Asymmetric Synthesis

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Nickel-Catalyzed Regio- and Enantioselective Annulation Reactions of 1,2,3,4-Benzothiatriazine-1,1(2*H*)-dioxides with Allenes**

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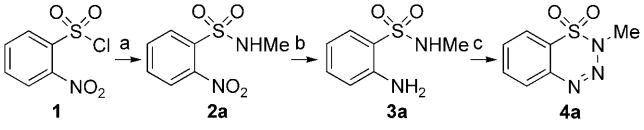
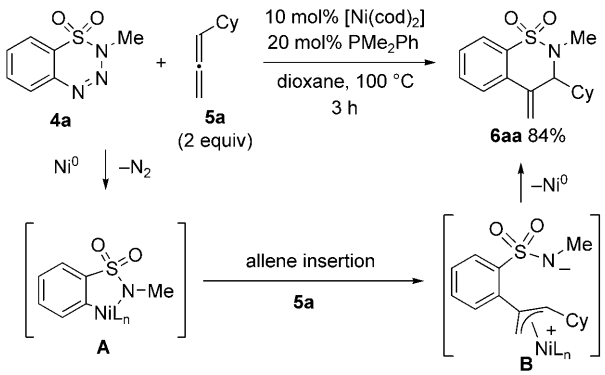
Transition metal complexes promote various annulation reactions, which provide efficient methods for the synthesis of heterocyclic molecules.[1] Such reactions often involve heteroatom-containing metalacycles as the key intermediate, and unsaturated organic compounds are incorporated into heterocyclic skeletons through migratory insertion and reductive elimination. It has been shown that heterocyclic compounds, such as triazoles,[2] phthalimides,[3a] phthalic anhydride,[3b] and isatoic anhydride[3c] serve as the precursor to heteroatom-containing metalacycles through oxidative addition to a low-valent transition metal, and the extrusion of gaseous molecules like N_2, CO, and CO_2.[4] We recently developed a nickel-catalyzed denitrogenative annulation reaction of 1,2,3-benzotriazin-4(3*H*)-ones with alkynes[5a] and allenes,[5b] in which a five-membered ring azanickelacycle was formed as the precursory platform. We next examined the use of 1,2,3,4-benzothiatriazine-1,1(2*H*)-dioxides as a triazo substrate for an annulation reaction because of the medicinal importance of the resulting 1,2-benzothiazine-1,1(2*H*)-dioxide derivatives.[6] Herein, we report the enantioselective synthesis of substituted 3,4-dihydro-1,2-benzothiazine-1,1(2*H*)-dioxides by the nickel-catalyzed denitrogenative annulation of 1,2,3,4-benzothiatriazine-1,1(2*H*)-dioxides with allenes.

The model substrate, 2-methyl-1,2,3,4-benzothiatriazine-1,1(2*H*)-dioxide (**4a**), can be readily prepared from *ortho*-nitrobenzenesulfonyl chloride (**1**), which is commercially available, in three steps (Scheme 1); **1** is coupled with methylamine and the resulting *ortho*-nitro-*N*-methylbenzenesulfonamide (**2a**) is reduced using zinc to give *ortho*-amino-*N*-methylbenzenesulfonamide (**3a**). The following HONO-mediated ring-closing reaction affords **4a** as a white solid.[7]



Scheme 1. a) NH_2Me, Et_3N, CH_2Cl_2, RT, 36 h, 89%; b) Zn, NH_4Cl, MeOH, RT, 6 h, 96%; c) $NaNO_2$, HCl, EtOH, 0°C, 9 h, 82%.

Initially, activation of the triazo moiety with nickel(0) was examined using achiral phosphines in the reaction with a mono-substituted allene, and PMe_2Ph was found to be a suitable ligand for the activation. A mixture of **4a** and cyclohexylpropa-1,2-diene (**5a**, 2 equiv) was heated in the presence of [Ni(cod)$_2$] (10 mol%) and PMe_2Ph (20 mol%) in 1,4-dioxane at 100°C. Substrate **4a** was consumed in 3 hours. Workup of the reaction mixture, followed by chromatographic isolation gave 3,4-dihydro-1,2-benzothiazine-1,1(2*H*)-dioxide (**6aa**) in 84% yield as a single regioisomer (Scheme 2). Other phosphine ligands, such as PMe_3, $PMePh_2$, PPh_3, and dppf gave inferior results. The annulation reaction is considered to consist of 1) oxidative addition of the N–N bond to nickel(0), 2) extrusion of N_2 to give five-membered ring azanickelacycle **A**, 3) insertion of an allene to form π-allylnickel intermediate **B**, and 4) allylic amidation at the more-substituted carbon[8,9] to release **6aa** and nickel(0).



Scheme 2. Ni^0-catalyzed denitrogenative annulation using achiral phosphine. cod = 1,5-cyclooctadiene.

Thus, the triazo moiety of **4a** could be activated by nickel(0), with the extrusion of N_2. We next examined chiral ligands using **4a** and **5a** as the substrates (Table 1). C_2-symmetric bidentate bisphosphine ligands, such as (*S*)-binap,[10] (*S*,*S*′,*R*,*R*′)-tangphos,[11] and (*R*,*R*)-Me-duphos,[12] were considerably inferior to PMe_2Ph in terms of reactivity (Table 1, entries 1–3). The yield and selectivity were both improved when unsymmetrical bidentate P,N-type ligands, such as (*S*,*S*)-*i*Pr-foxap,[13] were employed (Table 1, entries 5 and 6). Optically active **6aa** was formed stereoselectively along with a small amount of **7aa**. In particular, (*R*)-quinap[14] gave the best enantioselectivity for **6aa** (96%).

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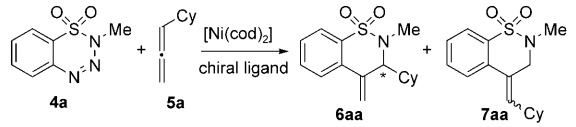
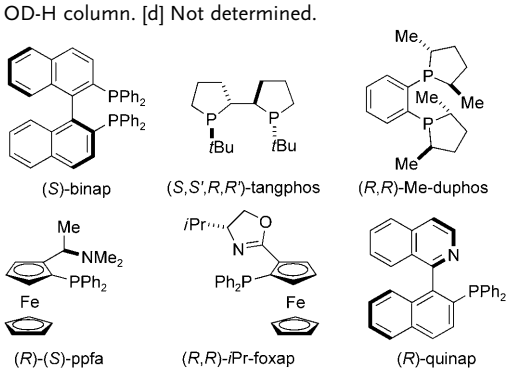
Table 1: Ni^0-catalyzed enantioselective annulation: Screening of chiral ligands.[a]



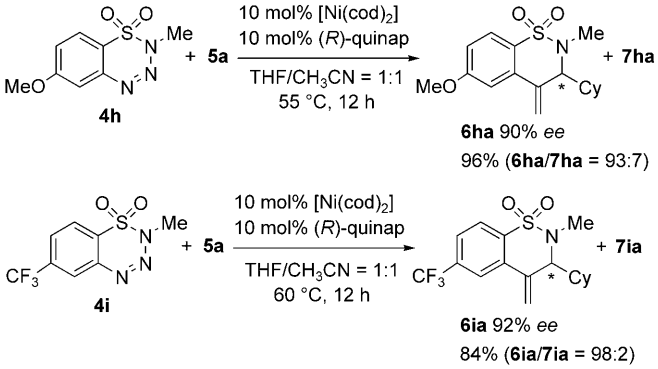
Entry[a]	Chiral ligand	Yield [%][b]	*ee* [%][c]
1	(*S*)-binap	< 5	–[d]
2	(*S*,*S*′,*R*,*R*′)-tangphos	< 5	–[d]
3	(*R*,*R*)-Me-duphos	13 (99:1)	52
4	(*R*)-(*S*)-ppfa	30 (97:3)	61
5	(*R*,*R*)-*i*Pr-foxap	92 (94:6)	92
6	(*R*)-quinap	87 (94:6)	96

[a] Conditions: **4a** (0.1 mmol), **5a** (0.2 mmol), [Ni(cod)$_2$] (10 mol%), chiral ligand (10 mol%) in 1,4-dioxane (1 mL) at 60°C for 6 h. [b] Total yield of isomers: the **6aa**/**7aa** ratio is given in parentheses. [c] Determined by HPLC analysis on a chiral stationary phase using a Chiralcel OD-H column. [d] Not determined.



The scope of the substituents on the nitrogen atom of **4** was examined in the reaction with **5a** using the nickel(0)/(*R*)-quinap catalyst (Table 2). Primary and secondary alkyl groups were suitable, and the corresponding products **6ba-ea** were produced with good regio- and enantioselectivities (Table 2, entries 1–4). On the other hand, *tert*-butyl-substituted substrate **4f** favored the formation of **7fa** (**6fa**/**7fa** = 13:87; Table 2, entry 5). Steric repulsion arising around the bulky *tert*-butyl group changed the preferred site of allylic amidation to the primary allylic carbon. *para*-Tolyl-substituted substrate **4g** was also converted into the corresponding product **6ga**, albeit in low yield (Table 2, entry 6).

Functionalized benzo groups were briefly examined (Scheme 3). Substrates **4h** and **4i**, which have electron-donating and electron-withdrawing ring substituents, both worked well with **5a** to furnish the corresponding products

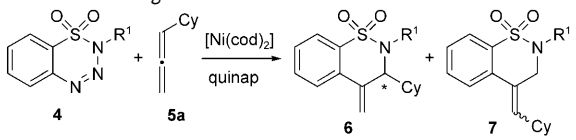


Scheme 3. Ni^0-catalyzed enantioselecitve annulation: Scope of the substituent on the benzene ring of **4**.

6ha and **6ia** with high yield and enantioselectivity, respectively.

Various monosubstituted allenes **5** were subjected to the annulation reaction with **4a** (Table 3). The reaction proceeded smoothly at 60°C to give **6** as the major product, except in the case of *tert*-butylpropa-1,2-diene (**5e**). The reaction of **5e** was slower at 60°C, probably owing to steric reasons, and thus required a higher temperature for it to proceed to completion. Enantioselectivities in the range 81–85% were observed with simple allenes that contain a primary, secondary, tertiary, or phenyl substituent (Table 3,

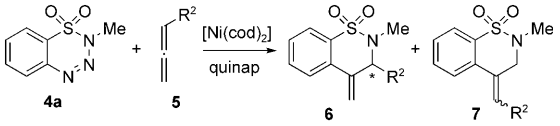
Table 2: Ni^0-catalyzed enantioselecitve annulation: Scope of the substituent on the nitrogen atom of **4**.[a]



Entry	**4**	R^1	**6**	**7**	Yield [%][b]	*ee* [%][c]
1	**4b**	Et	**6ba**	**7ba**	84 (92:8)	97
2	**4c**	Bn	**6ca**	**7ca**	74 (94:6)[d]	97
3	**4d**	PMB	**6da**	**7da**	69 (98:2)[d]	91
4	**4e**	*i*Pr	**6ea**	**7ea**	77 (91:9)[e]	88
5	**4f**	*t*Bu	**6fa**	**7fa**	67 (13:87)[f]	–[g]
6	**4g**	*p*-Tol	**6ga**	**7ga**	28 (88:12)	86

[a] Conditions: **4** (0.1 mmol), **5a** (0.2 mmol), [Ni(cod)$_2$] (10 mol%), (*R*)-quinap (10 mol%) in 1,4-dioxane (1 mL) at 100°C for 12 h unless otherwise noted. [b] Total yield of isomers: the **6**/**7** ratio is given in parentheses. [c] Determined by HPLC analysis using a chiral column. [d] Using toluene (1 mL). [e] Using [Ni(cod)$_2$] (20 mol%), (*R*)-quinap (20 mol%). [f] Using [Ni(cod)$_2$] (20 mol%), (*R*)-quinap (20 mol%) at 120°C. [g] Not determined. PMB = *para*-methoxybenzyl.

Table 3: Ni^0-catalyzed enantioselecitve annulation of **4a** with Allenes **5b–i**.[a]

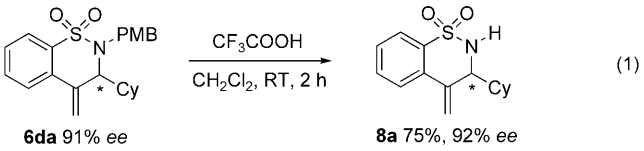


Entry	**5**	R^2	**6**	**7**	Yield [%][b]	*ee* [%][c]
1	**5b**	*n*-Hex	**6ab**	**7ab**	87 (96:4)	85
2	**5c**	CH_2Cy	**6ac**	**7ac**	92 (98:2)	81
3	**5d**	*c*-Pent	**6ad**	**7ad**	97 (97:3)	85
4	**5e**	*t*Bu	**6ae**	**7ae**	92 (87:13)[d]	84
5	**5f**	Ph	**6af**	**7af**	99 (86:14)	85
6	**5g**	$(CH_2)_2OTBS$	**6ag**	**7ag**	98 (91:9)	72
7	**5h**	$(CH_2)_2OBn$	**6ah**	**7ah**	91 (93:7)	73
8	**5i**	$(CH_2)_2N(Phth)$	**6ai**	**7ai**	95 (93:7)	76

[a] Conditions: **4a** (0.1 mmol), **5** (0.2 mmol), [Ni(cod)$_2$] (10 mol%), (*R*)-quinap (10 mol%) in THF/CH_3CN (0.5:0.5 mL) at 60°C for 3–12 h. [b] Total yield of isomers: the **6**/**7** ratio is given in parentheses. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 80°C.

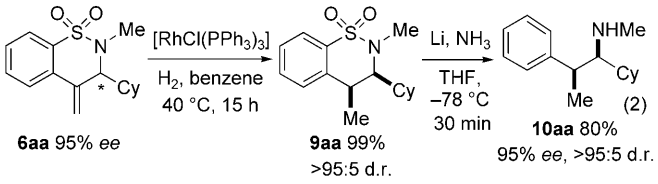
entries 1–5). Functional groups such as siloxy, benzyloxy, and *N*-phthalimidoyl groups on the alkyl chains were tolerated under the reaction conditions, although the enantioselectivities decreased to 72–76% *ee* (Table 3, entries 6–8).

The *para*-methoxybenzyl group in the product **6da** was easily removed on treatment with trifluoroacetic acid to give the unprotected 3,4-dihydro-1,2-benzothiazine-1,1(2*H*)-dioxide **8a** with retention of the enantiopurity [Eq. (1)].[15]



6da 91% *ee* **8a** 75%, 92% *ee* (1)

Furthermore, product **6aa** could be derivatized to β-methylphenethylamine **10aa** by stereoselective hydrogenation and subsequent reductive removal of the SO_2 moiety [Eq. (2)].[16] There are only a few reports in the literature on its preparation with high diastereo- and enantioselectivities.[17]



6aa 95% *ee* **9aa** 99% >95:5 d.r. **10aa** 80% 95% *ee*, >95:5 d.r. (2)

In summary, we have demonstrated that a highly reactive azanickelacycle can be generated from 1,2,3,4-benzothiatriazine-1,1(2*H*)-dioxide through extrusion of N_2. The azanickelacycle incorporates a variety of allenes in a regio- and enantioselective manner, providing a new synthetic route to substituted 3,4-dihydro-1,2-benzothiazine-1,1(2*H*)-dioxides, whose biological activities are of much interest.

Experimental Section

Typical procedure for the nickel-catalyzed annulation reaction: In an N_2-filled glove-box, **4a** (39.7 mg, 0.20 mmol), $[Ni(cod)_2]$ (5.6 mg, 0.02 mmol), (*R*)-quinap (8.8 mg, 0.02 mmol), 1,4-dioxane (2 mL), and **5a** (58 μL, 0.40 mmol) were added at room temperature to an oven-dried 4 mL vial containing a stirrer bar. The vial was sealed with a Teflon cap and taken out of the glove box. After being heated at 60 °C for 6 h, the reaction mixture was cooled to room temperature and stirred for 1 h in open air. The resulting mixture was passed through a pad of Florisil and eluted with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate 5:1) to give an isomeric mixture of **6aa** and **7aa** (50.7 mg, 0.17 mmol, 87% total yield, **6aa**/**7aa** = 94:6). The enantiomeric excess of the major isomer **6aa** was determined by HPLC analysis using a Chiralcel OD–H column.

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