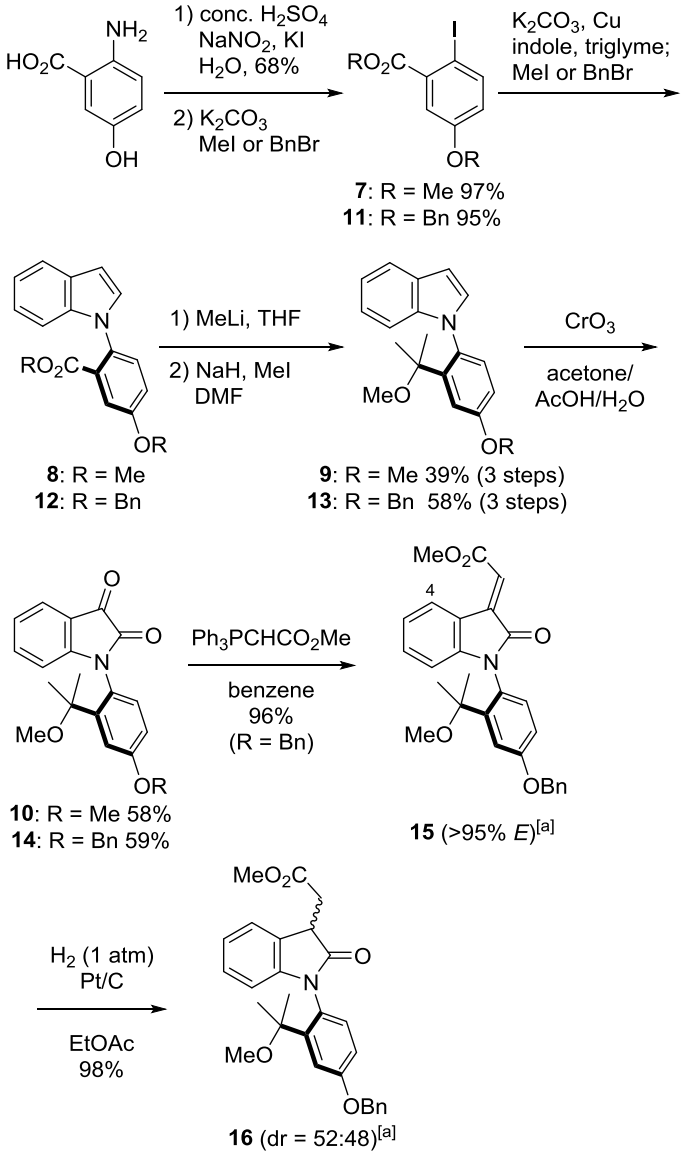
5a: R = Me
5b: R = Bn
5c: R = *m*-MPM
5d: R = Nap
5e: R = TBS

6a: R = Me
6b: R = Bn
6c: R = *m*-MPM
6d: R = Nap
6e: R = TBS

	protection					*oxidation*	
entry	reagents	solvent	temp.	indole	yield	isatin	yield
1	MeI, NaH	THF	0 °C → rt	**5a**	97%	**6a**	73%
2	BnCl, NaH	DMF	0 °C → rt	**5b**	93%	**6b**	60%
3	*m*-MPMBr, NaH	DMF	0 → 55 °C	**5c**	84%	**6c**	67%
4	NapBr, NaH	DMF	0 °C → rt	**5d**	–	**6d**	33%[a]
5	TBSOTf, 2,6-lutidine	CH_2Cl_2	–78 °C → rt	**5e**	81%	**6e**	68%

[a] 2 step yield.

Synthesis of *ortho*-monosubstituted *N*-aryl isatins 10 and 14, and oxindoles 15 and 16: We next synthesized *ortho*-monosubstituted *N*-aryl isatins **10** and **14**, and 3-alkylidene oxindole **15** and 3-alkyl oxindole **16** (Scheme 4). The three-step sequence involving C-N coupling of indole and iodoarene **7**, prepared from 2-amino-5-hydroxybenzoic acid according to the literature,[15] nucleophilic addition of MeLi, and subsequent methylation of the resulting *tert*-hydroxy group provided *N*-aryl indole **9**. Based on the *ortho*-disubstituted system, oxidation of this indole with CrO_3 gave the corresponding *N*-aryl isatin **10** in moderate yield. Synthesis of benzyl-protected *N*-aryl isatin **14** was conducted in a similar manner, and derivatives **15** and **16** were transformed from the resulting isatin **14** under conventional conditions. Wittig olefination of isatin **14** with phosphorane provided oxindole **15** in excellent yield as a single *E*-isomer, whose stereochemistry was confirmed by the NOESY correlation between the methyl group on the ester and the C4-hydrogen. Hydrogenation of the resulting alkene in **15** was performed with Pt/C in EtOAc under a hydrogen atmosphere (1 atm) to provide oxindole **16** as a diastereomeric mixture.[16]

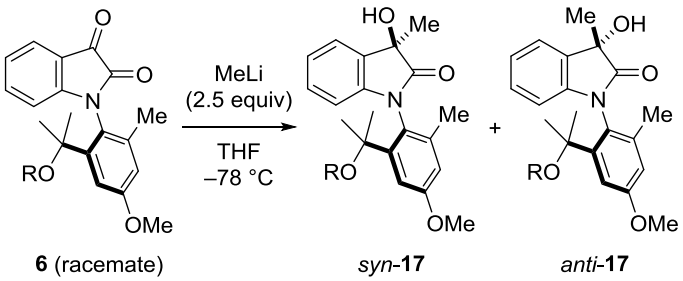


Scheme 4. Synthesis of isatins **10** and **14**, and oxindoles **15** and **16**. [a] Determined by ^{1}H NMR analysis after purification.

Nucleophilic addition to *ortho*-disubstituted *N*-aryl isatins 6a-e: At the outset, we examined the nucleophilic addition of MeLi to isatins **6a-e** in order to investigate the effect of the protective groups on the side chain in the *ortho*-position (Table 2). Treatment of methyl-protected isatin **6a** with 2.0 equiv of MeLi (LiBr free) in THF at –78 °C led to the corresponding adduct *syn*-**17a** and *anti*-**17a** in quantitative yield as a 75:25 mixture (entry 1). The relative stereochemistry was confirmed by X-ray crystallographic analysis and derivatizations as discussed below; MeLi attacked

from the less hindered diastereoface, as expected. To improve the diastereoselectivity, the reaction was examined using substrates with more hindered protective groups. Thus, the nucleophilic addition using benzyl surrogate **6b** was found to give **17b** in moderate yield with the same level of diastereoselectivity (*syn*:*anti* = 74:26, entry 2). The reactions of **6c** (R = *m*-MPM) and **6d** (R = Nap) with MeLi did not exhibit improved stereoselectivities (entries 3 and 4). To our surprise, the use of **6e** bearing a more hindered TBS group resulted in the formation of *anti*-**17e** as the major diastereomer, although the degree of diastereoselectivity was moderate (*syn*:*anti* = 39:61, entry 5). The exact origin of the stereochemical changeover observed in entry 5 is still obscure at present; however, we assumed that the top face of the carbonyl group in isatin **6e** would become accessible via a pyramidal amide structure, which was supported by X-ray crystallographic analysis of *syn*-**17e**,[17] although this is not direct evidence for the structure of **6e** in a solution. The relative stereochemistries of the resulting methyl adducts **17a-e** were determined by comparison of ^{1}H NMR spectra of the derivatives prepared from the major isomer of the TBS analogue *anti*-**17e**, whose epimer *syn*-**17e** was established by X-ray crystallographic analysis.[18] The axial chirality of the *ortho*-disubstituted oxindole system was found to be stable, as determined by heating **17a** (*syn*:*anti* = 75:25) in toluene at 105 °C for 19 h with no observed change in diastereomeric ratio. The results from Table 2 indicate that two diastereofaces of the carbonyl group would not be effectively discriminated by the *ortho*-disubstituted aryl group even though one side chain is a hindered [(alkoxy)dimethyl]methyl group. We attributed the low diastereoselectivity to the shielding the less hindered carbonyl face by the *ortho*-methyl group. In order to improve the diastereoselectivity, we next explored the diastereoselective reactions using *ortho*-monosubstituted *N*-aryl oxindole systems.

Table 2. Nucleophilic addition of MeLi to *ortho*-disubstituted isatins **6a-e**.[a]



6 (racemate) *syn*-**17** *anti*-**17**

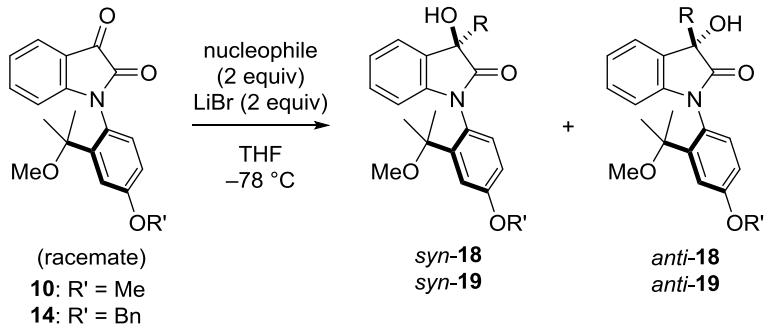
entry	substrate	R	product	yield[b]	*syn*:*anti*[c]
1[d,e]	**6a**	Me	**17a**	90%	75:25
2	**6b**	Bn	**17b**	78%	74:26
3[f]	**6c**	*m*-MPM	**17c**	76%	75:25
4[f]	**6d**	Nap	**17d**	90%	76:24
5	**6e**	TBS	**17e**	61%	39:61

[a] LiBr-free MeLi was used. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] 2.0 equiv of MeLi was used. [e] **6a** was recovered in 6% yield. [f] Reaction was carried out at –78 to –25 °C.

Nucleophilic addition to *ortho*-monosubstituted *N*-aryl isatins 10 and 14: Nucleophilic addition to isatin **10** or **14**[19] with various nucleophiles was next examined, and the results are shown in Table 3. *N*-Aryl isatin **10** was subjected to LiBr-free MeLi at –78 °C to generate the corresponding oxindole **18** in 70% yield with high diastereoselectivity (*syn*:*anti* = 88:12, entry 1). It is worth noting that the benzyl group on the lower aryl group was found to be essential for the high diastereoselectivity; the related reaction using benzyl surrogate **14** gave the corresponding methyl adduct **19a** in 85% yield with 92:8 diastereomeric ratio (entry 2). Addition of LiBr dramatically improved the yield of methyl adduct **19a** with the same level of diastereoselectivity (97% yield, dr = 94:6, entry 3). This trend was observed with other nucleophiles such as allyllithium and phenyllithium (entries 4 vs 5 and entries 6 vs 7). The reaction of *N*-aryl isatin **10** with EtLi under the optimized conditions provided the corresponding oxindole **19d** in 68% yield with high diastereoselectivity (*syn*:*anti* = 91:9, entry 8). The optimized conditions allowed for

introduction of a versatile functionality, a trimethylsilylethynyl moiety, to afford **19e** in 77% yield with high diastereoselectivity (*syn*:*anti* = 91:9, entry 9). Nucleophilic addition with a Grignard reagent resulted in diminished diastereoselectivity, probably due to the chelation of the organomagnesium reagents (entry 10). The addition of MeZnCl, prepared from $ZnCl_2$ and LiBr-free MeLi,[20] was also attempted; however, a low chemical yield and diastereomeric ratio were observed (7% yield, *syn*:*anti* = 81:19) along with 67% of unreacted **14** (entry 11). The polarity of solvent was also important in this reaction; less polar solvent systems such as THF-Et_2O resulted in slightly lower diastereoselectivities (*syn*:*anti* = 84:16, entry 12). In contrast, the addition of hexamethylphosphoramide (HMPA) enhanced the diastereoselectivity of adduct **19b**, which was obtained in 76% yield as a single diastereomer (entry 13). We finally achieved the remote asymmetric induction by taking advantage of the axial chirality.

Table 3. Nucleophilic addition of various nucleophiles to racemic *N*-aryl isatin **10** or **14**.[a]



(racemate)
10: R' = Me
14: R' = Bn

syn-**18**
syn-**19**

anti-**18**
anti-**19**

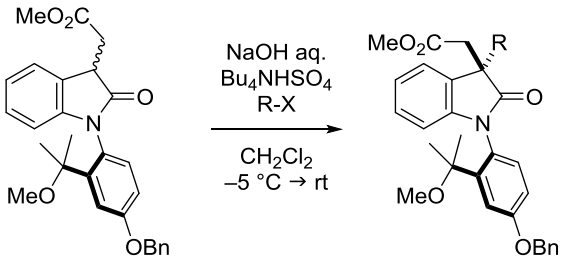
entry	substrate	R'	nucleophile	LiBr	product	yield[b]	*syn*:*anti*[c]
1[d]	**10**	Me	MeLi[e]	–	**18**	70%	88:12
2	**14**	Bn	MeLi[e]	–	**19a**	85%	92:8
3	**14**	Bn	MeLi[e]	+	**19a**	97%	94:6
4	**14**	Bn	PhLi[e]	–	**19b**	73%	86:14
5	**14**	Bn	PhLi[e]	+	**19b**	92%	88:12
6	**14**	Bn	CH_2=$CHCH_2$Li[f]	–	**19c**	77%	69:31
7	**14**	Bn	CH_2=$CHCH_2$Li[f]	+	**19c**	84%	68:32
8	**14**	Bn	EtLi[e]	+	**19d**	68%	91:9
9[g]	**14**	Bn	TMSC≡CLi	+	**19e**	77%	91:9
10	**14**	Bn	MeMgBr	+	**19a**	85%	55:45
11[h]	**14**	Bn	MeZnCl	+	**19a**	7%	81:19
12[i]	**14**	Bn	PhLi[e]	+	**19b**	98%	84:16
13[j]	**14**	Bn	PhLi[e]	+	**19b**	76%	>95:5

[a] Unless otherwise noted, reactions were conducted with 2 equiv of nucleophile and 2 equiv of LiBr at –78 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] 4 equiv of MeLi used. [e] LiBr-free nucleophile was used. [f] Prepared from allyltributyltin and *n*-BuLi. [g] Reaction was carried out at –78 to –10 °C. [h] *N*-Aryl isatin **14** was recovered in 67% yield. [i] THF/Et_2O (v/v = 1:1) was used. [j] 4 equiv of HMPA was used as a co-solvent.

The relative stereochemistry of the major diastereomer, *syn*-**19a**, was established by X-ray crystallographic analysis.[21] The relative stereochemistry of *syn*-**19d** was confirmed by NOESY analysis. The stereochemistry of *syn*-**19e** was determined by NOESY after transformation into *syn*-**19d**.[18] The stereochemistry of oxindoles **18**, **19b**, and **19c** could be tentatively assigned by assuming analogous diastereoselectivity.

Other transformations using *ortho*-monosubstituted *N*-aryl oxindoles: Having found a promising oxindole system bearing an *ortho*-monosubstituted aryl group, we moved to investigate the construction of a quaternary carbon center at C3 in the oxindole scaffold by alkylation or cycloaddition. Alkylation of oxindole **16** with an aqueous solution of NaOH and excess MeI in the presence of tetrabutylammonium hydrogensulfate provided *syn*-**20a** in 70% yield as a single diastereomer (Table 4, entry 1).[22] Allylation and prenylation were also effective to synthesize *syn*-**20b** and *syn*-**20c** in moderate to high yields with high diastereoselectivities (entries 2 and 3). The relative stereochemistry of the resulting allylation product *syn*-**20b** was determined by NOESY analysis of *syn*-**20c** after conversion by olefin cross metathesis with 2-methyl-2-butene.[18]

Table 4. Alkylation of oxindole **16** with several alkylation agents.



16 (dr = ca. 50:50)[a]

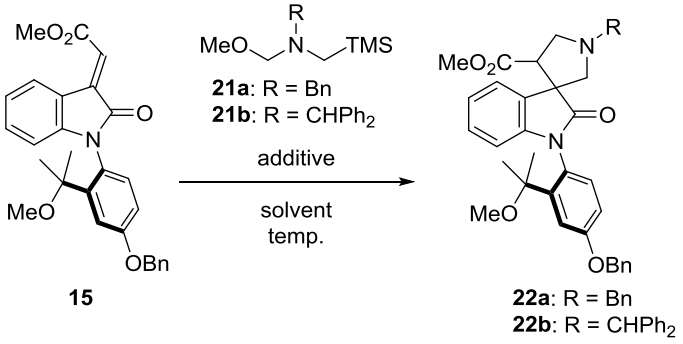
syn-**20a**: R = Me
syn-**20b**: R = allyl
syn-**20c**: R = prenyl

entry	R-X	yield	*syn*:*anti*[a]
1	methyl iodide	**20a** 70%	>95:5
2	allyl bromide	**20b** 85%	>95:5
3	prenyl bromide	**20c** 63%	>95:5

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.

We next examined the [3 + 2] cycloaddition of **15** with two different azomethyne ylides derived from *N*,*O*-acetals **21a**[23] and **21b** (Table 5). The reaction provided the corresponding [3 + 2] adducts **22a** and **22b** in excellent yields with low diastereoselectivities, irrespective of the steric hindrance of the azomethyne ylides and reaction conditions.[24]

Table 5. [3 + 2] cycloaddition of **15** with azomethyne ylides under various conditions.

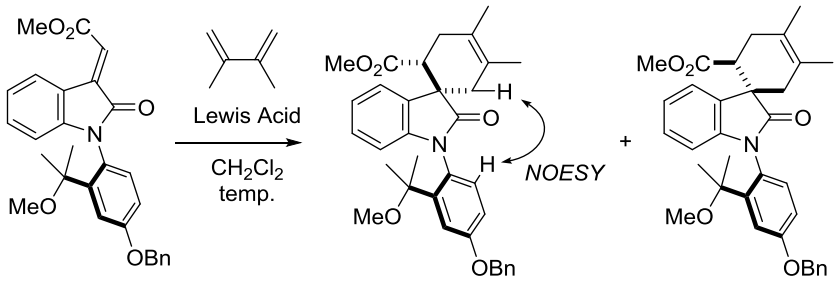


entry	*N*,*O*-acetal	additive	solvent	temp.		yield[a]	dr[b]
1	**21a**	CF_3CO_2H	toluene	rt	**22a**	quant.	65:35
2	**21a**	CF_3CO_2H	toluene	0 °C	**22a**	74%	61:39
3	**21a**	CF_3CO_2H	toluene	–40 → –5 °C	**22a**	86%	60:40
4	**21a**	AgF	MeCN	rt	**22a**	94%	57:43
5	**21a**	CsF	MeCN	rt	**22a**	52%	60:40
6	**21a**	LiF	MeCN	rt → 35 °C	**22a**	92%	62:38
7	**21b**	CF_3CO_2H	toluene	rt	**22b**	quant.	66:34

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of mixture of diastereomers after purification.

In contrast, the Diels-Alder cycloaddition of **15** with 2,3-dimethyl-1,3-butadiene in the presence of various Lewis acids gave the corresponding adduct in good yields with high facial selectivities (Table 6). Although the addition of $MgCl_2$ or LiBr afforded desired adduct **23** in low yield with good diastereoselectivity (*syn*:*anti* = 88:12, entries 1 and 2),[25] the reaction with $Sc(OTf)_3$ resulted in the formation of **23** in 91% yield with the same level of diastereoselectivity (entry 3). Changing the reaction conditions did not significantly affect the diastereoselectivities (entries 4-6). The relative stereochemistry of the resulting major diastereomer of Diels-Alder adduct *syn*-**23** was confirmed by NOESY analysis.[18]

Table 6. Diels-Alder reaction of **15** with 2,3-dimethylbutadiene in the presence of Lewis acids.



15 *syn*-**23** *anti*-**23**

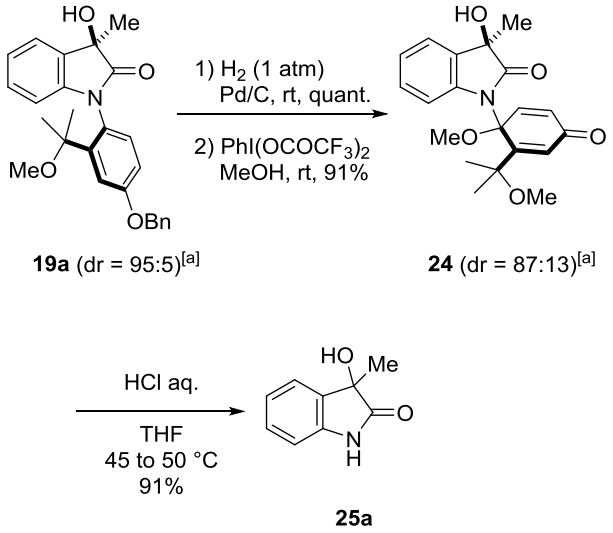
entry	Lewis Acid (eq)	temp.	**23** yield[a] (*syn*:*anti*)[b]	Recovered **15** yield[a]
1	$MgCl_2$ (2.0)	rt	35% (88:12)	62%
2	LiBr (14)	rt	48% (88:12)	39%
3	$Sc(OTf)_3$ (1.0)	rt	91% (87:13)	—
4[c]	$Sc(OTf)_3$ (1.0)	rt	92% (88:12)	—
5	$Sc(OTf)_3$ (1.0)	0 °C	72% (91:9)	29%
6	$Sc(OTf)_3$ (0.25)	rt	52% (87:13)	30%

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of mixture of isomer after purification. [c] Toluene was used as a solvent.

Removal of the aryl group: The final task was to remove the aryl moiety in the stereochemically defined oxindoles by oxidative cleavage of the C-N bond. Removal of the 4-(alkoxy)phenyl group on the nitrogen of amides has been easily achieved using CAN.[26,7q] However, we anticipated that it might be difficult to remove the aryl moiety, because the formation of the indispensable iminium intermediate could be interrupted by steric hindrance owing to the buttressing effect of the *ortho*-substituent(s) on the *N*-aryl group in our systems. Indeed, attempted cleavage of the C-N bond of *ortho*-disubstituted *N*-aryl oxindole **17a** or its phenol derivative did not give desired 3-hydroxy-3-methyloxindole **25a** with oxidants such as CAN, AgO/HNO_3, $PhI(OAc)_2$, $PhI(OCOCF_3)_2$, Fremy's salt, and IBX.

In contrast, removal of the aryl group in the *ortho*-monosubstituted system was achieved with $PhI(OCOCF_3)_2$.[27] Thus, deprotection of the benzyl group in **19a**[28] and subsequent oxidative cleavage using 2 equiv of $PhI(OCOCF_3)_2$ in MeOH at room temperature afforded *N*,*O*-acetal **24** in excellent overall yield (Scheme 5). Interestingly, introduction of the methoxy group took place stereoselectively (dr = 87:13), indicating that the axial chirality in **19a** was transmitted to the central

chirality of the *N*,*O*-acetal carbon with high diastereoselectivity. Hydrolysis of the resulting **24** under acidic conditions (1 M of HCl aq. at 45 to 50 °C) furnished the desired oxindole **25a** in 91% yield.



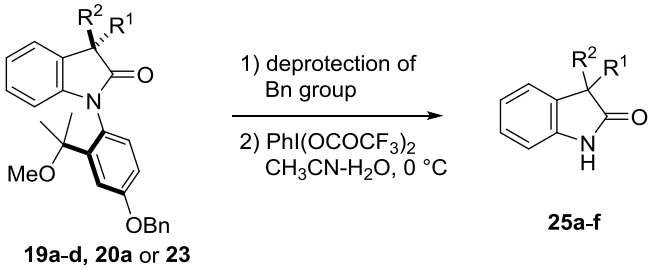
19a (dr = 95:5)[a] **24** (dr = 87:13)[a] **25a**

Scheme 5. Stepwise removal of the aryl moiety in oxindole **19a**. [a] Diastereomeric ratio was determined by ^{1}H NMR analysis.

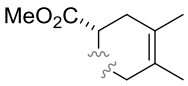
Oxidation and subsequent hydrolysis were carried out in a one-pot manner when aqueous MeCN was employed instead of MeOH (Table 7).[29] Deprotection of the benzyl group in the oxindoles under hydrogenolysis (method A: Pd/C, H_2) or under Lewis acidic conditions ($AlCl_3$ and Me_2NPh), followed by treatment of the resulting phenol with 1-1.3 equiv of $PhI(OCOCF_3)_2$ in aqueous MeCN at 0 °C furnished **25** in moderate to high overall yields. Especially in the case of acid-labile systems such as esters **20a** and **23**, the use of this one-pot method allowed for a clean transformation in high yield. In contrast, the stepwise method including hydrolysis with aqueous HCl resulted in a complex mixture for **25e** or the formation of desired **25f** in <41% yield. Pyrrolidine derivative **22a** smoothly underwent removal of the aryl moiety in the same manner after conversion of the *N*-benzyl group into a methoxycarbonyl group (Scheme 6).[30] To the best of our knowledge, this is the first example of the effective removal of an aryl moiety from amides after

atroposelective transformation; this procedure would be applicable to the oxidative cleavage of aryl groups in other acid-labile *N*-aryl amides as well.

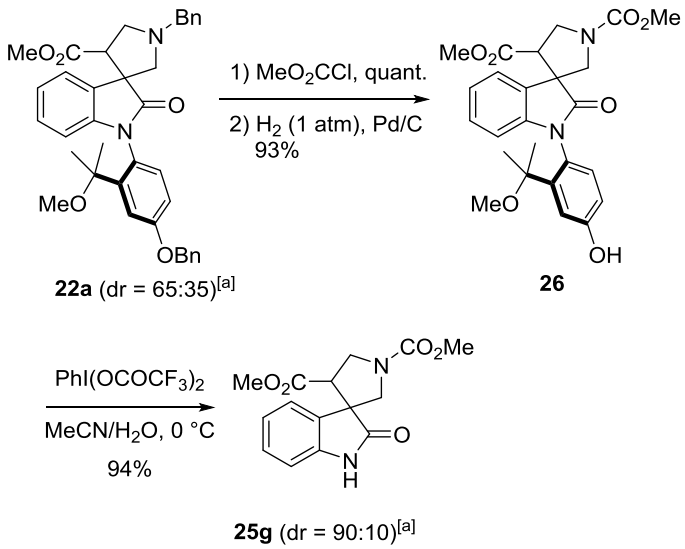
Table 7. Improved method for removal of aryl moiety.



19a-d, 20a or **23** **25a-f**

entry	substrate	R^1	R^2	deprotection method[a]	deprotection yield[b]	removal of aryl moiety	removal of aryl moiety yield[b]
1	**19a**	Me	OH	A	quant.	**25a**	83%
2	**19b**	Ph	OH	B	70%[c]	**25b**	50%
3	**19c**	allyl	OH	B	94%[c]	**25c**	55%
4	**19d**	Et	OH	A	quant.	**25d**	74%
5	**20a**	Me	CH_2CO_2Me	A	93%	**25e**	59%
6	**23**			A	quant.	**25f**	80%[d]

[a] Method A: H_2 (1 atm), Pd/C, MeOH, rt; Method B: $AlCl_3$, *N*,*N*-dimethylaniline, CH_2Cl_2, rt. [b] Isolated yield. [c] Combined yield of the corresponding phenol and isopropenylphenol derivatives. [d] dr = >95:5, determined by ^1H NMR analysis.



22a (dr = 65:35)[a] **26**

25g (dr = 90:10)[a]

Scheme 6. Removal of aryl moiety in **22a**. [a] Diastereomeric ratio was determined by ^1H NMR

analysis.

Conclusions

In summary, we developed a divergent approach towards the diastereoselective synthesis of 3,3-disubstituted oxindoles with a stereogenic center at C3, from newly designed axially chiral *N*-aryl oxindoles. Removal of the *p*-(benzyloxy)aryl moiety was achieved under mild conditions, implying that this protocol is applicable to other amide systems as well. Our method allows for the divergent and stereoselective incorporation of various functionalities at C3 into oxindole scaffolds of considerable synthetic and medicinal interest.[31]

Acknowledgments

This work was supported by the Uehara Memorial Foundation, and Grant-in-Aid for Young Scientists (B) (No. 21790026 and 23780115) and Grant-in-Aid for Scientific Research (C) (No. 25450151) from MEXT. We thank Dr. Kenji Yoza (Bruker AXS) for the X-ray crystallographic analysis.

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[16] Newly generated stereogenic center in **6** was found to be easily epimerized during the purification (diastereomeric ratio of the crude mixture = 88:12).

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[18] For details see, the Supporting Information.

[19] The rotational barrier of *N*-aryl isatins **14** for racemization was estimated to be 31.1 kcal/mol (298 K). For details, see the Supplementary data.

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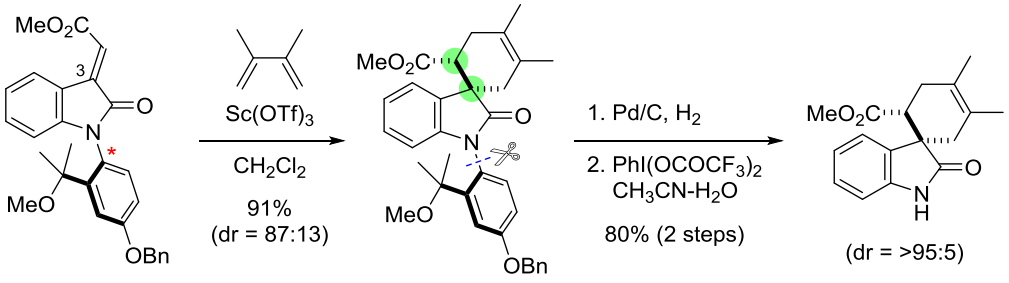
[29] For a related example of removal of *p*-siloxyphenyl group on an amine by oxidation with $PhI(OCOCF_3)_2$ in $MeCN/H_2O$ after deprotection of the silyl group, see: Y. Hayashi, W. Tsuboi, M. Shoji, N. Suzuki, *J. Am. Chem. Soc.* **2003**, *125*, 11208-11209.

[30] Based on the observation of high diastereoselectivities of cycloadducts **25f** (>95:5) and **25g** (90:10), we attributed that low diastereoselectivities of compounds **23** (88:12) and **22a** (65:35) were derived from the facial selectivities induced by the axial chirality. In addition, we did not detected epimerization of the α-carbonyl position under the reaction conditions of removal of the lower aryl moiety.

[31] We have demonstrated the synthesis of enantioenriched 3,3-disubstituted oxindole from a chiral non-racemic *N*-aryl isatin. Nucleophilic addition of MeLi and subsequent removal of the aryl moiety furnished 3-hydroxy-3-metheyloxindole in good overall yield without loss of stereochemical integrity. For details, see: ref [13].

Table of Contents



3,3-Disubstituted oxindoles were divergently synthesized by diastereoselective transformations including nucleophilic addition, alkylation, and cycloaddition using common, axially chiral *N*-aryl oxindoles. Notably, high diastereoselectivities (up to >95:5) were observed with *ortho*-monosubstituted *N*-aryl oxindoles to give various oxindole scaffolds, and facile removal of the *p*-(benzyloxy)aryl moiety in axially twisted amides was achieved by a mild, two-step sequence.