DOI: 10.1002/adsc.200505147

Stereoselective Synthesis of 3-Alkylideneoxindoles using Tandem Indium-Mediated Carbometallation and Palladium-Catalyzed Cross-Coupling Reactions

Reiko Yanada,[a] Shingo Obika,[a] Yusuke Kobayashi,[a] Tsubasa Inokuma,[a] Munetaka Oyama,[b] Kazuo Yanada,[c] Yoshiji Takemoto[a,*]

[a] Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
Fax: (+81)-75-753-4569, e-mail: takemoto@pharm.kyoto-u.ac.jp
[b] Division of Research Initiatives, International Innovation Center, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan
[c] Faculty of Pharmaceutical Sciences, Setsunan University, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan

Received: April 9, 2005; Accepted: July 1, 2005

This paper is dedicated to the memory of the late Professor Kiyoshi Tanaka.

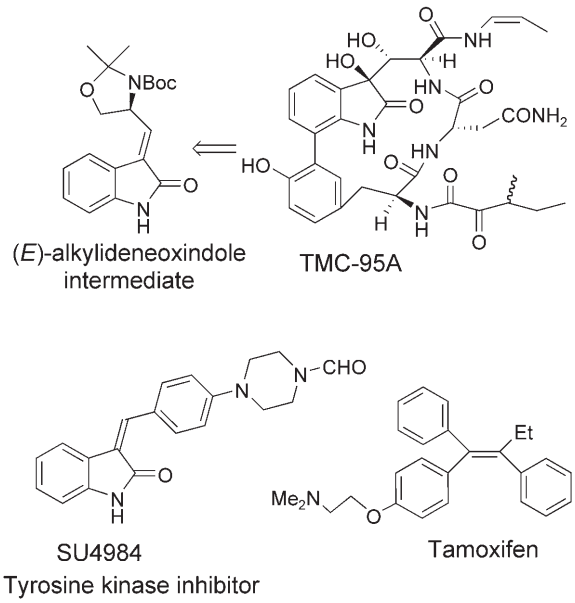
Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The first efficient methods for the stereoselective synthesis of various (*E*)-, (*Z*)-, and disubstituted 3-alkylideneoxindoles *via* radical cyclization reactions were investigated using tandem indium-mediated carbometallation and palladium-catalyzed cross-coupling reactions. The proper combination of substrates and reaction conditions is important for good yields. The key step is the first stereoselective carboindation reaction using the strong coordination ability of an indium cation to the amide carbonyl oxygen. We applied this method to the synthesis of TMC-95A precursor. A new *N*-debenzylation method with *N*-hydroxyphthalimide-O_2-$Co(OAc)_2$-$Mn(OAc)_2$ was also developed using a one-electron oxidation procedure.

Keywords: indium; oxindoles; palladium; radicals; stereoselective; vinylindium

Introduction

Various methods for regio- and stereoselective syntheses of substituted olefins have been developed using a wide variety synthetic methods.[1,2] On the other hand, oxindoles belong to an important class of natural indole alkaloids,[3] drug candidates[4] and metabolic intermediates. Among them, 3-alkylideneoxindoles are well known to be versatile compounds in terms of synthetic applicability and biological activity. For example, (*E*)-alkylideneoxindoles are important synthetic intermediates of TMC-95A[5] (Scheme 1). Much attention has also been directed to (*E*)- and (*Z*)-alkylideneoxindoles as promising inhibitors of tyrosine kinase such as SU4984 (Scheme 1),[6] cyclin-dependent protein kinase inhibitors,[7] and antirheumatic agents.[8] However, despite their importance, the stereoselective synthesis of (*E*)- and (*Z*)-3-alkylideneoxindoles remains difficult.[5,9] Stereoselective synthesis of disubstituted 3-alkylideneoxindoles has also not been achieved despite the fact that these compounds are expected to have unique biological activity due to their similarity to the anti-



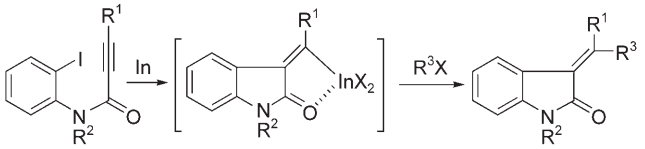
Scheme 1.

breast cancer drug tamoxifen. Therefore, the development of a stereoselective and diversity-oriented approach for the synthesis of (*E*)-, (*Z*)- and disubstituted 3-alkylideneoxindoles is highly demanded and a considerable challenge for the organic chemists. We have recently reported the stereoselective synthesis of 3-alkylideneoxindoles (Scheme 2).[10] Herein, we present a detailed account of the scope and limitations of this method. We have not only developed modified reaction conditions for the synthesis of (*E*)-, (*Z*)- and disubstituted 3-alkylideneoxindoles but have also developed the first oxidative radical approach for debenzylation of *N*-benzylamide with *N*-hydroxyphthalimide (NHPI)-O_2-$Co(OAc)_2$-$Mn(OAc)_2$.

Results and Discussion

In-Mediated Radical Cyclization of 2-Iodoynamides

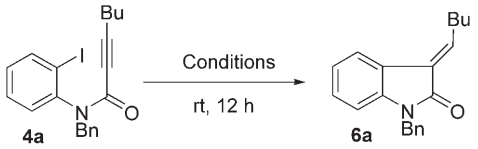
To initiate our examination of In-mediated radical cyclizations, 2-iodoalkynes **4a**–**4u** were synthesized in the usual manner in moderate yields as shown in Scheme 3.



Scheme 2.

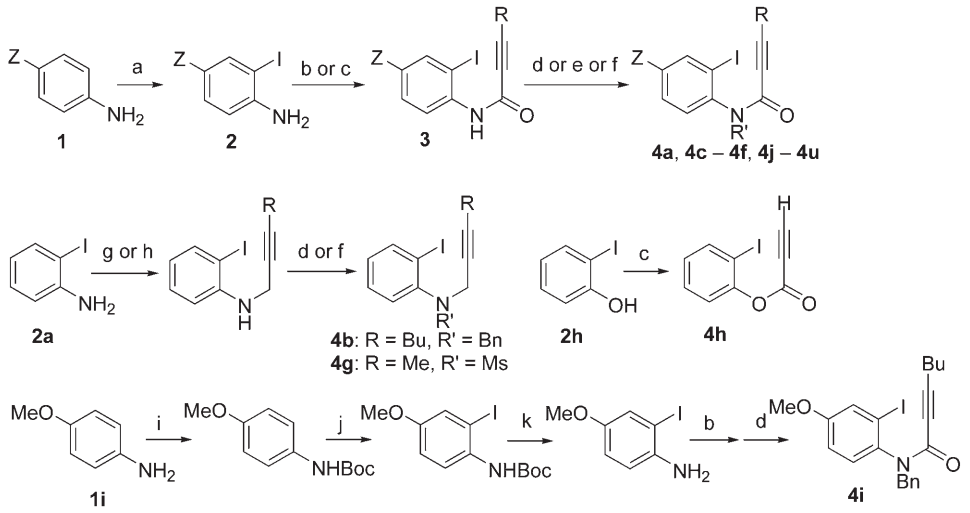
We initially focused on the cyclization of **4a** under the reaction conditions previously developed (In and I_2 in DMF).[11] Although the cyclization product (*E*)-**6a** was obtained exclusively, the chemical yield of **6a** was only 40% due to the recovery of the starting material **4a** in 45% yield (Table 1, 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*-radical cyclization smoothly proceeded to give (*E*)-**6a** in 81% yield as a single isomer (run 2). Furthermore, it was revealed that pyridinium tribromide ($Py \cdot HBr_3$) could be used for this reaction instead of Br_2 (run 3). We preferred to use $Py \cdot HBr_3$ due to its easy handling. In contrast, treatment of **4a** with In and NBS provided no desired product (run 4). In order to confirm whether these stereoselective cyclizations proceeded *via* a radical mechanism,[11c] the reaction of compound **4a** with In and $Py \cdot HBr_3$ was carried out in the presence of 2 equivs. of galvinoxyl as a radical scavenger. The yield of **6a** decreased to only 12% and most of the starting material **4a** (75%) was recovered. This result indicated that the cyclization proceeded *via* a radical mechanism by a single electron

Table 1. Optimization of reaction conditions.

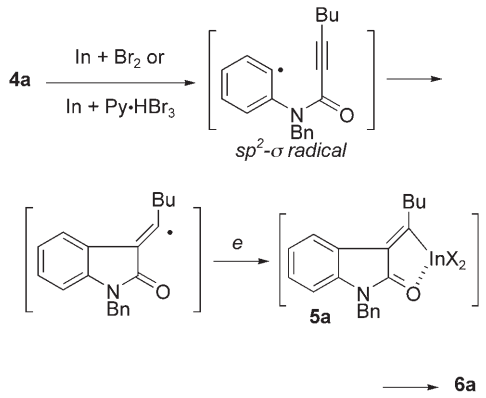


Run	Conditions	Yield [%]	
		6a (*E*:*Z*)	**4a**
1	In (2 equivs.) + I_2 (1 equiv.)	40 (*E*)	45
2	In (2 equivs.) + Br_2 (1 equiv.)	81 (*E*)	0
3	In (2 equivs.) + $Py \cdot HBr_3$ (1 equiv.)	80 (*E*)	0
4	In (2 equivs.) + NBS (1 equiv.)	0	80
5	InI (2 equivs.)	32 (*E*)	55
6	InBr (2 equivs.)	45 (*E*)	40
7	$InCl_3$ (0.1 equiv.) + $NaBH_4$ (2 equivs.)	19 (1.1:1)	50
8	Bu_3SnH (1.2 equivs.) + Et_3B (1.2 equivs.)	59 (2:1)	0

transfer process from indium.[12] These results suggest that this reaction proceeds by InX and/or InX_2 (X = I and Br) produced from the oxidation of In(0) with X_2. Therefore, we used commercially available InI and InBr instead of the combination of In and X_2. The reactions with these reagents gave (*E*)-**6a** as a single product but in lower yields (runs 5 and 6) because of the inferior solubility of commercially available InI and InBr in DMF. To clarify the origin of the exclusive formation of the (*E*)-isomer, **4a** was subjected to typical radical reaction conditions using metal hydrides such as $InCl_3$-$NaBH_4$,[13] and Bu_3SnH-Et_3B.[14] These reactions afforded a mixture of (*E*)- and (*Z*)-alkenes **6a** in a ratio of 1/1 to 2/1 (runs 7 and 8). It is thought that the In-mediated cyclization reaction with In-Br_2 or In-$Py \cdot HBr_3$ might effectively proceed *via* an sp^2-σ radical intermediate, and the (*E*)-selective alkene production was attributed to strong coordination of the indium atom to the amide carbonyl group of the intermediate **5a** (Scheme 4). It has been reported that similar coordination of indium reagents to a hydroxy group of the substrate can be used to control stereogenic centers.[15] The efficient formation of **6a** in the case of In-Br_2 and In-$Py \cdot HBr_3$ can be explained on the basis of redox potentials.[16] It is known that the oxidation potential of In(0) is more negative to the reduction potentials of Br_2 and I_2 and that the reduction potential of Br_2 is positive to that of I_2. Thus, cationic states of In can be formed in the presence of Br_2 or I_2 as a thermodynamically favorable process, and the formation is particularly promoted by Br_2. We tried to observe cyclic voltammograms of In with Br_2 and In with I_2 in DMF in order to obtain further information about the differences in the reactions, referring to previous results for SmI_2 and $SmBr_2$ showing remarkable potential differences.[17] However, no clear redox responses involving In ions were observed. This is presumably due to the less electro-active nature of In. Actually, electro-



Scheme 3. Preparation of 2-iodoalkynes **4a**–**4u**. *Reagents and conditions:* (a) benzyltrimethylammonium dichloroiodate ($BTMAICl_2$) (1.1 equivs.), $CaCO_3$ (1.3 equivs.), CH_2Cl_2: MeOH = 5:2, room temperature, 24 h; 83–97%; (b) 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (1.2 equivs.), $RCCCO_2H$ (1.1 equivs.), CH_3CN, room temperature, 16 h; 60–80%; (c) i) *n*-BuLi (1.1 equivs.), THF, −78 °C, 30 min, ii) $RCCCO_2Me$ (1.5 equivs.), 3 h; 50–70% except for **3l** (7%) and **3m** (27%); (d) BnBr (1.1 equivs.), Cs_2CO_3 (2 equivs.), TBAI (tetrabutylammonium iodide) (0.1 equiv.), DMF, room temperature, 13 h; 80–92%; (e) MeI (1.1 equivs.), NaH (1.1 equivs.), room temperature, 5 h; 90%; (f) MsCl (1.1 equivs.), Et_3N (1.5 equivs.), room temperature, 8 h; 78–80%; (g) 1-bromohept-2-yne (1.1 equivs.), K_2CO_3 (3 equivs.), acetone, reflux, 1.5 h, 79%; (h) 1-bromobut-2-yne (1.1 equivs.), K_2CO_3 (3 equivs.), acetone, reflux, 1.5 h, 79%; (i) Boc_2O (1.5 equivs.), Et_3N (1.1 equivs.), THF, room temperature, 5 h, 72%; (j) i) *t*-BuLi (2.2 equivs,), Et_2O, −78 °C, 30 min; ii) ICH_2CH_2I (1.5 equivs.), room temperature, 6 h, 79%; (k) CF_3CO_2H (1.2 equivs.), CH_2Cl_2, 0 °C → room temperature, 3 h, 91%.



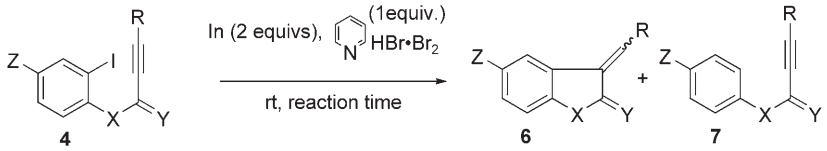
Scheme 4.

chemical data of In are scarcely available up to now. Finally, the optimal reaction conditions of runs 2 and 3 were used for the following examinations.

Scope and Limitation of the Reactants

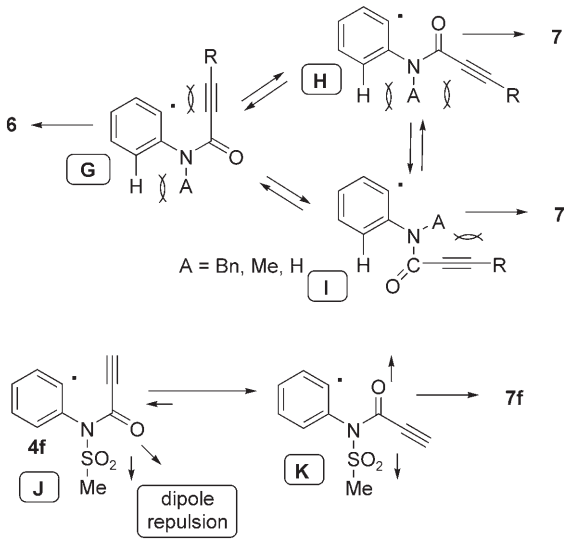
We next investigated the optimal amide moiety for the In-mediated reaction. The reaction of benzylamide **4a** with In and $Py \cdot HBr_3$ smoothly proceeded to give the cyclization product **6a** in good yield (Table 1, run 3). However when benzylaniline **4b** was used, the reaction could not yield the cyclization product but yielded compound **7b** (Table 2, run 1). It was proven that the amide carbonyl oxygen is necessary for the radical cyclization reaction with In. We examined several amides **4c**–**4e** bearing different protecting groups. The radical cyclization reaction smoothly proceeded to give **6c**–**6e**[18] (runs 2–4). It is thought that radical intermediates generated from **4c**–**4e** exist as a mixture of three rotamers **G**, **H** and **I** depicted in Scheme 5. In the case in which the *N*-protecting group is benzyl (A = Bn), rotamer **G** is predominant. When A is small, rotamers **H** and **I** are more stable than rotamer **G**. Then the proportion of rotamers **H** and **I** might increase according to the decrease of bulkiness of the *N*-substituents. Therefore, the hydrogenated products **7d**[19] and **7e** might be produced along with compounds **6d**[20] and **6e** (runs 3 and 4). In contrast to compound **4f**, compound **4g** bearing a methanesulfonyl group on the nitrogen atom smoothly gave the reductive radical cyclization products **6g** as a mixture of (*E*)- and (*Z*)-olefins. They tended to gradually isomerize to indole derivatives (run 6). A possible reason for compound **4f** giving not a cyclized product but compound **7f** is that intermediate **K** was more predominant than intermediate **J** because of the less dipole repulsion between amidecarbonyl and methanesulfonyl groups. We also applied this radical cyclization reaction to the iodo ester **4h**. The reaction proceeded to give benzofuran-2-one **6h**,[21] which is well known as a potential inhibitor of angiogenesis,[22] together with compound **7h** (run 7). We next investigated the reaction of *para*-substituted

Table 2. Reductive radical cyclization reaction.



Run	4	Z	X	Y	R	Time [h]	Yields [%]			
							6	(*E*: *Z*)	7	
1	**4b**	H	NBn	H,H	Bu	12		0	**7b**	60
2	**4c**	H	NBn	O	H	12	**6c**	68		0
3	**4d**	H	NMe	O	H	12	**6d**	40	**7d**	40
4	**4e**	H	NH	O	H	12	**6e**	39	**7e**	45
5	**4f**	H	NMs	O	H	12		0	**7f**	55
6	**4g**	H	NMs	H,H	Me	5	**6g**	88 (1 : 1.1)		0
7	**4h**	H	O	O	H	24	**6h**	40	**7h**	40
8	**4i**	OMe	NBn	O	Bu	20	**6i**	27		0
9	**4j**	Me	NBn	O	Bu	20	**6j**	58		0
10	**4k**	Cl	NBn	O	Bu	40		0	**7k**	91
11	**4l**	CF_3	NBn	O	Bu	40		0	**7l**	71
12	**4m**	CN	NBn	O	Bu	40		0	**7m**	72

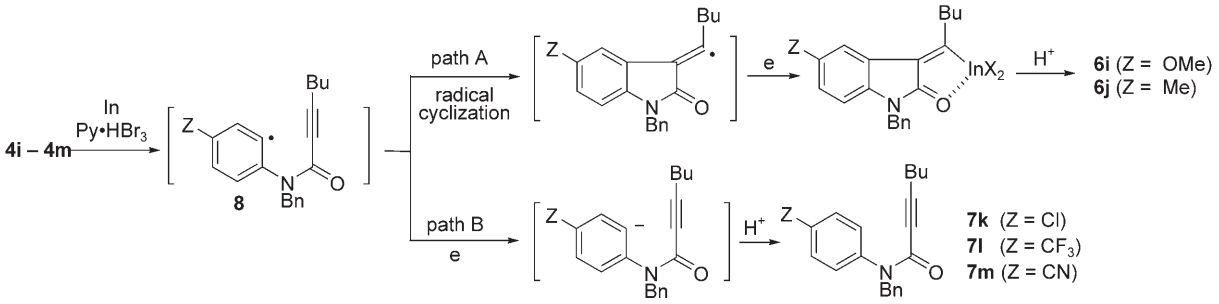
iodo-amides **4i**–**4m** in order to examine the substituent effects on aromatic ring and in order to synthesis 5-substituted indol-2-one derivatives as promising tyrosine kinase inhibitors.[6b, c] Reaction of compounds **4i** and **4j** bearing electron-donating groups (EDG) on the aromatic rings gave the desired cyclized products **6i** and **6j** but not in good yields (27% and 58%, respectively) accompanied by starting materials (20% and 39%) (runs 8 and 9). On the other hand, the reaction of compounds **4k**–**4m** bearing electron-withdrawing groups (EWG) on the aromatic rings gave no desired product but rather compounds **7k**–**7m** (runs 10–12). We propose the reaction mechanism illustrated in Scheme 6. Treatment of compounds **4i**–**4m** with In and Py·HBr_3 provides aryl radical intermediates **8**. It might be more difficult to dissociate the bond between an aromatic carbon and iodine when the aromatic ring has EDG. However, once the aryl radical **8** is formed, it is easily cyclized according to path A to give compounds **6i** and **6j** (runs 8 and 9). Since electron-releasing substituents will raise the energy of the singly occupied molecular orbital (SOMO), interaction of SOMO with the relatively low-lying LUMO of alkynes having electron-withdrawing groups would increase. In contrast to these results, it is easy to produce an aryl radical when Z is EWG, but this radical might have more electronic affinity. Then the reaction might proceed according to path B to produce compounds **7k**–**7m** (runs 10–12). It became clear that substituents on the aromatic rings significantly influence the reactivity of the aryl radical intermediates. In conclusion, an *N*-(iodophenyl)alkynylamide structure (Z = H) is the optimum structure for the In-mediated radical cyclization reaction.



Scheme 5.

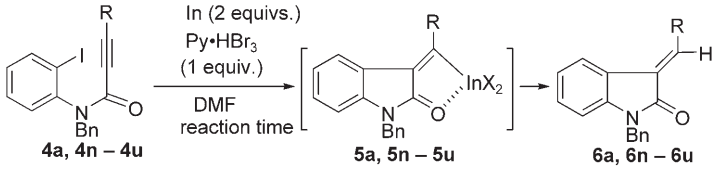
Stereoselective Synthesis of (*E*)-3-Alkylideneoxindoles

Having established the optimized reaction conditions and appropriate reactant structure, we next applied these conditions to synthesize various (*E*)-3-alkylideneoxindoles **6n**–**6u**. Representative results are shown in Table 3. The In-mediated cyclizations of **4a, 4n**–**4q** under the same reaction conditions gave the desired products **6a, 6n**–**6q** as single (*E*)-isomers in good yields (Table 3, runs 1–6). In the case of R = Me, both (*E*)- and (*Z*)-olefins were obtained (run 7). However, this problem was resolved only in that compound **4r** was added af-



Scheme 6. Reductive radical cyclization and reductive deiodination.

Table 3. Reductive radical cyclization reaction for the synthesis of (*E*)-alkenes.



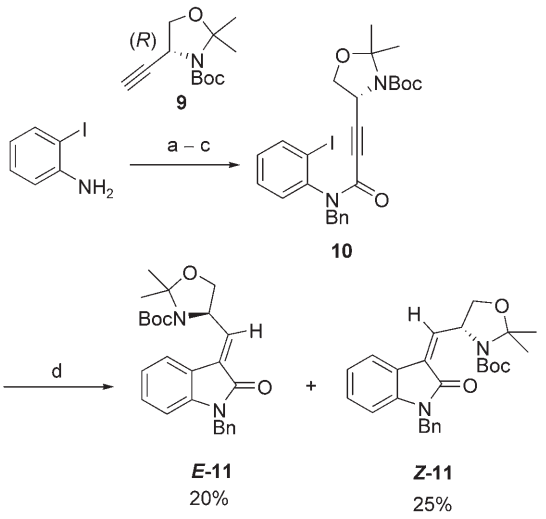
Run	**4**	R	Reaction time [h]	Yield [%] of **6** (*E*:*Z*)
1	**4a**	Bu	12	**6a** 80 (*E*)
2	**4a**	Bu	5	**6a** 80 (*E*)
3	**4n**	Et	24	**6n** 75 (*E*)
4[a]	**4o**	CH_2OBn	24	**6o** 70 (*E*)
5	**4p**	*p*-CF_3-C_6H_4	18	**6p** 75 (*E*)
6	**4q**	Ph	24	**6q** 80 (*E*)
7	**4r**	Me	24	**6r** 72 (1:1)
8	**4r**	Me	24	**6r** 70 (*E*)
9	**4s**	*p*-CH_3-C_6H_4	18	**6s** 84 (19:1)
10	**4t**	*p*-MeO-C_6H_4	18	**6t** 80 (10:1)
11	**4t**	*p*-MeO-C_6H_4	14	**6t** 80 (11:1)
12	**4u**		18	**6u** 70 (12:1)

[a] Two-fold amounts of In and Py·HBr_3 were used.

ter 5 minutes to the solution of In and Py·HBr_3 in DMF (run 8). In contrast, treatment of **4s**–**4u**, each bearing an electron-donating group (EDG) on the aromatic ring in the R group, with In and Py·HBr_3 predominantly provided the corresponding (*E*)-isomers **6s**–**6u** along with (*Z*)-isomers as minor products (runs 9–12). The ratio of *Z*/*E* was dependent on the substituents on the aromatic ring in the R group. Substrates bearing an electron-donating group in the R group tended to provide a (*Z*)-isomer as a minor adduct. Addition of water (20%) to the reaction mixture promoted the cyclization reaction (runs 2 and 11). It was found that during chromatography on silica gel (*Z*)-isomers were always eluted faster than (*E*)-isomers. In addition, the vinylic proton signals of (*E*)-isomers always appear at a lower field in the ^{1}H NMR spectrum than the corresponding signals of the (*Z*)-isomers due to the effect of the amide carbonyl oxygen.

Application to the Synthesis of a TMC-95A Precursor

We next applied the (*E*)-selective 3-alkylideneoxindole synthetic method to obtain a synthetic intermediate of TMC-95A as outlined in Scheme 7. (*E*)-**11**, an important TMC-95A intermediate, has been synthesized by some groups[5] but the ratio of (*E*)- to (*Z*)- was not high. We applied our procedure to the stereoselective synthesis of (*E*)-**11**. 2-Iodoaniline was reacted with triphosgene and sodium bicarbonate at room temperature,[23] resulting in the production of the corresponding isocyanate. Successive treatment of this isocyanate with lithium anion of compound **9**[24] in THF and with benzyl bromide in the presence of tetrabutylammonium iodide and cesium carbonate gave the desired ynamide **10** in 67% overall yield. In-mediated reaction of **10** under the optimal conditions proceeded smoothly, but unfortunately, a mixture of (*E*)- and (*Z*)-stereoisomers **11** was obtained in 20 and 25% yields, respectively. There are several possible reasons for this poor stereoselectivity of (*E*)-**11**.

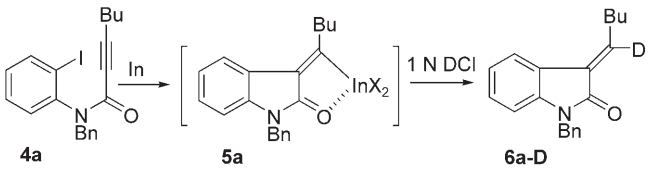


Scheme 7. Synthesis of a TMC-95A intermediate. a) triphosgene (0.33 equivs.), $NaHCO_3$ (excess), CH_2Cl_2/H_2O, room temperature, 2 h, 98%; b) *n*-BuLi (1.5 equivs.), **9** (1.5 equivs.), THF, $-78 \rightarrow -40\,^{\circ}C$, 4 h, 79%; c) BnBr (3 equivs.), TBAI (3 equivs.), Cs_2CO_3 (3 equivs.), DMF, room temperature, 3 h, 87%; d) In (2 equivs.), $Py \cdot HBr_3$ (1 equivs), DMF, room temperature, 6 h, 45%.

One possible reason is that only (*E*)-**11** was produced at the first stage of the radical cyclization reaction, but then an isomerization reaction from (*E*)-**11** to (*Z*)-**11** gradually took place at room temperature under these reaction conditions. Indeed, this isomerization reaction was confirmed using (*E*)-**11** under the reductive radical cyclization conditions.

Stereoselective Synthesis of (*Z*)-3-Alkylideneoxindoles

In order to confirm the existence of the vinylindium intermediate **5a**, the reaction mixture of **4a** was quenched with 1 N DCl, resulting in the production of the deuterated product (*E*)-**6a-D** (75% D) (Scheme 8). Since this observation confirmed the involvement of **5a**, we next examined the reaction of vinylindium intermediate **5c** and aryl halides in the presence of a palladium catalyst[11a,11c] (Table 4). Treatment of the vinylindium intermediate **5c**, prepared from **4c**, with 4-iodotoluene and 0.05 equivs. of $Pd(PPh_3)_4$ afforded the coupling product (*Z*)-**6 s** in 30% yield along with the protonated product **6c** (run 1). The low yield of **6 s** was attributed to the low reactivity of the vinylindium intermediate **5c**. Since the (*E*)-isomer **6s** could not be identified in the reaction mixture, the (*Z*)-selectivity was revealed to be very high. To improve the chemical yield, we tried to determine appropriate cross-coupling reaction conditions. We found that the addition of LiBr (3 equivs.)[11c,15f] together with $Pd(PPh_3)_4$[25] accelerated the coupling reaction to give the expected (*Z*)-alkene **6s** as a single isomer



Scheme 8.

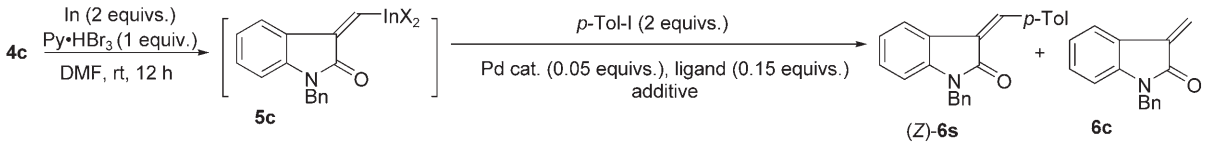
(run 2). This effect of LiBr could be explained as follows. The bromide anion of LiBr may coordinate to the indium atom of **5c** to form an indium ate complex (indates), whose In–C bond could be much more reactive than that of **5c** as an alkenyl donor. When we used $Pd(acac)_2$ as a ligandless palladium catalyst[26] with LiBr, (*Z*)-alkene **6s** was obtained in 60% yield as a single product (run 3). We accomplished a novel stereoselective synthesis of (*Z*)-3-alkylideneoxindole **6s** from **4c** by a tandem intramolecular carboindation and ligandless Pd-catalyzed cross-coupling reaction *via* **5c**. To improve the chemical yield of (*Z*)-**6s**, we continued to try to determine the optimum reaction conditions. After reductive radical cyclization of **4c**, tandem cross-coupling reaction of **5c** with *p*-tolyl iodide, $Pd(acac)_2$ (0.05 equivs.), and LiBr (1 equiv.) was examined at $50\,^{\circ}C$. The reaction produced the desired product (*Z*)-**6s** in only 10% yield (run 4). Our attention was directed to a more reactive Pd-carbon complex, $Pd(dba)_2$-NHC, developed recently.[27] The reaction of **4c** with $Pd(dba)_2$ and NHC [nitrogen heterocyclic carbene = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] in the presence of LiI and CuBr[28] proceeded smoothly even at $50\,^{\circ}C$, giving the desired adduct (*Z*)-**6s** in 75% yield (run 5). Although the Pd-NHC-catalyzed cross-coupling reaction did not occur without CuBr, use of 0.5 equivs. of CuBr along with 1 equiv. of LiI was sufficient to give the desired product (*Z*)-**6s** in good yield (run 6).

We applied this optimized method to the synthesis of some (*Z*)-alkenes. Table 5 shows representative results. Most of the reactions proceeded smoothly to give (*Z*)-alkenes in good yields (runs 1–3). When only 4-iodoanisole was used as an aryl halide, a mixture of (*Z*)- and (*E*)-alkene **6t** was obtained due to labile isomerization from (*Z*)- to (*E*)-isomer (run 4). We succeeded in obtaining compounds (*Z*)-**6** stereoselectively at a lower reaction temperature. Unfortunately, we did not succeed in the synthesis of **6v** using BuI as a cross-coupling reagent (run 5).

Stereoselective Synthesis of Disubstituted 3-Alkylideneoxindoles

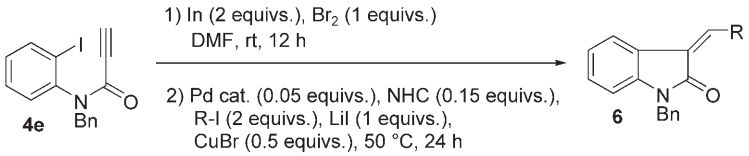
Tamoxifen, which has three aryl groups on the carbon-carbon double bond, is the most widely used antibreast cancer drug in clinical practice.[29] We anticipated that tamoxifen analogues **12** bearing tetrasubstitued olefins

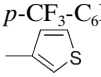
Table 4. Tandem carboindation and cross-coupling reaction for the synthesis of (*Z*)-alkenes.



Run	Pd cat., Ligand	Additive (equivs.)	Temperature [°C]	Reaction time [h]	Yield [%]	
					(*Z*)-**6 s**	**6c**
1	$Pd(PPh_3)_4$	–	100	7	30	30
2	$Pd(PPh_3)_4$	LiBr (3)	100	5	60	0
3	$Pd(acac)_2$	LiBr (3)	100	5	60	0
4	$Pd(acac)_2$	LiBr (3)	50	24	10	60
5	$Pd(dba)_2$, NHC	LiI (1), CuBr (1)	50	24	75	0
6	$Pd(dba)_2$, NHC	LiI (1), CuBr (0.5)	50	24	72	0

Table 5. Synthesis of (*Z*)-alkenes under new conditions.



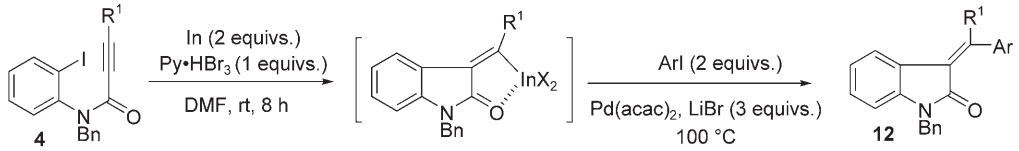
Run	R	Yield [%]	
		6	(*E* : *Z*)
1	Ph	**6q**	72 (*Z*)
2	*p*-CF_3-C_6H_4	**6p**	75 (*Z*)
3		**6u**	70 (*Z*)
4	*p*-MeO-C_6H_4	**6 t**	64 (1 : 2.4)
5	Bu	**6v**	0

could be prepared by using our new approach. Tandem cross-coupling reactions of **4** with several aryl iodides *via* a vinylindium intermediate were carried out in the presence of $Pd(acac)_2$ and LiBr at 100 °C. In all cases, the corresponding disubstituted 3-alkylideneoxindoles **12** were obtained in good yields with no contamination of other stereoisomers (Table 6, runs 1–6). Compound (*Z*)-**12a** was obtained from compound **4q** in high yield (run 1). The stereoisomer (*E*)-**12a** could also be prepared from **4s** by the same reaction procedure (run 2). The stereoselectivity of the products was unambiguously determined by a comparison of their ^1H NMR spectra. Regarding the effect of the amide carbonyl oxygen, the methyl proton signals bearing a phenyl ring of the (*Z*)-isomer appear at a lower field than the corresponding signal of the (*E*)-isomer. We also synthesized compounds (*Z*)-**12b** and (*E*)-**12b** (runs 3 and 4). It is notable that a *p*-methoxyphenyl group could be introduced with perfect retention of its configuration in the synthesis of **12c** (run 5) but not in the synthesis of **6t** (Table 5, run 4). Generally, the coupling reaction into disubstituted 3-alkylideneoxindoles **12** not only proceeded with perfect stereoselectivity but also gave 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 tamoxifen, widely used as an antibreast cancer drug. Stereoselective syntheses of tamoxifen analogues have been a subject of interest for organic and pharmaceutical chemists for many years.[30]

Debenzylation of 3-Alkylideneoxindoles by Oxidative Radical Reaction

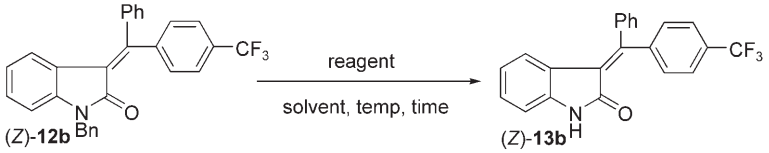
Crystal structures of the tyrosine kinase domain of FGFR1 (fibrobrast growth factor receptor 1) in complex with SU4984 and SU5402 were determined.[6a] It has been reported that oxindoles make two hydrogen bonds to the protein backbone of FGFR1K between N–H of the oxindoles and the carbonyl oxygen of Glu^{562} and between carbonyl oxygen of oxindoles and the amide pro-

Table 6. Tandem carboindation and cross-coupling reaction for the synthesis of disubstituted 3-alkylideneoxindoles.



Run	**4**	R^1	Ar	Reaction time [h]	Yield [%] of **12**	
1	**4q**	Ph	*p*-CH_3-C_6H_4	6	(*Z*)-**12a**	80
2	**4 s**	*p*-CH_3-C_6H_4	Ph	6	(*E*)-**12a**	80
3	**4q**	Ph	*p*-CF_3-C_6H_4	6	(*Z*)-**12b**	78
4	**4p**	*p*-CF_3-C_6H_4	Ph	5	(*E*)-**12b**	77
5	**4q**	Ph	*p*-MeO-C_6H_4	6	**12c**	73
6	**4q**	Ph		7	**12d**	70

Table 7. Debenzylation of 3-alkylideneoxindoles.

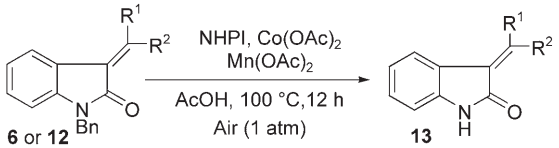


Run	Reagent	Solvent	Temperature	Time [h]	Yield [%] of **13b** (*E*:*Z*)
1	BBr_3	CH_2Cl_2	−78 °C	12	0
2	KO-*t*-Bu, O_2	DMSO	rt	6	0
3	CAN	$CH_3CN:H_2O=5:1$	rt	4	0
4	NBS, AIBN	chlorobenzene	reflux	12	95 (1:18)
5	NHPI, $Co(OAc)_2$, $Mn(OAc)_2$	AcOH	100 °C	12	93 (1:18)

ton of Ala[564]. Therefore, we examined some methods for debenzylation of compound (*Z*)-**12b** in order to obtain the deprotected oxindole compound (*Z*)-**13b**. We tried several deprotection methods. The reactions of (*Z*)-**12b** using the reagents like BBr_3,[31] KO*t*-Bu-O_2,[32] CAN,[33] NBS-AIBN,[34] and NHPI-O_2-metal system[35] were examined. The best and the same results were obtained when NBS-AIBN and NHPI-O_2-$Co(OAc)_2$-$Mn(OAc)_2$ reagent systems were used (Table 7, runs 4 and 5). A method for debenzylation from amide nitrogen with NBS-AIBN has already been reported.[34b] Ishii reported that an NHPI-O_2-metal system acts as a carbon radical-producing catalyst from the C–H bonds of alkanes, alkenes, alcohols, etc., under relatively mild conditions. We speculated that the reaction mechanism of this reagent system[35c] resembles the debenzylation mechanism using NBS-AIBN. We therefore examined the usefulness of this reagent system for oxidative radical debenzylation. Fortunately, debenzylation reaction proceeded smoothly with the use of this reagent system under air atmosphere to afford (*Z*)-**13b** almost stereoselectively (run 5).

Finally we applied this novel oxidative radical deprotection method to some oxindole derivatives in order to further develop deprotection methods. (*E*)-Oxindole **6a** and disubstituted oxindoles **12a** and **12b** were examined (Table 8). Their debenzylations proceeded smoothly to yield deprotected products in high yields along with small amounts of stereoisomers that were probably produced by thermal isomerization (runs 1–5). It was found that this NHPI-O_2-$Co(OAc)_2$-$Mn(OAc)_2$ system could

Table 8. Debenzylation of 3-alkylideneoxindoles.



Run	**6** or **12**	R^1	R^2	Yield [%]	
				13	(*E*:*Z*)
1	(*E*)-**6a**	Bu	H	(*E*)-**13c**	93 (99:1)
2	(*E*)-**12a**	*p*-CH_3-C_6H_4	Ph	(*E*)-**13a**	91 (96:4)
3	(*Z*)-**12a**	Ph	*p*-CH_3-C_6H_4	(*Z*)-**13a**	90 (4:96)
4	(*E*)-**12b**	*p*-CF_3-C_6H_4	Ph	(*E*)-**13b**	97 (93:7)
5	(*Z*)-**12b**	Ph	*p*-CF_3-C_6H_4	(*Z*)-**13b**	93 (5:95)

remove the benzyl group from the amide nitrogen under comparatively gentle conditions. It is expected that these debenzylated compounds may have tyrosine kinase activity, acts as a non-peptide antagonist of bombesin and GRP (gastrin releasing peptides),[36] and exhibit anti-rheumatic properties,[6] and cycline-dependent kinase (CDK) activity.[7]

Conclusion

In conclusion, we have developed the first efficient method for stereoselective and diversity-oriented synthesis of various (*E*)-, (*Z*)-, and disubstituted 3-alkylideneoxindoles using In-mediated carbometallation and Pd-catalyzed cross-coupling reaction under mild reaction conditions. The key step is the first stereoselective carboindation reaction using the strong coordination ability of an indium atom. We also applied this method to the synthesis of a TMC-95A precursor. A new method for debenzylation from amide nitrogen has also been developed using an NHPI-O_2-$Co(OAc)_2$-$Mn(OAc)_2$ system. Our method provides a versatile tool for the total synthesis of natural products and for random screening to find drug candidates.

Experimental Section

General

See the Supporting Information for the procedures used to prepare alkynes **4** and the characterization data of the compounds made. Metallic indium was purchased from Kojundo Chemical Laboratory Co., Ltd. All reactions were carried out under a positive pressure of argon or nitrogen.

Typical Procedure for Indium-Mediated Reductive Radical Cyclization

To a solution of iodoalkyne **4a** (41.8 mg, 0.10 mmol) in DMF were added indium(0) (22.8 mg, 0.20 mmol) and pyridinium bromide perbromide (31.9 mg, 0.10 mmol) and stirred for 12 h at room temperature under an argon atmosphere. After being quenched with water, the mixture was extracted with AcOEt and dried over $MgSO_4$. The residue was purified by column chromatography [silica gel, hexane/AcOEt (5/1)] to give **6a**; yield: 23.3 mg (80%).

Typical Procedure for Tandem Carboindation and Palladium-Catalyzed Cross-Coupling Reaction

To a solution of iodoalkyne **4c** (36.2 mg, 0.10 mmol) in DMF were added indium(0) (22.8 mg, 0.20 mmol) and pyridinium bromide perbromide (31.9 mg, 0.10 mmol) and stirred under at room temperature an argon atmosphere. After 12 h, to the solution were successively added 4-iodotoluene (43.6 mg, 0.20 mmol), palladium(II) acetylacetonate (1.52 mg, 5.0×10^{-3} mmol) and lithium bromide (17.2 mg 0.20 mmol) and the mixture was stirred at 100 °C for 5 h. After being quenched with water, the mixture was extracted with AcOEt and dried over $MgSO_4$. The residue was purified by column chromatography [silica gel, hexane/AcOEt (5/1)] to give (*Z*)-**6s**; yield: 19.5 mg (60%).

Typical Procedure for Copper-Mediated Mild Cross-Coupling Reaction

To a solution of iodoalkyne **4c** (36.2 mg, 0.10 mmol) in DMF were added indium(0) (22.8 mg, 0.20 mmol) and pyridinium bromide perbromide (31.9 mg, 0.10 mmol) and stirred at room temperature under an argon atmosphere. After 12 h, to the solution were successively added 4-iodotoluene (43.6 mg, 0.20 mmol), bis(dibenzylideneacetone)palladium(0) (2.88 mg, 5.0×10^{-3} mmol), NHC ligand (4.74 mg, 1.5×10^{-2} mmol), copper(I) bromide (7.15 mg, 0.05 mmol) and lithium iodide (13.3 mg 0.10 mmol) and the mixture was stirred at 50 °C for 24 h. After being quenched with water, the mixture was extracted with AcOEt and dried over $MgSO_4$. The residue was purified by column chromatography [silica gel, hexane/AcOEt (5/1)] to give (*Z*)-**6s**; yield: 23.4 mg (72%).

Synthesis of TMC-95A Intermediate

To a stirred solution of 2-iodoaniline (1.00 g, 4.57 mmol) in CH_2Cl_2 (20 mL) were added triphosgene (452 mg, 1.52 mmol) and a saturated aqueous solution of $NaHCO_3$ (20 mL) at 0 °C. After stirring at room temperature for 2 h, H_2O was added and aqueous layer was extracted with ether. The combined extracts were dried over $MgSO_4$, and then concentrated under reduced pressure. The crude isocyanate (1.10 g, 98%) was used for the next reaction without further purification. To a solution of **9**[24] (200 mg, 0.889 mmol) in THF (3.0 mL) was added a 1.58 M solution of *n*-butyllithium (0.56 mL, 0.889 mmol) in *n*-hexane. After the solution was stirred at −78 °C for 1 h, a solution of the isocyanate prepared above (145 mg, 0.593 mmol) in THF (3.0 mL) was added to the mixture. The reaction mixture was stirred at −78 °C for an additional hour, before warming to −40 °C. The mixture was then poured into a saturated aqueous solution of NH_4Cl and the mixture was extracted with diethyl ether. The combined organic extracts were dried and concentrated under vacuum and the crude product was purified by SiO_2 column chromatography (elution: 4 : 1 hexane/ethyl acetate) to give the debenzylation compound of **10** as a colorless oil; yield: 302 mg (79%).

Typical Procedure for Debenzylation by the NHPI-$Co(OAc)_2$-$Mn(OAc)_2$ Method

To a solution of (*Z*)-**12a** (45.5 mg, 0.10 mmol) in AcOH (1.0 mL) was added *N*-hydroxyphthalimide (16.3 mg, 0.10 mmol), cobalt(II) acetate (2.65 mg, 1.5×10^{-2} mmol) and manganese(II) acetate (1.73 mg, 1.0×10^{-2} mmol) and stirred for12 h at 100 °C. After being quenched with water, the mixture was extracted with AcOEt and dried over $MgSO_4$.

The residue was purified by column chromatography [silica gel, hexane/AcOEt (5/1)] to give (*Z*)-**13a**; yield: 32.8 mg (90%, *E*/*Z* = 4/96).

Acknowledgements

This work was supported in part by Grant-in-Aid for Scientific Research (B) and (C) from the Ministry of Education, Science, Sports, and Culture, Japan, and by the 21st Century COE Program "Knowledge Information Infrastructure for Genome Science".

References and Notes

[1] For example, olefin metathesis: a) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc*, **2000**, *122*, 8168–879; b) L. Anastasia, Y. R. Dumond, E. Negishi, *Eur. J. Org. Chem.* **2001**, 3039–3043; c) Q. Yao, Y. Zhang, *J. Am. Chem. Soc*, **2004**, *126*, 74–75; d) T. R. Hoye, C. S. Jeffrey, M. A. Tennakoon, J. Wang, H. Zhao, *J. Am. Chem. Soc*, **2004**, *126*, 10210–10211.

[2] For example, vinylic metal intermediates: a) M. Hojo, Y. Murakami, H. Aihara, R. Sakuragi, Y. Baba, A. Hosomi, *Angew. Chem. Int. Ed*. **2001**, *40*, 621–623; b) P. E. Tessier, A. J. Penwell, F. E. S. Souza, A. G. Fallis, *Org. Lett*. **2003**, *5*, 2989–2992; c) S. J. Patel, T. F. Jamison, *Angew. Chem. Int. Ed*. **2003**, *42*, 1364–1367; d) S. Ma, N. Jiao, L. Ye, *Chem. Eur. J.* **2003**, *9*, 6049–6056; e) N. Zhu, D. G. Hall, *J. Org. Chem.* **2003**, *68*, 6066–6069.

[3] a) T.-S. Kam, Y.-M. Choo, *Tetrahedron* **2000**, *56*, 6143–6150; b) A. Cane, M.-C. Tournaire, D. Barritault, M. Crumeyrolle-Arias, *Biochem. Biophys. Res. Commun.* **2000**, *276*, 379–384; c) M. Tsuda, T. Mugishima, K. Komatsu, T. Sone, M. Tanaka, Y. Mikami, M. Shiro, M. Hirai, Y. Ohizumi, J. Kobayashi, *Tetrahedron* **2003**, *59*, 3227–3230; d) C. Marti, E. M. Carreira, *Eur. J. Org. Chem*. **2003**, 2209–2219; e) S. Akai, T. Tsujino, E. Akiyama, K. Tanimoto, T. Naka, Y. Kita, *J. Org. Chem*. **2004**, *69*, 2478–2486.

[4] T. Y. Zhang, H. Zhang, *Tetrahedron Lett*. **2002**, *43*, 193–195 and references cited therein.

[5] a) D. Ma, Q. Wu, *Tetrahedron Lett*. **2000**, *41*, 9089–9093; b) S. Lin, S. J. Danishefsky, *Angew. Chem. Int. Ed*. **2001**, *40*, 1967–1970; c) M. Inoue, H. Furuyama, H. Sakazaki, M. Hirama, *Org. Lett*. **2001**, *3*, 2863–2865; d) S. Lin, S. J. Danishefsky, *Angew. Chem. Int. Ed*. **2002**, *41*, 512–515; e) M. Kaiser, M. Groll, C. Renner, R. Huber, L. Moroder, *Angew. Chem. Int. Ed*. **2002**, *41*, 780–783; f) B. K. Albrecht, R. M. Williams, *Org. Lett*. **2003**, *5*, 197–200; g) S. Lin, Z.-Q. Yang, B. H. B. Kwok, M. Koldobskiy, C. M. Crews, S. J. Danishefsky, *J. Am. Chem. Soc*. **2004**, *126*, 6347–6355.

[6] a) M. Mohammadi, G. McMahon, L. Sun, C. Tang, P. Hirth, B. K. Yeh, S. R. Hubbard, J. Schlessinger, *Science* **1997**, *276*, 955–960; b) L. Sun, N. Tran, F. Tang, H. App, P. Hirth, G. McMahon, C. Tang, *J. Med. Chem*. **1998**, *41*, 2588–2603; c) L. Sun, N. Tran, C. Liang, S. Hubbard, F. Tang, K. Lipson, R. Schreck, Y. Zhou, G. McMahon, C. Tang, *J. Med. Chem.* **2000**, *43*, 2655–2663; d) M. Vieth, D. J. Cummins, *J. Med. Chem*. **2000**, *43*, 3020–3032; e) H. N. Bramson, J. Corona, S. T. Davis, S. H. Dickerson, M. Edelstein, S. V. Frye, R. T. Gampe Jr., P. A. Harris, A. Hassell, W. D. Holmes, R. N. Hunter, K. E. Lackey, B. Lovejoy, M. J. Luzzio, V. Montana, W. J. Rocque, D. Rusnak, L. Schewchuk, J. M. Veal, D. H. Walker, L. F. Kuyper, *J. Med. Chem.* **2001**, *44*, 4339–4358; f) L. Sun, C. Liang, S. Shirazian, Y. Zhou, T. Miller, J. Cui, J. Y. Fukuda, J.-Y. Chu, A. Nematalla, X. Wang, H. Chen, A. Sistla, T. C. Luu, F. Tang, J. Wei, C. Tang, *J. Med. Chem.* **2003**, *46*, 1116–1119.

[7] C. L. Woodard, Z. Li, A. K. Kathcart, J. Terrell, L. Gerena, M. L. Sanchez, D. E. Kyle, A. K. Bhattacharjee, D. A. Nichols, W. Ellis, S. T. Prigge, J. A. Geyer, N. C. Waters, *J. Med. Chem*. **2003**, *46*, 3877–3882.

[8] R. P. Robinson, L. A. Reiter, W. E. Barth, A. M. Campeta, K. Cooper, B. J. Cronin, R. Destito, K. M. Donahue, F. C. Falkner, E. F. Fiese, D. L. Johnson, A. V. Kuperman, T. E. Liston, D. Malloy, J. J. Martin, D. Y. Mitchell, F. W. Rusek, S. L. Shamblin, C. F. Wright, *J. Med. Chem.* **1996**, *39,* 10–18.

[9] *E*:*Z* = 5:1–1:5, for example, a) M. Mori, Y. Ban, *Tetrahedron Lett*. **1979**, *20*, 1133–1136; b) M. R. Fielding, R. Grigg, C. J. Urch, *Chem. Commun.* **2000**, 2239–2240; c) A. Teichert, K. Jantos, K. Harms, A. Studer, *Org. Lett.* **2004**, *6*, 3477–3480.

[10] R. Yanada, S. Obika, M. Oyama, Y. Takemoto, *Org. Lett.* **2004**, *6*, 2825–2828.

[11] a) R. Yanada, N. Nishimori, A. Matsumura, N. Fujii, Y. Takemoto, *Tetrahedron Lett*. **2002**, *43*, 4585–4588; b) M. Ueda, H. Miyabe, A. Nishimura, O. Miyata, Y. Takemoto, T. Naito, *Org. Lett*. **2003**, *5*, 3835–3838; c) R. Yanada, Y. Koh, N. Nishimori, A. Matsumura, S. Obika, H. Mitsuya, N. Fujii, Y. Takemoto, *J. Org. Chem.* **2004**, *69*, 2417–2422; d) R. Yanada, S. Obika, N. Nishimori, M. Yamauchi, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 2331–2334.

[12] H. Miyabe, M. Ueda, A. Nishimura, T. Naito, *Org. Lett*. **2002**, *4*, 131–134.

[13] a) K. Inoue, A. Sawada, I. Shibata, A. Baba, *J. Am. Chem.* Soc. **2002**, *124*, 906–907; b) B. C. Ranu, S. Samanta, *Tetrahedron* **2003**, *59*, 7901–7904; c) B. C. Ranu, S. Samanta, *J. Org. Chem.* **2003**, *68*, 7130–7132; d) B. C. Ranu, S. Banerjee, A. Das, *Tetrahedron Lett.* **2004**, *45*, 8579–8581; e) C.-Y. Wang, H. Su, D.-Y. Yang, *Synlett* **2004**, 561–563.

[14] a) S. A. Brunton, K. Jones, *J. Chem. Soc. Perkin Trans. 1.* **2000**, 763–768; b) H. Ishibashi, T. Kobayashi, S. Nakashima, O. Tamura, *J. Org. Chem.* **2000**, *65*, 9022–9027; c) J.-P. Bouvier, G. Jung, Z. Liu, B. Guerin, Y. Guindon, *Org. Lett*. **2001**, *3*, 1391–1394; d) T. Ooi, M. Furuya, D. Sakai, Y. Hokke, K. Maruoka, *Synlett* **2001**, 541–543; e) H. Yorimitsu, K. Oshima, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 853–854.

[15] a) L. A. Paquette, T. M. Mitzel, *J. Am. Chem. Soc*. **1996**, *118*, 1931–1937; b) L. A. Paquette, G. D. Bennett, M. B.

Isaac, A. Chhatriwalla, *J. Org. Chem*. **1998**, *63*, 1836–1845; c) L. A. Paquette, R. R. Rothhaar, *J. Org. Chem*. **1999**, *64*, 217–224; d) S. Araki, F. Shiraki, T. Tanaka, H. Nakano, K. Subburaj, T. Hirashita, H. Yamamura, M. Kawai, *Chem. Eur. J*. **2001**, *7*, 2784–2790; e) R. Yanada, A. Kaieda, Y. Takemoto, *J. Org. Chem.* **2001**, *66*, 7516–7518; f) S. Araki, K. Ohnishi, F. Shiraki, T. Hirashita, *Tetrahedron Lett*. **2002**, *43*, 8033–8035.

[16] a) M. Shabangi, M. L. Kuhlman, R. A. Flowers II, *Org. Lett.* **1999**, *1*, 2133–2135; b) R. S. Miller, J. M. Sealy, M. Shabangi, M. L. Kuhlman, J. R. Fuchs, R. A. Flowers II, *J. Am. Chem. Soc*. **2000**, *122*, 7718–7722; c) M. L. Kuhlman, R. A. Flowers II, *Tetrahedron Lett.* **2000**, *41*, 8049–8052; d) B. W. Knettle, R. A. Flowers II, *Org. Lett*. **2001**, *3*, 2321–2324.

[17] Formal redox potentials: E^0 (I_2/I^-) = 0.54 V, E^0 (Br_2/Br^-) = 1.07 V, E^0 (Br_3^-/Br^-) = 1.05 V, E^0 (In^+/In) = −0.14 V, E^0 (In^{3+}/In) = −0.34 V. Data taken from: *CRC Handbook of Chemistry and Physics,* (ed.: D. R. Lide), CRC Press: Boca Raton, FL, 1997–1998, p.8–20 to 8–25.

[18] S. Rossiter, *Tetrahedron Lett*. **2002**, *43*, 4671–4673.

[19] C. B. Kanner, U. K. Pandit, *Tetrahedron* **1982**, *38*, 3597–3604.

[20] F. Amat-Guerri, R. Martínez-Utrilla, M. M. C. López-González, *Photochem. Photobiol.* **1990**, *50*, 361–375.

[21] R. Bloch, P. Orvane, *Tetrahedron Lett*. **1981**, #22#*37*, 3597–3600.

[22] E. Braud, M. Duflos, G. L. Baut, P. Renard, B. Pfeiffer, G. Tucker, *J. Enz. Inhibit. Med. Chem.* **2003**, *18*, 253–257.

[23] S. Uesato, Y. Hashimoto, M. Nishino, Y. Nagaoka, H. Kuwajima, *Chem. Pharm. Bull.* **2002**, *50*, 1280–1282.

[24] a) P. Garner, J. M. Park, *Org. Synth.* **1992**, *70*, 18–28; b) A. McKillop, R. J. K. Taylor, R. J. Watson, N. Lewis, *Synthesis* **1994**, 31–33; c) A. Dondoni, D. Perrone, *Synthesis* **1997**, 527–529; d) X. Serrat, G. Cabarrocas, S. Rafel, M. Ventura, A. Linden J. M. Villalgor, *Tetrahedron: Asymmetry* **1999**, *10*, 3417–3430.

[25] a) I. Pérez, J. P. Sestelo, L. A. Sarandeses, *Org. Lett*. **1999**, *1*, 1267–1269; b) N. Fujiwara, Y. Yamamoto, *J. Org. Chem*. **1999**, *64*, 4095–4101; c) T. Hirashita, H. Yamamura, M. Kawai, S. Araki, *Chem. Commun*. **2001**, 387–388; d) K. Takami, H. Yorimitsu, H. Shinokubo, S. Matsubara, K. Oshima, *Org. Lett*. **2001**, *3*, 1997–1999; e) I. Pérez, J. P. Sestelo, L. A. Sarandeses, *J. Am. Chem. Soc*. **2001**, *123*, 4155–4160; f) K. Takami, H. Yorimitsu, K. Oshima, *Org. Lett*. **2002**, *4*, 2993–2995; g) P. H. Lee, S. W. Lee, K. Lee, *Org. Lett*. **2003**, *5*, 1103–1106; h) T. Hirashita, Y. Hayashi, K. Mitsui, S. Araki, *J. Org. Chem*. **2003**, *68*, 1309–1313; i) U. Lehmann, S. Awasthi, T. Minehan, *Org. Lett*. **2003**, *5*, 2405–2408; j) S. W. Lee, K. Lee, D. Seomoon, S. Kim, H. Kim, H. Kim, E. Shim, M. Lee, S. Lee, M. Kim, P. H. Lee, *J. Org. Chem.* **2004**, *69*, 4852–4855; k) D. Rodriguez, J. P. Sestelo. L. A. Sarandeses, *J. Org. Chem.* **2004**, *69*, 8136–8139.

[26] Fu has reported Negishi reactions of organozirconium reagents under ligandless conditions: S. L. Wiskur, A. Korte, G. C. Fu, *J. Am. Chem. Soc*. **2004**, *126*, 82–83.

[27] W. A. Herrmann, *Angew. Chem. Int. Ed*. **2002**, *41*, 1290–1309.

[28] S. P. H. Mee, V. Lee, J. E. Baldwin, *Angew. Chem. Int. Ed.* **2004**, *43*, 1132–1136.

[29] a) V. C. Jordan, *J. Med. Chem.* **2003**, *46*, 883–908; b) V. C. Jordan, *J. Med. Chem.* **2003**, *46*, 1081–1111.

[30] a) J. Kirk, S. K. Syed, A. L. Harris, M. Jarman, B. D. Roufogalis, I. J. Stratford, J. Camichael, *Biochem. Pharmacol*. **1994**, *48*, 277–285; b) C. D. M. A. van den Koedijk, M. A. Blankenstein, J. H. H. Thijssen, *Biochem. Pharmacol*. **1994**, *47*, 1927–1937; c) K. Itami, T. Kamei, J. Yoshida, *J. Am. Chem. Soc*. **2003**, *125*, 14670–14671; d) I. Shiina, M. Suzuki, K. Yokoyama, *Tetrahedron Lett*. **2004**, *45*, 965–967; e) C. Zhou, R. C. Larock, *J. Org. Chem.* **2005**, ASAP.

[31] E. Paliakov, L. Strekowski, *Tetrahedron Lett*. **2004**, *45*, 4093–4095.

[32] a) A. A. Haddach, A. Kelleman, M. V. Deaton-Rewolinski, *Tetrahedron Lett*. **2002**, *43*, 399–402; b) R. Gigg, R. Conant, *J. Chem. Soc. Chem. Commun*. **1983**, 465–466.

[33] a) S. D. Bull, S. G. Davies, G. Fenton, A. W. Mulvaney, R. S. Prasad, A. D. Smith, *Chem. Commun*. **2000**, 337–338; b) S. D. Bull, S. G. Davies, G. Fenton, A. W. Mulvaney, R. S. Prasad, A. D. Smith, *J. Chem. Soc. Perkin Trans. 1,* **2000**, 3765–3774.

[34] a) M. S. Anson, J. G. Montana, *Synlett* **1994**, 219–220; b) S. R. Baker, A. F. Parsons, M. Wilson, *Tetrahedron Lett*. **1998**, *39*, 331–332.

[35] a) Y. Tashiro T. Iwahama, S. Sakaguchi, Y. Ishii, *Adv. Synth. Catal.* **2001**, *343*, 220–225; b) Y. Ishii, S. Sakaguchi, T. Iwahama, *Adv. Synth. Catal.* **2001**, *343*, 393–427; c) Y. Ishii, S. Sakaguchi, *J. Synth. Org. Chem. Jpn.* **2003**, *61,* 1056–1063; d) K. Hirase, S. Sakaguchi, Y. Ishihi, *J. Org. Chem.* **2003**, *68*, 5974–5976.

[36] J. J. Valentine, S. Nakanishi, D. L. Hageman, R. M. Snider, R. W. Spencer, F. J. Vinick, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 333–338.

