CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201203701

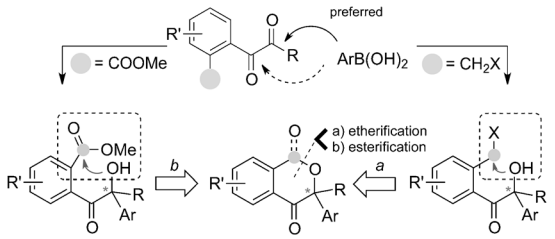
Rhodium-Catalyzed Enantioselective Addition to Unsymmetrical α-Diketones: Tandem One-Pot Synthesis of Optically Active 3-Tetrasubstituted Isochroman Derivatives

Ting-Shun Zhu, Jian-Ping Chen, and Ming-Hua Xu*[a]

Isochromans (3,4-dihydro-1*H*-isochromene) constitute an important class of oxygenated heterocycles that are found in a wide range of naturally occurring products and biologically active compounds.[1] Although numerous synthetic strategies have been developed for the construction of these structural motifs, only a limited number of stereoselective methods for preparing chiral 1- or 3-substituted isochromans have been reported.[2] Particularly with respect to chiral quaternary carbon-containing isochromans, which have already shown unique pharmaceutical properties,[3] to the best of our knowledge, there are no examples of their straightforward enantioselective synthesis.[4,5] Thus, the development of new catalytic systems that are capable of the efficient synthesis of highly optically active isochroman derivatives with a quaternary carbon stereogenic center is highly desirable. In this communication, we report a highly practical and efficient asymmetric approach to chiral 3-tetrasubstituted isochroman derivatives, 4-isochromanones, and 1,4-isochromandiones through a tandem 1,2-addition/cyclization one-pot sequence that is catalyzed by a simple Rh/sulfur-olefin catalyst.

We have recently designed a new family of chiral ligands, sulfur-olefins, and successfully employed them in the rhodium-catalyzed asymmetric 1,4-addition of aryl boronic acids to α,β-unsaturated carbonyl compounds.[6,7] With the extremely simple structure of the chiral *N*-sulfinyl cinnamylamine ligand, we developed a highly enantioselective 1,2-addition of arylboronic acids to α-ketoesters and α-diketones. A variety of highly enantioenriched tertiary α-hydroxy carbonyl derivatives were easily accessed under mild conditions at room temperature.[6d]

In considering isochroman frameworks, we envisioned an intramolecular heterocyclization protocol. If a highly regio- and enantioselective 1,2-addition of unsymmetrical α-diketones can be achieved,[8] the resulting α-hydroxy ketone product might be appropriately designed as a precursor capable of intramolecular etherification or esterification of the newly formed hydroxyl function to give the corresponding 3-tetrasubstituted isochromanones (Scheme 1).



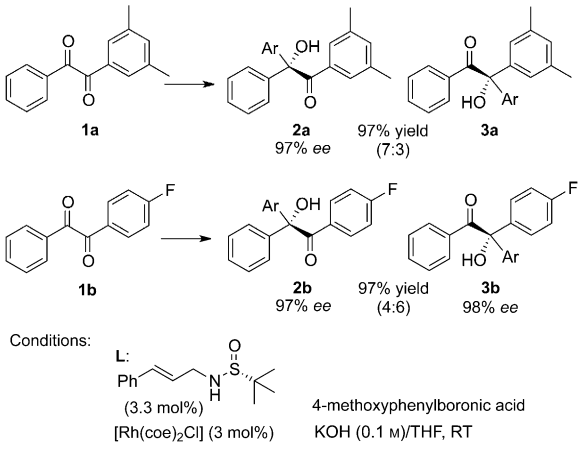
Scheme 1. Proposed intramolecular heterocyclization.

We began our studies by examining the reactions of unsymmetrical α-diketones **1a** and **1b** with 4-methoxyphenylboronic acid in the presence of $[Rh(coe)_2Cl]_2$ (1.5 mol%; coe = cyclooctene) and chiral *N*-sulfinyl cinnamylamine ligand (3.3 mol%) in aqueous KOH (0.1 M)/THF at room temperature. To our delight, the reactions proceeded smoothly and gave the expected tertiary α-hydroxyketones **2** and **3** in nearly quantitative yield with 7:3 and 4:6 regioselectivity, respectively. Notably, both regioisomers were obtained with excellent enantiomeric excesses (97–98% *ee*). These results suggested the possibility of a highly regio- and enantioselective 1,2-addition to unsymmetrical α-diketones that have large differences in the steric and electronic properties of each ketone moiety (Scheme 2).

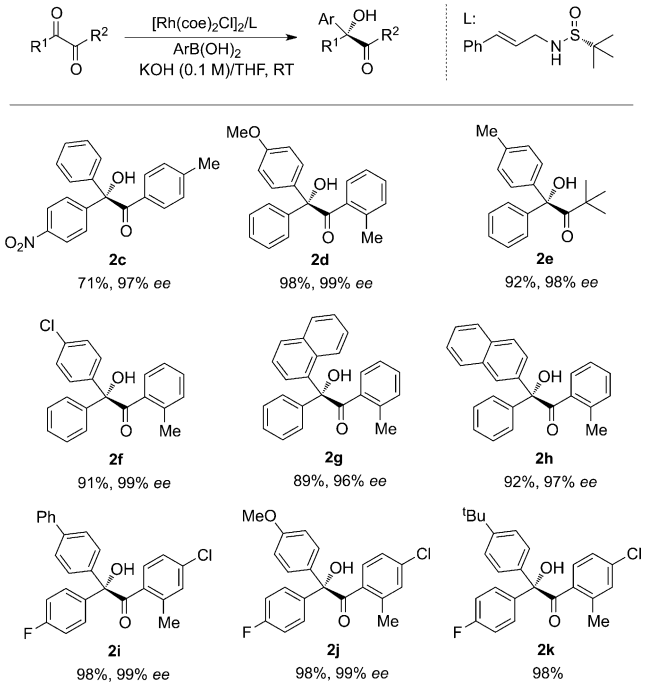
In order to investigate the potential of this highly regio- and enantioselective reaction, we prepared a variety of different substituted benzils. As expected, the use of a substrate with large electronic differences between the two substituents on the benzene ring led to a great enhancement of the regioselectivity. In the case of 1-(4-nitrophenyl)-2-*para*-tolylethane-1,2-dione, the sole regioisomer **2c** was observed with 97% *ee* (Scheme 3). The regiochemistry is in accordance with the observation by Inoue et al.[8b] that the addition of arylstannane to benzil derivatives with a nitro group was completely regioselective. On the other hand, the significant influence of steric hindrance is seen in the addition. With *ortho*-methyl-substituted unsymmetrical benzils, reactions with different aryl boronic acids afforded the desired tertiary α-hydroxyketones in high yields with excellent regioselectivity (>99:1) and enantioselectivities (96–99% *ee*; **2d**, **2f**–**k**). When 3,3-dimethyl-1-phenylbutane-1,2-dione was

[a] T.-S. Zhu, J.-P. Chen, Prof. Dr. M.-H. Xu
Shanghai Institute of Materia Medica
Chinese Academy of Sciences
555 Zuchongzhi Road, Shanghai 201203 (P.R. China)
Fax: (+86) 21-50807388
E-mail: xumh@mail.shcnc.ac.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201203701.



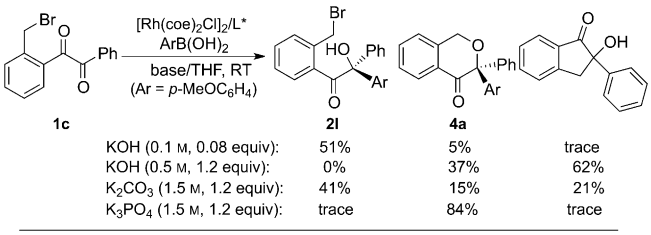
Scheme 2. Initial attempts at the Rh-catalyzed 1,2-addition to unsymmetrical α-diketones.

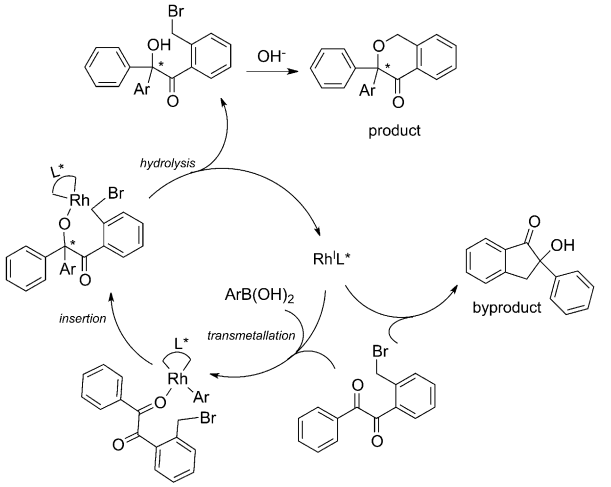


Scheme 3. Regio- and enantioselective 1,2-addition to unsymmetrical α-diketones. Reactions were carried out with α-diketone (0.25 mmol) and arylboronic acid (1.5 equiv) in the presence of Rh (3 mol%), ligand (3.3 mol%), and KOH (0.1 M, 0.08 equiv) in of THF (1.0 mL) for 3 h. Yields of isolated product are shown, and *ee* was determined by chiral HPLC analysis. For **2k**, an accurate *ee* measurement was not achieved due to the lack of full baseline resolution of its racemic compound, see the Supporting Information for details.

employed, the same high level of regio- and enantioselectivity was obtained (**2e**). In all these cases, a strong regioselectivity favoring addition to the less hindered and more electron deficient carbonyl group was found.

Encouraged by the above success, we then turned our attention to the construction of isochroman frameworks. Initially, the benzil **1c**, with an *ortho*-bromomethyl substituent on one benzene ring, was prepared and subjected to 1,2-addition under the above conditions. However, the result was disappointing. The reaction gave the expected isochroman **4a**[9] in only 5% yield, but yielded mostly the uncyclized addition product **2l** (Scheme 4). Typically, the catalytic cycle is proposed to involve aryl rhodium intermediate formation through transmetallation, followed by insertion and hydroly-

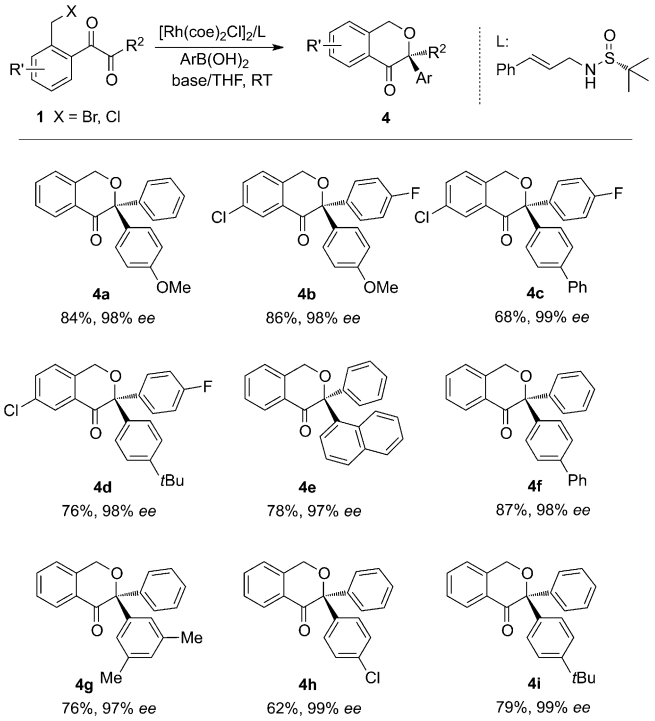




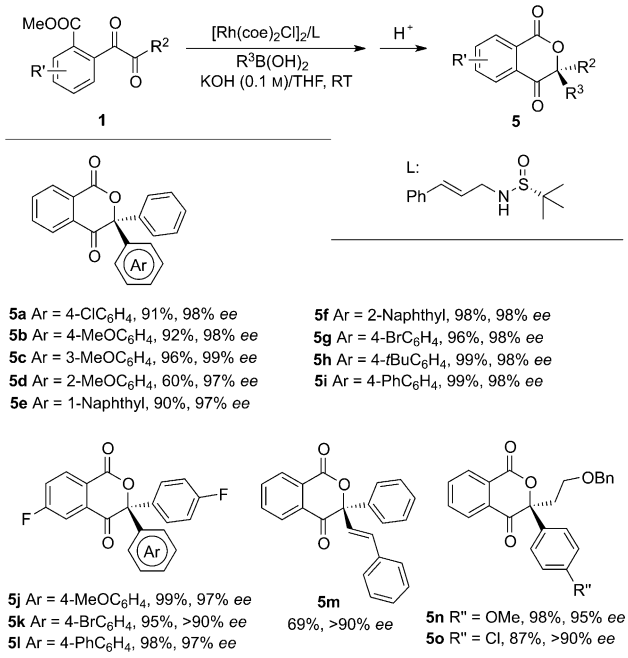
Scheme 4. Initial attempts at the 1,2-addition/etherification.

sis steps. However, the use of KOH (0.5 M) or K_2CO_3 (1.5 M) led to the significant formation of the unexpected racemic indanone byproduct, which is likely initiated by the oxidative addition of the Rh^I species into the C–Br bond of the substrate, although the exact intermediate and its coordination status remains unclear at this time. These results clearly indicate that the base has an important influence on the tandem reaction. Fortunately, after careful screening of the basic conditions, we were pleased to find that the addition–etherification tandem reaction proceeded smoothly and gave **4a** in good yield (84%) and enantioselectivity (98%) when performed with 1.2 equivalents of K_3PO_4 (1.5 M; Scheme 5). Moreover, it seemed that chloride substrates were not prone to Rh-oxidative addition; they also underwent the effective addition–etherification process to give the corresponding 4-isochromanones in good yields and excellent *ee* under proper conditions (**4e–i**, Scheme 5). In comparsion, the use of a chlorine leaving group allowed the reaction to proceed more efficiently with diverse arylboronic acids. The stereochemistry of the products was assigned according to our previous report.

Following the success of the one-pot asymmetric synthesis of 4-isochromanone, we decided to explore the possibility of



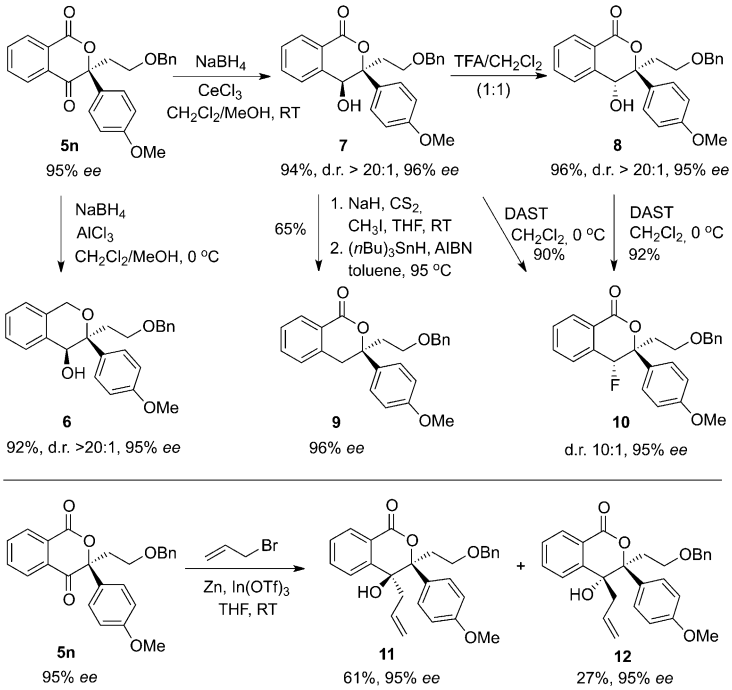
Scheme 5. One-pot synthesis of 4-isochromanones by tandem 1,2-addition/etherification. Reactions were carried out with α-diketone (0.25 mmol), and arylboronic acid (2 equiv) in the presence of Rh (3 mol%), ligand (3.3 mol%), and base in THF (1.0 mL) for 3 h. For products **4a–d** with bromide substrates (X = Br), K_3PO_4 (1.5 M, 1.2 equiv) was used; for products **4e–i** with chloride substrates (X = Cl), KOH (0.1 M, 0.08 equiv) was used. Et_3N (0.1 mL) and KI (50 mg, 1.2 equiv) were added after the addition. Yields of isolated product are shown, and *ee* was determined by chiral HPLC analysis.



Scheme 6. One-pot synthesis of 1,4-isochromandiones by tandem 1,2-addition/esterification. Reactions were carried out with α-diketone (0.25 mmol) and arylboronic acid (1.5 equiv) in the presence of Rh (3 mol%), ligand (3.3 mol%), and KOH (0.1 M, 0.08 equiv) in THF (1.0 mL) for 3 h, then acidified with H_2SO_4 (0.1 mL conc.) in CH_3OH (1 mL) and stirred for a further 1 h. Yields of isolated product are shown, and *ee* was determined by chiral HPLC analysis. For **5k**, **5m**, and **5o** accurate *ee* measurements were not achieved due to the lack of full baseline resolution of their racemic compounds, see the Supporting Information for details.

a tandem 1,2-addition–esterification to generate chiral 1,4-isochromandiones. Accordingly, α-diketone substrates with an ester substituent (COOMe) at the *ortho* position of one ketone phenyl ring were prepared and evaluated. The results are summarized in Scheme 6. As anticipated, the rhodium-catalyzed enantioselective 1,2-addition can only take place at the less sterically congested ketone, giving the desired adducts with excellent *ee* under the same reaction conditions shown in Scheme 3. Subsequently, by adding a small amount of H_2SO_4 (conc.), the tandem intramolecular esterification was found to proceed smoothly and was complete within 1 h, giving the cyclized product **5** in high yield and maintaining enantioselectivity. It is noteworthy that a broad range of arylboronic acids with distinct steric and electronic properties can be successfully employed in the reaction (**5a–l**). Furthermore, alkenylboronic acids can also participate in the regio- and enantioselective 1,2-addition. Performing the one-pot reaction with styrylboronic acid led to the desired, functionalized product **5m** with high enantioselectivity, albeit in moderate yield (69%). To further expand the reaction scope, we turned to an α-diketone substrate with a linear alkyl group on one carbonyl. Remarkably, in the cases of **5n** and **5o**, the 3-alkyl-3-aryl 1,4-isochromandiones with high enantioselectivities were equally accessed with the tandem one-pot sequence under the same mild conditions. In addition, useful functional groups, such as benzyloxy, were introduced. Thus, this method allows the efficient and stereoselective installation of versatile substituents at the 3-position and provides access to highly enantioenriched 1,4-isochromandiones.

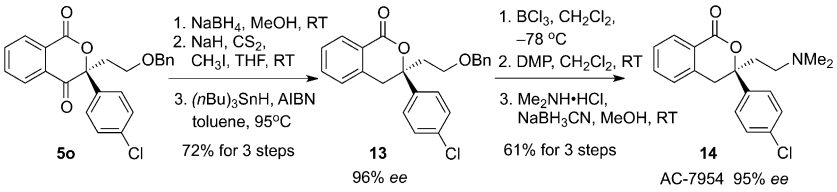
To further explore the synthetic utility of this chemistry, a series of functional group transformations were studied (Scheme 7). When the addition product **5n**, with a 3-alkyl-3-aryl quarternary stereogenic center, was subjected to $AlCl_3$- or $CeCl_3$-mediated $NaBH_4$ reduction, the corresponding 4-hydroxyl-isochroman (**6**) and -isochromanone (**7**) were generated as single stereoisomers in 94% and 92% yield, respectively. Interestingly, the 4-hydroxyl group of **6** underwent a complete epimerization in trifluoroacetic acid, likely through a cationic intermediate, giving epimer **8** in 96% yield with 95% *ee*. Furthermore, by using Barton's radical deoxygenation procedure, removal of the hydroxyl group in **7** was easily accomplished, providing 1-isochromanone **9** in a relatively good yield with no racemization detected. It is noteworthy that the DAST (diethylaminosulfur trifluoride)-mediated dehydroxyfluorination of both **7** and **8** gave mainly the same fluoride product, (4*R*)-**10**, without losing optical purity (95% *ee*). This suggests that the reactions undergo a typical S_N1 process,[10] and the stereoselectivity is



Scheme 7. Synthetic applicability towards various isochroman derivatives. TFA = trifluoroacetic acid, AIBN = 2-2′-azobisisobutyronitrile, Tf = trifluoromethanesulfonyl.

again attributed to the steric differentiation at 3-position. In addition, an attempt to use a carbon nucleophile was also carried out. Treatment of **5n** with an allylzinc reagent in the presence of $In(OTf)_3$[11] gave two diastereoisomers, **11** and **12**, in a 2:1 ratio, which were readily separated by column chromatography. Thus, the isochroman architecture with two contiguous quarternary stereocenters that is otherwise difficult to access was established in a stereoselective fashion.[12]

Finally, a particularly fascinating synthetic application of the methodology was demonstrated. As illustrated in Scheme 8, the adduct **5o** was readily converted to **14** (AC-7954),[3a–c] a drug lead that is a highly selective nonpeptidic agonist of the urotensin-II receptor,[13] by two linear process with a total of six steps in good yield. To our knowledge, the asymmetric route to AC-7954 is unprecedented,[14] and the known procedure to synthesize its racemic compound is somewhat inefficient,[3a–c] which has largely limited the availability of this interesting class of compounds. From this point of view, our current strategy represents a potentially valuable enantioselective approach to the generation of a wide range of isochroman-based urotensin-II agonists.



Scheme 8. The first asymmetric synthesis of AC-7954. DMP = Dess–Martin periodinane.

In summary, we have developed an efficient and general catalytic one-pot protocol for the synthesis of an interesting class of isochroman derivatives. A great variety of highly enantioenriched tetrasubstituted isochromanones have been efficiently generated by this method under exceptionally mild conditions. The key transformation relies on the stereoselective creation of tertiary α-hydroxyketones from a rhodium-catalyzed highly regio- and enantioselective 1,2-addition of arylboronic acids to unsymmetrical α-diketones by using an extremely simple chiral *N*-sulfinyl cinnamylamine ligand. Moreover, the first asymmetric synthesis of the non-peptide urotensin II receptor agonist AC-7954 has been successfully achieved by taking advantage of this reaction. Further investigations of the application of this strategy in biologically interesting, oxygen-containing heterocyclic compound syntheses are ongoing in our laboratory.

Experimental Section

General procedure for the synthesis of 4a–i: Under an Ar atmosphere, a solution of the α-diketone compound (0.25 mmol), $[RhCl(coe)_2]_2$ (2.7 mg, 0.0075 mmol of Rh), *N*-sulfinyl cinnamylamine ligand (2.0 mg, 0.00825 mmol), and arylboronic acid (0.5 mmol) in THF (1.0 mL) was stirred at room temperature for 30 min. Aqueous KOH (0.2 mL, 0.1 M, 0.02 mmol) was then added to the mixture. After stirring at room temperature for 3 h, KI (50 mg, 1.2 equiv) and Et_3N (0.1 mL) were added, the mixture was stirred for an additional 1 h, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the corresponding addition products **4e–i**.

General procedure for the synthesis of 5: Under an Ar atmosphere, a solution of the α-diketone compound (0.25 mmol), $[RhCl(coe)_2]_2$ (2.7 mg, 0.0075 mmol of Rh), *N*-sulfinyl cinnamylamine ligand (2.0 mg, 0.00825 mmol), and arylboronic acid (0.375 mmol) in THF (1.0 mL) was stirred at room temperature for 30 min. Aqueous KOH (0.2 mL, 0.1 M, 0.02 mmol) was then added to the mixture. After stirring at room temperature for 3 h, MeOH (1 mL) and H_2SO_4 (conc., 0.1 mL),were added, the mixture was stirred for another 1 h, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the corresponding addition product **5**.

Acknowledgements

Financial support from the National Natural Science Foundation of China (20972172, 21021063), and the Chinese Academy of Sciences is greatly acknowledged.

Keywords: AC-7954 · asymmetric catalysis · domino reactions · isochromans · rhodium

[1] a) M. D. Ennis, N. B. Ghazal, R. L. Hoffman, M. W. Smith, S. K. Schlachter, C. F. Lawson, W. B. Im, J. F. Pregenzer, K. A. Svensson,

R. A. Lewis, E. D. Hall, D. M. Sutter, L. T. Harris, R. B. McCall, *J. Med. Chem.* **1998**, *41*, 2180; b) D. A. Bianchi, E. G. Sutich, T. S. Kaufman, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 757; c) D. A. Bianchi, N. E. Blanco, N. S. Carrillo, T. S. Kaufman, *J. Agric. Food Chem.* **2004**, *52*, 1923; d) M. Tobe, T. Tashiro, M. Sasaki, H. Takikawa, *Tetrahedron* **2007**, *63*, 9333; e) K. Trisuwan, V. Rukachaisirikul, Y. Sukpondma, S. Phongpaichit, S. Preedanon, J. Sakayaroj, *Tetrahedron* **2010**, *66*, 4484.

[2] a) P. Maity, H. D. Srinivas, M. P. Watson, *J. Am. Chem. Soc.* **2011**, *133*, 17142; b) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198; c) N. T. Patil, L. M. Lutete, H. Wu, N. K. Pahadi, I. D. Gridnev, Y. Yamamoto, *J. Org. Chem.* **2006**, *71*, 4270; d) S.-F. Zhu, X.-G. Song, Y. Li, Y. Cai, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 16374; e) M. Fujita, Y. Yoshida, K. Miyata, A. Wakisaka, T. Sugimura, *Angew. Chem.* **2010**, *122*, 7222; *Angew. Chem. Int. Ed.* **2010**, *49*, 7068; f) M. Leibeling, D. C. Koester, M. Pawliczek, S. C. Schild, D. B. Werz, *Nat. Chem. Biol.* **2010**, *6*, 199; g) A. Orue, E. Reyes, J. Vicario, L. Carrillo, U. Uria, *Org. Lett.* **2012**, *14*, 3740; h) M. Terada, Y. Toda, *Angew. Chem. Int. Ed.* **2012**, *51*, 2093.

[3] a) G. E. Croston, R. Olsson, E. A. Currier, E. S. Burstein, D. Weiner, N. Nash, D. Severance, S. G. Allenmark, L. Thunberg, J.-N. Ma, N. Mohell, B. O'dowd, M. R. Brann, U. Hacksell, *J. Med. Chem.* **2002**, *45*, 4950; b) F. Lehmann, E. A. Currier, R. Olsson, U. Hacksell, K. Luthman, *Bioorg. Med. Chem.* **2005**, *13*, 3057; c) F. Lehmann, E. A. Currier, R. Olsson, J.-N. Ma, E. S. Burstein, U. Hacksell, K. Luthman, *Bioorg. Med. Chem.* **2010**, *18*, 4844; d) M. P. Costi, A. Gelain, D. Barlocco, S. Ghelli, F. Soragni, F. Reniero, T. Rossi, A. Ruberto, C. Guillou, A. Cavazzuti, C. Casolari, S. Ferrari, *J. Med. Chem.* **2006**, *49*, 5958; e) Y. Shishido, H. Wakabayashi, H. Koike, N. Ueno, S. Nukui, T. Yamagishi, Y. Murata, F. Naganeo, M. Mizutani, K. Shimada, Y. Fujiwara, A. Sakakibara, O. Suga, R. Kusano, S. Ueda, Y. Kanai, M. Tsuchiya, K. Satake, *Bioorg. Med. Chem.* **2008**, *16*, 7193; f) K. Kuramochi, K. Fukudome, I. Kuriyama, T. Takeuchi, Y. Sato, S. Kamisuki, K. Tsubaki, F. Sugawara, H. Yoshida, Y. Mizushina, *Bioorg. Med. Chem.* **2009**, *17*, 7227; g) Y. Uto, Y. Kiyotsuka, Y. Ueno, Y. Miyazawa, H. Kurata, T. Ogata, T. Deguchi, M. Yamada, N. Watanabe, M. Konishi, N. Kurikawa, T. Takagi, S. Wakimoto, K. Kono, J. Ohsumi, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 746; h) M. Fichtner, E. Lee, E. Tomlinson, D. Scott, P. Cornelius, T. A. Patterson, P. A. Carpino, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2738.

[4] For a report on the enantioselective synthesis of spirocyclic benzopyranones by [4+2] annulation, see: D. Hojo, K. Noguchi, M. Hirano, K. Tanaka, *Angew. Chem.* **2008**, *120*, 5904; *Angew. Chem. Int. Ed.* **2008**, *47*, 5820.

[5] For examples of achiral synthesis of 3-quarternary isochroman derivatives, see: a) M. Altemöller, J. Podlech, D. Fenske, *Eur. J. Org. Chem.* **2006**, 1678; b) D. Soorukram, T. Qu, A. G. M. Barrett, *Org. Lett.* **2008**, *10*, 3833; c) G. Liu, J. M. Wurst, D. S. Tan, *Org. Lett.* **2009**, *11*, 3670; d) S. Ueno, M. Ohtsubo, R. Kuwano, *Org. Lett.* **2010**, *12*, 4332; e) Y. Lu, D.-H. Wang, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 5916; f) Y. Lu, D. Leow, X. Wang, K. M. Engle, J.-Q. Yu, *Chem. Sci.* **2011**, *2*, 967; g) K. Fujiwara, T. Kurahashi, S. Matsubara, *Chem. Lett.* **2011**, *40*, 322; h) Y. Ochi, T. Kurahashi, S. Matsubara, *Org. Lett.* **2011**, *13*, 1374; i) N. Kern, A. Blanc, J.-M. Weibel, P. Pale, *Chem. Commun.* **2011**, *47*, 6665; j) L. Wei, J. Zhang, *Chem. Commun.* **2012**, *48*, 2636.

[6] a) S.-S. Jin, H. Wang, M.-H. Xu, *Chem. Commun.* **2011**, *47*, 7230; b) W.-Y. Qi, T.-S. Zhu, M.-H. Xu, *Org. Lett.* **2011**, *13*, 3410; c) S.-S. Jin, H. Wang, T.-S. Zhu, M.-H. Xu, *Org. Biomol. Chem.* **2012**, *10*, 1764; d) T.-S. Zhu, S.-S. Jin, M.-H. Xu, *Angew. Chem.* **2012**, *124*, 804; *Angew. Chem. Int. Ed.* **2012**, *51*, 780.

[7] For recent reports on chiral sulfur-olefin ligands by other groups, see: a) T. Thaler, L.-N. Guo, A. K. Steib, M. Raducan, K. Karaghiosoff, P. Mayer, P. Knochel, *Org. Lett.* **2011**, *13*, 3182; b) X. Feng, Y. Wang, B. Wei, J. Yang, H. Du, *Org. Lett.* **2011**, *13*, 3300; c) G. Chen, J. Gui, L. Li, J. Liao, *Angew. Chem.* **2011**, *123*, 7823; *Angew. Chem. Int. Ed.* **2011**, *50*, 7681; d) F. Xue, X. Li, B. Wan, *J. Org. Chem.* **2011**, *76*, 7256; e) N. Khiar, A. Salvador, A. Chelouan, A. Alcudia, I. Fernández, *Org. Biomol. Chem.* **2012**, *10*, 2366; f) X. Feng, Y. Nie, J. Yang, H. Du, *Org. Lett.* **2012**, *14*, 624.

[8] For reported non-asymmetric addition examples, see: a) G. R. Ganci, J. D. Chisholm, *Tetrahedron Lett.* **2007**, *48*, 8266; b) S. Oi, M. Moro, H. Fukuhara, T. Kawanishi, Y. Inoue, *Tetrahedron* **2003**, *59*, 4351; c) S. Miyamura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 2255.

[9] CCDC-899346 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] a) M. M. Bio, M. Waters, G. Javadi, Z. J. Song, F. Zhang, D. Thomas, *Synthesis* **2008**, 891; b) S. Bresciani, D. O'Hagan, *Tetrahedron Lett.* **2010**, *51*, 5795.

[11] X.-W. Sun, M.-H. Xu, G.-Q. Lin, *Org. Lett.* **2006**, *8*, 4979.

[12] The configurations of the newly formed stereogenic carbon centers at the 4-position of compounds **6**, **7**, **8**, **10**, **11**, and **12** were assigned by NOE experiments; see the Supporting Information for details.

[13] For a review on UII receptor modulators as potential drugs, see: B. E. Maryanoff, W. A. Kinney, *J. Med. Chem.* **2010**, *53*, 2695.

[14] Resolution of enantiomers by HPLC using preparative chiral column has been reported, see ref. [3a].

Received: October 17, 2012
Revised: November 12, 2012
Published online: December 12, 2012

