

Enantioselective Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-ones by Nickel-Catalyzed Denitrogenative Annulation of 1,2,3-Benzotriazin-4(3*H*)-ones with Allenes

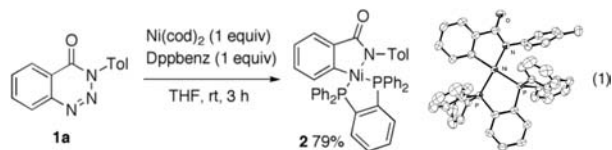
Motoshi Yamauchi, Masao Morimoto, Tomoya Miura, and Masahiro Murakami*

Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Katsura, Kyoto 615-8510, Japan

Received November 11, 2009; E-mail: murakami@sbchem.kyoto-u.ac.jp

Transition-metal-catalyzed annulation reactions continue to provide many powerful synthetic methodologies for the construction of heterocyclic compounds.¹ Heterometalacyclic complexes often act as key intermediates, which subsequently incorporate unsaturated compounds through insertion and reductive elimination to afford heterocyclic skeletons. It has been reported that heterocyclic compounds such as triazoles,² phthalimides,^{3a} phthalic anhydride,^{3b} and isatoic anhydrides^{3c} can be exploited as the precursory platform to generate heterometalacyclic intermediates through oxidative addition to a low-valent transition metal and subsequent extrusion of gaseous molecules such as N₂, CO, and CO₂.⁴ We recently developed a Ni-catalyzed denitrogenative annulation of 1,2,3-benzotriazin-4(3*H*)-ones (**1**) with alkynes.⁵ A five-membered azanickelacycle was postulated as the intermediate. Our continued investigations have led us to isolate and characterize the postulated azanickelacycle complex. Herein, we report on its stoichiometric reaction with allenes, which has successfully been extended to a catalytic asymmetric denitrogenative annulation of 1,2,3-benzotriazin-4(3*H*)-ones.

N-Tolyl-1,2,3-benzotriazin-4(3*H*)-one (**1a**)⁶ was treated with equimolar amounts of Ni(cod)₂ and 1,2-bis(diphenylphosphino)benzene (Dppbenz) in THF at room temperature for 3 h. Recrystallization of the reaction mixture from CH₂Cl₂/hexane afforded azanickelacycle **2** as dark-brown crystals in 79% yield (eq 1): The



five-membered cyclic structure of **2** was unambiguously determined by single-crystal X-ray analysis. Ni(II) complex **2** has square-planar geometry, and the N atom of the amidate moiety is bound to the Ni center in an η¹ fashion. Presumably, oxidative insertion of Ni(0) into the N–N(tolyl) bond of **1a** and subsequent retroinsertion of N₂ furnished **2**.

Next, we examined the reactivity of azanickelacycle **2**, which led us to discover that allene functionality was successfully incorporated into the precursory skeleton. Thus, when 3 equiv of nona-1,2-diene (**3a**) was reacted with **2** in THF at 60 °C, an isomeric mixture of 3,4-dihydroisoquinolin-1(2*H*)-ones **4aa** and **5aa** in a 54:46 ratio was obtained (99% total yield; eq 2):

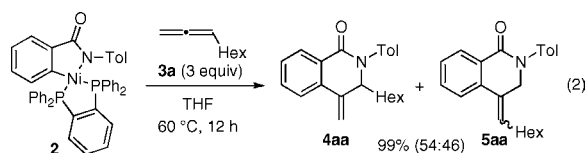


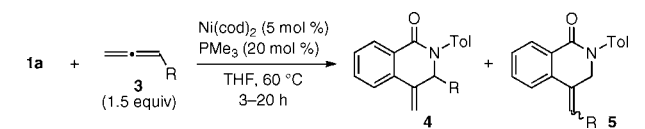
Table 1. Ni(0)-Catalyzed Annulation of *N*-Aryl-1,2,3-benzotriazin-4(3*H*)-ones **1** with Nona-1,2-diene (**3a**)^a

entry	1	R ¹	R ²	R ³	4	5	% yield ^b
1	1a	Tol	H	H	4aa	5aa	94 (94:6) ^c
2	1b	Ph	H	H	4ba	5ba	90 (91:9) ^d
3	1c	4-MeOC ₆ H ₄	H	H	4ca	5ca	76 (94:6) ^e
4	1d	4-ClC ₆ H ₄	H	H	4da	5da	83 (93:7) ^{f,h}
5	1e	2-MeOC ₆ H ₄	H	H	4ea	5ea	94 (95:5) ^{c,i}
6	1f	Ph	MeO	MeO	4fa	5fa	79 (95:5) ^{c,j}
7	1g	Ph	H	CO ₂ Me	4ga	5ga	88 (85:15) ^g

^a Conditions: **1** (0.2 mmol), **3a** (0.3 mmol), Ni(cod)₂ (5 mol %), and PMe₃ (20 mol %) in THF (2 mL) at 60 °C for 3–16 h. ^b Total yield of isomers; the **4/5** ratio is given in parentheses. ^c Z/E > 95:5. ^d Z/E = 78:22. ^e Z/E = 83:17. ^f Z/E = 86:14. ^g Z/E = 80:20. ^h Using dioxane (2 mL) at 80 °C. ⁱ Using 10 mol % Ni(cod)₂ and 40 mol % PMe₃. ^j Using 10 mol % Ni(cod)₂ and 40 mol % PMe₃ in dioxane (2 mL) at 80 °C.

The possibility of developing a catalytic reaction incorporating allenes was then pursued (Table 1). When a mixture of **1a** and **3a** (1.5 equiv) in THF was heated at 60 °C for 3 h in the presence of a Ni catalyst (5 mol %) prepared from Ni(cod)₂ and PMe₃ (Ni/P = 1:4), the product **4aa** resulted in preference to **5aa** (94%, **4aa/5aa** = 94:6; entry 1). Other phosphine ligands such as PCy₃, Prt-Bu₃, PPh₃, and Dppbenz gave inferior results. Under the conditions involving PMe₃ as the ligand, a wide variety of aryl substituents on the N atom afforded the corresponding 3,4-dihydroisoquinolin-1(2*H*)-ones **4ba–ea** in yields ranging from 76 to 94% with high regioselectivities, suggesting less steric and electronic impact of the aryl group (R¹) (entries 2–5). The 4-methoxyphenyl group of **4ca** was readily removed by treatment with cerium ammonium nitrate to furnish the nonprotected 3,4-dihydroisoquinolin-1(2*H*)-one.⁷ Benzotriazinones **1f** and **1g** having electron-donating and -withdrawing ring substituents also participated in the reaction (entries 6 and 7).

Terminal allenes having a variety of R substituents were subjected to the annulation reaction of **1a**. The regioselectivity was significantly affected by the sterics of the R substituent (Table 2). As with simple nona-1,2-diene **3a**, functionalized allenes **3b–e** having one primary substituent exhibited good regioselectivity to give the corresponding 3,4-dihydroisoquinolin-1(2*H*)-ones **4ab–ae** in good yields (entries 1–4). On the other hand, cyclohexylpropa-1,2-diene (**3f**) afforded a mixture of regioisomers **4af** and **5af** in a 55:45 ratio (entry 5).⁸ Allene **3g** bearing a *tert*-butyl group gave the insertion products in favor of **5ag** (**4ag/5ag** = 18:82; entry 6), and complete regioselectivity for **5** was observed with trialkylsilyl-substituted allene **3h** (entry 7). Whereas reductive elimination at

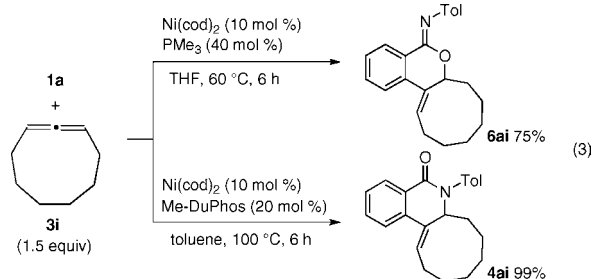
Table 2. Ni(0)-Catalyzed Annulation of *N*-Tolyl-1,2,3-benzotriazin-4(3*H*)-one (**1a**) with Allenes **3**^a

entry	3	R	4	5	% yield ^b
1	3b	(CH ₂) ₂ OBN	4ab	5ab	91 (94:6) ^{c,e}
2	3c	(CH ₂) ₂ OSi <i>t</i> -BuMe ₂	4ac	5ac	81 (93:7) ^c
3	3d	(CH ₂) ₂ OH	4ad	5ad	76 (91:9) ^d
4	3e	(CH ₂) ₃ CN	4ae	5ae	95 (92:8) ^c
5	3f	<i>c</i> -Hex	4af	5af	89 (55:45) ^{c,f}
6	3g	<i>t</i> -Bu	4ag	5ag	99 (18:82) ^c
7	3h	Si <i>t</i> -BuMe ₂	4ah	5ah	82 (0:100) ^c

^a The reaction conditions were the same as those in Table 1. ^b Total yield of isomers; the 4/5 ratio is given in parentheses. ^c *Z/E* > 95:5. ^d *Z/E* = 67:23. ^e Using dioxane (2 mL) at 80 °C. ^f Using 10 mol % Ni(cod)₂ and 40 mol % PMe₃.

the more-substituted carbon is generally preferred for electronic reasons, the steric bulk of the *tert*-butyl and trialkylsilyl groups favors reductive elimination at the less-substituted carbon.

The use of 1,3-disubstituted allenes was also examined. To our surprise, the product outcome varied with the ligand employed. Thus, whereas the use of PMe₃ furnished the imino ester **6ai** in 75% yield,⁹ the bidentate phosphine ligand (*R,R*)-Me-DuPhos afforded **4ai** as the sole product in 99% yield at 100 °C (eq 3).^{10,11}

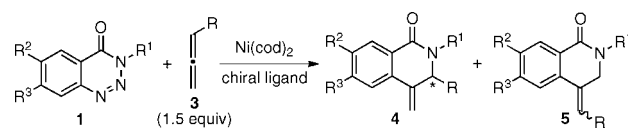


Next, the catalytic reaction was extended to an asymmetric version, and various chiral ligands were examined using **1a** and **3a** (Table 3). Whereas bidentate phosphine ligands such as (*R,R*)-Me-DuPhos and (*S,S,R,R*)-TangPhos exhibited reasonable enantioselectivities, the regioselectivities were poor (entries 1 and 2). The regio- and enantioselectivities both became acceptable when the phosphino-oxazoline ligand (*S,S*)-*i*-Pr-FOXAP was employed (entry 3).¹² Lowering the reaction temperature to 60 °C led to the best result (96%, 90% ee, **4aa/5aa** = 98:2; entry 4). The asymmetric process worked well with a sterically and electronically diverse array of *N*-aryl substituents (entries 5–11). The reaction tolerated the presence of a variety of functional groups (entries 12–19).

In summary, a denitrogenative annulation reaction of 1,2,3-benzotriazin-4(3*H*)-ones with allenes provides a unique method for the regio- and enantioselective synthesis of substituted 3,4-dihydroisoquinolin-1(2*H*)-ones, which are found in a wide variety of plant alkaloids and bioactive compounds.¹³ Further studies to expand the reaction scope are in progress.

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Supporting Information Available: Experimental procedures, spectral data for the new compounds, and details of the X-ray analysis

Table 3. Ni(0)-Catalyzed Enantioselective Annulation Reaction of *N*-Aryl-1,2,3-benzotriazin-4(3*H*)-ones **1** with Allenes **3**^a

entry	1	3	chiral ligand	<i>T</i> (°C)	4	% yield ^b	ee (%) ^c
1	1a	3a	Me-DuPhos	80	4aa	95 (83:17)	78
2	1a	3a	TangPhos	80	4aa	96 (66:34)	91
3	1a	3a	<i>i</i> -Pr-FOXAP	80	4aa	99 (97:3)	87
4	1a	3a	<i>i</i> -Pr-FOXAP	60	4aa	96 (98:2)	90
5	1b	3a	<i>i</i> -Pr-FOXAP	60	4ba	99 (97:3)	91
6	1c	3a	<i>i</i> -Pr-FOXAP	60	4ca	99 (96:4)	92
7	1d	3a	<i>i</i> -Pr-FOXAP	60	4da	94 (95:5)	93
8	1e	3a	<i>i</i> -Pr-FOXAP	60	4ea	98 (98:2)	91 ^d
9	1f	3a	<i>i</i> -Pr-FOXAP	60	4fa	99 (94:6)	92 ^d
10	1g	3a	<i>i</i> -Pr-FOXAP	60	4ga	95 (95:5)	97
11	1h (R ¹ , R ² , R ³ = 4-CF ₃ C ₆ H ₄ , H, H)	3a	<i>i</i> -Pr-FOXAP	60	4ha	92 (93:7)	93
12	1i (R ¹ , R ² , R ³ = CONPh ₂ , H, H)	3a	<i>i</i> -Pr-FOXAP	40	4ia	81 (99:1)	95 ^e
13	1j (R ¹ , R ² , R ³ = 2-thienyl, N-Ph, H)	3a	<i>i</i> -Pr-FOXAP	60	4ja	95 (98:2)	96
14	1a	3b	<i>i</i> -Pr-FOXAP	60	4ab	98 (94:6)	91
15	1a	3c	<i>i</i> -Pr-FOXAP	60	4ac	92 (95:5)	91
16	1a	3d	<i>i</i> -Pr-FOXAP	60	4ad	91 (92:8)	97
17	1a	3e	<i>i</i> -Pr-FOXAP	60	4ae	99 (94:6)	93 ^d
18	1a	3f	<i>i</i> -Pr-FOXAP	60	4af	76 (73:27)	96
19	1a	3j (R = (CH ₂) ₂ N(phth))	<i>i</i> -Pr-FOXAP	60	4aj	99 (96:4)	97

^a Conditions: **1** (0.2 mmol), **3** (0.3 mmol), Ni(cod)₂ (10 mol %), and chiral ligand (20 mol %) in THF (2 mL) for 12 h. ^b Total yield of isomers; the 4/5 ratio is given in parentheses. ^c Determined by HPLC analysis using a chiral column. ^d Using CH₃CN. ^e Using 20 mol % Ni(cod)₂.

of Ni(II) complex **2** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) The enantiomeric excess of **4ai** was low (19% ee).
- (11) Treatment of **6ai** with Ni(cod)₂ (10 mol %) and (*R,R*)-Me-DuPhos (20 mol %) in toluene at 100 °C caused isomerization to **4ai** (97% yield), indicating that **4ai** is the thermodynamically more stable isomer.
- (12) (*S,S*)-*i*-Pr-FOXAP = (*S,S*)-[2-(4'-isopropylloxazolin-2'-yl)ferrocenyl]diphenylphosphine. See: Miyake, Y.; Nishibayashi, Y.; Uemura, S. *Synlett* **2008**, 1747.
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