Organic LETTERS

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Indium-Mediated Asymmetric Intramolecular Allenylation of *N-tert*-Butanesulfinyl Imines: Efficient and Practical Access to Chiral 3-Allenyl-4-aminochromanes

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Supporting Information

ABSTRACT: An efficient method for the preparation of highly optically active 3-allenyl- and 3-vinyl-4-aminochromanes by In-mediated intramolecular cyclization has been developed. The synthetic utilities of the approach were demonstrated by the construction of various chiral polycyclic heterocycles, especially the interesting spiroheterocyclic compound **9** and steroid analogue **10**.

Chromanes are an important class of oxygenated heterocycles; they have been frequently found as a key structural unit in many biologically active molecules and natural products.[1] Among them, 4-aminochromanes are particularly known as a unique class of compounds in drug discovery programs.[2] For example, chroman-4-amine sulfonamide (I) is a potential K^+ channel blocker with good selectivity over the block of *h*ERG;[2a] compound II is a potent JAK3 inhibitor, showing in vivo efficacy in an acute mechanistic mouse IL-2 model;[2b] compound III exhibits modest antibacterial properties against *Staphylococcus aureus*[2c] (Figure 1). Due to their biological significance, much

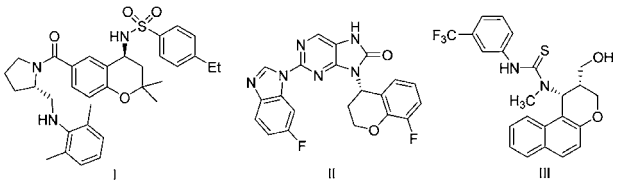
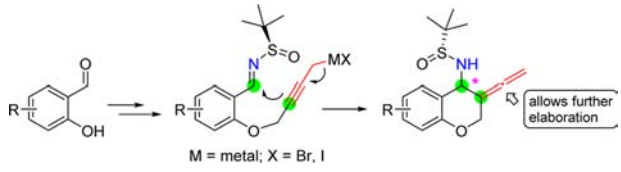


Figure 1. Chiral 4-aminochromanes with biological activities.

interest has been focused toward variable synthesis of a diverse range of 4-aminochromanes. It is, however, surprising that efficient methods for stereoselective preparation of optically active 4-amino substituted chromanes have been less developed,[1,3,4] and in fact, only a limited number of reports mainly involving catalytic reduction[3] and chiral auxiliary[4] methodology have been documented. Herein, we present a highly efficient asymmetric approach for the rapid construction of optically pure 4-amino substituted chromanes bearing an interesting allenyl functionality at the 3-position via indium-mediated diastereoselective intramolecular cyclization of alkyne-tethered *N-tert*-butanesulfinyl imines at rt.

With respect to enantioselective access to chiral amines, *N-tert*-butanesulfinyl imine chemistry has been intensively investigated and proven to be an attractive strategy with excellent performance in reaction stereocontrol and the ease of introduction and removal of the auxiliary.[5] In recent years, we have succeeded in preparing a series of structurally diverse chiral amines using this protocol.[6] In considering 4-amino substituted chromane frameworks, we were intrigued by the idea of metal-mediated asymmetric intramolecular allenylation of related *N-tert*-butanesulfinyl imines having a propargylic halide unit linked to phenolic oxygen (Scheme 1). It is worth mentioning that

Scheme 1. Synthetic Proposal



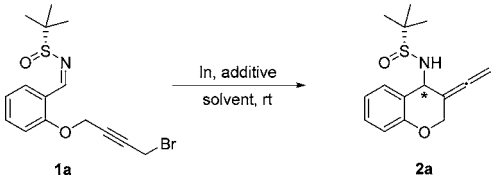
incorporation of a neighboring allenyl function[7] would allow further extensive elaboration of the 4-aminochromane molecules to achieve diversity in structures.

Our investigation was initiated by evaluating the feasibility of the intramolecular allenylation of **1a**, which was readily generated from the substitution reaction of salicylaldehyde with 1,4-dibromo-2-butyne followed by condensation with (*R*)-*N-tert*-butanesulfinylamide. To our delight, the designed reaction proceeded in the presence of indium in THF at rt for 24 h, leading to the formation of **2a** in a moderate yield (43%) with an exciting 97% de (Table 1, entry 2). A simple comparative trial indicated that a zinc-mediated reaction could only exhibit poor efficiency (entry 1). To improve the yield, we started to optimize the reaction conditions. Based on our experience, we first adopted iodized salts as additives to promote the reaction

Received: June 24, 2014
Published: July 28, 2014

   dx.doi.org/10.1021/ol501815e | *Org. Lett.* 2014, 16, 4118–4121

Table 1. Screening and Optimization of the Reaction Conditions[a]



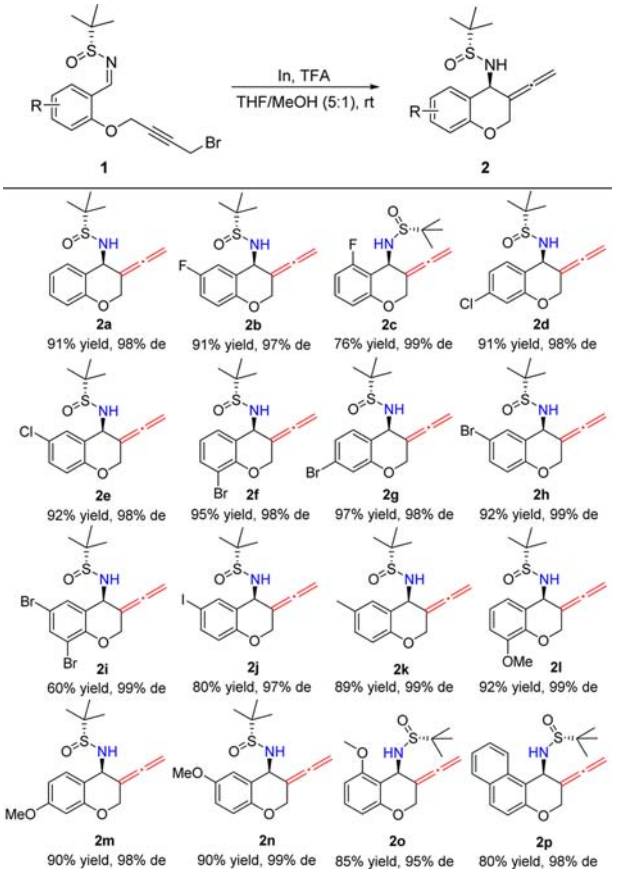
entry	solvent	additive	time (h)	yield (%)[b]	de (%)[c]
1[d]	THF	–	24	<5	–
2	THF	–	24	43	97
3	THF/H_2O (1:1)	NaI	24	73	96
4	THF/H_2O (1:1)	CuI	24	58	94
5	THF/H_2O (1:1)	KI	24	87	96
6	THF	TFA	6	72	98
7	THF	AcOH	6	89	95
8	THF	HCl	24	trace	–
9	MeOH	TFA	0.4	78	69
10[e]	THF/MeOH (2:1)	TFA	1	80	94
11[e]	THF/MeOH (5:1)	TFA	1	91	98
12[e,f]	THF/MeOH (5:1)	TFA	2	88	95

[a]The reaction was performed with 0.1 mmol of **1a**, 0.2 mmol of In, and 4 equiv of additives in 2 mL of solvent at rt unless noted. [b]Isolated yield. [c]The diastereoselectivity of the product was measured as the enantiomeric excess for the oxidate derivative of **2a**; determined by chiral HPLC analysis. [d]Zn was used instead of In. [e]2.4 mL of solvent were added. [f]2 equiv of TFA were used.

because it is likely that the iodide anion in aqueous solution will displace bromine in the substrate to generate a propargylic iodide in situ, thus facilitating the easy formation of reactive propargylindium.[6d] Indeed, increases in yields were obviously observed, but it led to a slight decline in the stereoselectivity (entries 3–5). We then examined several frequently used protic acids as the additives (entries 6–8); they are generally applied to improve reactions by activating the imines.[8] Pleasingly, there was a small increase in de (98%) when TFA was employed; however, the reaction yield was less satisfactory (72%, entry 6). After extensive study of the solvent effect, we found that the reaction could proceed smoothly and complete in a short time (0.4 h) albeit with moderate de (entry 9). Interestingly, when a mixed solvent of THF/MeOH (2:1) was used, the reaction proceeded well to give an improved yield as well as diastereoselectivity (entry 10). Further optimization of the solvent ratio to 5:1 led to the attainment of both excellent yield (91%) and diastereoselectivity (98% de) (entry 11). Nevertheless, the use of 2 equiv of TFA was less effective (entry 12).

With the optimal reaction conditions established, we next turned our attention to evaluate the reaction generality. As indicated in Scheme 2, a wide range of *N*-sulfinyl imines with diverse substituents were synthesized and tested. To our delight, in all cases, intramolecular allenylation of these substrates took place smoothly at rt to provide the corresponding 3-allenyl-4-aminochromane products in good yields with excellent diastereoselectivities (95–99% de). Reactions of electron-donating group substituted imines proceeded with equally high efficiency and diastereoselectivity as when electron-withdrawing substituents were introduced (see products **2k–o** and **2b–j**). Moreover, it was found that substitution at each position of the phenyl ring (*ortho*, *meta*, or *para*) did not affect the results. Also notably, the tolerance of the chloro (**2d–e**), bromo (**2f–i**), and iodo group (**2j**) provided an opportunity for further function-

Scheme 2. In-Mediated Intramolecular Allenylation of *N-tert*-Butanesulfinyl Imines[a,b,c]



[a]The reaction was performed with 0.1 mmol of **1**, 0.2 mmol of In and 4 equiv of TFA in 2.4 mL of solvent at rt. [b] Isolated yield. [c] The diastereoselectivity of the product was measured as enantiomeric excess for the oxidate derivatives of **2**.

alization via metal-catalyzed cross-coupling reactions. In addition, substrates with sterically congested electrophilic sites can also readily undergo cyclization while maintaining excellent diastereoselectivity (see products **2o** and **2p**), demonstrating that the reaction is nicely broad in scope.

The absolute configuration of the obtained 4-aminochromane was determined to be (*S*) by X-ray crystallographic analysis of the cyclized product **2a** (Figure 2). Conversion of the allenylation products to the corresponding free amines has been examined. For example, removal of the *N-tert*-butanesulfinyl group in **2a** under acidic conditions readily gave the desired amine without loss of optical purity (97% ee). To rationalize the observed stereochemistry, we proposed a six-membered ring transition

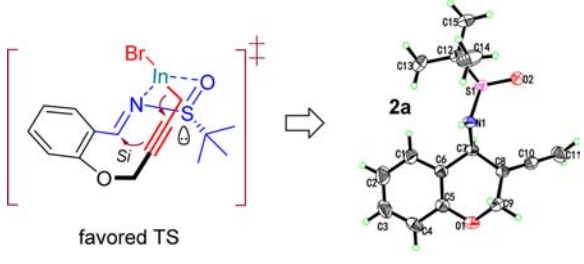


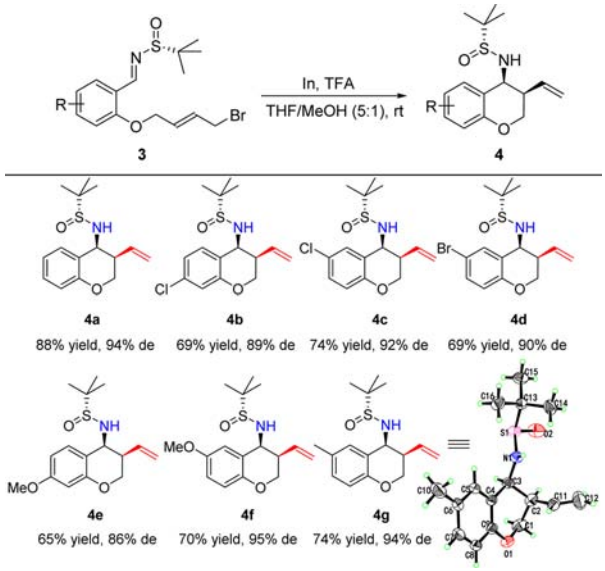
Figure 2. Transition state proposal for stereocontrol.

dx.doi.org/10.1021/ol501815e | *Org. Lett.* 2014, 16, 4118–4121

state model involving propargyl indium coordination with the imine nitrogen and oxygen concurrently (Figure 2). As depicted, an *si*-face attack is much more favored to avoid the steric hindrance of *tert*-butyl.

Encouraged by the above success, we conceived to extend the reaction system to intramolecular allylation by replacing the alkyne unit with the corresponding alkene unit. A similar process with chiral hydrazone as the auxiliary has been successfully reported by Cook;[4c] although excellent diastereoselectivities can be achieved, the removal of the chiral source seems to be a little troublesome. Therefore, alkene substrates **3** were readily prepared. Gratifyingly, under the same conditions, the desired allylation products having two contiguous stereogenic centers can be obtained in moderate yields (65%−88%) while maintaining a relatively high level of diastereoselectivity (up to 95% de with *syn*-conformation) (Scheme 3). Similarly as in allenylation reactions, the electronic properties seem have no significant impact on the stereoselectivity. As an example, the removal of *N*-sulfinyl in **4a** was carried out with ease under acidic conditions (0.2 M HCl in EtOAc, 87% yield) and proved to be much more convenient as compared with hydrazones.[4c] The stereochemistry of two newly formed centers were measured as (3*R*, 4*S*) by the X-ray structure of **4g**.

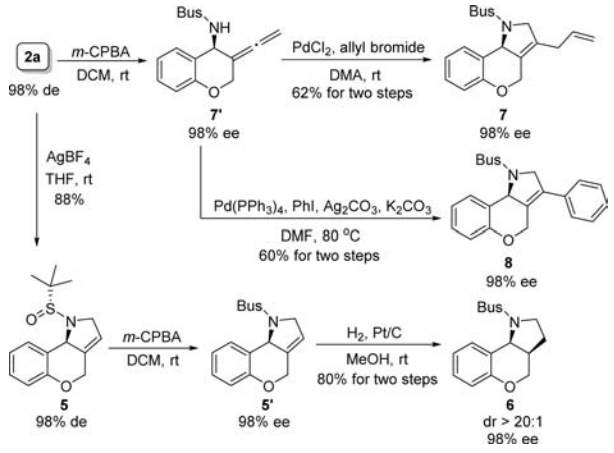
Scheme 3. In-Mediated Intramolecular Allylation of *N*-*tert*-Butanesulfinyl Imines[a,b,c]



[a]The reaction was performed with 0.1 mmol of **3**, 0.2 mmol of In and 4 equiv of TFA in 2.4 mL of solvent at rt. [b] Isolated yield. [c] The diastereoselectivity of the product was measured as enantiomeric excess for the oxidate derivatives of **4**.

To demonstrate the synthetic utility of this method, we conducted the allenylation reaction on a gram scale. Much to our delight, it went smoothly and provided **2a** in 86% yield. Subsequently, we sought to convert **2a** into more valuable molecules based on the amino and allenyl functionalities. As illustrated in Scheme 4, a further cyclization reaction promoted by $AgBF_4$ smoothly led to pyrroline product **5** in 88% yield without loss of optical purity.[9] A subsequent oxidation/hydrogenation[10] sequence allowed the generation of hexahydrochromeno[4,3-*b*]pyrrole **6** in good yield with high diastereoselectivity (dr >20:1). Furthermore, similar hydroamination processes accompanied by a coupling reaction mediated by

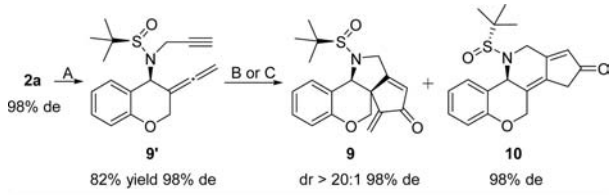
Scheme 4. Synthetic Applicability of Allenylation Product



$PdCl_2$ and $Pd(PPh_3)_4$ provided **7** and **8** respectively. It should be noted that the ee's of the attained tricyclic heterocycles remained essentially unchanged.

Inspired by the above annulation protocol,[11] we were also keen to explore the construction of complex polycyclic frameworks. A two-step, sequential *N*-propargylation/allenic Pauson−Khand reaction was developed and found to be applicable to 3-allenyl-4-aminochromanes. As shown in Scheme 5, **2a** was rapidly transformed into interesting polycyclic chromane compounds **9** and **10**. By using different transition metal complexes ($Mo(CO)_6$ or $Co_2(CO)_8$), a remarkable reversal of Pauson−Khand cyclization in allenic π-bond selectivity was observed.[12] Fortunately, their structures were confirmed by X-ray crystallographic analysis (Figure 3). It was found that compound **9** bears an unusual but rather intriguing spiroheterocyclic skeleton, while compound **10** has a ring system similar to steroids, which are a common mother nucleus of many important drug molecules such as hydrocortisone, digoxin, and spironolactone.[13] From the bioisosteric replacement strategy point of view, these novel chromane-based polycyclic compounds may lead to the design of new promising molecules for drug research and development.

Scheme 5. Further Synthetic Applicability of 2a[a]



conditions	metal complexes	yield (%)[b]	**9**:**10** ratio
B	$Mo(CO)_6$	63	3:1
C	$Co(CO)_8$	73	1:3

[a]Condition A: LiHMDS, propargyl bromide, THF, −78 °C to rt. Condition B: $Mo(CO)_6$, DMSO, CO, toluene, 100 °C. Condition C: (1) $Co_2(CO)_8$, DCM, rt. (2) NMO, MeCN, rt. [b]Total yield of **9** and **10**.

In summary, we have successfully developed an indium-mediated highly diastereoselective intramolecular cyclization process to prepare enantiomerically enriched 3-allenyl- or 3-vinyl-4-aminochromanes. The transformation is rapid and practical; it can be performed at rt using a broad range of *N*-sulfinyl substrates bearing corresponding alkyne and alkene

dx.doi.org/10.1021/ol501815e | *Org. Lett.* 2014, 16, 4118−4121

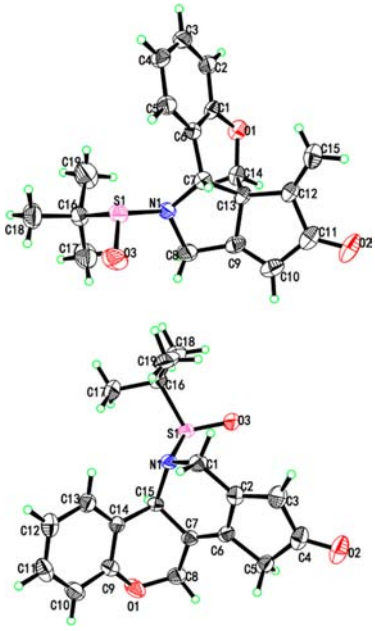


Figure 3. X-ray structures of compounds **9** (top) and **10** (bottom).

units. Notably, the 4-aminochromane products are versatile and valuable synthons, and they can undergo further cyclization to produce more complicated polycyclic heterocycles. Further work will be devoted to the application of this methodology to the synthesis of potential biological agents.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization, copies of HPLC and NMR spectra, and crystallographic data for **2a**, **4g**, **9**, and **10** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (21325209) and the Shanghai Municipal Committee of Science and Technology (14XD1404400).

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(9) The *N*-sulfinyl in **5** can also be easily removed under acidic conditions; see the results in the SI.

(10) A slight ee drop (to 95%) was observed in the hydrogenation process when Pd/C was used as the catalyst. However, with Pt/C as the catalyst, the enantioselectivity remained unchanged (98% ee).

(11) For two recent reports for the synthesis of cyclic benzo-fused amines using *tert*-butanesulfinyl imine chemistry, see: (a) Fustero, S.; Lázaro, R.; Aiguabella, N.; Riera, A.; Simón-Fuentes, A.; Barrio, P. *Org. Lett.* **2014**, *16*, 1224. (b) Fustero, S.; Lázaro, R.; Herrera, L.; Rodriguez, E.; Nateu, N.; Barrio, P. *Org. Lett.* **2013**, *15*, 3770.

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(13) Removal of *N*-sulfinyl in **9** and **10** were also investigated. It seems **9** is very sensitive to acidic conditions and decomposes quickly, while conversion of **10** to its free amine was successful; see the results in the SI.