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Diastereoselective synthesis of 3,3-disubstituted oxindoles from atropisomeric *N*-aryl oxindole derivatives

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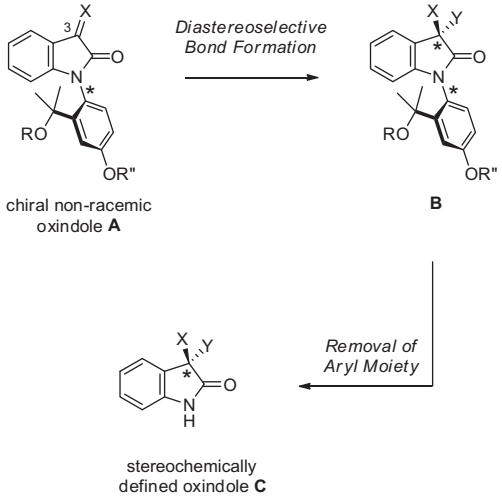
ABSTRACT

Diastereoselective synthesis of 3,3-disubstituted oxindoles has been examined by transformations involving nucleophilic addition, alkylation, and cycloaddition using chiral racemic *N*-aryl oxindoles bearing C–N axial chirality. The most striking features of this approach are high diastereoselectivities (up to >95:<5) when using *ortho*-monosubstituted *N*-aryl oxindoles and easy removal of the *p*-(benzyloxy)aryl moiety in the axially twisted amides by a mild two-step sequence.

3,3-Disubstituted oxindoles having a stereogenic center at C3 are attractive targets in organic synthesis because of their significant biological activities and wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and pharmaceuticals.[1] Hence, numerous methods based on enantioselective transformations have been established for constructing the oxindole skeleton.[2] Diastereoselective synthesis has not been attempted frequently because of the positions of introduced chiral auxiliary limited.[3] During the course of our studies on the stereocontrolled synthesis of 3,3-disubstituted oxindole,[4] we designed a chiral non-racemic *N*-aryl oxindole **A** with axial chirality on the C–N bond as a new chiral building block (Scheme 1) and attempted to use it for the diastereocontrolled synthesis of various oxindole scaffolds.[5] After the diastereomeric bond formation, removal of the aryl moiety in **B** by oxidative cleavage of the C–N bond would afford a stereochemically defined oxindole **C**. Herein, we report diastereoselective transformations involving nucleophilic addition, alkylation, and cycloaddition using chiral racemic oxindoles, which are relatively easier to synthesize than the non-racemic ones, and discuss the facial selectivity. The most striking features of this approach are as follows: (1) high diastereoselectivities (up to >95:<5) are observed when using *ortho*-monosubstituted *N*-aryl oxindoles and (2) the *p*-(benzyloxy)aryl moiety in the twisted amides can be removed by a two-step sequence involving oxidation under mild conditions, that is, oxidation in the presence of $PhI(OCOCF_3)_2$, in $MeCN–H_2O$ at 0 °C.

Results of the nucleophilic addition of isatin **1**[6,7] with various nucleophiles are presented in Table 1. Treatment of **1** with 2 equiv of MeLi (LiBr free) afforded the corresponding oxindole **2a** in good yield with high diastereoselectivity (*syn*:*anti* = 92:8, entry 1), while



Scheme 1. General scheme for stereocontrol of the C3-stereogenic center of oxindole by axial chirality.

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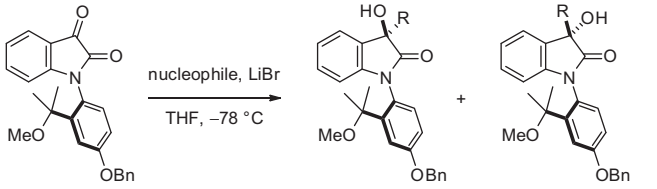
Table 1
Nucleophilic addition of various nucleophiles to racemic isatin **1**



1 (racemate) *syn*-**2** *anti*-**2**

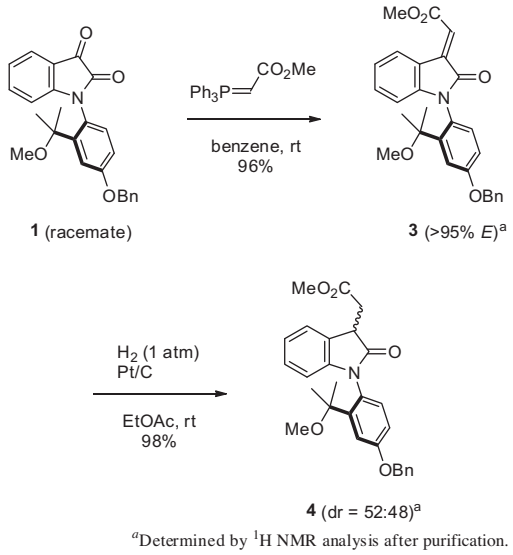
Entry	Nucleophile		Yield (%)	(syn:anti)[a]
1[b]	MeLi	**2a**	85	(92:8)
2	MeLi	**2a**	97	(94:6)
3	EtLi	**2b**	68	(91:9)
4	PhLi	**2c**	92	(88:12)
5	CH_2=$CHCH_2Li$	**2d**	84	(68:32)
6[c]	TMSC≡CLi	**2e**	77	(91:9)
7[b]	MeMgBr	**2a**	85	(55:45)
8[d]	PhLi	**2c**	98	(84:16)
9[e,f]	PhLi	**2c**	76	(>95:<5)

[a] Determined by ^{1}H NMR analysis.
[b] In the absence of LiBr.
[c] Reaction was carried out at −78 to −10 °C.
[d] Et_2O was used as a co-solvent.
[e] HMPA was used as a co-solvent.
[f] Unreacted isatin **1** was recovered in 19% yield.

the related reaction in the presence of LiBr afforded the same product in a much higher yield (97%) but with almost the same level of diastereoselectivity (entry 2). The relative stereochemistry of the major diastereomer, *syn*-**2a**, was confirmed by X-ray crystallographic analysis.[8] Thus, it was apparent that MeLi attacked from the less hindered face, as expected. Although the allylation of **1** resulted in a low diastereoselectivity, other nucleophiles, including lithium trimethylsilylacetylide, gave excellent results (entries 3–6).[9] Nucleophilic addition with a Grignard reagent (MeMgBr) resulted in a diminished diastereoselectivity, probably because of chelation between the metal center of the nucleophile and the methoxy group on the side chain (entry 7).[10] Solvent polarity also played a significant role in this reaction. A slight decrease in diastereoselectivity was observed when the reaction was performed in THF–Et_2O, although the yield of **2c** was high (entry 8). In contrast, **2c** was obtained in 76% yield as a single diastereomer when the reaction was carried out in the presence of the polar hexamethylphosphoramide (HMPA) (entry 9). Thus, the remote asymmetric induction utilizing the axial chirality was achieved.

We next focused on the construction of the quaternary carbon center at C3 by alkylation or cycloaddition. Substrates **3** and **4** for these reactions were prepared as shown in Scheme 2. Wittig olefination of **1** with the phosphorane afforded the corresponding oxindole **3** as the single *E*-isomer in excellent yield. Hydrogenolysis of the resulting **3** by Pt/C in EtOAc under hydrogen atmosphere (1 atm) gave oxindole **4** as a diastereomeric mixture.[11]

Alkylation of **4** with an aqueous solution of NaOH and excess MeI in the presence of tetrabutylammonium hydrogen sulfate gave **5a** in 70% yield as a single diastereomer (Fig. 1).[12] Allylation and prenylation were also effective for the diastereoselective synthesis of **5b** and **5c** in moderate-to-high yields. [3+2] Cycloaddition of **3** with azomethine ylide, however, did not afford the desired level of diastereoselectivity. Thus, the azomethine ylide generated in situ from *N*-benzyl-*N*-methoxymethyl-*N*-trimethylsilylmethylamine[13] and TFA in toluene was treated with α,β-unsaturated oxindole **3** to obtain the desired pyrrolidine derivative **6a** in quantitative yield, albeit with low diastereoselectivity (dr = 65:35). The steric hindrance of the protective group in the azomethine ylide,



Scheme 2. Preparation of oxindoles **3** and **4**.

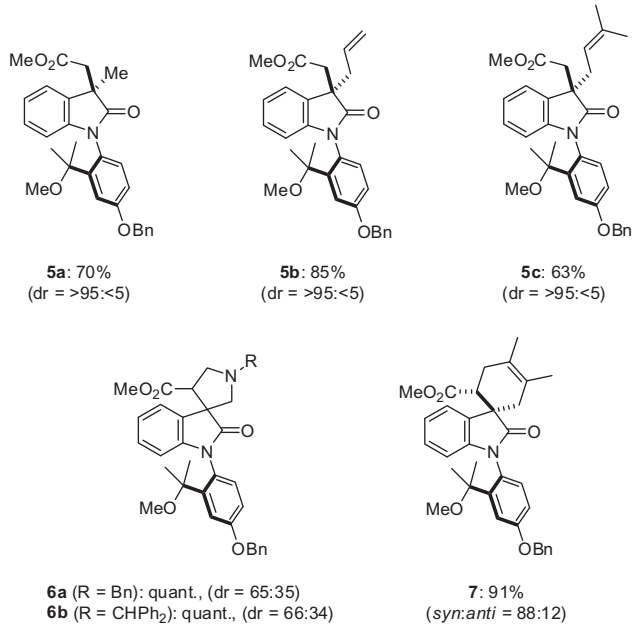
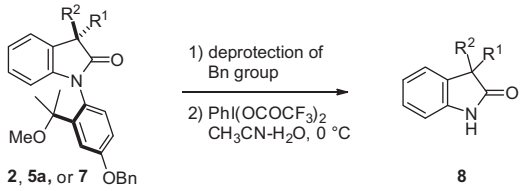


Figure 1. Alkylation of oxindole **4** and cycloaddition of α,β-unsaturated oxindole **3**.

nevertheless, did not affect the stereoselectivity (**6b**: dr = 66:34). In contrast, the Diels–Alder cycloaddition of **3** with excess 2,3-dimethyl-1,3-butadiene in the presence of 1.0 equiv of $Sc(OTf)_3$ at room temperature gave the corresponding adduct **7** in 91% yield with high facial selectivity (*syn*:*anti* = 88:12).

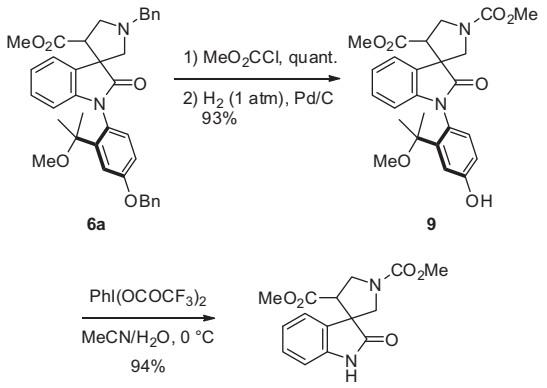
Finally, the aryl moiety had to be removed by an oxidative cleavage of the C–N bond. After intensive studies, $PhI(OCOCF_3)_2$ was found to be effective for this purpose (Table 2).[14–16] Deprotection of the benzyl group in the *N*-aryl oxindoles by hydrogenolysis (method A: Pd/C, H_2) or under Lewis acidic conditions (method B: $AlCl_3$ and Me_2NPh), followed by treatment of the resulting phenol with 1–1.3 equiv of $PhI(OCOCF_3)_2$ in the aqueous MeCN at 0 °C, led to the formation of **8** in moderate-to-high overall yield.[17] In particular, the use of this method allowed for clean transformation in the case of acid-labile systems such as ester series **5a** and **7**. The aryl

Table 2
Removal of *p*-(benzyloxy)aryl moiety



Entry	Substrate	R^1	R^2	Deprotection method[a]	Yield	Removal of aryl moiety	Yield (%)
1	**2a**	Me	OH	A	Quant.	**8a**	83
2	**2b**	Et	OH	A	Quant.	**8b**	83
3	**2c**	Ph	OH	B	70%[b]	**8c**	50
4	**2d**	Allyl	OH	B	94%[b]	**8d**	55
5	**5a**	Me	CH_2CO_2Me	A	83%	**8e**	59
6	**7**	MeO_2C		A	Quant.	**8f**	80[c]

[a] Method A: H_2 (1 atm), Pd/C, MeOH, rt; Method B: A1C1$_3$, *N*,*N*′-dimethylaniline, CH_2C1_2, rt.
[b] Combined yield of the corresponding phenol and isopropenylphenol derivatives.
[c] dr = >95:<5, determined by ^{1}H NMR analysis.



Diastereomeric ratio was determined by ^{1}H NMR analysis.

Scheme 3. Removal of aryl moiety in **6a**.

moiety in pyrrolidine derivative **6a** was smoothly removed in the same manner after conversion of the *N*-benzyl group into a methoxycarbonyl group (Scheme 3).[17] Thus, the sequential transformation could be performed under mild conditions to remove the *p*-(benzyloxy)phenyl group bearing a hindered *ortho*-substituent, even though it was introduced in the axially twisted amide system. To the best of our knowledge, this is the first example of the effective removal of an aryl moiety from the core amide after atroposelective transformation,[18] and this procedure would be applicable to the oxidative cleavage of the aryl group in other acid-labile *N*-aryl amides as well.

In summary, we have developed a method for the diastereoselective synthesis of 3,3-disubstituted oxindoles that incorporate a stereogenic center at C3, from newly designed chiral *N*-aryl oxindoles. Since a variety of reagents can be used in a highly stereoselective manner, various oxindole derivatives, which would be useful building blocks for alkaloid synthesis, can be obtained from a common *N*-aryl oxindole intermediate. Removal of the *p*-(benzyloxy)aryl moiety is possible even under mild conditions, which implies that this protocol is applicable to other amide systems as well. Asymmetric synthesis of chiral non-racemic oxindoles and application to the synthesis of oxindole alkaloids will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.092.

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6. Isatin **1** bearing *ortho*-monosubstituted aryl group was prepared from commercially available 2-iodo-5-hydroxybenzoic acid and indole in good overall yield as a racemic form. See the Supplementary data.
7. The rotational barrier of *N*-aryl isatins **1** for racemization was estimated to be 31.1 kcal/mol. For details, see the Supplementary data.
8. Crystallographic data for *syn*-**2a** have been deposited in the Cambridge Crystallographic Data Centre (CCDC 895008).
9. Relative stereochemistry of *syn*-**2b** was determined by NOESY analysis. The stereochemistry of *syn*-**2e** was determined by NOESY analysis after transformations into *syn*-**2b**. Oxindoles **2c** and **2d** could be tentatively assigned by assuming an analogous diastereoselectivity.
10. MeZnCl was also used for this reaction, however low chemical yield and diastereomeric ratio were observed (7% yield, *syn*:*anti* = 81:19) along with 67% of unreacted **1**.
11. Newly generated stereogenic center in **4** was found to be easily epimerized during the purification (diastereomeric ratio of the crude mixture = 88:12).
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16. Oxidative cleavage of the C–N bond in **2a** or its phenol derivative was not effective when CAN, $PhI(OAc)_2$, PhI(OH)OTs, Fremy's salt, or DDQ was used.
17. Based on the observation of high diastereoselectivities of cycloadducts **8f** (>95:<5) and **8g** (90:10), we attributed that lower disatereoselectivities of compounds **6a** (65:35) and **7** (88:12) 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.
18. Transformation to phenol is crucial for achievement of removal of the lower aryl moiety. Direct oxidative cleavage from benzyl-protected *N*-aryl oxindole with various oxidants did not succeed. Related unsuccessful results were reported in Ref. 5e,j.