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Asymmetric Synthesis of Aminochromanes via Intramolecular Indium-Mediated Allylation of Chiral Hydrazones

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Abstract

The asymmetric intramolecular indium-mediated cyclization reaction delivers chromanes with excellent diastereoselectivity (68–91% yield, dr >99:1). The reaction was efficient for aryl substrates with both electron withdrawing or donating groups. Carboxylic acid additives were found to be necessary for optimal reaction.

Graphical Abstract

Chiral amine compounds display unique biological properties and this has inspired a great deal of effort in the development of asymmetric methods for their synthesis.ⁱ Furthermore, the increased need for enantiopure medicinal compounds and the rapid advancement for the field of asymmetric synthesis encourages the development of synthetic methods that utilize reagents and promoters of low relative toxicity.ⁱⁱ Indium has emerged as a metal of high potential in organic synthesis because of its unique properties. For example, indium metal is relatively unaffected by air or oxygen at ambient temperatures and can be handled safely without apparent toxicity. Allyl indium reagents are also tolerant of many functional groups and display low basicity and selective nucleophilicity, which permits excellent chemoselective transformations.ⁱⁱⁱ Despite its extensive utility in intermolecular C-C bond formation, the corresponding intramolecular cyclizations are somewhat limited. Examples include the cyclization of enynes,^{iv} cyclization of tethered propargyl bromides to carbonyl compounds,^v Pd/In-mediated cyclization,^{vi} atom-transfer cyclization,^{vii} intramolecular allylindation of terminal alkynes^{viii} and cyclization via hydrometallation of alkynes.^{ix} As part of our continued effort to expand the synthetic utility of organoindium reagents, we disclose for the first time an efficient asymmetric indium-mediated intramolecular cyclization of chiral hydrazone derivatives and its application toward the synthesis of chromane antibiotics.

Supporting Information Available: Experimental procedures, characterization data and ¹H and ¹³C NMR spectra for all new compounds. Crystallographic data for **3a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Hydrazones are relatively stable imine equivalents and are significantly less reactive than imines. Consequently, there are fewer reports of organometallic addition to hydrazones than to imines.^x Due to their greater reactivity, imines are also prone to hydrolytic degradation and tend to be unstable during purification or prolonged storage. This is particularly problematic for aliphatic imines.^{xi} This limits their utility as precursors for chiral amine compounds. Therefore, addition of carbon fragments to C=NX bonds (where X = stabilizing group) and related compounds are increasingly being used for the synthesis of chiral amines.^{xii} Practical catalytic, enantioselective addition to C=N bonds are highly desirable.^{xiii} Chiral auxiliaries offer a useful approach for chiral amine synthesis. The use of a stabilizing group allows a chiral auxiliary to be incorporated and cleaved without affecting the efficiency of the process.^{xiv,xv}

We have reported several examples of highly efficient stereoselective intermolecular allylations of chiral hydrazones.^{xvi} Considering the excellent success obtained in diastereoselective allylation we sought to develop an intramolecular variation of the reaction. Chromanes and related compounds have attracted interest due to their occurrence in many biological compounds. Vitamin E components,^{xvii} cromakalim,^{xviii} chromane antibiotics,^{xix} to name a few, are examples of chromanes with desirable biological properties. We envisioned that an allylic bromide tethered hydrazone would provide the framework for entry into the core chromane structure.

Many indium-mediated allylation reactions are found to be optimal with at least 50% excess allyl halide (halide:In, 3:2). Thus the extension of this reaction to an intramolecular cyclization is not necessarily straightforward as it is inherently restricted to one equivalent of the allyl halide. Protic acid additives have been shown to improve such reactions.^{xx} Thus, our initial studies scrutinized the influence of different Lewis acid and protic acid additives on the outcome of the cyclization. To investigate the intramolecular indium-mediated allylation reaction we first examined the cyclization of **1a** which was easily prepared from the condensation of the corresponding aldehyde with chiral hydrazine followed by reaction with 1,4-dibromo-2-butene.^{xxi} The results of our initial screen are summarized in Table 1. Treating **1a** with two equivalents of indium metal in THF at room temperature was completely ineffective and the starting material was recovered intact (entry 1). Similarly, in the presence of protic acids HCl, H₃PO₄ and methane sulfonic acid no reaction ensued (entries 2–4). As we have previously shown,^{xvi} indium(III) Lewis acids are effective in promoting the intermolecular allylation of hydrazones and the addition of In(OTf)₃ and InBr₃ was tested as well (entries 5 and 6). To our disappointment these reactions also failed affording only trace amounts of **2a**. Furthermore, a mixture of at least three stereoisomers was produced with poor selectivity. However, when 6 equivalents of trifluoroacetic acid was added the reaction proceeded with good efficiency to produce **2a** as a single isomer. The stereochemistry of the product was confirmed by the X-ray crystal structure of the *N*-trifluoroacetate derivative **3** (see supporting information). The *cis*-stereochemistry was also observed in an analogous racemic cyclization.^{xx}

The observation that carboxylic acid had a pronounced effect on the cyclization of **1a** led us to investigate other carboxylic acids as additives. As shown in Table 1, the addition of BOC-protected amino acids demonstrated a similar enhancement of reactivity and selectivity

shown by TFA. The chiral amino acid derivatives of *L*-proline and *L*-phenylalanine provided complete control of the stereoselectivity however the yields were low (entries 8 and 9). No influence of the stereochemistry of the amino acid on the selectivity of the reaction was observed. We were pleased to discover that the simple glycine derivative was more effective and provided the highest observed yields (entries 10–13). Optimal reaction was obtained with two equivalents each of BOC-Gly-OH and indium metal affording a 72% isolated yield of **2a** (entry 12). We have determined that both proton and carboxylate are required for best reaction as both simple protic acids (*vide supra*) as well as carboxylate salts (not shown) were ineffective. This may suggest that the carboxylate bridges between the hydrazone and the allylic indium species that would be formed upon reduction of the allyl bromide. However, this is only supposition and no further evidence has yet been obtained to conclude the role of acid. No reaction was observed in the absence of reducing In(0) metal.

Under the established optimal reaction conditions a variety of chiral hydrazones were efficiently converted into the corresponding cyclized products (Table 2). Substitution on the ring was well tolerated. Substrate **1d**, having an electron-donating group *para*- to the allyl ether moiety and *meta*- to the hydrazone resulted in the highest yield (91%, entry 3). On the other hand, placing an electron-donating group *meta*- to the allyl ether moiety and *para*- to the hydrazone resulted in lower yield (68%, entry 4). In general, all reactions proceeded with good to excellent yield and complete stereocontrol to give the *cis*-products. Although the cyclization of aliphatic hydrazones was not attempted based on analogous intermolecular allylation reactions it should be feasible.^{xvi}

The role of TFA in both promoting the reaction and controlling the stereochemical outcome is unknown but may involve multiple roles in templating and activating the transition state. Group 13 metal halides are well known to form bridged dimers which would likely be unable to cyclize in the intramolecular allylation. The carboxylic acid may help in breaking up aggregated organometallic intermediates. As illustrated in Figure 1, a chair transition state involving the allylic indium and imine moieties would afford the *cis*-aminochromane product. The acid may aid in activating the reaction through hydrogen bonding to the oxazolidinone carbonyl while simultaneously enhancing the nucleophilicity of the allylindium by donation from the acid carbonyl to the indium metal.

To demonstrate the synthetic utility of this stereoselective intramolecular cyclization methodology, **2b** was elaborated into a key intermediate (**5**, Scheme 1) for the synthesis of a chromane antibiotic (**6**) discovered by Pharmacia to have shown modest activity against *S. aureus*.^{xix} Reductive cleavage of the hydrazine was accomplished by acylating with trifluoroacetic anhydride followed by treatment with SmI₂ to give **4** in good yield. Ozonolysis of the olefin and hydrolysis of the trifluoroacetate provided amino alcohol **5** with good efficiency. Compound **5** was previously prepared by a nitron cycladdition approach with poor stereoselectivity.^{xix} Spectroscopic data was identical to that reported in the literature.

In conclusion, we have developed the first asymmetric indium-mediated intramolecular cyclization of hydrazones. This method proceeded with good chemical yield and excellent stereocontrol in the presence of simple carboxylic acids. The stereochemistry of the product

was established by X-ray crystallography analysis. We have applied this method to the synthesis of the key intermediate of a chromane antibiotic via core structure **4**. It should be pointed out that **4** possesses latent functionality in the olefin that could be utilized for further manipulation. Thus a variety of subsequent modifications could be envisioned to generate a diverse library of compounds with potential biological applications.

Experimental Section

Cyclization of hydrazone **1a** to afford **2a**.

To an oven-dried Schlenk flask under argon was added indium powder (133.2 mg, 1.16 mmol), hydrazone **1a** (250 mg, 0.58 mmol) and dry THF (10.0 ml). BOC-Gly-OH (235.7 mg, 1.16 mmol) was added and the reaction mixture was stirred for 12 h at room temperature. The mixture was concentrated and purified by flash chromatography eluting initially with 20% ethyl acetate in hexanes and then 80% dichloromethane in hexanes. Compound **2a** was obtained in 72% yield: 147.2 mg (0.42 mmol); mp 108–110 °C; $[\alpha]_{20}^D = -97.6$ ($c = 0.3$ in THF); IR (film): 1747, 2962 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.03$ (d, $J = 8.4$ Hz, 1H), 7.72–7.68 (m, 2H), 7.49–7.45 (m, 1H), 7.31–7.27 (m, 1H), 7.05 (d, $J = 8.8$ Hz, 1H), 6.05–5.96 (m, 1H), 5.41–5.35 (m, 2H), 5.21 (d, $J = 2.8$ Hz, 1H), 4.70 (d, $J = 10.0$ Hz, 1H), 4.67 (d, $J = 10.0$ Hz, 1H), 4.31–4.27 (m, 1H), 3.60–3.57 (m, 1H), 3.11–3.07 (m, 1H), 2.93–2.87 (m, 1H), 2.15–2.11 (m, 1H), 1.87–1.81 (m, 1H), 0.65 (d, $J = 6.8$ Hz, 3H), 0.56 (d, $J = 7.2$, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 158.5, 152.6, 134.0, 133.9, 130.0, 128.7, 128.5, 126.9, 123.4, 121.7, 119.0, 118.8, 113.0, 63.8, 63.2, 61.2, 49.1, 38.7, 27.8, 17.4, 15.8$; HRMS Calc'd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3$ ($\text{M}+\text{Na}$) $^+$: 375.1685; Found: 375.1684.

Preparation of 2,2,2-trifluoro-N-(2,3-dihydro-2-vinyl-1H-benzo[f]chromen-1-yl)acetamide (**4**).

To a solution of **ent-3** (100 mg, 0.22 mmol) in MeOH under argon was added a solution of SmI_2 (20 mL, 0.1 M in THF) and the reaction mixture was stirred for 45 min. The solution was opened to air and stirred for an additional 5 min. Concentration followed by flash chromatography (10:1 hexanes/ethyl acetate) gave **4** (63 mg, 90%) as a white solid; mp 166–168 °C; $[\alpha]_{20}^D = -222.8$ ($c = 0.35$ in THF); IR (film): 1693 cm^{-1} ; ^1H NMR (400 MHz) $\delta = 7.77$ – 7.72 (m, 2H), 7.65 (dd, $J = 8, 0.8$ Hz, 1H), 7.52– 7.48 (m, 1H), 7.39– 7.35 (m, 1H), 7.05 (d, $J = 8$ Hz, 1H), 6.33 (d, $J = 4$ Hz, 1H), 5.93– 5.85 (m, 1H), 5.79 (dd, $J = 8, 4$ Hz, 1H), 5.30 (d, $J = 4$ Hz, 1H), 5.21 (d, $J = 15$ Hz, 1H), 4.41 (ddd, $J = 15, 4, 1.6$ Hz, 1H), 4.01 (t, $J = 12$ Hz, 1H), 3.10– 3.04 (m, 1H); ^{13}C NMR (100 MHz) $\delta = 156.9$ (d, $J_{\text{CF}} = 40$ Hz), 152.9, 132.7, 132.0, 131.0, 129.0, 128.5, 127.8, 120.1 (d, $J_{\text{CF}} = 144$ Hz), 120.1, 110.8, 76.6, 64.0, 43.7, 40.4; HRMS Calc'd for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{NO}_2$ ($\text{M}+\text{Na}$) $^+$: 344.0874; Found: 344.0876.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- i (a). Friestad GK; Mathies AK *Tetrahedron* 2007, 63, 2541–2569.(b)Kobayashi S; Ishitani H *Chem. Rev* 1999, 99, 1069. [PubMed: 11749440] (c)Bloch R *Chem. Rev* 1998, 98, 1407. [PubMed: 11848938] (d)Enders D; Reinhold U *Tetrahedron: Asymmetry* 1997, 8, 1895.(e)Denmark SE; Nicaise OJ-C *Chem. Commun* 1996, 999.
- ii (a). Li C-J *Chem. Rev* 1993, 93, 2023(b)Noyori R *Green Chem.*, 2003, 5, G37(c)Lindstrom UM; *Chem. Rev* 2002, 102, 2751 [PubMed: 12175267] (d)Yanada R; Obika S; Nishimori N; Yamauchi M; Takemoto Y *Tetrahedron Lett.* 2004, 45, 2331(e)Li C-J *Acc. Chem. Res* 2002, 35, 533. [PubMed: 12118992]
- iii (a). Alonso F; Beletskaya IP; Yus M *Chem. Rev* 2002, 102, 4009 [PubMed: 12428984] (b)Ranu BC; Dutta J; Guchhait SK *J. Org. Chem* 2001, 66, 5624. [PubMed: 11485495]
- iv. Lee PH; Kim S; Lee K; Seomoon D; Kim H; Lee S; Kim M; Han M; Noh K; Livinghouse T *Org. Lett* 2004, 6, 4825. [PubMed: 15606076]
- v. Kang H-Y Kim Y-T; Yu Y-K; Cha JW; Cho YS; Koh HY *Synlett* 2004, 45.
- vi (a). Kang S-K; Lee S-W; Jung J; Lim Y J. *Org. Chem* 2002, 67, 4376 [PubMed: 12054979] (b)Nguyen VC; Kim Y-T; Yu Y-K; Kang H-Y *Bull. Korean Chem. Soc* 2005, 26, 711.
- vii (a). Yanada R; Nishimori N; Matsumura A; Fujii N; Takemoto Y *Tetrahedron Lett.* 2002, 43, 4585(b)Cook GR; Hayashi R; *Org. Lett* 2006, 8, 1045. [PubMed: 16524264]
- viii (a). Nair V; Ros S; Jayan CN; Pillai BS *Tetrahedron* 2004, 60, 1959(b)Salter MM; Sardo-Inffiri S *Synlett* 2002, 2068.
- ix. Takami K; Yorimitsu H; Oshima K *Org. Lett* 2002, 4, 2993. [PubMed: 12182607]
- x (a). Kobayashi S; Hamada T; Manabe K; *J. Am. Chem. Soc* 2002, 124, 5640 [PubMed: 12010028] (b)Friestad GK; Ding H *Angew. Chem. Int. Ed* 2001, 40, 4491(c)Burk MJ; Feaster JE; *J. Am. Chem. Soc* 1992, 114, 6266(d)Kadota J; Park J-Y; Yamamoto Y *Chem. Commun* 1996, 841.
- xi. Jacobsen MF; Ionita L; Skrydstrup T *J. Org. Chem* 2004, 69, 4792. [PubMed: 15230604]
- xii (a). Friestad GK; Shen Y; Ruggles EL *Angew. Chem. Int. Ed* 2003, 42, 5061(b)Friestad GK; Qin GK, *J. Am. Chem. Soc* 2001, 123, 9922. [PubMed: 11583567]
- xiii (a). Saaby S; Fang X; Gathergood N; Jørgensen KA; *Angew. Chem., Int. Ed* 2000, 112, 4280(b)Saaby S; Bayo P; Aburel PS; Jørgensen KA *J. Org. Chem* 2002, 67, 4352 [PubMed: 12054974] (c)Johannsen M *Chem. Commun* 1999, 2233.
- xiv (a). Maryanoff BE; Zhang H,-C; Cohen JH; Turchi IJ; Maryanoff CA *Chem. Rev* 2004, 104, 1431 [PubMed: 15008627] (b)Weinreb SM; *Top. Curr. Chem* 1997, 190, 131(c)Weinreb SM; Orr RK *Synthesis* 2005, 1205.
- xv (a). Friestad GK *Eur. J. Org. Chem* 2005, 3157(b)Enders D; Reinhold U *Tetrahedron: Asymmetry* 1997, 8, 1895(c)Davis FA; Zhou P; Chen B-C *Chem. Soc. Rev* 1998, 27, 13(d)Bloch R *Chem.Rev* 1998, 98, 1407 [PubMed: 11848938] (e)Ellman JA; Owens TD; Tang TP; *Acc. Chem. Res* 2002, 35, 984 [PubMed: 12437323] (f)Job A; Janeck CF; Bettray W; Peters R; Enders D *Tetrahedron* 2002, 58, 2253(g)Zhou P; Chen B; Davis FA; *Tetrahedron* 2004, 60, 8003(h)Friestad GK *Eur. J. Org. Chem* 2005, 3157(i)Ogawa C; Sugiura M; Kobayashi S; *J. Org. Chem* 2002, 67, 5359. [PubMed: 12126428]
- xvi. Cook GR; Maity BC; Kargbo R *Org. Lett*, 2004, 6, 1741. [PubMed: 15151403]
- xvii (a). Couladouros EA; Moutsos VI; Lampropoulou M; Little JL; Hyatt JA *J. Org. Chem* 2007, 72, 6735 [PubMed: 17685653] (b)Trost BM, Shen HC, Surivet JP, *Angew. Chem., Int. Ed* 2003, 42, 3943(c)Tietze LF; Sommer KM; Zinngrebe J; Stecker F *Angew. Chem., Int. Ed* 2004, 43, 2.
- xviii. Rovnyak GC; Ahmed SZ; Ding CZ; Dzwonczyk S; Ferrara FN; Humphreys WG; Grover GJ; Santafianos D; Atwal KS; Baird AJ; McLaughlin LG; Normandin DE; Sleph PG; Traeger SC *J. Med. Chem* 1997, 40, 24. [PubMed: 9016325]
- xix (a). Zhao Q; Han F; Romero DL *J. Org. Chem* 2002, 67, 3317 [PubMed: 12003541] (b)Broggini G; Folcio F; Sardone N; Sonzogni M; Zeechi G; *Tetrahedron: Asymmetry* 1996, 7, 797.
- xx. Kang H-Y; Yu Y-K *Bull. Korean Chem. Soc* 2004, 25, 1627.
- xxi. See supporting information.

Figure 1.
Possible transition state for the carboxylic acid promoted In-mediated allylation.

Scheme 1.
Synthetic route to intermediate **5**.

Table 1.Affect of additives on the cyclization of **1a**.^a

entry	additive (equiv)	time (h)	yield (%) ^b	dr ^c
1	none	10	0	—
2	aq HCl (6)	10	0	---
3	H ₃ PO ₄ (6)	10	0	---
4	CH ₃ SO ₃ H (6)	10	0	---
5	In(OTf) ₃ (1.3)	48	<5	---
6	InBr ₃ (1.3)	48	<5	---
7	TFA (6)	10	68	>99:1
8	BOC- <i>L</i> -Pro-OH (1.3)	12	10	>99:1
9	BOC- <i>L</i> -Phe-OH (1.3)	12	20	>99:1
10	BOC- Gly-OH (1.0)	12	60	>99:1
11	BOC- Gly-OH (1.5)	12	65	>99:1
12	BOC- Gly-OH (2)	12	72	>99:1
13	BOC- Gly-OH (6)	12	65	>99:1

^aSee experimental section for details.^bIsolated yield.^cDiastereomer ratio of the major isomer **2a** shown vs. three other possible isomers. Determined by ¹H NMR.

Table 2.Indium/carboxylic acid-mediated cyclization of chiral hydrazones.^a

entry	substrate	product	yield (%) ^b
1			70
2			86
3			91
4			68
5			78
6			89

entry	substrate	product	yield (%) ^b
7			82
8			82
9			82
10			78

^aSee experimental section for details.

^bIsolated yield.