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Stereoselective Synthesis of 3-Alkylideneoxindoles Using Tandem In-Mediated Carbometalation and Pd-Catalyzed Cross-Coupling Reaction

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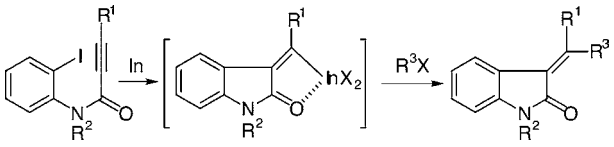
ABSTRACT



Efficient methods for stereoselective synthesis of various (*E*)-, (*Z*)-, and disubstituted 3-alkylideneoxindoles were investigated using tandem In-mediated carbometalation and ligandless Pd-catalyzed coupling reaction.

Oxindoles are important constituents of natural indole alkaloids,[1] drug candidates,[2] and metabolic intermediates. Among them, 3-alkylideneoxindoles are well-known to be versatile compounds in terms of biological activity and synthetic applicability. For example, (*E*)-alkylideneoxindoles are important synthetic intermediates of TMC-95A[3] as well as drug candidates of tyrosine kinase inhibitors[4] and anti-rheumatic compounds.[5] Similarly, much attention has been directed to (*Z*)-alkylideneoxindoles as promising inhibitors of tyrosin kinase[4] and cyclin-dependent protein kinases.[6] However, despite their importance, stereoselective synthesis of these (*E*)- and (*Z*)-3-alkylideneoxindoles remains a difficult problem.[3,7] In addition, stereoselective synthesis of 3-disubstituted 3-alkylideneoxindoles, which are expected to have unique biological activity, has not been achieved.

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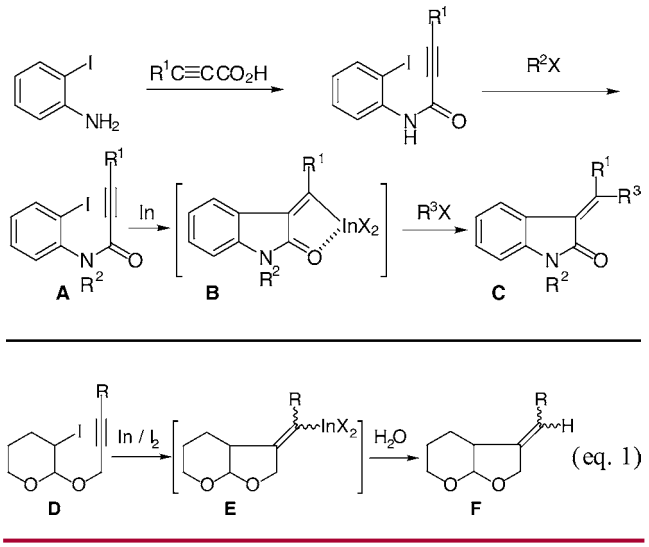
Therefore, development of a stereoselective and diversity-oriented approach for synthesis of such 3-alkylideneoxindoles (**A**→**C**) are in high demand (Scheme 1). We have already

Scheme 1



reported reductive cyclization of **D** with In and iodine to prepare 3-alkylidenehexahydrofuro[2,3-*b*]pyrans **F**.[8] The intramolecular carboindation of **D** occurred via vinylindium intermediate **E** to give a mixture of (*E*)- and (*Z*)-isomers **F** in good yield with moderate stereoselectivity (1/1−8/1) of *E*/*Z* (eq 1). We expected that in the case of iodo-ynamide **A**, stereochemically defined alkene **C** would be obtained predominantly if the indium atom coordinates to the amide-carbonyl group in **B**. Here we report the first stereoselective synthesis of (*E*)-, (*Z*)-, and disubstituted 3-alkylideneoxindoles **C** using tandem indium-mediated carbometalation and palladium-catalyzed cross-coupling reaction.

We initially examined the cyclization of **1a** under the reaction conditions developed previously (In and I_2 in DMF, Table 1).[8a,c] Although the cyclization product **3a** was obtained exclusively, the chemical yield of **3a** was only 40% due to recovery of the starting material **1a** in 45% yield (run 1). After optimization of the reaction conditions, we found that additives had a dramatic effect on the reaction rate. When Br_2 was added to the reaction mixture instead of I_2, 5-*exo* cyclization proceeded smoothly to give (*E*)-**3a** in 81% yield as a single isomer (run 2).[9,10] Furthermore, it was revealed that pyridinium tribromide (Py·HBr_3) could be used for this reaction instead of Br_2, but the combination of In and NBS provided no desired product (runs 3 and 4). We preferred to use Py·HBr_3 due to its easy handling. To investigate the

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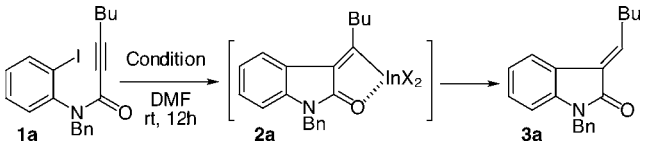
Table 1. Reductive Radical Cyclization Reaction



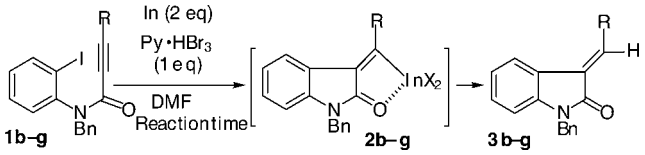
run	condition	yield (%) **3a** (*E*:*Z*)	**1a**
1	In (2 equiv) + I_2 (1 equiv)	40 (*E*)	45
2	In (2 equiv) + Br_2 (1 equiv)	81 (*E*)	0
3[a]	In (2 equiv) + Py·HBr_3 (1 equiv)	80 (*E*)	0
4	In (2 equiv) + NBS (1 equiv)	0	80
5	Bu_3SnH (1.2 equiv) + Et_3B (1.2 equiv)	59 (2:1)	0
6	$InCl_3$ (0.1 equiv) + $NaBH_4$ (2.0 equiv)	19 (1.1:1)	50

[a] Reaction mixture of compound **1** (1 mmol), In (2 mmol), Py·HBr_3, or Br_2 (1 mmol) in DMF (2 mL) was stirred for 12 h at room temperature under an argon atmosphere.

potentiality of other reagents, **1a** was treated with Bu_3SnH[11] and $InCl_3$−$NaBH_4$,[12] affording the mixture of (*E*)- and (*Z*)-alkenes **3a** in a ratio of 1/1 to 2/1 (runs 5 and 6). These results suggests that the (*E*)-selective production in the In-mediated reaction was due to strong coordination of the indium atom to the amidecarbonyl group of the intermediate **2a**. It has been reported that the coordination of indium reagents to a hydroxy group of the substrate can be used to control stereogenic centers.[13]

Having established the optimized reaction conditions for **3a**, we next applied these conditions to synthesize various (*E*)-3-alkylideneoxindoles **3b**−**g**. Representative results are shown in Table 2. Except for **1f** and **1g**, the In-mediated

Table 2. Reductive Radical Cyclization Reaction for Synthesis of (*E*)-Alkenes



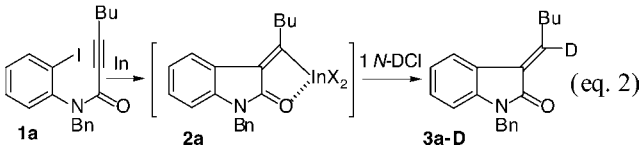
run	**1**	R	reaction time (h)	**3**	yield (%) (*E*:*Z*)
1	**1b**	Et	24	**3b**	75 (*E*)
2[a]	**1c**	CH_2OBn	24	**3c**	70 (*E*)
3	**1d**	*p*-CF_3−Ph	18	**3d**	75 (*E*)
4	**1e**	Ph	24	**3e**[7a]	80 (*E*)
5	**1f**	*p*-CH_3−Ph	18	**3f**	84 (19:1)
6	**1g**	*p*-MeO−Ph	18	**3g**	80 (10:1)

[a] Two folds of In and Py·HBr_3 was used.

cyclizations of **1b**−**e** under the same conditions gave the desired products **3b**−**e** as single isomers in good yields (runs 1−4). In contrast, treatment of **1f** and **1g**, each bearing an

electron-donating group on the aromatic ring in the R group, with In and Py·HBr_3 provided the corresponding (*E*)-isomers **3f**−**g** along with (*Z*)-isomers as minor products (runs 5 and 6). The ratio of *Z*/*E* was dependent on the substituents on the aromatic ring in the R group. Substrates bearing a more electron-donating group in the R group tended to provide a (*Z*)-isomer with a higher *Z*/*E* ratio.

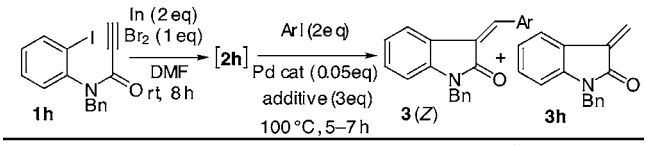
To confirm the existence of the vinylindium intermediate **2a**, the reaction mixture of **1a** was quenched with 1*N*-DCl, resulting in the production of the deuterated product (*E*)-**3a-D** (75% D) (eq 2). Since this observation confirmed the



involvement of **2a**, we next examined the reaction of vinylindium intermediate **2h** and aryl halides in the presence of a palladium catalyst to give (*Z*)-alkenes **3** stereoselectively (Table 3). Pd-catalyzed cross-coupling reactions of vinylindiums and aryl halides have already been reported by Sarandeses, Yamamoto, Araki, Oshima, and our group.[8a,8c,14] Treatment of the vinylindium intermediate **2h** prepared from **1h** with 4-iodotoluene and 0.05 equiv of $^6Pd(PPh_3)_4$[14b] afforded the coupling product (*Z*)-**3f** in 30% yield along with the protonated product **3h** (run 1). Since the (*E*)-isomer **3f** could not be identified in the reaction mixture, the (*Z*)-selectivity was revealed to be very high. To improve the chemical yield, we examined cross-coupling reactions with various palladium catalysts other than $Pd(PPh_3)_4$. Although the reaction of **2h** with $Pd(acac)_2$ gave a mixture of (*Z*)-alkene **3f** and **3h**, we found that the addition of LiBr (3 equiv),[8c,13] together with $Pd(acac)_2$, accelerated the coupling reaction, giving the expected (*Z*)-alkene **3f** as a single isomer in 60% yield (runs 2 and 3). The same subjection of vinylindium **2h** to the coupling reaction with several aryl iodides produced the corresponding (*Z*)-alkenes **3e**, **3d**, and **3i** exclusively (runs 4−6). In this way, we accomplished a novel stereoselective synthesis of several (*Z*)-3-alkylideneoxindoles **3** from **1h** by a tandem intramolecular carboindation and ligandless Pd-catalyzed cross-coupling reaction[15] via **2h**, though the chemical yields of (*Z*)-**3** need to be improved. This ligandless process should be a useful method from the viewpoint of cost, purification of the reaction mixture, and atom economy.

Having succeeded in the synthesis of (*E*)- and (*Z*)-3-alkylideneoxindoles, we finally undertook the stereoselective synthesis of disubstituted 3-alkylideneoxindoles **4**. Tandem cross-coupling reactions of **1e** with several aryl iodides via vinylindium **2e** were carried out under the conditions in the presence of $Pd(acac)_2$ and LiBr. In all cases, the corresponding disubstituted 3-alkylideneoxindoles **4** were obtained in good yields with no contamination of other stereoisomers. Since stereoisomer **4a** (*E*) of **4a** (*Z*) could be prepared starting from **1f** and iodobenzene by the same procedure, the stereoselectivity was unambiguously determined by a comparison of their ^1H NMR spectra. In addition, it is notable that a *p*-methoxyphenyl group could be introduced with perfect retention of the configuration in the synthesis of **4c**, in sharp contrast to the synthesis of **3g**. Generally, the coupling reaction into disubstituted 3-alkylideneoxindoles **4** proceeded not only with perfect stereoselectivity but also in better yield than that of the corresponding (*Z*)-adducts. Consequently, this method provides an efficient route to disubstituted 3-alkylideneoxindoles, which can be regarded as oxindole analogues of the anti-breast cancer drug tamoxifen.[16] In summary, we have developed the first efficient methods for stereoselective and diversity-oriented synthesis

Table 3. Tandem Carboindation and Cross-Coupling Reaction for (*Z*)-Alkenes



run	Ar	Pd cat.	additive	yield (%) 3 (*Z*)		3 h
1	*p*-CH_3Ph	$Pd(PPh_3)_4$	–	**3 f**	30	30
2	*p*-CH_3Ph	$Pd(acac)_2$	–	**3 f**	32	28
3	*p*-CH_3Ph	$Pd(acac)_2$	LiBr	**3 f**	60	0
4	Ph	$Pd(acac)_2$	LiBr	**3e**[7a]	60	0
5	*p*-CF_3Ph	$Pd(acac)_2$	LiBr	**3 d**	78	0
6		$Pd(acac)_2$	LiBr	**3 i**	55	0

(9) We tried to observe the cyclic voltammograms of In with I_2 and In with Br_2 in DMF to consider the differences in the reactions, referring to the previous results of SmI_2 and $SmBr_2$, which showed remarkable potential differences.[10] However, no clear redox responses involving In ions were observed. This is presumably due to the less electroactive nature of In. Actually, the electrochemical data of In have been scarcely available up to now.

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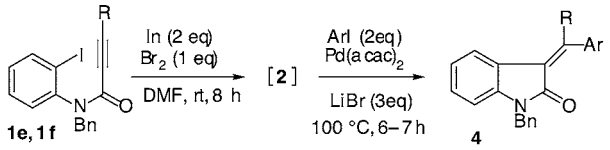
Table 4. Tandem Carboindation and Cross-Coupling Reaction for Disubstituted 3-Alkylideneoxindoles



run	**1**	R	Ar	yield (%) **4**	
1	**1 e**	Ph	*p*-CH_3Ph	**4a** (*Z*)	80
2	**1 e**	Ph	*p*-CF_3Ph	**4 b**	78
3	**1 e**	Ph	*p*-MeOPh	**4 c**	73
4	**1 e**	Ph		**4 d**	70
5	**1 f**	*p*-CH_3Ph	Ph	**4a** (*E*)	80

of various (*E*)-, (*Z*)-, and disubstituted 3-alkylideneoxindoles using tandem In-mediated carbometalation and ligandless Pd-catalyzed coupling reaction. The key step is the first stereoselective carboindation reaction of **1a**−**g** using the strong coordination ability of an indium atom. Our method provides a versatile tool for the total synthesis of natural products and for random screening to find drug candidates.

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Supporting Information Available: Information on general experimental procedures and on characteristics of synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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