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Metal-Catalyzed Cascade Rearrangements of 3-Alkynyl Flavone Ethers

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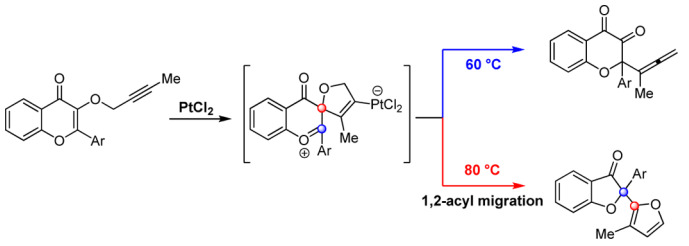
ABSTRACT



Metal-mediated rearrangements of 3-alkynyl flavone ethers are reported. The overall process involves 5-*endo* enyne cyclization to a platinum-containing spiro-oxocarbenium intermediate which may be trapped with methanol to produce spirodihydrofurans or further rearranged to afford either allenyl chromanediones or benzofuranones.

As part of our interest in the chemical reactivity of 3-flavone ethers, we have reported the scandium triflate catalyzed Claisen rearrangement of 3-allyloxyflavone ethers such as **1** to access 3,4-chromanediones **2**.[1] In the current study, we investigated the possibility for metal-catalyzed alkynyl-Claisen (Saucy–Marbet) rearrangements of the corresponding 3-alkynyl flavone ethers **3** to access allenyl-chromanediones **4**. Use of transition metal catalysts such as Au(I),[2] Ag(I),[3] Pd(II),[4] Rh(I),[5] Cu(I),[6] and Fe(III)[7] for alkynyl-Claisen rearrangements has been reported. Subsequent one-pot cascade reactions to access heterocycles including furans, pyrroles, 2*H*-pyrans, and dihydropyridines have also been reported by the Kirsch[2b,3b–3d] and Jiang laboratories.[4b,6,7] Moreover, Kozlowski and co-workers have reported the first asymmetric Saucy–Marbet rearrangement of propargyl-substituted indoles to afford allenyl oxindoles or spirolactones

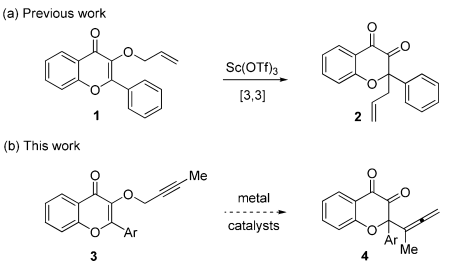


Figure 1. Metal-catalyzed rearrangement of 3-flavone ethers.

(1) Marie, J.-C.; Xiong, Y.; Min, G. K.; Yeager, A. R.; Taniguchi, T.; Berova, N.; Schaus, S. E.; Porco, J. A., Jr. *J. Org. Chem.* **2010**, *75*, 4584–4590.

(2) (a) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979. (b) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925–3927. (c) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132–8133. (d) Mauleón, P.; Krinsky, J. L.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 4513–4520.

(3) (a) Grissom, J. W.; Klingberg, D.; Huang, D.; Slattery, B. J. *J. Org. Chem.* **1997**, *62*, 603–626. (b) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151–2153. (c) Menz, H.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 4795–4797. (d) Harschneck, T.; Kirsch, S. F. *J. Org. Chem.* **2011**, *76*, 2145–2156.

(4) (a) Nevado, C.; Echavarren, A. M. *Tetrahedron* **2004**, *60*, 9735–9744. (b) Huang, H.; Jiang, H.; Cao, H.; Zhao, J.; Shi, D. *Tetrahedron* **2012**, *68*, 3135–3144.

(5) (a) Saito, A.; Kanno, A.; Hanzawa, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3931–3933. (b) Okazaki, E.; Okamoto, R.; Shibata, Y.; Noguchi, K.; Tanaka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 6722–6727.

(6) Cao, H.; Jiang, H.; Yao, W.; Liu, X. *Org. Lett.* **2009**, *11*, 1931–1933.

(7) Jiang, H.; Yao, W.; Cao, H.; Huang, H.; Cao, D. *J. Org. Chem.* **2010**, *75*, 5347–5350.

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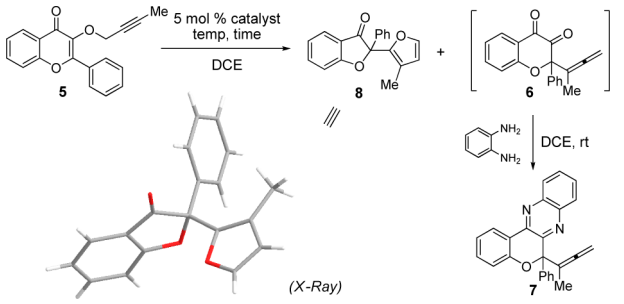
Table 1. Metal Catalyst Screening



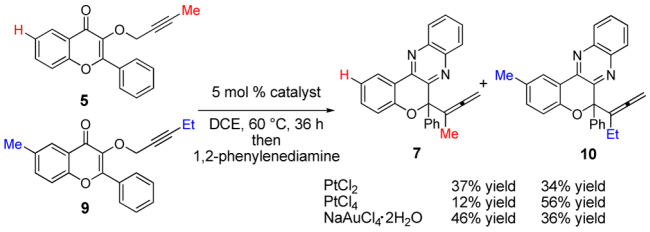
entry	metal	t (°C)	time (h)	yield 7	yield 8	yield 5
1	$AuCl_3$	60	36	53%	14%	33%
2	$NaAuCl_4 \cdot 2H_2O$	60	36	50%	trace	–
3	$NaAuCl_4 \cdot 2H_2O$	80	60	74%	trace	–
4	$PtCl_2$	60	36	21%	–	60%
5	$PtCl_4$	60	36	40%	28%	24%
6	$PtCl_2$	80	60	–	53%[a]	–
7	$PtCl_4$	80	60	–	44%[a]	–
8	$Rh_2(tfa)_4$	80	36	–	24%[a]	–

[a] The remaining mass balance is the cleavage product 3-hydroxyflavone.

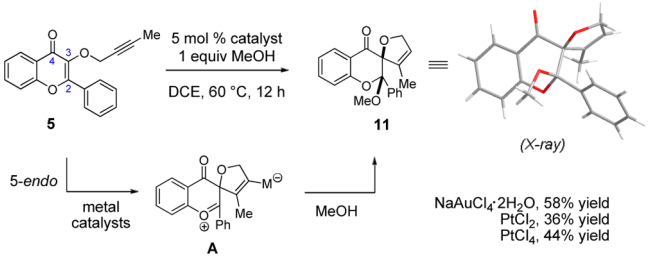
catalyzed by Pd(II)/BINAP.[8] In this Communication, we report metal-catalyzed rearrangements of 3-alkynyl flavone ethers which led to the identification of an unexpected cascade rearrangement pathway.

We began our evaluation of the alkynyl Claisen rearrangement of 3-alkynyl flavone ether **5** with a series of alkynophilic metals (Table 1). Among a panel of catalysts screened, $AuCl_3$ was found to catalyze the reaction to produce allenyl 3,4-chromanedione **6** which was condensed with 1,2-phenylenediamine[1] to provide chromenoquinoxaline **7**. Aurate salts proved to be efficient catalysts; in particular, 5 mol % of $NaAuCl_4 \cdot 2H_2O$ at elevated temperatures cleanly catalyzed the rearrangement of substrate **5** which was followed by diamine condensation to afford **7** in 74% yield (entry 3). In addition to the allene **7**, a small amount of furanyl benzofuranone **8** (*vide infra*) was also observed in the $AuCl_3$-catalyzed reaction (entry 1). The structure of **8** was confirmed by X-ray crystal structure analysis[9] (Table 1). Use of platinum catalysis also led to the formation of **8**. At 60 °C, $PtCl_4$ afforded both **7** (40%) and **8** (28%) (entry 5).[10] At a higher reaction temperature, $PtCl_2$ was highly efficient in producing benzofuranone **8**.

Scheme 1. Crossover Experiments



Scheme 2. Intermolecular Trapping of an Oxocarbenium Intermediate



$Rh_2(tfa)_4$[11] also promoted the rearrangement to afford **8** in 24% yield along with a significant amount of propargyl ether cleavage to yield 3-hydroxyflavone as a side product.[9] Rare earth triflate catalysts ($Sc(OTf)_3$ and $La(OTf)_3$) which were found to be workable for 3-allyloxyflavone ethers[1] were not effective for substrates such as **5**.[9]

In order to probe the reaction mechanism, crossover experiments were conducted to exclude the possibility of an intermolecular reaction pathway (Scheme 1). In the event, rearrangement of an equimolar mixture of butynyl ether **5** and pentynyl ether **9** in the presence of metal catalysts ($PtCl_2$, $PtCl_4$, or $NaAuCl_4$, 60 °C) resulted in the sole production of chromenoquinoxalines **7** and **10** after condensation with 1,2-phenylenediamine. The absence of crossover products by mass spectrometric[9] analysis of the crude reaction mixture strongly suggests an intramolecular pathway as opposed to an ion pair mechanism.[1,12]

Further mechanistic insights were gained by treatment of substrate **5** with Au(III) or Pt catalysts in the presence of methanol which afforded spirodihydrofuran **11**[9] as a single diastereomer (36–58% yield, Scheme 2). The formation

(8) (a) Cao, T.; Deitch, J.; Linton, E. C.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 2448–2451. (b) Cao, T.; Linton, E. C.; Deitch, J.; Berritt, S.; Kozlowski, M. C. *J. Org. Chem.* **2012**, *77*, 11034–11055.

(9) See Supporting Information for complete experimental details.

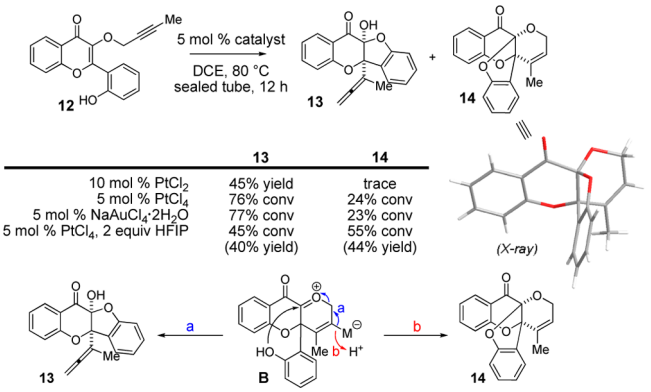
(10) For $PtCl_2$- and $PtCl_4$-catalyzed hydroarylation of alkynes, see: Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055–1058.

(11) Gainer, M. J.; Bennett, N. R.; Takahashi, Y.; Looper, R. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 684–687.

(12) For a representative crossover study, see: Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 2603–2605.

(13) For transition-metal-catalyzed 5-*endo* cyclization of alkynes and 1,5-enynes, see: (a) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350–5352. (b) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963. (c) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991–5994. (d) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1141–1144. (e) Brazeau, J.-F.; Zhang, S.; Colomer, I.; Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 2742–2749.

Scheme 3. Intramolecular Trapping of an Oxocarbenium Intermediate

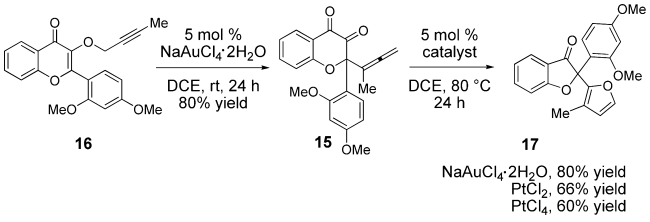


of product **11** indicates that the metal catalysts preferentially activate the alkyne of flavone ether substrates such as **5** toward 5-*endo*[13] and not 6-*endo* enyne cyclization. In the case of $PtCl_4$ additional bidentate coordination of the metal catalyst to the C-3 flavone ether and C-4 carbonyl oxygens[14] may contribute to lower nucleophilicity at C-2, thereby rendering attack at C-3 more preferable to produce platinum-containing oxocarbenium intermediate **A**[15] which afforded spirodihydrofuran **11** after reaction with methanol. The observed diastereoselectivity may be explained by steric shielding of the β face of the oxonium intermediate by the vinyl methyl group, leading to diastereoselective addition of methoxide to the α face.[9]

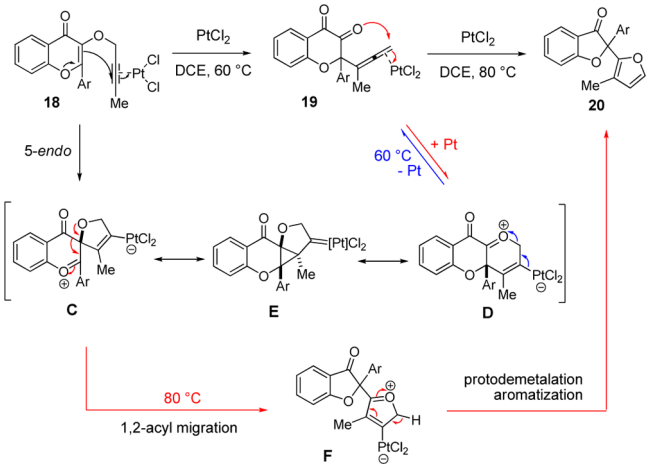
We also evaluated a 3-alkynyl flavone ether substrate bearing an internal nucleophile (Scheme 3). Treatment of 2′-hydroxyflavone ether **12** with $PtCl_2$ afforded allene **13** (45%) along with a trace amount of the bridged dihydropyran product **14**, the structure of which was confirmed by X-ray crystal structure analysis.[9] Both **13** and **14** are presumably derived from intramolecular trapping of oxocarbenium **B** (*vide infra*) by the adjacent 2′-hydroxyl group. Use of $PtCl_4$ and $NaAuCl_4 \cdot H_2O$ as catalysts favored the formation of **14**. Eventually, we found that addition of 1,1,1,2,2,2-hexafluoroisopropanol (HFIP) as the proton source[16] provided tetracycle **14** in 44% yield, conceivably by promoting protodemetalation (Scheme 3, pathway **b**) versus elimination (pathway **a**).

Additional mechanistic information was also obtained from allenyl chromanedione substrate **15**, derived from alkynyl flavone ether **16** using Au(III)-catalyzed rearrangement. When **15** was resubjected to rearrangement conditions at 80 °C, benzofuranone **17** was isolated in 60−80% yield (Scheme 4), suggesting that allenyl chromanedione substrates may also participate in the metal-

Scheme 4. Preparation and Rearrangement of an Allenyl Chromanedione



Scheme 5. Proposed Mechanistic Pathway



catalyzed cycloisomerization cascade to produce benzofuranone products (Scheme 5).[17]

Based on our experimental results, we propose the overall mechanistic pathway shown in Scheme 5. Following initial 5-*endo* enyne cyclization[18] of alkynyl flavone ether **18**, the resulting platinum-containing spiro-oxocarbenium intermediate **C** may undergo pinacol-type 1,2-rearrangement[19] to form dipole **D**,[20] possibly *via* a cyclopropyl platinacarbene intermediate **E**.[21] Dipole **D** may further fragment to yield allenyl chromanedione **19** through platinum dissociation

(14) Tang, H.; Wang, X.; Yang, S.; Wang, L. *Rare Met.* **2004**, *23*, 38–42.

(15) Li, G.; Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 6944–6945.

(16) Roth, K. E.; Blum, S. A. *Organometallics* **2010**, *29*, 1712–1716.

(17) For platinum- and gold-catalyzed 6-*endo* cycloisomerization of allenes, see: (a) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485–4488. (b) Kong, W.; Fu, C.; Ma, S. *Chem. Commun.* **2009**, *0*, 4572–4574.

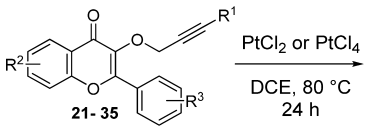
(18) For reviews on metal-catalyzed enyne cycloisomerization, see: (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296. (b) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 5916–5923. (c) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847–7870. (d) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (e) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315.

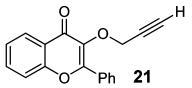
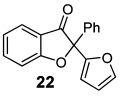
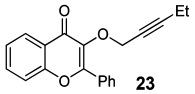
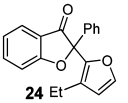
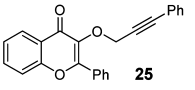
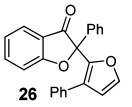
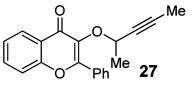
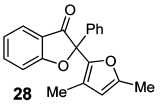
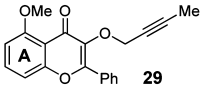
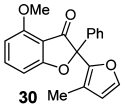
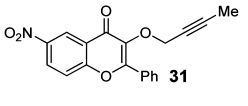
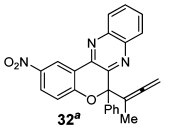
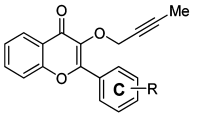
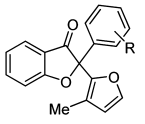
(19) For examples of metal-catalyzed cycloisomerization involving pinacol-type rearrangement, see: (a) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2310–2313. (b) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398–6399. (c) Tang, J.; Bhunia, S.; Sohel, S. M. A.; Lin, M.; Liao, H.; Datta, S.; Das, A.; Liu, R. *J. Am. Chem. Soc.* **2007**, *129*, 15677–15683. (d) Crone, B.; Kirsch, S. F. *Chem.—Eur. J.* **2008**, *14*, 3514–3522. (e) Shu, X.-Z.; Liu, X.-Y.; Ji, K. G.; Xiao, H.-Q.; Liang, Y.-M. *Chem.—Eur. J.* **2008**, *14*, 5282–5289.

(20) Kusama, H.; Suzuki, Y.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2006**, *8*, 895–897.

(21) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757–5766.

Table 2. Substrate Scope



entry	substrate	product	yield%
1			$PtCl_2$, 20% $PtCl_4$, 10%
2			$PtCl_2$, 43% $PtCl_4$, 31%
3			$PtCl_2$, 31% $PtCl_4$, 43%
4			$PtCl_2$, 70% $PtCl_4$, 65%
5			$PtCl_2$, 80% $PtCl_4$, 64% (12 h)
6			$PtCl_2$, 18% $PtCl_4$, 12% (12 h)
7	 **33** R = 2'-CF_3 **35** R = 2'-MeO **16** R = 2',4'-MeO	 **34** R = 2'-CF_3 **36** R = 2'-MeO **17** R = 2',4'-MeO	$PtCl_2$ **34**: NR **36**: 53% (48 h) **17**: 67% (24 h)

[a] Products obtained after condensation with 1.5 equiv of 1,2-phenylenediamine.

(Scheme 5, blue arrow). At elevated temperatures, intermediate **C** may rearrange *via* a formal 1,2-acyl migration to obtain oxocarbenium **F**[22] which after protodemetalation and aromatization may afford **20** as the thermodynamic product (Scheme 5, red arrow). Conceivably, allenyl chromanedione **19** may also undergo metal catalyzed 6-*endo* cycloisomerization[17] to yield oxocarbenium intermediates **D** and **C**, which following similar pathways may produce benzofuranone **20** (Scheme 5, red arrow).

Regarding substrate scope, substitutions at the terminal position of the alkyne such as hydrogen as well as alkyl and phenyl groups (Table 2, **21**, **23**, **25**, entries 1−3) were tolerated, although substrates with terminal alkynes suffered low yields from side reactions presumably due to metal vinylidene formation. Flavone ether **27** derived from a secondary propargylic alcohol was also reactive affording the 2,3,5-trisubstituted furanyl benzofuranone **28** in high yield (entry 4). 5-Methoxy substrate **29**, with increased electron density on the flavone A-ring, underwent smooth acyl migration to afford benzofuranone **30** in high yield (entry 5). In contrast, electron-withdrawing groups found in substrates such as **31** disfavored acyl migration. In this instance, only allenyl chromenoquinoxaline **32** was isolated following diamine condensation even at an elevated reaction temperature (entry 6). Electron-rich C-rings found in substrates **16** and **35** favored the cascade process producing benzofuranones by increasing nucleophilicity at C-3 and stabilizing the forming positive charge in the proposed spiro-oxocarbenium intermediate **C** (entry 7, *cf*. Scheme 5). In contrast, the electron-poor 2′-trifluoromethyl flavone ether **33** was not a useable substrate and did not afford appreciable amounts of benzofuranone **34** (entry 7).

In summary, evaluation of the metal-catalyzed alkynyl Claisen (Saucy−Marbet) rearrangements of 3-alkynyl flavone ethers led to the discovery of a 1,2-acyl migration cascade which afforded novel furanyl benzofuranones. Mechanistic studies have revealed that the rearrangement is likely initiated by 5-*endo* enyne cyclization to a platinum-containing spiro-oxocarbenium intermediate, which may be intercepted by methanol to produce spirodihydrofurans or further rearranged to afford allenyl chromanediones at 60 °C and benzofuranones at elevated reaction temperatures. Further studies including asymmetric reaction development and diverse nucleophilic trapping of spiro-oxocarbenium intermediates are currently in progress and will be reported in future publications.

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Supporting Information Available. Experimental procedure and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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