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Construction of Spiro-Fused 2-Oxindole/ α-Methylene- γ-Butyrolactone Systems with Extremely High Enantioselectivity via Indium-Catalyzed Amide Allylation of *N*-Methyl Isatin

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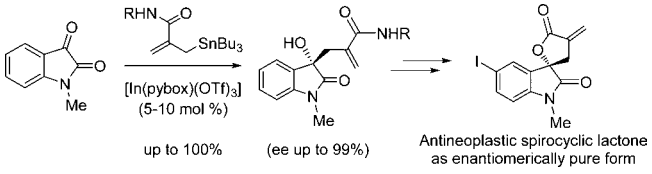
ABSTRACT



A remarkably effective method allowing an extremely high enantioselective synthesis of the spiro-fused 2-oxindole/α-methylene-γ-butyrolactones is described. The key strategy lies in the use of indium-catalyzed asymmetric amide allylation of *N*-methyl isatin with functionalized allylstannanes, which can lead to the antineoplastic spirocyclic lactones in almost enantiopure forms.

In recent years, spiro-fused 2-oxindoles have extensively been recognized as biologically important targets that have received unprecedented attention from the synthetic and medicinal communities due to the fact that these chemical motifs would be expected to serve as potential scaffolds engaging a variety of related systems to generate potential clinical candidates.[1] In this regard, spiro-fused 2-oxindole/ α-methylene-γ-butyrolactone systems have recently emerged as an entry to a novel class of promising variants for future drug discovery,[2−4] since these types of substructures found in naturally occurring sesquiterpene lactones can act as a highly efficient Michael acceptor to give rise to potent biological activities applicable to a wide range of human diseases (Figure 1).[5,6] Despite the particularly appealing prospects for unique and reliable design of the molecular systems, development of a methodology for the chemical synthesis of these spirocyclic lactones is substantially less advanced and the subject of stereocontrol to produce their single enantiomers has represented a formidable challenge to synthetic organic chemists.[7] Pioneering work reported

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(1) (a) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104–6155. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748–8758. (c) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219.
(2) Rana, S.; Natarajan, A. *Org. Biomol. Chem.* **2013**, *11*, 244–247.
(3) Shanmugam, P.; Viswambharan, B. *Synlett* **2008**, 2763–2768.
(4) Heindel, N. D.; Minatelli, J. A. *J. Pharm. Sci.* **1981**, *70*, 84–86.
(5) (a) Kitson, R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426–9451. (b) Bachelier, A.; Mayer, R.; Klein, C. D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5605–5609.
(6) (a) Takahashi, M.; Sudo, T.; Murata, Y.; Sengoku, T.; Yoda, H. *Nat. Prod. Commun.* **2013**, *8*, 889–896. (b) Takahashi, M.; Atsumi, J.; Sengoku, T.; Yoda, H. *Synthesis* **2010**, 3282–3288.
(7) (a) Wang, Q.-L.; Peng, L.; Wang, F.-Y.; Zhang, M.-L.; Jia, L.-N.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2013**, *49*, 9422–9424. (b) Shanmugam, P.; Vaithiyanathan, V. *Tetrahedron* **2008**, *64*, 3322–3330.

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by Heindel involved nonstereoselective Reformatsky condensation of isatin and its iodinated derivative to obtain racemic mixtures of the corresponding spirocyclic lactones (**1A**,**B**) as antineoplastic drug candidates, one of which proved to be highly potent against the P-388 lymphocytic leukemia and human carcinoma of the nasopharynx.[4]

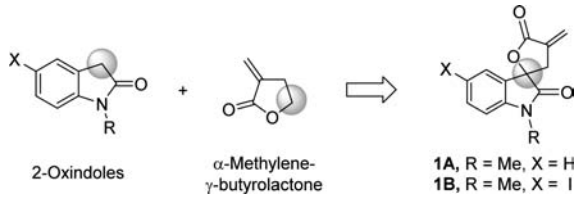
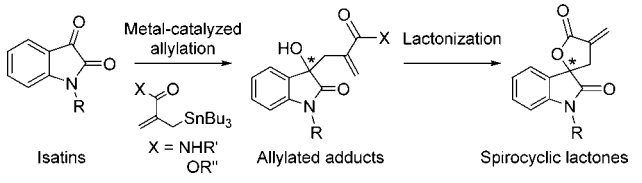


Figure 1. Schematic representation of antineoplastic spiro-fused 2-oxindole/α-methylene-γ-butyrolactones.

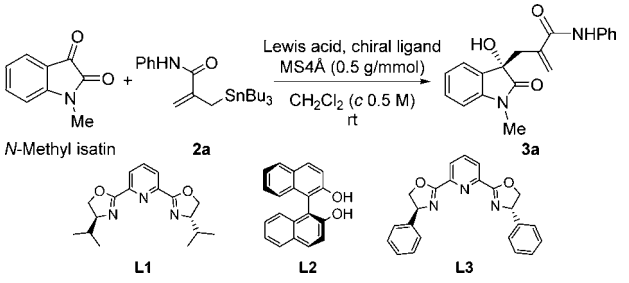
Nevertheless, the chemical inhomogeneities in molecular chirality of these substances may cause significant uncertainties in quantitative studies, thereby impeding accurate biological evaluation of its intrinsic property. Thus, it is of great interest to establish synthetic approaches to enantiomerically pure forms of the spirocyclic lactones in an effort to shed light on the biological importance of this class of molecules. Here, we report a remarkably effective method allowing for highly enantioselective synthesis of the spirocyclic lactones using a strategy based on metal-catalyzed asymmetric allylation of isatins with functionalized β-carbonyl allylstannanes and subsequent lactonization (Scheme 1).[8,9]

Scheme 1. A Strategy for Enantioselective Construction of Spirocyclic Lactone Systems



According to our previous work, indium-catalyzed allylation of aldehydes with β-amido allyltributylstannanes could be effectively utilized to generate α-methylene-γ-butyrolactones in satisfactorily high yields with good to high levels of enantioselectivity.[10] In this study, an indium(III) complex of 2,6-bis[4′-(*S*)-isopropyloxazolin-2-yl]pyridine[11] [(*S*,*S*)-isopropyl-pybox, **L1**] would be expected to serve as a potential chiral catalyst for exerting a significant degree of stereochemical control on the amide allylation of isatins to afford enantiomerically enriched products.[12] Therefore, we initially carried out the reaction of *N*-methyl isatin with 1.2 equiv of *N*-phenyl-β-amido allyltributylstannane **2a** in the presence of 10 mol % of [In(**L1**)(OTf)$_3$] and activated 4 Å molecular sieves in dichloromethane at rt. After a period of 3 h, we observed complete consumption of the substrate and clean formation of the desired allylated adduct **3a** as an optically active form with an isolated yield of 97%. The degree of asymmetric induction could be evaluated by HPLC analysis on a Chiralpak IC chiral stationary phase, showing the current reaction system allowed a significantly high enantiomeric excess value (84% ee) to be obtained (Table 1, entry 1). A further increase of the catalyst loading to 20 mol % could reduce the reaction time to 2 h for completion, resuting in almost quantitative product formation (99% isolated yield), but failed to furnish higher enantioselectivity (77% ee) (Table 1, entry 2). With a catalyst loading as low as 5 mol %, the reaction also proceeded smoothly to provide **3a** in 99% isolated yield with an enantioselectivity of 82% ee (Table 1, entry 3). Encouraged by the above results, we next screened chiral catalysts available for the combination of various Lewis acids with chiral ligands to find the optimum conditions for this asymmetric process.

Table 1. Metal and Ligand Effects for the Amide Allylation with **2a**[a]

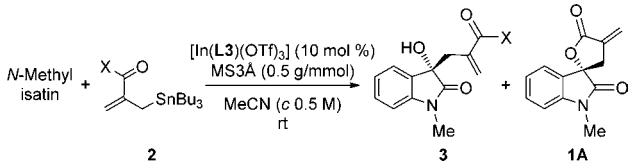


entry	Lewis acid	chiral ligand	catalyst loading (mol %)	t (h)	yield[b] (%)	ee[c] (%)
1	In(OTf)$_3$	**L1**	10	3	97	84
2	In(OTf)$_3$	**L1**	20	2	99	77
3	In(OTf)$_3$	**L1**	5	4	99	82
4	Sc(OTf)$_3$	**L1**	10	23	100	10
5	Yb(OTf)$_3$	**L1**	10	14	98	9
6	Sm(OTf)$_3$	**L1**	10	95	45	7
7	InCl$_3$	**L1**	10	5	100	18
8	In(OTf)$_3$	**L2**	10	1	90	7
9	In(OTf)$_3$	**L3**	10	3	99	97
10	In(OTf)$_3$	**L3**	20	2	99	97
11	In(OTf)$_3$	**L3**	5	4	98	96

[a] All reactions were carried out in CH_2Cl_2 (c 0.5 M) under nitrogen with 1.2 equiv of **2a** in the presence of 4 Å molecular sieves. [b] Yields of the isolated product. [c] The ee values were determined by HPLC analysis with a Daicel Chiralpak IC.

(8) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293.
(9) For stoichiometric allylation with stannylated reagents, see: (a) Tanaka, K.; Yoda, H.; Isobe, Y.; Kaji, A. *Tetrahedron Lett.* **1985**, *26*, 1337–1340. (b) Tanaka, K.; Yoda, H.; Isobe, Y.; Kaji, A. *J. Org. Chem.* **1986**, *51*, 1856–1866.
(10) (a) Suzuki, T.; Atsumi, J.; Sengoku, T.; Takahashi, M.; Yoda, H. *J. Organomet. Chem.* **2010**, *695*, 128–136. (b) Suzuki, T.; Sengoku, T.; Takahashi, M.; Yoda, H. *Tetrahedron Lett.* **2008**, *49*, 4701–4703.
(11) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846–848.

Table 2. Substrate Scope of Reagents for Allylation of **2**[a]



2 3 1A

entry	2	X	t (h)	product	yield[b] (%)	ee[c] (%)
1	**2a**	NHPh	3	**3a**	100	98
2	**2b**	NHC_5H_{11}	4	**3b**	88	95
3	**2c**	NH(1-naph)	4	**3c**	95	98
4	**2d**	NH(*p*-tolyl)	3	**3d**	99	99
5	**2e**	NMePh	72	**3e**	37[d]	66
6	**2f**	OMe	72	**1A**	46[d]	83

[a] All reactions were carried out in MeCN (*c* 0.5 M) under nitrogen with 1.2 equiv of **2** in the presence of 3 Å molecular sieves. [b] Yields of the isolated product. [c] The ee values were determined by HPLC analysis with Daicel Chiralpaks IB (for **1A**), IC (for **3a**, **3b**, and **3d**), IE (for **3e**), and IF (for **3c**). [d] Large amounts of the starting materials were recovered intact after prolonged reaction times.

As shown in Table 1, the use of chiral catalysts prepared with other Lewis acids such as $Sc(OTf)_3$, $Yb(OTf)_3$, $Sm(OTf)_3$, and $InCl_3$ was found ineffective even under comparable conditions (Table 1, entries 4–7). Thus, the choice of the $In(OTf)_3$-based catalytic system appeared to be crucial to achieve high yield and enantioselectivity for the given asymmetric processes. With this idea in mind, we then focused on the use of other types of readily available chiral ligands [(*S*)-1,1′-bi(2-naphthol) **L2** and (*S,S*)-phenyl-pybox **L3**, Table 1] as practical alternatives to **L1**. When **L2** was used for the reaction, **3a** was obtained in 90% isolated yield after a period of 1 h. In this case, the chiral catalyst failed to control the stereospecific reaction properly, and the ee value was very low (Table 1, entry 8). On the other hand, the reaction carried out with **L3** proceeded to completion in 3 h for a catalyst loading of 10 mol %, affording an excellent isolated yield and enantiomeric excess of the product (99%, 97% ee) (Table 1, entry 9), while increasing the catalyst loading up to 20 mol % had little notable effect on the reaction outcome (Table 1, entry 10). Performing the reaction in the presence of 5 mol % of this catalyst resulted in the complete conversion within 4 h, which allowed the product to be generated with almost the same high enantioselectivity (96% ee) (Table 1, entry 11). From the examples above, it appears that [In(**L3**)$(OTf)_3$] is the most effective catalyst driving the reaction to reach the practical levels of efficiencies.

It is noteworthy at this point that the yield and enantioselectivity of this amide allylation could be further improved to 100% and 98% ee, respectively, simply by replacing the solvent by acetonitrile with a catalyst loading of 10 mol % and activated 3 Å molecular sieves (Table 2, entry 1). With these optimized conditions in hand, we then examined the scope of the allylation with different β-carbonyl allylstannanes **2b**–**f** (Table 2, entries 2–6). When *N*-pentyl- and *N*-(1-naphthyl)-β-amido derivatives **2b** and **2c** were treated under the given conditions involving the use of 10 mol % of [In(**L3**)$(OTf)_3$], the corresponding allylated adducts were formed in very high chemical and enantiomeric yields (88%, 95% ee for **3b** and 95%, 98% ee for **3c**), respectively (Table 2, entries 2 and 3), indicating the utility of this catalytic system to effect the enantioselective transformation for a wide range of functionalities. In fact, the above optimal conditions also proved to be more effective for *N*-(*p*-tolyl) analogue **2d** and led to a virtually quantitative formation of the product **3d**, which culminated in an extremely high degree of asymmetric induction with an excellent enantioselectivity of 99% ee (Table 2, entry 4).

Subsequently, we examined whether the current catalytic system could be applied to *N,N*-disubstituted β-amido derivative **2e** that lacks the amide NH proton. Under identical conditions, the reaction required a very long time to result in incomplete consumption of the substrate and afforded a much lower yield of the product **3e** with a moderate degree of enantioselectivity (37%, 66% ee) (Table 2, entry 5). The loss of the stereochemical integrity could be understood in terms of a change in specific binding interactions of the stannylated reagent with chiral catalyst–substrate association over the course of the reaction, thus suggesting that the NH-containing amide functionality would play an important role in enhancing enantioselectivity. To verify this assumption, an attempt was made to use methyl ester derivative **2f**. In this case, the reaction occurred at a much slower rate and did not proceed beyond 46% conversion even after a period of 72 h, giving primarily the spirocyclic lactone **1A**, instead of the expected product **3f**.[2,10] The degree of stereocontrol in this allylation process could be temporarily deduced from an ee value of **1A**, which was found to be significantly lower (83% ee) as determined by HPLC analysis on a Chiralpak IB (Table 2, entry 6). Thus, it can be seen that the presence of the secondary amide substituents in the stannylated reagents should serve as a major element to form highly ordered transition states, making it possible to precisely differentiate two enantiotopic faces of the carbonyl moiety.[13]

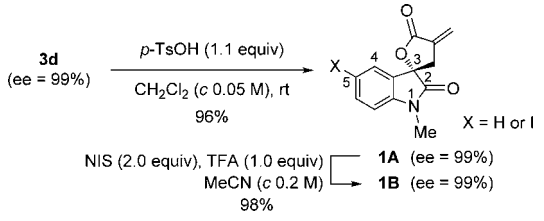
After installing the stereogenic center with perfect control of the remarkably high π-facial selectivity of the indium-catalyzed amide allylation, our next objective was to convert enantiomerically enriched acyclic 2-oxindoles **3** into **1A** in an efficient and practical fashion with complete retention

(12) (a) Gutierrez, E. G.; Wong, C. J.; Sahin, A. H.; Franz, A. K. *Org. Lett.* **2011**, *13*, 5754–5757. (b) Hanhan, N. V.; Sahin, A. H.; Chang, T. W.; Fettinger, J. C.; Franz, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 744–747.

(13) Considering our preliminary observation that addition of the ligands resulted in a dramatic acceleration in overall reaction rate as compared with the case without their use (taking 24 h to reach completion under analogous conditions), these ligands would be essential elements to interact considerably with the reaction components. Furthermore, we also observed that a comparative experiment using propiophenone substrate failed to give any allylated product. Therefore, it appears that the ketoamide structural motif of *N*-methyl isatin is responsible for preferential formation of the critical transition states with appropriate geometries.

of stereochemistry. This is exemplified in Scheme 2 for the reaction of **3d** with an ee of 99%, prepared under the conditions described above (Table 2, entry 4). Upon exposure to 1.1 equiv of *p*-toluenesulfonic acid in dichloromethane at rt, this material readily cyclized at rt to furnish the desired lactone in 96% yield. Remarkably, the product, purified by silica-gel column chromatography, was found to retain the constant level of optical purity as determined on the basis of the chiral HPLC analysis, thereby demonstrating that **3d** could be efficiently converted into **1A** without loss of the optical purity.[14]

Scheme 2. Chemical Transformation of **3d** to **1B**



At the final stage of the work, our synthetic effort was focused on introduction of an iodine atom onto the aromatic nucleus of **1A** to explore further derivatization to access 5-iodinated 2-oxindole of the spirocyclic lactone, the synthetic racemate of which has been implicated as a promising cytotoxic antineoplastic drug candiate according to Heindel's report.[4] To this end, we subjected enantiomerically enriched (99% ee) lactone **1A** to treatment with 2.0 equiv of *N*-iodosuccinimide (NIS) in the presence of 1.0 equiv of TFA in acetonitrile at rt.[15] Under these conditions, this substrate underwent smooth conversion to reach completion after 15 h at rt, affording an iodinated material **1B** as the sole product of the reaction. This product was purified by silica-gel column chromatography to obtain a 98% isolated yield of **1B** and then fully characterized on the basis of elemental analysis and spectral data. In the ^{1}H NMR spectrum, one can see the complete disappearance of the characteristic resonance assignable to the C5 aromatic proton when compared to that of **1A**. This can be attributed to site-selective installation of an iodine substituent taking place only at the most desired C5 position of the aromatic system, and thus the chemical structure of **1B** was clearly identified as the 5-substituted derivative. In this regard, it is indeed important to note that the iodination proceeds with complete preservation of the C3 stereochemistry throughout this transformation. As confirmed by the chiral HPLC analysis on the Chiralpak IB, this product was obtained in a respectable optical purity (99% ee) comparable to that of the parent compound. Considering the exact coincidence of the absolute ee values given for **3d**, **1A**, and **1B**, it can be concluded that the reaction sequence described above should offer an ideal approach to the chiral version of the target molecules.

To provide a comprehensive structural description of the spirocyclic lactone systems, including determination of the absolute configuration, X-ray structural analysis was carried out on a single crystal of **1B**, which was grown from a chloroform/hexane solution.[16] As expected, this compound crystallizes in the chiral space group C_2 and contains the 5-iodinated aromatic ring structure (see the Supporting Information), consistent with its ^{1}H NMR analysis. Anomalous dispersion attributed to the iodine atoms allowed the absolute configuration of the undefined stereocenter to be unambiguously assigned as *S* with certainty by the structure refinement processes, where a satisfactory Flack parameter value of 0.098(16) was given for the correct configuration.[17,18]

In conclusion, we have described asymmetric construction of the spirocyclic lactone systems with perfect stereocontrol (>99%, 99% ee) via indium-catalyzed amide allylation of *N*-methyl isatin. This report represents not only the first asymmetric synthesis of the spirocyclic lactones but also the first catalytic asymmetric amide allylation of isatins, making versatile platforms for new types of diversely structured chiral 2-oxindoles as new attractive drug candidates. Further exploration of the extended scope of the amide allylation to isatin derivatives as well as mechanistic elucidation of the origins of the enantioselectivity will be addressed elsewhere.

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Supporting Information Available. X-ray structure of (*S*)-**1B**, experimental details, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) In fact, partial and complete racemization took place when the reaction was carried out with $BF_3 \cdot OEt_2$ and TfOH, respectively. This indicates the benzylic quaternary stereocenter of the allylated adduct would have low tolerance to Lewis acids and strong Brønsted acids.

(15) Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* **2002**, *43*, 5047–5048.

(16) Crystal data for **1B**: monoclinic, space group C_2 (No. 5), a = 20.2766(10) Å, b = 11.0112(6) Å, c = 13.5295(6) Å, $\alpha = \gamma = 90°$, β = 123.314(2)°, V = 2524.3(2) Å^3, Z = 8, ρ = 1.869 Mg m^{-3}, $\mu(Cu_{K\alpha})$ = 19.953 cm^{-1}, T = 173 K; in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0716 ($I > 2\sigma(I)$), wR_2 = 0.1939, and GOF = 1.056 for 3514 reflections and 327 parameters (CCDC deposition number 953629).

(17) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876–881.

(18) All the absolute stereochemistries for **3a**, **3b**, **3c**, and **3e** were established to be *S*, by comparison of the optical rotations of the relevant lactonization products **1A** that could be obtained without loss of configurational integrity.

The authors declare no competing financial interest.