A Journal of the Gesellschaft Deutscher Chemiker

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201800567
Angew. Chem. 10.1002/ange.201800567

Link to VoR: http://dx.doi.org/10.1002/anie.201800567
http://dx.doi.org/10.1002/ange.201800567

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10.1002/anie.201800567

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Highly Enantioselective Tandem Michael Addition of Tryptamine-Derived Oxindoles to Alkynones: Concise Synthesis of Strychnos Alkaloids

Weigang He,† Jiadong Hu,† Pengyan Wang,† Le Chen, Kai Ji, Siyu Yang, Yin Li, Zhilong Xie and Weiqing Xie*

Abstract: A highly enantioselective tandem Michael addition of oxindole derived from tryptamine to alkynone is developed by taking advantage of $Sc(OTf)_3$-chiral *N,N'*-dioxide catalyst. The reaction enables facile preparation of enantioenriched spiro[pyrrolidine-3,3'-oxindole], which provides a novel strategy for the synthesis of monoterpenoid indole alkaloids. As a demonstration, the asymmetric synthesis of strychnos alkaloids [(-)-tubifoline, (-)-tubifolidine, (-)-dehydrotubifoline] is achieved in 10-11 steps.

Monoterpenoid indole alkaloids constitute a large family of indole alkaloids that widely distributed in nature.[1] Those alkaloids feature complex structure, including polycyclic ring system, consecutive stereocenters, and quaternary carbon centers. Additionally, this subclass of indole alkaloids exhibited important biological profiles, which has been a rich source for medicine development. For example, reserpine and vinblastine have been used for treatment of cardiovascular disease and cancer respectively.[1] In this respect, spiro[pyrrolidine-3,3'-oxindole] has been recognized as a privileged skeleton widely present in indole alkaloids[2,3] (Figure 1, strychnofoline,[2a] formosanine[2b]) and pharmaceutical molecules with diverse biological activities.[3] Therefore, numerous strategies including various enantioselective catalyzed methodologies have been reported for the construction of this scaffold.[3]

Strychnos alkaloids belong to the monoterpenoid indole alkaloid incorporated with a cyclohexane fused spiro[pyrrolidine-3,3'-oxindoline] framework and a bridged D ring. Since the milestone synthesis of strychnine by Woodward,[4] the challenging complicate structure of strychnos alkaloids has long served as inspiration and testament for new synthetic methodologies and strategies.[5] Biologically, spirooxindole and strychnos alkaloids share the same biosynthetic precursor (strictosidine).[6] Although spiro[pyrrolidine-3,3'-oxindole] contains the core structure (A, B and C rings) presented in those two type of indole alkaloids (Figure 1), its application in synthesis of strychnos alkaloids has never been explored.[3,5,7]

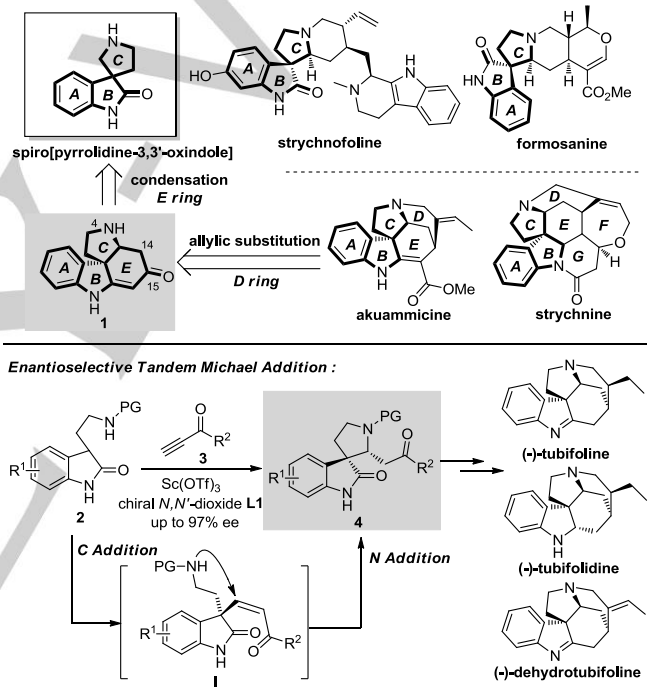

Figure 1. Monoterpenoids Incorporated with Spiro[pyrrolidine-3,3'-oxindole scaffold and Enantioselective Tandem Michael Addition that Enables Asymmetric Synthesis of Strychnos Alkaloids.

As a continuation of our work on synthesis of indole alkaloids,[8] we hypothesized that the enone **1** could serve as a versatile building block for the synthesis of strychnos alkaloids by forging the bridged D ring via allylic substitution after reduction of the enone moiety. Retrosynthetically, this intermediate could be accessed by the intramolecular condensation of spiro[pyrrolidine-3,3'-oxindole] **4** (Figure 1). Drawn inspirations from previous work on tandem mixed Michael addition[9] and enantioselective addition of oxindole to alkynone[10], we surmised that tandem Michael addition of tryptamine-derived oxindole **2** to alkynone **3** through intermolecular carbon-Michael addition followed by intramolecular aza-Michael addition via oxindole **I** would give rise to the desired spirooxindole **4**. Herein, we report the

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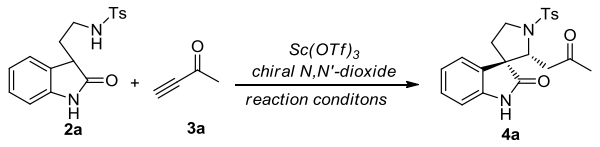
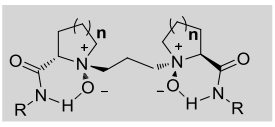
10.1002/anie.201800567

enantioselective construction of spiro[pyrrolidine-3,3'-oxindoline] via this tandem process promoted by $Sc(OTf)_3$-chiral *N,N'*-dioxide.[11] Furthermore, the implementation of this new strategy in the synthesis of strychnos alkaloids is also demonstrated.

Table 1. Optimization of Reaction Conditions.[a]



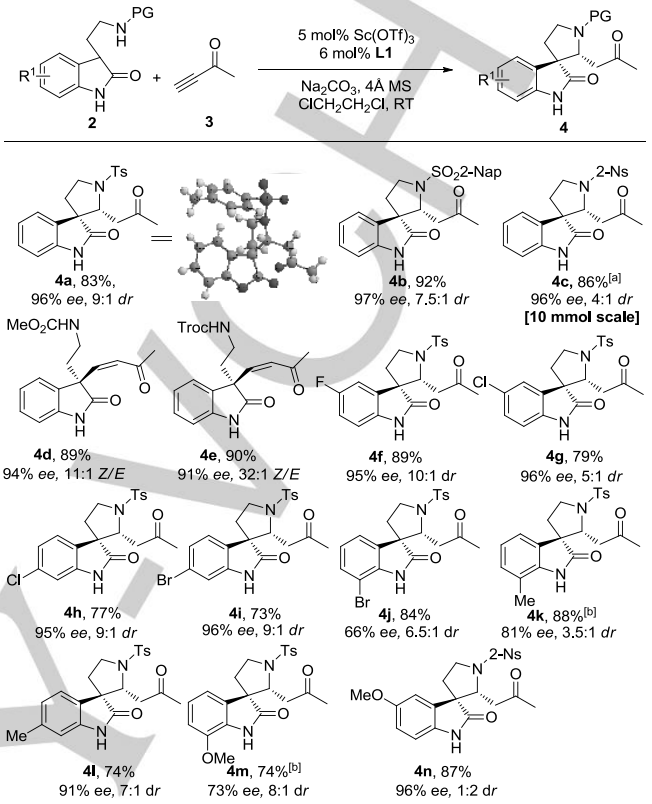
entry	ligand	base	solvent	time (h)	yield[b] (%)	ee[c] (%)	dr[c]
1	**L1**	Na_2CO_3	$ClCH_2CH_2Cl$	60	83	96	9:1
2	**L2**	Na_2CO_3	$ClCH_2CH_2Cl$	84	78	96	8:1
3	**L3**	Na_2CO_3	$ClCH_2CH_2Cl$	60	93	96	5:1
4	**L4**	Na_2CO_3	$ClCH_2CH_2Cl$	72	73	87	3:1
5	**L5**	Na_2CO_3	$ClCH_2CH_2Cl$	60	94	93	5:1
6	**L1**	Na_2CO_3	CH_2Cl_2	48	84	96	5:1
7	**L1**	Na_2CO_3	$CHCl_3$	60	85	96	8:1
8	**L1**	Na_2CO_3	THF	48	27	86	4:1
9	**L1**	K_2CO_3	$ClCH_2CH_2Cl$	72	93	95	5:1
10	**L1**	Cs_2CO_3	$ClCH_2CH_2Cl$	48	76	13	1:1
11	**L1**	K_3PO_4	$ClCH_2CH_2Cl$	48	95	87	2:1



L1: R = 2,4,6-trimethylphenyl, n = 2
L2: R = 2,6-diethyl-4-methylphenyl, n = 2
L3: R = 2,6-diisopropylphenyl, n = 2
L4: R = phenyl, n = 2
L5: R = 2,4,6-trimethylphenyl, n=1

[a] Reaction conditions: Reactions were performed with **2a** (0.1 mmol), **3a** (0.11 mmol), base (0.1 mmol), $Sc(OTf)_3$ (5 mol %) and ligand (6 mol %) in solvent (1.0 mL) under dry air condition at RT. [b] Isolated yields. [c] Determined by HPLC on ChiralPak IC column. Ts = *p*-toluenesulfonyl.

We initially focused on optimizing the reaction conditions of the tandem Michael addition of tryptamine derived oxindole **2a** to alkynone **3a** using $Sc(OTf)_3$-chiral *N,N'*-dioxide catalyst.[10e] Delightfully, the desired product **4a** could be isolated in 83% yield with 96% ee and 9:1 dr using **L1** as ligand (Table 1, entry 1). Various chiral *N,N'*-dioxide ligands were subsequently surveyed, while none of them gave better results than **L1** (Table 1, entries 2 to 5). Solvent screening revealed that 1,2-dichloroethane was the solvent of choice (Table 1, entries 6 to 8 and Supporting Information). Next, different inorganic and organic bases were evaluated, which showed that Na_2CO_3 gave superior outcome in terms of enantioselectivity and diastereoselectivity (Table 1, entries 9 to 11 and supporting information).

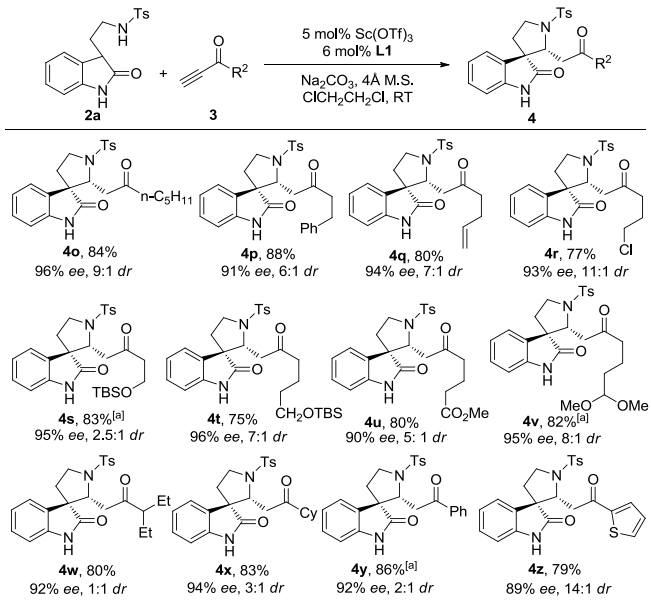


[a] The reaction was carried out with $NaHCO_3$ as base at 50 °C. [b] The reaction was performed with CH_2Cl_2 as solvent. Nap = naphthalene; 2-Ns = 2-nitrobenzensulfonyl; Troc = 2,2,2-trichloroethoxycarbonyl.

Scheme 1. Substrate Scope with Respect to Oxindole.

Upon identifying the optimal reaction conditions, an array of tryptamine-derived oxindole was examined to expand the substrate scope. The protecting group attached to the primary amine was crucial for the tandem process. Sulfonyl-protected oxindoles could smoothly be converted to the desired products in excellent enantioselectivities (Scheme 1, **4a** to **4c**). Carbamate-protected oxindoles only delivered carbon-Michael addition product. This could be ascribed to the reduced nucleophilicity of the nitrogen which impeded the aza-Michael addition (Scheme 1, **4d** and **4e**). Those products together with the isolation of the carbon-Michael addition intermediate for **4a** (see Supporting Information) strongly suggested the reaction started with intermolecular carbon-Michael addition followed by intramolecular aza-Michael addition. Electron-withdrawing groups (F, Cl and Br) on indole were compatible with the reaction conditions, affording corresponding spirooxindole in excellent enantioselectivities (Scheme 1, **4f** to **4i**). To our satisfactory, electron-donating substituents such as Me, OMe was also tolerated, providing spirooxindole **4l** and **4n** in 91% ee and 96% ee respectively. However, bromine or other electron donating groups (Me, OMe) on the C-7 of oxindole were

detrimental for the reaction, resulting in moderate enantioselectivities. The structure of the product was firmly established by X-ray crystallographic analysis of **4a**.[12]

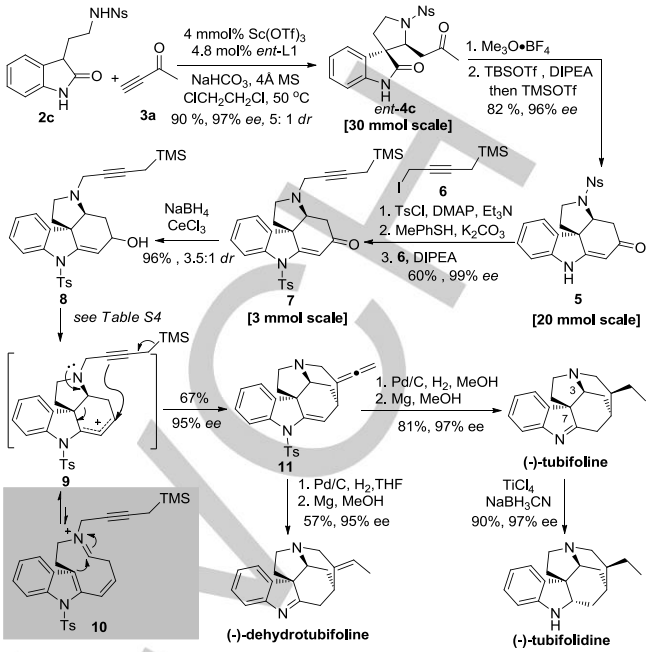


[a] The reaction was performed with CH_2Cl_2 as solvent. Cy = cyclohexanyl; Ph = phenyl.

Scheme 2. Substrate Scope of Alkynone.

Furthermore, different alkynone was extensively explored as the reaction partner to afford synthetically useful spirooxindoles. As depicted in Scheme 2, both linear and branched aliphatic alkynone could be transfer to corresponding spirooxindole in good to excellent enantioselectivities (Scheme 2, 90% to 96% ee for **4o**-**4x**). To our delight, different functional groups such as olefin, halide, TBS-protected hydroxyl, ester and acetal were tolerated (Scheme 2, **4p**-**4v**), which allowed further manipulations for constructing advanced intermediates. Aromatic alkynone also compatible with the reaction conditions, albeit with decreased enantioselectivities (Scheme 2, **4y** and **4z**).

Having established a reliable protocol for constructing enantioenriched spiro[pyrrolidine-3,3'-oxindole], we turned our attention to the synthesis of strychnos alkaloids [(-)-tubifoline, (-)-tubifolidine, (-)-dehydrotubifoline][13-15] by following the strategy depicted in Figure 1. The synthesis commenced with the preparation of spirooxindole *ent*-**4c** on decal gram scale using this newly developed protocol (Scheme 3). Subsequently, intramolecular condensation of the methyl ketone with oxindole of *ent*-**4c** to forge the E ring proved to be quite challenging due to the rapid racemization of *ent*-**4c** under acidic or basic conditions.[7] After extensive screening of the reaction conditions, we found that activation of the amide with Meerwein salt, followed by formation of silyl enol ether and treatment with TMSOTf in one pot smoothly delivered the tetracyclic product **5** in 82% yield over two steps without loss of enantiopurity.



Scheme 3. Asymmetric Synthesis of Strychnos Alkaloids.

With the key tetracyclic intermediate **5** in hand, we subsequently focused on building up the bridged D ring via allylic substitution (Scheme 3). First, installation of propargyl silane onto enone **7** could be achieved in 60% yield via a sequence of Tosyl-protection, removal of 2-Nosyl, and alkylation of the resulted secondary amine with propargyl iodide **6**. Subsequent reduction of enone **7** mediated by $NaBH_4/CeCl_3$ led to allyl alcohol **8**, setting the stage for the critical ring closure. The cyclization of **8** was unexpectedly problematic as the allyl cation intermediate **9** might involve in ring opening/cyclization process via iminium **10**, which resulted in dramatic erosion of enantiopurity. After carefully optimizing the reaction conditions (see Supporting Information, Table S4), it was revealed that the racemization could be totally supressed by performing the reaction in the presence of excessive $SnCl_4$ (5.0 equiv) at low temperature. Subsequent hydrogenation of allene **11** over Pd/C in MeOH followed by the deprotection of Tosyl promoted by Mg in MeOH furnished (-)-tubifoline in 81% yield. Reduction of (-)-tubifoline with $NaBH_3CN/TiCl_4$ gave (-)-tubifolidine in 90% yield.[16] On the other hand, semi-hydrogenation of allene **11** followed by removal of Tosyl provided (-)-dehydrotubifoline in 57% yield.

In conclusion, an enantioselective construction of spiro[pyrrolidine-3,3'-oxindole] was described by employing tandem Michael addition of oxindole derived from tryptamine to alkynone promoted by $Sc(OTf)_3$-chiral *N,N'*-dioxide. This protocol enabled asymmetric total synthesis of strychnos alkaloids [(-)-tubifoline, (-)-tubifolidine, (-)-dehydrotubifoline] in 10 to 11 steps, which featured an intramolecular condensation to form the E ring and a $SnCl_4$-promoted allylic substitution to forge the bridged D ring. Further application of this strategy in asymmetric synthesis of other type of monoterpenoid alkaloids is

currently pursued in our laboratory and the results will be reported in due course.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (grand No. 21722206, 21672171), the Scientific Research Foundation of Northwest A&F University. Financial support from the Open Fund of State Key Laboratory of Bioorganic & Natural Products is also acknowledged.

Keywords: tandem Michael addition, spiro[pyrrolidine-3,3'-oxindole], $Sc(OTf)_3$-chiral *N,N'*-dioxide, strychnos alkaloids, tubifoline

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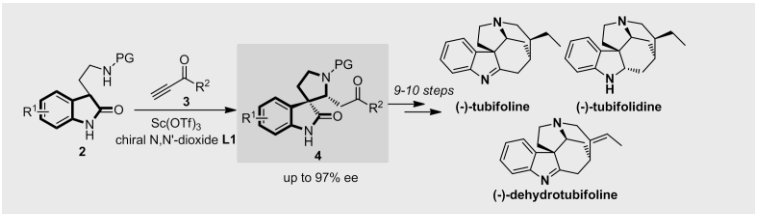

A novel strategy for synthesizing strychnos alkaloids is enabled by $Sc(OTf)_3$-chiral *N,N'*-dioxide catalyzed enantioselective tandem Michael addition of oxindole derived from tryptamine to alkynone.

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