J|A|C|S COMMUNICATIONS

Published on Web 12/15/2009

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

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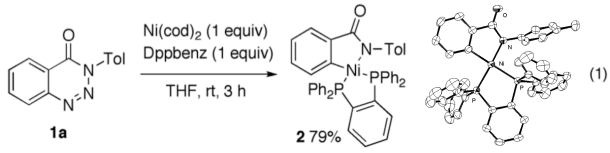
Transition-metal-catalyzed annulation reactions continue to provide many powerful synthetic methodologies for the construction of heterocyclic compounds.[1] Heterometalacyclic complexes often act as key intermediates, which subsequently incorporate unsaturated compounds through insertion and reductive 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 N_2, CO, and CO_2.[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.

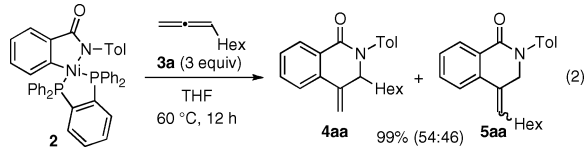
N-Tolyl-1,2,3-benzotriazin-4(3*H*)-one (**1a**)[6] was treated with equimolar amounts of $Ni(cod)_2$ and 1,2-bis(diphenylphosphino)benzene (Dppbenz) in THF at room temperature for 3 h. Recrystallization of the reaction mixture from CH_2Cl_2/hexane afforded azanickelacycle **2** as dark-brown crystals in 79% yield (eq 1): The



(1)

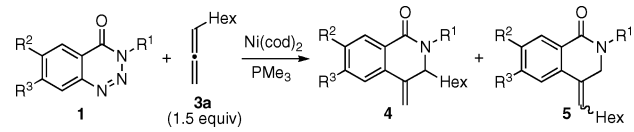
five-membered cyclic structure of **2** was unambiguously determined by single-crystal X-ray analysis. Ni(II) complex **2** has square-planar geometry, and the N atom of the amidate moiety is bound to the Ni center in an η^1 fashion. Presumably, oxidative insertion of Ni(0) into the N−N(tolyl) bond of **1a** and subsequent retroinsertion of N_2 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):



(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-$MeOC_6H_4$	H	H	**4ca**	**5ca**	76 (94:6)[e]
4	**1d**	4-ClC_6H_4	H	H	**4da**	**5da**	83 (93:7)[f,h]
5	**1e**	2-$MeOC_6H_4$	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_2Me	**4ga**	**5ga**	88 (85:15)[g]

[a] Conditions: **1** (0.2 mmol), **3a** (0.3 mmol), $Ni(cod)_2$ (5 mol %), and PMe_3 (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 % PMe_3. [j] Using 10 mol % $Ni(cod)_2$ and 40 mol % PMe_3 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 PMe_3 (Ni/P = 1:4), the product **4aa** resulted in preference to **5aa** (94%, **4aa**/**5aa** = 94:6; entry 1). Other phosphine ligands such as PCy_3, P*t*-Bu_3, PPh_3, and Dppbenz gave inferior results. Under the conditions involving PMe_3 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 (R^1) (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

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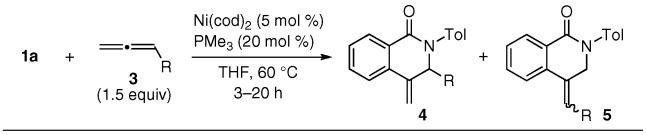
Table 2. Ni(0)-Catalyzed Annulation of *N*-Tolyl-1,2,3-benzotriazin-4(3*H*)-one (**1a**) with Allenes **3**[a]

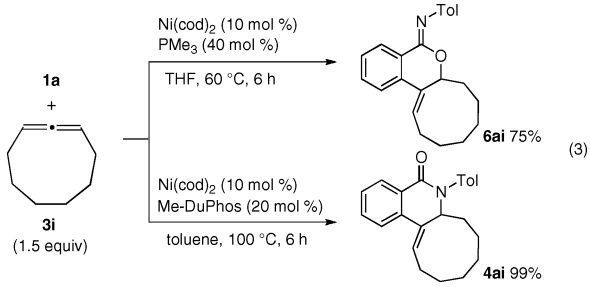


entry	3	R	4	5	% yield[b]
1	**3b**	$(CH_2)_2OBn$	**4ab**	**5ab**	91 (94:6)[c,e]
2	**3c**	$(CH_2)_2OSi$*t*-$BuMe_2$	**4ac**	**5ac**	81 (93:7)[c]
3	**3d**	$(CH_2)_2OH$	**4ad**	**5ad**	76 (91:9)[d]
4	**3e**	$(CH_2)_3CN$	**4ae**	**5ae**	95 (92:8)[c]
5	**3f**	*c*-Hex	**4af**	**5af**	89 (55:45)[c,f]
6	**3g**	*t*-Bu	**4ag**	**5ag**	99 (18:82)[c]
7	**3h**	Si*t*-$BuMe_2$	**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 % PMe_3.

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 PMe_3 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]



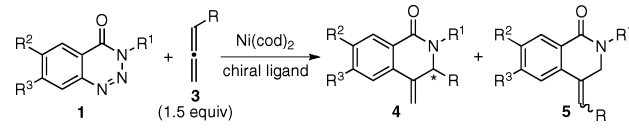
Next, the catalytic reaction was extended to an asymmetric version, and various chiral ligands were examined using **1a** and **3a** (Table 3). Whereas bidentate phosphine ligands such as (*R*,*R*)-Me-DuPhos and (*S*,*S*,*R*,*R*)-TangPhos exhibited reasonable enantioselectivities, the regioselectivities 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).

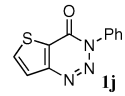
In summary, a denitrogenative annulation reaction of 1,2,3-benzotriazin-4(3*H*)-ones with allenes provides a unique method for the regio- and enantioselective synthesis of substituted 3,4-dihydroisoquinolin-1(2*H*)-ones, which are found in a wide variety of plant alkaloids and bioactive compounds.[13]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

Acknowledgment. This work was supported in part by MEXT, the Mitsubishi Chemical Corporation Fund, the Sumitomo Foundation, and the Astellas Award in Synthetic Organic Chemistry, Japan.

Supporting Information Available: Experimental procedures, spectral data for the new compounds, and details of the X-ray analysis of Ni(II) complex **2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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	*T* (°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*-Pr-FOXAP	80	**4aa**	99 (97:3)	87
4	**1a**	**3a**	*i*-Pr-FOXAP	60	**4aa**	96 (98:2)	90
5	**1b**	**3a**	*i*-Pr-FOXAP	60	**4ba**	99 (97:3)	91
6	**1c**	**3a**	*i*-Pr-FOXAP	60	**4ca**	99 (96:4)	92
7	**1d**	**3a**	*i*-Pr-FOXAP	60	**4da**	94 (95:5)	93
8	**1e**	**3a**	*i*-Pr-FOXAP	60	**4ea**	98 (98:2)	91[d]
9	**1f**	**3a**	*i*-Pr-FOXAP	60	**4fa**	99 (94:6)	92[d]
10	**1g**	**3a**	*i*-Pr-FOXAP	60	**4ga**	95 (95:5)	97
11	**1h** (R^1, R^2, R^3 = 4-$CF_3C_6H_4$, H, H)	**3a**	*i*-Pr-FOXAP	60	**4ha**	92 (93:7)	93
12	**1i** (R^1, R^2, R^3 = $CONPh_2$, H, H)	**3a**	*i*-Pr-FOXAP	40	**4ia**	81 (99:1)	95[e]
13	 **1j**	**3a**	*i*-Pr-FOXAP	60	**4ja**	95 (98:2)	96
14	**1a**	**3b**	*i*-Pr-FOXAP	60	**4ab**	98 (94:6)	91
15	**1a**	**3c**	*i*-Pr-FOXAP	60	**4ac**	92 (95:5)	91
16	**1a**	**3d**	*i*-Pr-FOXAP	60	**4ad**	91 (92:8)	97
17	**1a**	**3e**	*i*-Pr-FOXAP	60	**4ae**	99 (94:6)	93[d]
18	**1a**	**3f**	*i*-Pr-FOXAP	60	**4af**	76 (73:27)	96
19	**1a**	**3j** (R = $(CH_2)_2N$(phth))	*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 CH_3CN. [e] Using 20 mol % $Ni(cod)_2$.

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(6) We developed a facile route to **1** from *N*-H-1,2,3-benzotriazin-4(3*H*)-one, which is commercially available. For details of the Ullmann-type coupling reaction with aryl halides, see the Supporting Information.
(7) See the Supporting Information for details.
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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′-isopropyloxazolin-2′-yl)ferrocenyl]diphenylphosphine. See: Miyake, Y.; Nishibayashi, Y.; Uemura, S. *Synlett* **2008**, 1747.
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JA909603J