J|A|C|S COMMUNICATIONS

Published on Web 01/22/2009

Stereocontrolled Synthesis of Complicated Oxacyclic Compounds via Platinum-Catalyzed [4 + 2]-Cycloadditions and Annulations of Enynals with Allylic Alcohols

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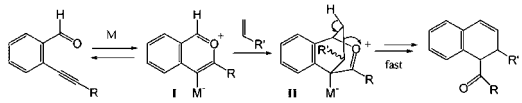
Metal-catalyzed cycloaddition reactions are powerful tools in organic synthesis to access complex molecular frameworks.[1] In the presence of electrophilic metals, common 2-alkynylbenzaldehydes form metal-benzopyrilium intermediates **I** that undergo [4 + 2] cycloaddition with alkenes to form cycloadducts **II**.[2,3] These species suffer kinetic instability and undergo rapid rearrangement to give 1,2-dihydronaphalene or naphthalene products. Metal-free [4 + 2]-cycloadducts resembling **II** were also too unstable to isolate.[4,5] The high reactivity of this species allows its interception with enynals of special types that however only gave distinct [3 + 2]-cycloadducts.[6] We sought new approaches for elaboration of intermediates **II** because of their skeletal complexity. Herein, we report the synthesis of complex oxacyclic compounds through diversified interceptions of intermediate **II** with 2-substituted allylic alcohol; this work first reveals the high diastereoselectivity of the benzopyrilium-alkene [4 + 2] cycloadditions.

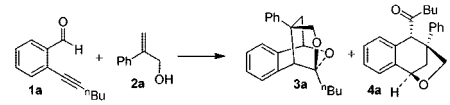


As shown in Table 1, treatment of 2-alkynylbenzaldehydes (**1a**) with 2-phenylallyic alcohol (**2a**) with $PtCl_2$/CO catalyst (10 mol %) in hot toluene (70 °C, 4 h) provided tetracyclic ketal **3a** and oxacyclic ketone **4a** in 35% and 7%, respectively; both species were obtained as a single stereoisomer. Gratifyingly, the use of 1,4-dioxane solvent greatly improved the yields of **3a** and **4a** to 62% and 12%, respectively. Other solvents gave the following yields: benzene (40% **3a**, 8% **4a**), THF (52% **3a**, 12% **4a**) and MeCN (0% for **3a** and **4a**). Commonly used gold catalysts AuCl, $AuCl_3$, and $PPh_3AuCl/AgSbF_6$ in dioxane at 23 °C led to complete consumption of starting **1a** with low yields of desired **3a** (<14%). The molecular structures of **3a** and **4a** are inferred through X-ray diffraction studies[7] of their related analogues **3i** and **6h**.

We examined the cycloaddition reactions of various aldehyde substrates **1a**−**d** with allylic alcohols **2b**−**d** to assess the generality of tetracyclic ketal synthesis; the results are depicted in Table 2. All reactions were performed in 1,4-dioxane at 80 °C (2 h) except entry 3 that employed siloxy **2d** in wet and hot toluene. Entries 1−3 showed the suitability of this cycloaddition to allylic alcohols **2b**−**2c** or siloxy species **2d** (R^2 = Me, *n*-Bu, $TMSCH_2$), providing ketals **3b**−**3d** in 61−72% yields. The cycloadditions are also extendible to various 2-alkynylbenzaldehydes **1b** and **1c**, producing ketals **3e**−**3h** efficiently (69−78% yields) except for **3i** that was obtained in 41% yield. The X-ray structure of ketal **3i** is provided in Supporting Information.

Table 3 depicts a notable change of chemoselectivity when we examined this platinum catalysis on nonaromatic enynals **5b**−**f**. On the basis of catalyst screening,[8] $PtCl_2$/CO is less efficient as $PtCl_2$/AgOTf (10/20 mol %), which implements a new annulation of these enynals with allylic alcohols **2a**−**c** in toluene at 23 °C (16 h). Particularly notable is the formation of a single stereoisomer for oxacyclic products **6a**−**g** and **6i** despite their molecular complexity;

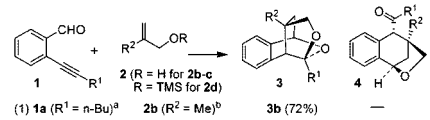
Table 1. Stereocontrolled Formation of Stable [4 + 2]-Cycloadducts



entry	catalyst (mol %)[a]	condition	product (yields)[b]
1	$PtCl_2$(10)/CO	toluene (80 °C, 4 h)	**3a** (35%), **4a** (7%)
2	$PtCl_2$(10)/CO	1,4-dioxane (80 °C, 2 h)	**3a** (62%), **4a** (12%)
3	AuCl (5)	1,4-dioxane (23 °C, 20 min)	**3a** (11%)
4	$AuCl_3$ (5)	1,4-dioxane (23 °C, 20 min)	**3a** (14%)
5	$AuClPPh_3$ (%)/$AgSbF_6$ (5)	1,4-dioxane (23 °C, 20 min)	**3a** (12%), **4a** (2%)

[a] [**1a**] = 0.17 M, **2a** (2.5 equiv). [b] Product yields are reported after silica column chromatography.

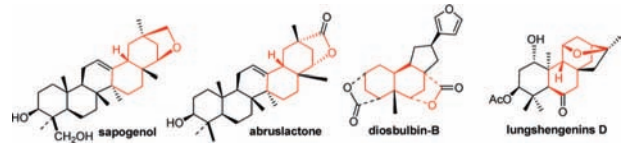
Table 2. Stereocontrolled [4 + 2] Cycloadditions of 2-Alkynylbenzaldehydes with Allylic Alcohols



(1) **1a** (R^1 = n-Bu)[a]	**2b** (R^2 = Me)[b]	**3b** (72%)	—
(2) **1a** (R^1 = n-Bu)	**2c** (R^2 = n-Bu)	**3c** (64%)	—
(3) **1a** (R^1 = n-Bu)	**2d** (R^2 = $TMSCH_2$)	**3d** (61%); **3b**(4%)	—
(4) **1b** (R^1 = Me)	**2b** (R^2 = Me)	**3e** (73%)	—
(5) **1b** (R^1 = Me)	**2c** (R^2 = n-Bu)	**3f** (69%)	—
(6) **1c** (R^1 = CH_2OBn)	**2b** (R^2 = Me)	**3g** (75%)	—
(7) **1c** (R^1 = CH_2OBn)	**2c** (R^2 = n-Bu)	**3h** (78%)	—
(8) **1d** (R^1 =)	**2b** (R^2 = Me)	**3i** (41%)	**4i** (18%)

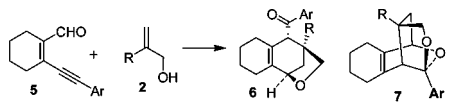
[a] [aldehyde] = 0.17 M, alcohol (2.5 equiv), 1,4-dioxane, $PtCl_2$ (10 mol %), CO (1 atm), 80 °C, 2 h. [b] Product yields are reported after silica column chromatography.

elucidation of product frameworks relies on an X-ray structure of one diastereomer of compound **6h**. The results in entries 1−2 and 5−6 reveal that the electron-rich phenylethynyl substituents of enynals **5b**−**d** gave better yields (67−80%) of annulation products **6b**, **6e**, and **6f** as compared to **6a** (61% yield) given from parent species **5a**. This new catalytic annulation is extendible to allylic alcohols **2c** and **2a** (R = *n*-Bu, Ph; entries 3−4), giving tricyclic ketones **6c**−**6d** and **6g** in reasonable yields. The use of acyclic enynal **5f** gave bicyclic ketone **6h** in 42% yield. This new annulation provides a rapid construction of the tricyclic cores of natural compounds represented by sapogenol,[9a] abruslactone,[9b] diosbulbin-B,[9c] and lungshengenins D.[9d]



10.1021/ja809560c CCC: $40.75

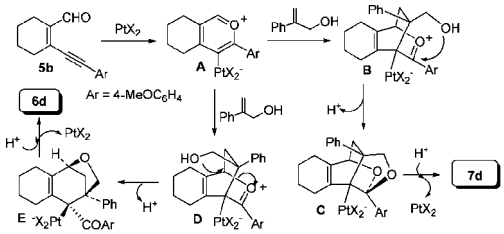
Table 3. Platinum-Catalyzed Annulation of Enynals with Allylic Alcohols



(1)	**5a** (Ar = Ph)	**2b** (R = Me)	**6a** (61%)	—
(2)	**5b** (Ar = 4-$MeOC_6H_4$)	**2b**	**6b** (80%)	—
(3)	**5b**	**2c** (R = n-Bu)	**6c** (69%)	—
(4)	**5b**	**2a** (R = Ph)	**6d** (51%)	**7d** (18%)
(5)	**5c** (Ar = 3,5-$Me_2C_6H_3$	**2b**	**6e** (67%)	—
(6)	**5d** (Ar = 3,4--$(MeO)_2C_6H_3$)	**2b**	**6f** (78%)	—
(7)	**5d**	**2a**	**6g** (71%)	—
(8)	**5e** (Ar = 4-$MeOC_6H_4$)	**2b**	**6h** (75%, dr = 1)	—
(9)	**5f** (Ar = 4-$MeOC_6H_4$)	**2b**	**6i** (42%)	—

[a] [aldehyde] = 0.17 M, alcohol (2.5 equiv), toluene, $PtCl_2$ (10 mol %), AgOTf (20 mol %), 23 °C, 16 h. [b] Product yields are reported after silica column chromatography.

Scheme 1

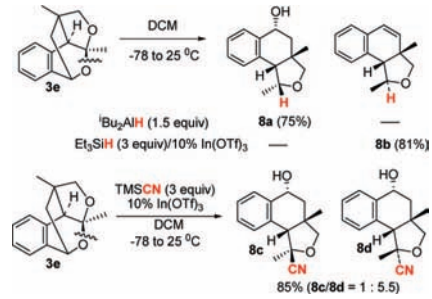


The isolation of ketal species **7d** enabled us to elucidate the formation mechanism of tricyclic oxacyclic species **6d**, generated from a subtle annulation of enynal **5b** with 2-phenylallylic alcohol. As shown in Scheme 1, a minor proportion of pyrilium **A** undergoes [4 + 2]-cycloaddition with the *si*-face of allylic alcohol, giving intermediate **B** with a tethered alcohol to trap this species through formation of ketal species **C** that ultimately gives observed ketal **7d**. We envisage that a major proportion of pyrilium species **A** undergoes cycloaddition with the *re* face of allylic alcohol to give adduct **D**, of which the tethered alcohol facilitates dissociation of the ketone via an intramolecular S_N2 attack, producing species **E** with controlled stereochemistry. With this reaction model, we conclude that the distinct pathways in Tables 2 and 3 stem from separate diastereofacial faces in the cycloadditions of allylic alcohols with benzopyrilium and pyrilium intermediates, arising from 2-alkynylbenzaldehydes **1a**−**d** and enynals **5a**−**f**, respectively.

Scheme 2 shows selected examples for stereocontrolled cleavage of the ketal functionality of species **3e**. Treatment of this ketal with $^{i}Bu_2AlH$[10] (1.5 equiv) gave fused tricyclic tetrahydrofuran **8a** in 75% yield. With our own efforts, we found that Et_3SiH (3 equiv)/10% $In(OTf)_3$ and TMSCN (3 equiv)/10% $In(OTf)_3$ effected cleavage of the ketal ring of species **3a**, with retention of stereochemistry, giving **8b** (81%) and **8d** (ca. 72%) exclusively.

Before this work, the [4 + 2]-cycloadducts from benzopyriliums (or pyriliums) and alkenes are merely a hypothetic intermediate without actual use. Our new strategy to intercept [4 + 2]-cycload-

Scheme 2



ducts involves the use of 2-substituted allylic alcohols. For nonaromatic enynals, we obtained distinct tricyclic oxacyclic ketones due to occurrence of a new annulation reaction. The values of such cycloadditions and annulations are reflected by their high diastereoselectivities and chemoselectivities. New approaches to intercept [4 + 2]-cycloadducts from benzopyriliums and alkynes are under current investigations.[11]

Acknowledgment. The authors thank to the National Science Council, Taiwan for supporting this work.

Supporting Information Available: Experimental procedures, X-ray crystallographic data of compounds **3i** and **6h**, NMR spectra, and spectra data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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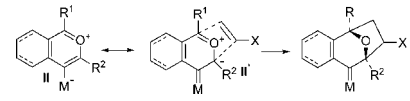
(6) Benzopyrilium **II** is also characterized by a carbenoid carbonyl ylide form **II′**, which undergoes [3 + 2]-cycloaddition reaction with alkenes, ultimately giving stable oxacyclic compounds. Such [3 + 2] cycloadditions are applicable to enol ethers or 2-alkynylbenzaldehydes of special types; see: (a) Kusama, H.; Funami, H.; Shido, M.; Hara, Y.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 2709. (b) Oh, C. H.; Lee, J. H.; Lee, S. J.; Kim, J., II; Hong, C. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 7505. (c) Shin, S.; Gupta, A. K.; Rhim, C. Y.; Oh, C. H. *Chem. Commun.* **2005**, 4429. .



(7) Crystallographic data of compounds **3i** and **6h** are provided in Supporting Information.

(8) Catalyst screening for the transformation of enynal **5a** into oxacyclic ketone **6a** is provided in Table S1 (Supporting Information).

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(11) Distinct oxacyclic species were produced from 2-alkynylbenzaldehydes, water, and 2-substituted allylsilanes using $PtCl_2$/CO catalyst, see: Bhunia, S.; Wang, K.-C.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2008**, *47*, 5063.

JA809560C