JOC*Article*

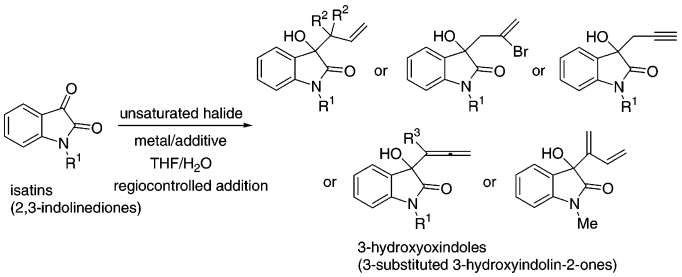
Metal-Mediated Entry to Functionalized 3-Substituted 3-Hydroxyindolin-2-ones via Regiocontrolled Carbonylallylation, Bromoallylation, 1,3-Butadien-2-ylation, Propargylation, or Allenylation Reactions of Isatins in Aqueous Media

Benito Alcaide,*,† Pedro Almendros,*,‡ and Raquel Rodríguez-Acebes†

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, Spain, and Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006-Madrid, Spain

alcaideb@quim.ucm.es; iqoa392@iqog.csic.es

Received January 21, 2005



Reactions of 2,3-indolinediones (isatins) with stabilized organometallic reagents were investigated in aqueous media. Isatins and a variety of stabilized organic halides undergo coupling under Barbier-type conditions in the presence of different metals (indium, tin, zinc) and additives (ammonium chloride, hydrobromic acid, bismuth(III) chloride, hafnium(IV) chloride). The regiochemistry of the processes (carbonylallylation, bromoallylation, 1,3-butadien-2-ylation, propargylation, or allenylation reactions) were generally excellent. On this basis, simple and fast protocols for the synthesis of the potentially bioactive 3-substituted 3-hydroxyoxindole moiety were developed.

Introduction

3-Substituted 3-hydroxyindolin-2-ones are important substrates for studies of biological activity as well as useful synthetic intermediates for drug candidates and alkaloids. As a consequence, development of practical methods for their preparation is of interest. The 3-substituted 3-hydroxyoxindole moiety is present in several pharmacologically active alkaloids such as celogentin K,[1] donaxaridine,[2] convolutamydines,[3] dioxibrassinine,[4] welwitindolinone C,[5] TMC-95s,[6] and 3′-hydroxyglucoisatisin,[7] in addition to several others. On the other hand, the development of new carbon−carbon bond-forming reactions is of particular interest in organic synthesis. Among the most fundamental and important reactions for constructing carbon−carbon bonds are the allylation and the propargylation/allenylation of aldehydes and ketones (carbonyls) with organometallic reagents. For example, Sakurai-, Grignard-, and Barbier-type reactions have been widely utilized for the allylation[8] or propargylation/allenylation[9] of carbonyls, in which chemo- and regioselectivities of the desired alcohols are highly dependent on the nature of the metals employed. Although many

† Universidad Complutense de Madrid.
‡ Instituto de Química Orgánica General.

(1) Suzuki, H.; Morita, H.; Shiro, M.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 2489.

(2) (a) Rasmussen, H. B.; MacLeod, J. K. *J. Nat. Prod.* **1997**, *60*, 1152. (b) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. *Tetrahedron* **2004**, *60*, 3493.

(3) (a) Kamano, Y.; Zhang, H.-P.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Pettit, G. R. *Tetrahedron Lett.* **1995**, *36*, 2783. (b) Miah, S.; Moody, C. J.; Richards, I. C.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2405.

(4) (a) Monde, K.; Sasaki, K.; Shirata, A.; Takasugi, M. *Phytochemistry* **1991**, *30*, 2915. (b) Suchy, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentova, E. *J. Org. Chem.* **2001**, *66*, 3940.

(5) Jiménez, J. I.; Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1999**, *62*, 569.

(6) (a) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Juroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990. (b) Lin, S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 512. (c) Albrecht, B. K.; Williams, R. M. *Org. Lett.* **2003**, *5*, 197. (d) Lin, S.; Yang, Z.-Q.; Kwok, B. H. B.; Koldobskiy, M.; Crews, C. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6347. (e) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2004**, *6*, 2849.

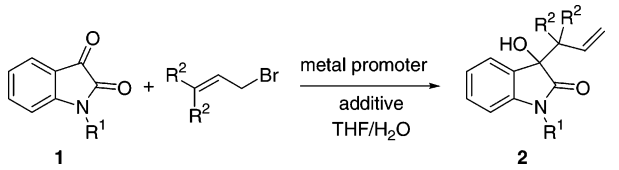
(7) (a) Fréchard, A.; Fabre, N.; Péan, C.; Montaut, S.; Fauvel, M.-T.; Rollin, P.; Fourasté, I. *Tetrahedron Lett.* **2001**, *42*, 9015.

10.1021/jo050130w CCC: $30.25
Published on Web 03/22/2005

efforts have been made in these fields into various types of carbonylic compounds, the bromoallylation, the allenylation, or the 1,3-butadien-2-ylation of isatins have not been reported yet. Furthermore, the information available on the use of oxindoles as building blocks on the propargylation and allylation reactions is still very scarce.[10] Nair first reported the allylmetalation of isatins in anhydrous dimethylformamide,[11] while Gong described more recently the allylation of isatin in aqueous environment.[12] The only known propargylation example is the addition of propargylindium to isatins described by Nair, but the synthetic interest is diminished owing to the low regioselectivity of the propargylic/allenic reaction site.[11a]

The appealing properties of organometallic reactions in aqueous media include their synthetic advantages (many reactive functional groups, such as hydroxy, amine, and carboxylic functions, do not require the protection−deprotection protocol in such reactions, and many water-soluble compounds do not need to be converted into their derivatives and can be reacted directly), its potential as an environmentally benign chemical process (the use of anhydrous flammable solvents can be avoided and the burden of solvent disposal may be reduced), as well as an unique reactivity and selectivity that are not often attained under dry conditions, making them profitable in many cases.[13] On the other hand, two general protocols are available for the metal-promoted carbonyl addition with use of organic halides: the stepwise Grignard procedure where the metal reagent is preformed and then added to the carbonyl compound or the in situ Barbier procedure where the organometallic species is formed in the presence of the carbonyl. Continuing with our work on the synthesis of nitrogenated compounds of biological interest,[14] we decided to pursue a convenient approach for the regiocontrolled incorporation of new substituents at the indole ring. In this context, we wish to report now details of the manner in which isatins and a variety of stabilized organic halides undergo coupling under Barbier-type conditions in aqueous media.

TABLE 1. Allylation Reaction of Isatins 1 in Aqueous Media



entry	isatin	R^1	R^2	metal	additive	*T* (°C)	*t* (h)[a]	product[b]	yield[c] (%)
1	**1a**	H	H	Zn		20	48	**2a**	35
2	**1a**	H	H	Sn		20	20	**2a**	31
3	**1a**	H	H	In		20	1	**2a**	95
4	**1a**	H	H	In		0	2	**2a**	100
5	**1a**	H	H	Zn	NH_4Cl	20	24	**2a**	83
6	**1a**	H	H	Sn	NH_4Cl	20	24	**2a**	40
7	**1a**	H	H	In	NH_4Cl	20	4	**2a**	42
8	**1a**	H	H	In	$HfCl_4$	0	0.3	**2a**	100
9	**1a**	H	Me	In	$HfCl_4$	0	0.3	**2b**	86
10	**1b**	Me	H	Zn	NH_4Cl	20	48	**2c**	74
11	**1b**	Me	H	In		20	4	**2c**	90
12	**1b**	Me	H	In	NH_4Cl	20	0.5	**2c**	99
13	**1b**	Me	H	In	$HfCl_4$	0	0.5	**2c**	100

[a] Reaction progress was followed by TLC but could also be noted by the disappearance of the yellow color of the appropriate isatin. [b] Analysis of the ^1H NMR spectra (300 MHz) of the crude reaction mixtures revealed compounds **2** as the only detected isomer. [c] Yield of pure, isolated product with correct analytical and spectral data.

Results and Discussion

α-Keto lactams **1** may be considered similar to α-amino aldehydes, most of which are relatively unstable chemically in a number of addition reactions. A model reaction of isatin **1a** was carried out by the treatment of a THF/H_2O (1:1) solution of α-keto lactam **1a** with allyl bromide in the presence of zinc at room temperature, to give regioselectively the adduct **2a** in 35% yield (Table 1, entry 1). Preliminary results encouraged us to screen other metals for the above reaction for better yield. The tin-promoted allylation also afforded the homoallylic alcohol **2a** in a low 31% yield (Table 1, entry 2). We were pleased to find that use of indium under appropriate conditions gave **2a** in quantitative yield (Table 1, entry 4). The ionic strength enhancement of the reaction solvent provided by the ammonium chloride increased the yield of **2a** for the zinc and tin-promoted reactions (Table 1, entries 5 and 6). However, slightly lower yield was obtained in the allylindation (Table 1, entry 7). The addition of a catalytic quantity of hafnium(IV) chloride accelerated the process, affording the 3-allyl 3-hydroxyindolin-2-one **2a** in quantitative yield after 20 min (Table 1, entry 8). Similar results were obtained in the metal-mediated allylation reaction on using *N*-methylisatin **1b** or prenyl bromide (Table 1, entries 9−13).

(8) For recent reviews of allylmetal additions, see: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Roush, W. R.; Chemler, C. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 11. (c) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10. (d) Thomas, E. J. *Chem. Commun.* **1997**, 411. (e) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (f) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(9) For reviews, see: (a) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (b) Yamamoto, H. In *Comprehensive Organic Synthesis;* Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.3. (c) Panek, J. S. In *Comprehensive Organic Synthesis;* Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, p 595.

(10) (a) For a review on indium- and gallium-mediated reactions, including isatins, see: Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959. (b) For a review on the chemistry of isatins and bioactive derivatives, see: Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, 273. (c) For the first investigations of the Reformatsky reaction on isatins, see: Myers, F. J.; Lindwall, H. G. *J. Am. Chem. Soc.* **1938**, *60*, 644. (d) 3-Alkenyl 3-hydroxyindolin-2-ones can be obtained by a Claisen rearrangement; see ref 2a.

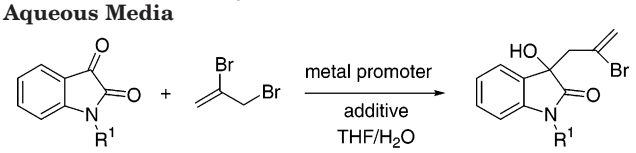
(11) (a) Nair, V.; Ros, S.; Jayan, C. N.; Viji, S. *Synthesis* **2003**, 2542. (b) Nair, V.; Ros, S.; Jayan, C. N. *Tetrahedron* **2001**, *57*, 9453. (c) Nair, V.; Ros, S.; Jayan, C. N. *J. Chem. Res., Suynop.* **2001**, 551.

(12) Gong, J. H.; Lee, K. Y.; Son, J. S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2003**, *24*, 507.

(13) For recents reviews on organic reactions in aqueous media, see: (a) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (b) Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2002**, *8*, 4095. (c) Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299. (d) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (e) Lubineau, A.; Augé, J. *Top. Curr. Chem.* **1999**, *206*, 1. (f) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: New York, 1998.

(14) See, for instance: (a) Alcaide, B.; Almendros, P.; Alonso, J. M. *J. Org. Chem.* **2004**, *69*, 993. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodríguez-Acebes, R. *J. Org. Chem.* **2004**, *69*, 826. (c) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem. Eur. J.* **2003**, *9*, 5793. (d) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2003**, *5*, 3795. (e) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Chem. Eur. J.* **2003**, *9*, 3415.

TABLE 2. Bromoallylation Reaction of Isatins 1 in Aqueous Media



entry	isatin	R^1	metal	additive	T (°C)	t (h)[a]	product	yield[b] (%)
1	**1a**	H	In		20	168	**3a**	20
2	**1a**	H	Zn		20	168	**3a**	*c*
3	**1a**	H	Bi		20	168	**3a**	*d*
4	**1a**	H	Sn		20	27	**3a**	30
5	**1a**	H	Sn	NH_4Cl	20	24	**3a**	49
6	**1a**	H	Sn	HBr	5	48	**3a**	65
7	**1a**	H	Sn	$HfCl_4$	5	22	**3a**	62
8	**1a**	H	Sn	$BiCl_3$	5	20	**3a**	67
9	**1b**	Me	Sn	$BiCl_3$	5	18	**3b**	74
10	**1b**	Me	Sn	$BiCl_3/NH_4Cl$	5	20	**3b**	56

[a] Reaction progress was followed by TLC but could also be noted by the disappearance of the yellow color of the appropriate isatin. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] The bromoallylation reaction proceeded with concomitant γ-lactam ring-opening. See the Supporting Information for details. [d] Decomposition products of the starting isatin were observed.

In contrast to the carbonylallylation, the analogous reaction involving bromoallylmetals has been scarcely investigated,[15] despite the fact that it can provide useful intermediates, the corresponding bromohomoallylic alcohols.[16] Since indium-mediated allylation of aldehydes has attracted much interest among organic chemists due to its compatibility with many common organic functional groups and stability under aqueous conditions, we decided to introduce the bromovinyl moiety on the indole ring via indium-promoted Barbier-type bromoallylation of isatins in an aqueous environment. Unfortunately, when the reaction of isatin **1a** with 2,3-dibromopropene was conducted in the presence of indium in aqueous tetrahydrofuran, the corresponding bromoallylated product **3a** was formed after 7 days in only 20% yield (Table 2, entry 1). Next, using a standard protocol we screened different metal mediators (zinc, tin, and bismuth). No coupling product was observed when zinc and bismuth were used. The bromohomoallylic alcohol **3a** was achieved through the tin-mediated bromoallylation in a low 30% yield (Table 2, entry 4). Since the incorporation of water-stable additives could improve both yield and conversion rate, we explored further the metal-promoted bromoallylation of ketone **1a** in the presence of different additives. The addition of ammonium chloride to the aqueous medium containing tin, 2,3-dibromopropene, and isatin **1a** was effective, achieving the bromohomoallylic alcohol **3a** in a 49% yield after 1 day of reaction (Table 2, entry 5). This encouraging observation prompted us to investigate different Lewis or protic acids as additives. When the above reaction was mediated by tin and was conducted in a THF/H_2O (1:1) solution at 5 °C in the presence of a catalytic quantity of hydrobromic acid, it gave rise to the bromohomoallyl alcohol **3a** in a reasonable 65% yield after 2 days of reaction (Table 2, entry 6). The addition of bismuth(III) chloride or hafnium(IV) chloride to the aqueous environment of the tin-promoted bromoallylation reaction of isatins shortened reaction times while maintaining good yields (Table 2, entries 7−9). The effect of the amount of 2,3-dibromopropene on the conversion rate as well as on the yield was studied, and it was found that the efficiency of the process did increase on increasing the molar ratio between the allyl halide and tin from 1:1 to 2:1.

Once we had established the best reaction conditions to carry out the allylation and bromoallylation reactions, our aim was to evaluate the feasibility of other related metal-mediated Barbier-type reactions in isatins, studying the regiochemistry of the connection (e.g., allenylation vs propargylation). However, it is not easy to control selectivity between Barbier-type propargylation and allenylation with propargylic halides. The reaction of propargyl bromide with metals has been proposed to generate an equilibrium between the allenyl and propargyl organometallics. This metallotropic rearrangement often results in poor regioselection in the final organic product because both organometallic species can react with the carbonyl compounds. Tuning the regioselectivity of the reaction of propargylmetals with carbonyl compounds toward the synthesis of either acetylenic or allenic products remains an important challenge in organic synthesis. In this context, the preparation of homopropargylic and allenic alcohols from transient allenylindium reagents or propargylic stannanes respectively, described by Marshall,[17] and the regioselective synthesis of allenic and homopropargylic alcohols through the indium-mediated reaction of trialkylsilyl propargyl bromide with aldehydes reported by Loh,[18] are noteworthy.

The aim of achieving full control of regiochemistry prompted us to seek an aqueous metal-induced propargylation/allenylation reaction. For this purpose, isatins **1** were treated with prop-2-ynyl bromides, bearing substituents of varying steric demand at C3, and a broad variety of metals and reaction conditions in aqueous media. While the chemical yield of the addition was generally good, the regioselectivity of the process was a function of the nature of both the metal and the propargyl bromide, and in many cases of the additive as well. The regioselectivity of the carbon−carbon bond formation were initially investigated through the tin-mediated reaction between the isatin **1a** and propargyl bromide in aqueous tetrahydrofuran at room temperature. In the event, the 3-substituted 3-hydroxyoxindole moiety was obtained after several days of reaction; however, the observed regioselectivity was very poor (48:52) in favor of the allenic product (Table 3, entry 1). Surprisingly, the regiochemical preference was reversed both on the indium-promoted as well as the zinc-mediated reactions, with the expected alcohols **4a** and **5a** being obtained as a mixture of regioisomers in a ratio of **4a**:**5a** = 78:22 and 93:7, respectively (Table 3, entries 2 and 3). Interestingly,

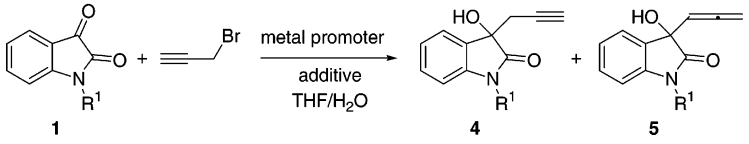
(15) (a) Trost, B. M.; Coppola, B. P. *J. Am. Chem. Soc.* **1982**, *104*, 6879. (b) Mandai, T.; Nokami, J.; Yano, T.; Yoshinaga, Y.; Otera, J. *J. Org. Chem.* **1984**, *49*, 172. (c) Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248.

(16) See, for example: (a) Trost, B. M.; Corte, J. R.; Gudiksen, M. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3662. (b) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790.

(17) (a) Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630. (b) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798. (c) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 696. (d) Marshall, J. A.; Yu, R. H.; Perkins, J. E. *J. Org. Chem.* **1995**, *60*, 5550.

(18) Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 13042.

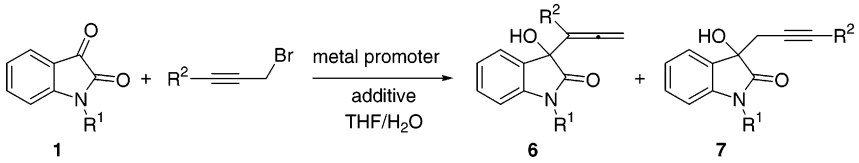
TABLE 3. Regioselective Propargylation Reaction of Isatins 1 in Aqueous Media



entry	isatin	R^1	metal	additive	T (°C)	t (h)[a]	**4:5** ratio[b]	yield[c] (%)
1	**1a**	H	Sn		20	216	**4a:5a** (48:52)	25
2	**1a**	H	In		20	168	**4a:5a** (78:22)	40
3	**1a**	H	Zn		20	216	**4a:5a** (93:7)	46
4	**1a**	H	Sn	NH_4Cl	20	24	**4a:5a** (46:54)	32
5	**1a**	H	In	NH_4Cl	20	2	**4a:5a** (82:18)	57
6	**1a**	H	Zn	NH_4Cl	20	1	**4a:5a** (100:0)	64
7	**1a**	H	Zn	$HfCl_4$	20	168	**4a:5a** (100:0)	59
8	**1a**	H	Zn	$HfCl_4/NH_4Cl$	0	4	**4a:5a** (100:0)	100
9	**1b**	Me	Zn	NH_4Cl	20	2	**4b:5b** (100:0)	69
10	**1b**	Me	Zn	$HfCl_4/NH_4Cl$	0	6	**4b:5b** (100:0)	90

[a] Reaction progress was followed by TLC but could also be noted by the disappearance of the yellow color of the appropriate isatin. [b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [c] Yield of pure, isolated product (or mixture of regioisomers, when applicable) with correct analytical and spectral data.

TABLE 4. Regioselective Allenylation Reaction of Isatins 1 in Aqueous Media



entry	isatin	R^1	R^2	metal	additive	T (°C)	t^a (h)	**6:7** ratio[b]	yield[c] (%)
1	**1a**	H	Me	In		20	1	**6a:7a** (100:0)	75
2	**1a**	H	Me	Sn		20	18	**6a:7a** (100:0)	42[d]
3	**1a**	H	Me	In		5	2	**6a:7a** (100:0)	90
4	**1a**	H	Me	In	NH_4Cl	20	12	**6a:7a** (100:0)	50
5	**1a**	H	Me	In	NH_4Cl	5	24	**6a:7a** (100:0)	57
6	**1a**	H	Me	Sn	NH_4Cl	5	36	**6a:7a** (82:18)	57
7	**1a**	H	Me	Sn	$HfCl_4$	5	6	**6a:7a** (72:28)	60
8	**1b**	Me	Me	In		20	0.5	**6b:7b** (100:0)	87
9	**1b**	Me	Me	In		5	1	**6b:7b** (100:0)	90
10	**1b**	Me	Me	Sn	$BiCl_3$	5	19	**6b:7b** (88:12)	48
11	**1b**	Me	Ph	In		20	1	**6c:7c** (95:5)	78
11	**1b**	Me	Ph	In		5	2	**6c:7c** (100:0)	82

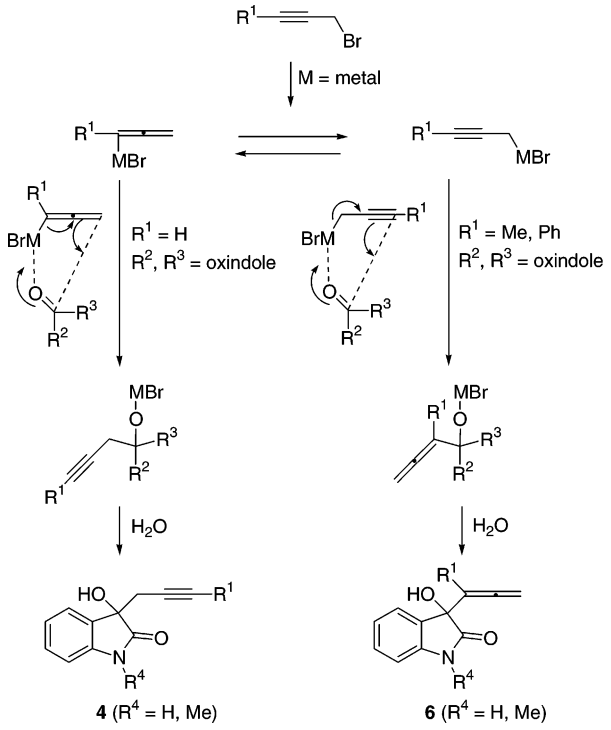
[a] Reaction progress was followed by TLC but could also be noted by the disappearance of the yellow color of the appropriate isatin. [b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [c] Yield of pure, isolated product (or mixture of regioisomers, when applicable) with correct analytical and spectral data. [d] Decomposition products arising from the γ-lactam ring opening were observed.

just by changing the system solvent in the zinc-induced reaction (a saturated aqueous solution of NH_4Cl in THF was used instead of aqueous tetrahydrofuran), the α-allenol **4a** was obtained after just 1 h of reaction as single isomer in a reasonable 64% yield (Table 3, entry 6). Simply by adding 20 mol % of hafnium(IV) chloride to the above reaction mixture the α-allenic alcohol **4a** was obtained in quantitative yield after 4 h at 0 °C (Table 3, entry 8). Similarly, it was obtained the 3-propargyl 3-hydroxyindolin-2-one **4b** (Table 3, entries 9 and 10).

Our next aim was to find a carbonyl propargylation/allenylation method that proceeds in a highly regioselective fashion by the use of 3-substituted 2-propynyl bromides through choice of reaction conditions. Contrary to the above results obtained in the indium-mediated propargylation reaction using propargyl bromide itself, excellent regioselectivities can be obtained when the indium-promoted reactions were carried out in the presence of propargyl bromides bearing an aliphatic or an aromatic substituent at the terminal position. Metal-promoted reactions of isatins **1** with 1-bromo-2-butyne or 1-bromo-3-phenyl-2-propyne afforded the α-allenols **6** as essentially regioisomerically pure products. The indium-mediated reactions were found to proceed faster in the absence of additives. The tin-induced allenylation reaction was accelerated by the addition of Lewis acids, but proceeded with moderate regioselectivity. The results are summarized in Table 4.

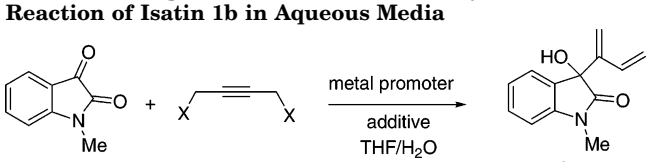
It may be inferred that different steric effects in the organometallic reagents derived from differently substituted propargyl bromides may be responsible for the different regiochemical preference of the propargyl/allenylmetals involved in the reaction, stabilizing one of the intermediates of the metallotropic equilibrium rather than the other. Probably, the isomerization of propargylmetal to allenylmetal species is restricted by the steric effect of a substituent (R^1 = CH_3 or C_6H_5) in the bromopropyne (Scheme 1).

SCHEME 1



In contrast to the allylation and propargylation/allenylation, the analogous reaction involving butadienylmetals has been much less investigated.[19] Therefore, we were interested in exploring the metal-mediated 1,3-butadien-2-ylation of isatins in aqueous media using 1,4-dibromo-2-butyne, 1,4-dichloro-2-butyne, or 1,4-bis(methanesulfonyl)-2-butyne.[20] The indium-mediated reaction between the isatin **1b** and 1,4-dibromo-2-butyne in aqueous tetrahydrofuran (1:1) at room temperature afforded the 3-(1,3-butadien-2-yl) 3-hydroxyindolin-2-one **8** in 44% yield as the only regio- and stereoisomer (Table 5, entry 1). However, when the Barbier-type reaction was conducted in a THF/H_2O (1:5) mixture the coupling was not as efficient as before (14% yield) (Table 5, entry 2). A higher proportion of THF beyond the 1:1 ratio in the solvent did not seem to improve the yield further. The ionic strength enhancement of the reaction solvent provided by the ammonium chloride was counterproductive for the indium-mediated 1,3-butadien-2-ylation. Thus, moving from THF/H_2O (1:1) to THF/NH_4Cl (aq satd) (1:1) decreased the yield of **8** to 11% (Table 5, entry 3). When the above coupling was promoted by zinc in THF/NH_4Cl (aq satd) (1:5), it gave rise to the 1,3-butadien-2-yl alcohol **8** in 20% yield (Table 5, entry 4). The yield was slightly lower by performing the zinc-mediated reaction in THF/H_2O (1:1) (Table 5, entry 5). Next, we explored 1,4-dichloro-2-butyne and 1,4-bis(methanesulfonyl)-2-butyne as Barbier-type 1,3-butadien-2-ylating reagents, rather than 1,4-dibromo-2-butyne.

TABLE 5. Regioselective 1,3-Butadien-2-ylation Reaction of Isatin 1b in Aqueous Media



entry	X	metal	THF/H_2O ratio	additive	T (°C)	t^a (h)	yield^b (%)
1	Br	In	1:1		20	4	44
2	Br	In	1:5		20	4	14
3	Br	In	1:1	NH_4Cl	20	14	11
4	Br	Zn	1:5	NH_4Cl	20	24	20
5	Br	Zn	1:1		20	24	15
6	MsO	In	1:1	NaI	20	24	25
7	Cl	In	1:1		20	48	*c*

[a] Reaction progress was followed by TLC but could also be noted by the disappearance of the yellow color of the isatin. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] Decomposition products arising from the γ-lactam ring-opening were observed.

The bismesylate was then reacted with isatin **1b**, sodium iodide, and indium in aqueous THF to afford the corresponding (buta-1,3-dien-2-yl)methanol derivative **8** in moderate yield (up to 25%) (Table 5, entry 6). Products arising from the γ-lactam ring-opening rather than coupling adducts were observed in the metal-mediated reaction of isatin **1b** with 1,4-dichloro-2-butyne (Table 5, entry 7). These results suggest that the metal-promoted carbonyl-1,3-butadien-2-ylation in aqueous media may be quite sensitive to various factors.

From a mechanistic point of view, the results of the metal-mediated 1,3-butadien-2-ylation process of isatins could be explained as illustrated in Scheme 2. It may be reasonable to postulate a metallotropic rearrangement between the propargylmetal and allenylmetal species. Their reactions with electrophiles suffer from competing reaction. Thus, both intermediates from this equilibrium are able to react with the isatin derivative, leading to the (buta-1,3-dien-2-yl)methanol **8** or homoallenic alcohol **9**, probably via the participation of six-membered, cyclic transition structures. It seems reasonable to propose that the regiochemical preference observed on the metal-promoted reactions of 1,4-dibromo-2-butyne or 1,4-bis(methanesulfonyl)-2-butyne with isatin **1b** must be controlled by steric effects.[21] Probably, the isomerization of propargylmetal to allenylmetal is prohibited by the steric effect of both ML_n substituents. Thus, the propargylmetal reagent undergoes nucleophilic addition to produce exclusively allenyl compounds, which after protiodemetalation gave 1,3-butadien-2-yl alcohol **8** (Scheme 2).

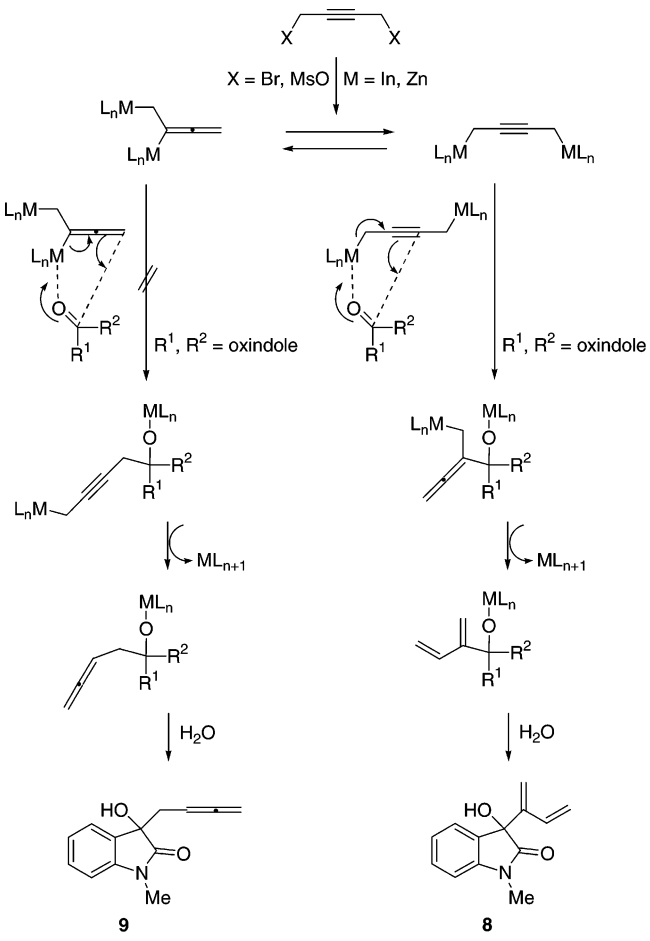
The use of THF as cosolvent was necessary to increase the solubility of both starting material and product in every single addition reaction. Sometimes, the above addition reactions benefit from the presence of additives. The lone pairs of the carbonyl oxygen atom can be considered as hard Lewis base sites. Coordination of these lone pairs to Lewis acids lowers the electron density at the oxygen atom and lowers the energy of the lowest unoccupied molecular orbital, the C=O π^* orbital, activating the group toward nucleophilic attack. Because the

(19) (a) Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *J. Org. Chem.* **2002**, *67*, 1925. (b) Lu, W.; Ma, J.; Yang, Y.; Chan, T. H. *Org. Lett.* **2000**, *2*, 3469. (c) Luo, M.; Iwabuchi, Y.; Hatakeyama, S. *Chem. Commun.* **1999**, 267. (d) Nishiyama, T.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Tetrahedron Lett.* **1998**, *39*, 43. (e) Soundararajan, R.; Li, G.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 100.

(20) For the addition of allenylmethylsilane on isatin in the presence of titane, see: Hojo, M.; Murakami, C.; Aihara, H.; Tomita, K.; Miura, K.; Hosomi, A. *J. Organomet. Chem.* **1995**, *499*, 155.

(21) A reviewer pointed out the unstability of the bis organometallic intermediate on the two adjacent carbons.

SCHEME 2



proton is the smallest possible Lewis acid, it may be possible that in the dilute acidic medium provided by the presence of hydrobromic acid in the bromoallylation reaction, protonation of the carbonyl occurs, facilitating the addition process by the nucleophile. It is to be presumed that the ionic strength enhancement of the reaction solvent provided by the ammonium chloride accelerated the process.[22] Although the role of the bismuth- and hafnium-derived additives is not completely understood, it may be explained in terms of Lewis acid which activates both the carbonyl group as well as the softness of these reagents. A transmetalation of the initially formed organometallic reagent with bismuth(III) chloride or hafnium(IV) chloride as Lewis acids may be involved.[23]

Conclusions

In conclusion, we have achieved efficient Barbier-type carbonyl-allylation, bromoallylation, 1,3-butadien-2-ylation, propargylation, or allenylation reactions of 2,3-indolinediones (isatins) in aqueous media, which proceeded with full regiocontrol. The simple reaction protocols for achieving functionalized adducts, in combination with the chemical and biological interest of the 3-substituted 3-hydroxyoxindole moiety, makes these processes very appealing. The current work is directed to use these unsaturated alcohols for the synthesis of spiroindolones.

Experimental Section

General Methods. The same experimental techniques were used as previously reported.[14]

Indium Promoted Reaction between Allyl Bromides and Isatins 1 in an Aqueous Medium Containing $HfCl_4$. General Procedure for the Synthesis of Homoallylic Alcohols 2. The appropriate allyl bromide (1.0 mmol) was added to a well-stirred suspension of the corresponding 2,3-indolinedione **1** (0.5 mmol), indium powder (115 mg, 1.0 mmol), and hafnium(IV) chloride (32 mg, 0.1 mmol) in THF/H_2O (1:1, 5 mL) at 0 °C. The mixture was stirred at the same temperature until complete disappearance of the α-keto-γ-lactam (TLC). Saturated aqueous sodium hydrogen carbonate (2.5 mL) was added, and the mixture was allowed to warm to room temperature before being extracted with ethyl acetate (3 × 3 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate or ethyl acetate/dichloromethane mixtures gave analytically pure compounds **2**. Spectroscopic and analytical data for some representative forms of **2** follow.[24]

3-Allyl-3-hydroxy-1,3-dihydro-2*H*-indol-2-one, 2a.[11b] From 73 mg (0.5 mmol) of 2,3-indolinedione **1a** was obtained 93 mg (100%) of compound **2a**.

Tin-Promoted Reaction between 2,3-Dibromopropene and Isatins 1 in an Aqueous Medium Containing $BiCl_3$. General Procedure for the Synthesis of Bromohomoallylic Alcohols 3. 2,3-Dibromopropene (300 mg, 1.5 mmol) was added to a well-stirred suspension of the corresponding 2,3-indolinedione **1** (0.5 mmol), tin powder (89 mg, 0.75 mmol), and bismuth(III) chloride (31 mg, 0.1 mmol) in THF/NH_4Cl (aq satd) (1:5, 5 mL) at 5 °C. After 20 h, saturated aqueous sodium hydrogen carbonate (2.5 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature before being extracted with ethyl acetate (3 × 3 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate or ethyl acetate/dichloromethane mixtures gave analytically pure compounds **3**. Spectroscopic and analytical data for some representative forms of **3** follow.

3-(2-Bromoallyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one, 3a. From 73 mg (0.5 mmol) of 2,3-indolinedione **1a** was obtained 89 mg (67%) of compound **3a** as a colorless oil after purification by flash chromatography (ethyl acetate/dichloromethane, 1/4). ^{1}H NMR (acetone-d_6): δ 9.39 (br s, 1H), 7.42 (dd, 1H, J = 7.4, 1.3 Hz), 7.25 (td, 1H, J = 7.7, 1.4 Hz), 7.01 (td, 1H, J = 7.5, 1.1 Hz), 6.90 (d, 1H, J = 7.8 Hz), 5.61 and 5.40 (d, each 1H, J = 1.7 Hz), 3.18 (d, 2H, J = 0.7 Hz). ^{13}C NMR (acetone-d_6): δ 178.6, 143.0, 130.9, 130.3, 126.7, 126.1, 122.5, 122.0, 110.6, 76.5, 49.2. IR ($CHCl_3$, cm^{-1}): ν 3424, 3297, 1711. MS (EI), *m/z*: 269 (M^+ + 1, 100), 267 (M^+ − 1, 98). Anal. Calcd for $C_{11}H_{10}BrNO_2$: C, 49.28; H, 3.76; N, 5.22. Found: C, 49.40; H, 3.72; N, 5.18.

Zinc-Promoted Reaction between Propargyl Bromide and Isatins 1 in an Aqueous Medium Containing NH_4Cl and $HfCl_4$. General Procedure for the Synthesis of Homoproparagylic Alcohols 4. Propargyl bromide (178 mg,

(22) Modification in the diastereomeric ratio or acceleration of the process has been reported on changing the ionic strength of the solvent in the allylation of enantiopure 2-aminoaldehydes: (a) Chappell, M. D.; Halcomb, R. L. *Org. Lett* **2000**, *2*, 2003. In a recent paper on the allylation of mucohalic acids, it has been suggested that the role NH_4Cl plays is perhaps 2-fold: (1) to activate the carbonyl group and (2) to polish the metal surface. See: (b) Zhang, J.; Blazecka, P. G.; Berven, H.; Belmont, D. *Tetrahedron Lett.* **2003**, *44*, 5579.

(23) For an allyltin−indium trichloride transmetalation, see: Li, X.-R.; Loh, T.-P. *Tetrahedron: Asymmetry* **1996**, *7*, 1996.

(24) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

1.5 mmol) was added to a well-stirred suspension of the corresponding 2,3-indolinedione **1** (0.5 mmol), zinc powder (195 mg, 3.0 mmol), and hafnium(IV) chloride (32 mg, 0.1 mmol) in THF/NH_4Cl (aq satd) (1:5, 5 mL) at 0 °C. The mixture was stirred at the same temperature until complete disappearance of the α-keto-γ-lactam (TLC). Saturated aqueous sodium hydrogen carbonate (2.5 mL) was added, and the mixture was allowed to warm to room temperature before being extracted with ethyl acetate (3 × 3 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to gave analytically pure compounds **4**. Spectroscopic and analytical data for some representative forms of **4** follow.

3-Hydroxy-3-(2-propynyl)-1,3-dihydro-2*H*-indol-2-one, 4a.[11b] From 73 mg (0.5 mmol) of 2,3-indolinedione **1a** was obtained 93 mg (100%) of compound **4a**.

Indium-Promoted Reaction between 3-Substituted 2-Propynylbromides and Isatins 1. General Procedure for the Synthesis of α-Allenic Alcohols 6. The appropriate propargyl bromide (1.5 mmol) was added to a well-stirred suspension of the corresponding 2,3-indolinedione **1** (0.5 mmol) and indium powder (344 mg, 3.0 mmol) in THF/H_2O (1:1, 5 mL) at 5 °C. After 2 h, saturated aqueous sodium hydrogen carbonate (2.5 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature before being extracted with ethyl acetate (3 × 3 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate or ethyl acetate/dichloromethane mixtures gave analytically pure compounds **6**. Spectroscopic and analytical data for some representative forms of **6** follow.

3-(2,3-Butadien-2-yl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one, 6a. From 73 mg (0.5 mmol) of 2,3-indolinedione **1a** was obtained 90 mg (90%) of compound **6a** as a colorless solid. Mp: 179−180 °C (hexanes/ethyl acetate). ^1H NMR (acetone-d_6): δ 9.24 (br s, 1H), 7.18 (dd, 1H, J = 7.4, 1.2 Hz), 7.10 (td, 1H, J = 7.7, 1.3 Hz), 6.87 and 6.77 (td, each 1H, J = 7.5, 1.0 Hz), 4.98 (s, 1H), 4.69 (qd, 2H, J = 3.1, 1.3 Hz), 1.59 (t, 3H, J = 3.1 Hz). ^{13}C NMR (acetone-d_6): δ 207.1, 178.7, 143.1, 132.6, 130.5, 126.0, 123.1, 110.9, 102.0, 78.5, 77.6, 14.3. IR ($CHCl_3$, cm^{-1}): ν 3423, 3296, 1955, 1714. MS (EI), *m/z*: 202 (M^+ + 1, 7), 201 (M^+, 100). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.52; H, 5.54; N, 7.00.

3-Hydroxy-1-methyl-3-(1-phenylpropadienyl)-1,3-dihydro-2*H*-indol-2-one, 6c. From 112 mg (0.70 mmol) of 2,3-indolinedione **1b** was obtained 158 mg (82%) of compound **6c** as a colorless solid. Mp: 106−108 °C (hexanes/ethyl acetate). ^1H NMR ($CDCl_3$): δ 7.30 (m, 2H), 7.15 (m, 5H), 7.04 (td, 1H, J = 7.6, 1.0 Hz), 6.77 (d, 1H, J = 7.3 Hz), 5.28 (s, 2H), 3.12 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 206.9, 176.3, 143.7, 133.1, 130.1, 129.2, 128.4 (2C), 128.2 (2C), 127.6, 124.9, 123.2, 108.5, 108.0, 77.1, 81.3, 26.3. IR ($CHCl_3$, cm^{-1}): ν 3295, 1953, 1712. MS (EI) *m/z*: 278 (M^+ + 1, 15), 277 (M^+, 100). Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.07; H, 5.41; N, 5.10.

Indium-Promoted Reaction between 1,4-Dibromo-2-butyne and Isatin 1b. 1,4-Dibromo-2-butyne (212 mg, 1.0 mmol) was added to a well-stirred suspension of the α-keto lactam **1b** (81 mg, 0.5 mmol) and indium powder (115 mg, 1.0 mmol) in THF/H_2O (1:1, 5 mL) at room temperature. After 4 h, saturated aqueous sodium hydrogen carbonate (2.5 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate (3 × 3 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/dichloromethane (1:40) as an eluent gave 48 mg (44%) of compound **8**.

3-(1,3-Butadien-2-yl)-3-hydroxy-1-methyl-1,3-dihydro-2*H*-indol-2-one, 8. Colorless solid. Mp: 119−120 °C (hexanes/ethyl acetate). ^1H NMR: δ 7.37 (td, 1H, J = 7.7, 1.3 Hz), 7.30 (m, 1H), 7.10 (td, 1H, J = 7.6, 1.0 Hz), 6.88 (d, 1H, J = 7.8 Hz), 6.06 (ddd, 1H, J = 17.5, 11.2, 1.0 Hz), 5.58 and 5.50 (s, each 1H), 5.21 (dd, 1H, J = 17.6, 1.2 Hz), 4.99 (dd, 1H, J = 11.0, 1.0 Hz), 3.25 (s, 3H). ^{13}C NMR: δ 176.7, 145.1, 143.9, 133.3, 130.2, 129.6, 124.6, 123.5, 116.8, 114.1, 108.7, 78.0, 26.5. IR ($CHCl_3$, cm^{-1}): ν 3295, 1718. MS (EI), *m/z*: 216 (M^+ + 1, 7), 215 (M^+, 100). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.41; H, 6.05; N, 6.55.

Acknowledgment. We thank the DGI-MCYT (Project BQU2003-07793-C02-01) for financial support. R.R.-A. thanks the MCYT for a predoctoral grant.

Supporting Information Available: Compound characterization data and experimental procedures for compounds **2b**,**c**, **3b**, **4b**, **6b**, and **7b**,**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050130W