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Synthetic Methods

Pt^{II}-Catalyzed Synthesis of 9-Oxabicyclo[3.3.1]nona-2,6-dienes from 2-Alkynyl-1-carbonylbenzenes and Allylsilanes by an Allylation/Annulation Cascade[**]

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Allylsilanes commonly undergo [3+2] or [2+2] annulation reactions with aldehydes to give substituted tetrahydrofurans or oxetans,[1] an approach that has been applied to the syntheses of natural products.[2] New [3+2] and [4+2] annulations were reported for aldehyde substrates bearing an α- or β-siloxy group,[3] but these annulations required 1.0–5.0 equivalents of a Lewis acid ($BF_3{\cdot}Et_2O$, $TiCl_4$, or $SnCl_4$).[2–4] Our objective was to explore new annulations of allysilanes with functionalized aldehydes by using soft-acid-metal species in catalytic proportions.[4,5] Herein, we report a one-pot Pt^{II}-catalyzed synthesis of 9-oxabicyclo[3.3.1]nona-2,6-dienes by a tandem allylation/annulation reaction of the oxo-alkyne functionalities with 2-substituted allylsilanes (see Table 1). The importance of this new synthesis is that it provides easy access to two classes of bioactive molecules, **I**–**IV** and **V**, which are comprised of the oxatricyclic framework that showed biological effects in the central nervous system,[6] as well as HIV-1 inhibitory activities[7] (Figure 1).

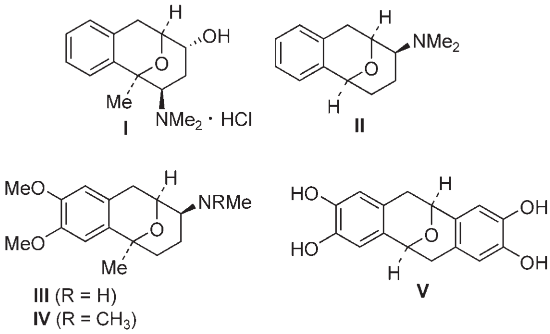
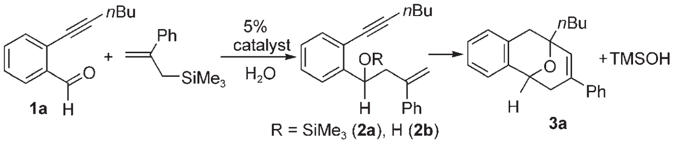


Figure 1. Bioactive molecules bearing 9-oxabicyclo[3.3.1]nona-2,6-diene frameworks.

We selected commonly used Au^I, Ag^I, and Pt^{II} species for screening and used each at a 5 mol% loading. Although these catalysts were reported to be catalytically active for the addition of allylsilanes to aldehydes and imines,[4] our results reveal that AgOTf, $[PPh_3AuSbF_6]$, and $[PPh_3AuOTf]$ are less efficient than platinum catalysts.[8] Treatment of 2-alkynylbenzaldehyde **1a** with $PtCl_2$ (5 mol%) in hot toluene (Table 1, entry 1) gave oxatricyclic species **3a** and siloxy species **2a** in 32% and 39% yields, respectively. In the presence of water (2 equiv) and CO (1 atm), the yield of compound **3a** was greatly improved to 88% (Table 1, entry 3); this reaction presumably involves a $[PtCl_2(CO)]$ species, which increases the electrophilicity of the platinum.[9] Notably, water participates in this catalytic reaction because it provides one hydrogen atom for species **3a**, and one OH group for the accompanying Me_3SiOH product. Efficient annulation was also attained with a $PtCl_2$/2 AgOTf catalyst in wet toluene to give compound **3a** in a 91% yield. Under mild conditions (toluene, 50 °C, 3 h), we isolated homoallylic alcohol **2b** and siloxy derivative **2a** in significant amounts (Table 1, entry 5), thus verifying them as reaction intermediates; these intermediates were converted into compound **3a** with $PtCl_2$/CO upon additional heating (Table 1, entry 6). The proposed structure of oxatricyclic species **3a** was inferred from ^1H NOE spectra, and confirmed from the X-ray crystallographic structure of related compound **3c**.[10]

Table 1: Catalytic activities for platinum and gold catalysts.



Entry	Substrate	Catalyst	Conditions[a]	H_2O (equiv)	Products (Yields [%])[b]
1	**1a**	$PtCl_2$	80 °C,15 h	–	**3a** (32), **2a** (39)
2	**1a**	$PtCl_2$/CO	80 °C,15 h	–	**3a** (41), **2a** (43)
3	**1a**	$PtCl_2$/CO	80 °C,15 h	2	**3a** (80)
4	**1a**	$PtCl_2$/ 2 AgOTf[c]	80 °C,12 h	2	**3a** (91)
5	**1a**	$PtCl_2$/CO	50 °C, 3 h	2	**1a** (14), **2a** (38), **2b** (42)
6	**2a**+**2b**	$PtCl_2$/CO	80 °C,12 h	2	**3a** (85)

[a] Toluene, [**1a**] = 0.26 м, [CO] = 1 atm, 5 mol% catalyst, silane [1.5 equiv]. [b] Yields are for products isolated after column chromatography. [c] 5 mol% $PtCl_2$ and 11 mol% AgOTf.

The results in Table 2 show the scope of this oxatricyclic synthesis by annulations of 2-alkynylbenzaldehydes **1a**–**1j**

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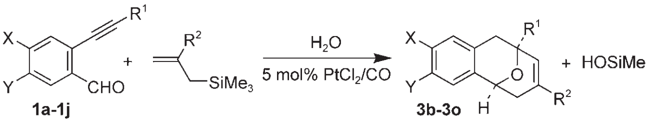
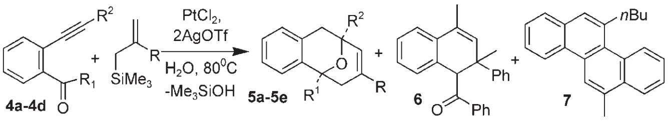
Table 2: Annulation of 2-alkynylbenzaldehydes with allylsilanes.



Entry	Enynal[a]	Silane	*t* [h]	Products (Yields [%])[c]
	X, Y = H			
1	R^1 = Ph (**1b**)	R^2 = Ph	20	**3b** (75)
2	R^1 = 4-MeOC_6H_4-(**1c**)	R^2 = Ph	24	**3c** (78)
3	R^1 = Cy (**1d**)	R^2 = Ph	10	**3d** (88)
4	R^1 = Me (**1e**)	R^2 = Ph	15	**3e** (72)
5	R^1 = H (**1f**)	R^2 = Ph	14 (10[b])	**3f** (12, 31[b])
6	R^1 = *n*Bu (**1a**)	R^2 = 4-$CF_3C_6H_4$	12	**3g** (68)
7	R^1 = *n*Bu (**1a**)	R^2 = 4-MeOC_6H_4	12	**3h** (60)
8	R^1 = *n*Bu (**1a**)	R^2 = 2-thienyl	13	**3i** (81)
9	R^1 = *n*Bu (**1a**)	R^2 = Me	2	**3j** (63[b])
10	R^1 = Me (**1e**)	R^2 = Me	1	**3k** (80)
	R^1 = *n*Bu, Y = H			
11	X = CF_3 (**1g**)	R^2 = Ph	10	**3l** (68)
12	X = OMe (**1h**)	R^2 = Ph	14 (12[b])	**3m** (34, 78[b])
	R^1 = *n*Bu, X = H			
13	Y = CF_3 (**1i**)	R^2 = Ph	15	**3n** (70)
14	Y = OMe (**1j**)	R^2 = Ph	20	**3o** (82)

[a] 80 °C, [substrate] = 0.26 M, [CO] = 1 atm, catalyst (5 mol%), silane (1.5 equiv). [b] These values were obtained with 5% $PtCl_2$/11% AgOTf. [c] Yields are for products isolated after column chromatography. Cy = cyclohexyl.

Table 3: Annulation of 2-alkynyl-1-ketonylbenzenes with allylsilanes.



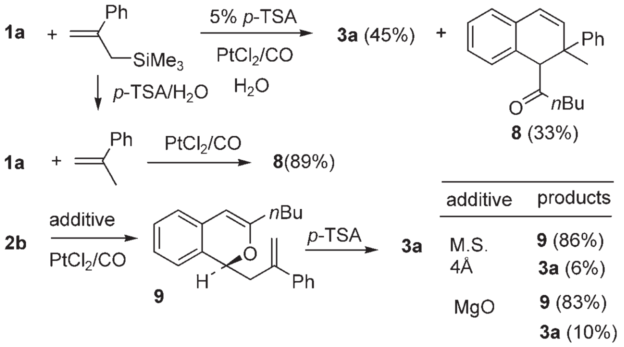
Entry	Ketones[a]	Silanes	*t* [h]	Products (Yields [%])[c]
1	R^1 = R^2 = Me (**4a**)	R = Ph	12	**5a** (66)
2	R^1 = Me, R^2 = *n*Bu (**4b**)	R = Ph	10	**5b** (83)
3	R^1 = Me, R^2 = Ph (**4c**)	R = Ph[b]	11	**5c** (63), **6** (22, d.r. = 1:1)
4	R^1 = R^2 = *n*Bu (**4d**)	R = Ph	11	**5d** (82)
5	**4b**	R = Me	6	**5e** (57), **7** (24)

[a] [substrate] = 0.26 M, 5% $PtCl_2$/11% AgOTf, silane (1.5 equiv). [b] 2.0 equiv of silane used. [c] Yields are for products isolated after column chromatography.

with various allylsilanes and water; the reactions were run with 5 mol% $PtCl_2$/CO in wet toluene. In three reactions (Table 2, entries 5, 9, and 12) we used $PtCl_2$/2 AgOTf (5/11 mol%) to improve the product yields. The reactions of substrates **1b**–**1e**, in which the R^1 substituent of the aldehyde is varied (Table 2, entries 1–4), gave oxatricyclic products **3b**–**3e** in good yields (72–88%). However, the unsubstituted analogue gave **3f** in 31% yield (Table 2, entry 5). The annulations of aldehydes **1a** and **1e** with various 2-substituted allylsilanes proceeded smoothly in wet toluene to give expected products **3g**–**3k** in 60–81% yields (Table 2, entries 6–10). The reaction is also compatible with different substituents (X and Y) on the phenyl rings of aldehydes **1g**–**1j**, and satisfactory yields (> 68%) were obtained for their annulated products **3l**–**3o**.

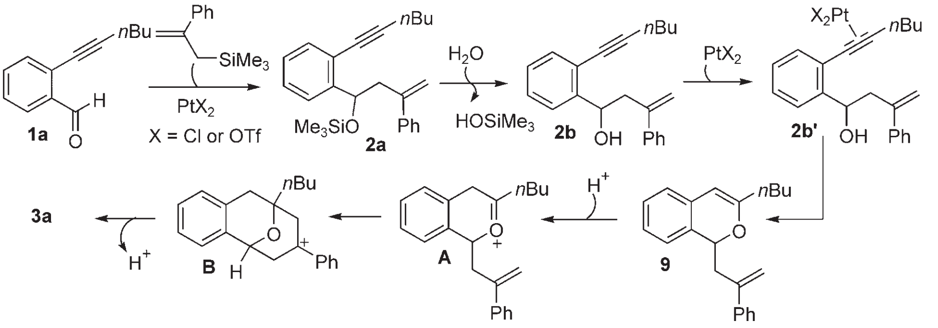
Although ketones are generally inactive in the Lewis acid promoted annulation with allylsilanes, ketones **4a**–**4d** were compatible with this new method. The results in Table 3 show that the $PtCl_2$/2 AgOTf mixture (5/11 mol%) efficiently catalyzed the annulation of these ketones with 2-(phenylallyl)trimethylsilane to give desired oxacyclic compounds **5a**–**5d** (63–83% yields) in wet toluene (100 °C, 10–12 h). We obtained 1,2-dihydronaphthalene species **6** as a side product (22% yield, d.r. = 1:1) with **4c** as the substrate (Table 3, entry 3).[11] The annulation of compound **4b** with 2-(methyl)allyltrimethylsilane gave desired product **5e** and chrysene **7** in 57% and 24% yields, respectively.[12]

To clarify the role of the Brønsted acid (Scheme 1), we added *p*-toluenesulfonic acid (*p*-TSA, 5 mol%) to a mixture of aldehyde **1a**, 2-(phenylallyl)trimethylsilane, and $PtCl_2$/CO (5 mol%) in wet toluene (80 °C, 12 h), and obtained oxatricyclic product **3a** and 1,2-dihydronaphthalene **8** (d.r. = 1.7:1) in 45% and 33% yields, respectively. The use of stronger Brønsted acids, such as HCl or HOTf, led to complete decomposition of starting aldehyde **1a**. The formation of species **8** has been rationalized by work in an early report by Yamamoto and co-workers.[13,14b,c] As proposed, the Brønsted acid catalyzes the hydrative decomposition of 2-(phenylallyl)trimethylsilane to 1-methylstyrene.[13] The results (Table 1, entry 1–6) show that of 1,2-dihydronaphthalene **8** is not isolated. In a separate experiment, we found that treatment of alcohol **2b** with $PtCl_2$/CO in dry toluene (80 °C, 12 h) predominantly gave 1*H*-isochromene **9** in 83–86% yields in the presence of either 4 Å molecular sieves or a proton-scavenger such as MgO. Additional treatment of 1*H*-isochromene **9** with *p*-TSA (1 mol%) in hot toluene (80 °C, 0.5 h) gave desired oxatricyclic product **3a** in a 96% yield. On the basis of these observations, we concluded that the concentration of the free Brønsted acid was rather small in the $PtCl_2$/CO/H_2O system, but it is necessary for the final annulation step.



Scheme 1. Control experiments to clarify the role of the Brønsted acid.

Accordingly, we propose a plausible mechanism (Scheme 2) that involves an initial Pt^{II}-catalyzed addition[4e] of the allysilane to the aldehyde to give siloxy product **2a**. In this wet system, we envisage that PtX$_2$ ($X = Cl$, OTf) enhances the hydrolysis of this siloxy species to give alcohol **2b**. A second Pt^{II}-catalyzed reaction of this alcohol, involving the hydroalkoxylation of the alkyne, is expected to give 1*H*-isochromene **9**,[14] which subsequently undergoes protonation to give oxonium intermediate **A**. The final annulation is completed upon addition of the tethered alkene of species **A** to its oxonium center to give oxabicyclic tertiary cation **B**, which then loses a proton regioselectively to produce desired **3a**. Herein, the alkene regioselectivity of **3a** is attributed to its less strained framework, having an energy that is approximately 2.91 kcal mol^{-1} less than the other olefin isomer.[15]



Scheme 2. A proposed mechanism for the formation of 9-oxabicyclo[3.3.1]nona-2,6-dienes.

In summary, we report a new platinum-catalyzed synthesis of 9-oxabicyclo[3.3.1]nona-2,6-dienes from readily available 2-alkynyl-1-carbonylbenzenes, allylsilanes, and water. This reaction sequence is proposed to proceed through a series of three reactions, including allylation of the carbonyl group,[4] hydroalkoxylation of the alkyne,[15] and a new ene-oxonium annulation.[16,17] The value of this new annulation is indicated by the easy access to bioactive molecules comprised of the same oxatricyclic framework. The synthesis of enantiomeric oxatricyclic products by using chiral platinum catalysts is under current investigation.

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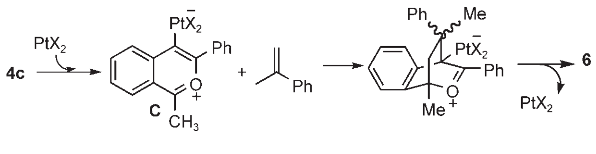
[8] In wet dichloroethane (25°C, 12 h), AgOTf, PPh$_3$AuSbF$_6$, and [PPh$_3$AuOTf] led to complete consumption of starting aldehyde **1a**, but only [PPh$_3$AuOTf] gave desired oxatricyclic species **3** in a 25% yield.

[9] For the PtCl$_2$/CO catalysis, see a) A. Fürstner, C. Aïssa, *J. Am. Chem. Soc.* **2006**, *128*, 6306; b) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024; c) B. P. Taduri, S. M. A. Sohel, H.-M. Cheng, G.-Y. Lin, R.-S. Liu, *Chem. Commun.* **2007**, 2530–2532; d) H.-K. Chang, S. Datta, A. Das, R.-S. Liu, *Angew. Chem.* **2007**, *119*, 4828; *Angew. Chem. Int. Ed.* **2007**, *46*, 4744.

[10] The x-ray crystallographic data for compound **3c** has been deposited at the Cambridge Crystallographic Data Center (CCDC-677837 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif), and ^{1}H NOE spectra of key compounds are provided in the Supporting Information.

[11] 1,2-dihydronaphthalene **6** was formed from [4+2] cycloaddition of benzopyrinium **C** and 1-methylstyrene (see below); this olefin arose from decomposition of allylsilane with a Brønsted acid when water was present.[13] In a control experiment, we obtained compound **6** (86% yield) from PtCl$_2$/CO-catalyzed cyclization of **4c** with 1-methylstyrene in hot toluene. See the leading paper: N. Asao, T. Kasahara, Y. Yamamoto, *Angew. Chem.* **2003**, *115*, 3628; *Angew. Chem. Int. Ed.* **2003**, *42*, 3504.



[12] For the mechanism of formation of chrysene **7**, see A. Das, H.-H. Liao R.-S. Liu, *J. Org. Chem.* **2007**, *72*, 9214.

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[15] The calculations were done with Gaussian-98 package at level B3LYP/6-31+G*; details are provided in the Supporting information.

[16] For metal-catalyzed addition of a tethered phenol or enol to an enol ether of 1*H*-isochromenes, see: A. Beeler, S. Su, C. A. Singleton, J. A. Proco, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 1413.

[17] Ketones are generally inactive toward metal-catalyzed allylation reactions.[1] The high yields of oxatricyclic products **5a**–**5d** may arise from addition of allylsilane to benzopyrilium species **C**,[11] rather than by the mechanism proposed in Scheme 2. We thank one reviewer for this valuable comment.