

# Generation of $\alpha,\beta$ -Unsaturated Platinum Carbenes from Homopropargylic Alcohols: Rearrangements to Polysubstituted Furans

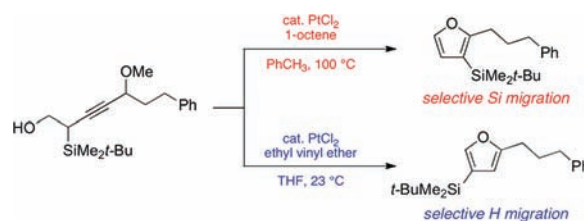
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## ABSTRACT



A number of diversely substituted furans are synthesized via a cycloisomerization process that goes through a unique metal carbene species. Both ligand structure and the nature of the leaving group are evaluated. The characteristics of the carbene intermediate can be modulated, resulting in highly selective hydrogen or silicon group migrations.

Cycloisomerizations that are initiated by the coordination of an alkyne to a  $\pi$ -acidic metal—often Au or Pt complexes—have been well-documented over the past decade.<sup>1</sup> The general processes, typically commencing with nucleophilic addition to the activated alkyne, involve a number of metal-associated intermediates. These metal-based species display a wide range of characteristics, spanning from carbene-like to vinylmetal-like, among several others. Our capacity to understand these intermediates, and consequently modulate their reactivity, would greatly enable the development of synthetically useful transformations. Proceeding with that directive in alignment with our investigations of alkyne

activation using platinum catalysis,<sup>2</sup> we have been interested in new modes of Pt carbene generation. Herein we describe our studies in this area in the context of a unique, mild cycloisomerization to form polysubstituted furans, with the ability to achieve selective and predictable substitution patterns.<sup>3–5</sup> We also illustrate the likely intermediacy of platinum carbenes by demonstrating chemoselective migrations<sup>4a,b</sup> simply based on the coordination environment established by the reaction conditions.

In a conventional reaction manifold, alkyne activation is followed by attack from a nucleophilic species. For the large majority of cases, this nucleophilic attack will generate a resulting electrophile (e.g., a carbocation arising from a nucleophilic alkene), which is then captured by the electron-rich metal center.<sup>1b,f,j</sup> By appropriately positioning a leaving group at the propargylic site (i.e., X, Scheme 1) as an alternative electrophilic component, however, coordination of the alkyne by a  $\pi$ -acidic metal complex could induce a stepwise pathway leading to carbene intermediate

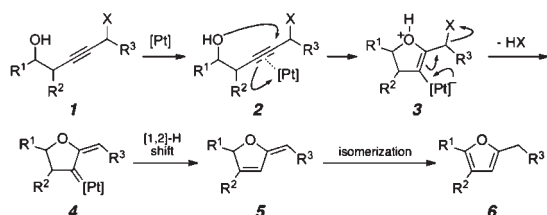
(1) For select reviews, see: (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (c) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (d) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (e) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (f) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (g) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (h) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (i) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903. (j) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.

(2) Rooke, D. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11926–11928.

(3) For select reviews on heterocycle synthesis based on cycloisomerizations, see: (a) Kirsch, S. F. *Synthesis* **2008**, 3183–3204. (b) See ref 1h.

4.<sup>6</sup> A 1,2-hydrogen shift would then occur to form alkene **5**, which would subsequently isomerize<sup>4c-g</sup> to the thermodynamically stable furan (**6**).<sup>7</sup> On the basis of this mechanistic hypothesis, we anticipated the appropriate conditions could facilitate carbene formation, and perhaps also dictate the reactivity of this carbene.

Scheme 1



As a test case for this study, we synthesized homopropargylic alcohol **7**<sup>8</sup> and subjected it to a variety of alkyne activation conditions. We found that PtCl<sub>2</sub>, in combination with an olefinic ligand, produced furan **8** in a range of yields (Table 1).<sup>9</sup> The alkene ligand was necessary for optimal reactivity, as ligands such as Et<sub>3</sub>N, pyridine, PPh<sub>3</sub>, and CO were less effective. Based on our observations of the differential reactivity of 0.05 and 1.0 equiv alkene ligand, we

(4) For select examples of metal-catalyzed cyclization approaches to furans, see: (a) Dudnik, A. S.; Xia, Y.; Li, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 7645–7655. (b) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440–1452. (c) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966–5968. (d) Seiler, B.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 13089–13102. (e) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687–7692. (f) Hashmi, A. S. K.; Schwarz, L.; Choi, J. –H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285–2288. (g) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409–5412. (h) Yoshida, M.; Al-Amin, M.; Shishido, K. *Synthesis* **2009**, 2454–2466. (i) Barluenga, J.; Riesgo, L.; Vicente, R.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2008**, *130*, 13528–13529. (j) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925–3927. (k) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531–4534. (l) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165. (m) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450–3451. (n) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655–3661. (o) Aponick, A.; Li, C. –Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624–4627. (p) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002–5005 and the references therein.

(5) For select reviews on regioselective syntheses of polysubstituted heterocycles, see: (a) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095–3110. (b) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076–2080. (c) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850–852. (d) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238–6241. (e) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955–2020.

(6) A recent report described a similar mode of carbene generation toward the formation of polycyclic compounds via [3 + 2] cycloadditions. See: Saito, K.; Sogou, H.; Suga, T.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 689–691.

(7) For related cycloisomerizations of alkynyl azides, see: (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261. (b) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5349–5352. (c) Xia, Y.; Huang, G. *J. Org. Chem.* **2010**, *75*, 7842–7854. (d) Wetzell, A.; Gagosz, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7354–7358.

(8) See Supporting Information for experimental details.

(9) For select examples of the use of alkene ligands in platinum catalysis, see: (a) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423–15430. (b) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022–15023.

reasoned that the variance was in part due to inconsistent solubilization of the catalyst.<sup>10</sup> Ultimately, we found that readily soluble Zeise's dimer ([C<sub>2</sub>H<sub>4</sub>)PtCl<sub>2</sub>)<sub>2</sub>) was the optimal catalyst for this transformation, affording furan **8** in 90% isolated yield at 1.5 mol % catalyst loading at room temperature in 5 min.

Table 1. Optimization for Pt-Catalyzed Furan Formation

entry	ligand	equiv	time (h)	yield (%) <sup>a</sup>
1	none	N/A	7–20	83
2	CO	1.0 atm	24	0
3	Et <sub>3</sub> N	0.05	72	3
4		1.0	72	0
5	pyridine	0.05	72	20
6		1.0	72	0
7	PPh <sub>3</sub>	0.05	4	65
8		1.0	30	0
9	methyl acrylate	0.05	14	63
10		1.0	7.5	90
11	ethyl vinyl ether	0.05	8	75
12		1.0	1.5	82
13	1-octene	0.05	3	83
14		1.0	1	87
15		0.05	66	32
16		1.0	48	25
17		0.05	66	31
18		1.0	1	86
19		0.05	24	54
20		1.0	2.5	91
21	[(C <sub>2</sub> H <sub>4</sub> )PtCl <sub>2</sub> ) <sub>2</sub> (1.5 mol %) <sup>b</sup>	N/A	5 min	90(90 <sup>c</sup> )

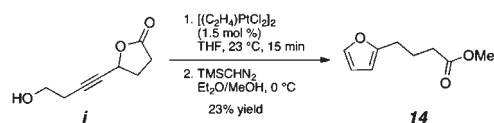
<sup>a</sup> Yield determined by GC with 4,4'-*tert*-butylbiphenyl as the internal standard. <sup>b</sup> Used instead of PtCl<sub>2</sub>. <sup>c</sup> Isolated yield.

The nature of the propargylic leaving group is important. As depicted in Table 2, strongly dissociative leaving groups caused a noticeable erosion in yield. Esters were also ineffective (entry 4), as competing known processes of propargylic carboxylates were likely occurring.<sup>11,12</sup> In all of these cases, the strong leaving group would be prone to immediate ionization once the alkyne coordinates to the

(10) The variable times required for the ligandless conditions (entry 1) also suggest complications due to solubilization.

(11) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750–2752.

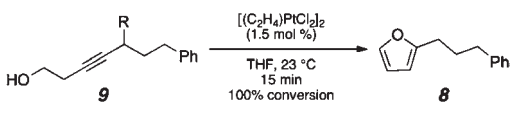
(12) Lactone **i**, which is geometrically constrained from undergoing an analogous [3,3]-rearrangement, did produce the furan product. Yields were still modest, however, underscoring the importance of a weaker leaving group being necessary for generating these carbene species effectively.



(13) The efficacy of alkoxy leaving groups could arise from a facile proton transfer process that generates an oxonium leaving group. Additionally, the benign byproduct alcohol could be inconsequential relative to the strongly acidic byproducts that would arise from the substrates with more electron-withdrawing leaving groups.

metal center, which would conflict with the desired reactivity. Alkoxy groups appeared to be optimal in these systems, only capable of ionization once the putative vinylplatinum species is generated.<sup>13,14</sup> It should be noted that a hydroxyl moiety was an adequate leaving group (entry 5), although the yields were somewhat diminished.

**Table 2.** Leaving Group Influence on Reactivity

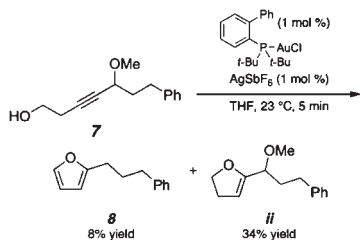


entry	R	yield (%) <sup>a</sup>
1	Cl	5
2	OTs	37
3	OSO <sub>2</sub> CH <sub>3</sub>	61
4	OAc	9
5	OH	84
6	OMe	90 <sup>b</sup>

<sup>a</sup>Determined by GC with 4,4'-di-*tert*-butylbiphenyl as internal standard. <sup>b</sup>Isolated yield.

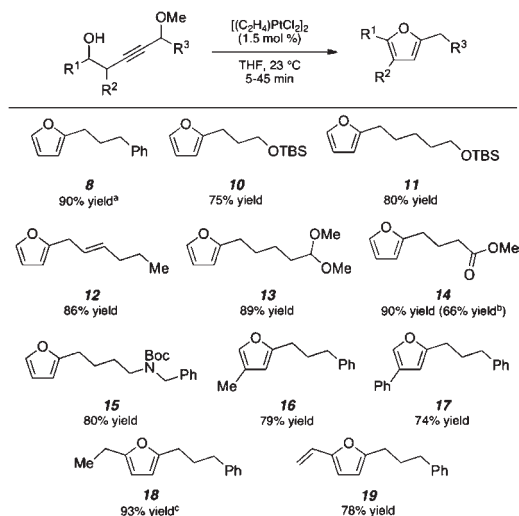
With the optimal cycloisomerization conditions in hand, a diverse array of furans were synthesized (Figure 1). Mono-, di-, and trisubstituted furans with differential substitution patterns were readily accessed in good to excellent yields. The reaction tolerates silyl ethers, esters, carboxylic acids, alkenes, and acetals, establishing its high functional group compatibility. The formation of furan **12** highlights the mild nature of the transformation, as the unconjugated alkene was formed in good yield without any observable isomerization. Branching at the nucleophilic alcohol was also tolerated, although the reaction required elevated temperatures in cases of increased steric encumbrance (e.g., **18**). Stereochemical orientation across a cyclohexane ring was inconsequential, as both alcohols **20** and **21** cleanly isomerized to form fused furan **22** (eq 1).

(14) (a) Gold catalysts also displayed reactivity, but the hydroalkoxylation product (**ii**) was the major component. This observation is consistent with the lesser metal-based donation that is generally seen in catalytic Au systems relative to Pt. For a relevant discussion, see: Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403.

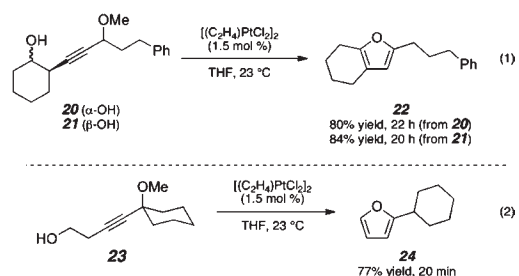


(b) We considered the possibility that compound **ii** was an intermediate toward the furan product under the Pt-catalyzed conditions. Although enol ether **ii** could be observed as a product at low temperature, subjecting it to the reaction conditions, as well as multiple variants of these conditions, never produced furan **8**. See the Supporting Information for details.

Finally, a tertiary ether was also a suitable substrate, leading to  $\alpha$ -branched 2-substituted furan **24** (eq 2).



**Figure 1.** Pt-catalyzed cycloisomerizations to furans. <sup>a</sup>Using 0.5 mol % [(C<sub>2</sub>H<sub>4</sub>)PtCl<sub>2</sub>]<sub>2</sub>. <sup>b</sup>Using carboxylic acid starting material; isolated after subsequent treatment with TMSCHN<sub>2</sub>. <sup>c</sup>Reaction performed at 50 °C.

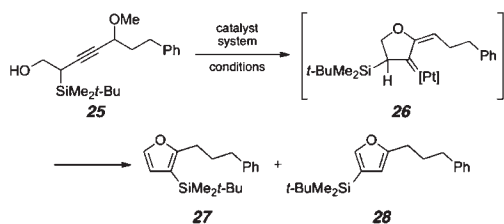


Toward further probing the nature of the putative intermediacy of the platinum carbene, we then evaluated migratory aptitudes based on the platinum catalyst precursor. On the basis of our and others' silyl migration studies,<sup>2,4a</sup> we hypothesized that an  $\alpha$ -silyl group would be capable of migration as the termination step of these cycloisomerizations.<sup>15,16</sup> To that end, propargylsilane **25**, which we anticipated would lead to intermediate carbene **26**, was subjected to a number of catalytic conditions (Table 3). There was a noticeable solvent effect; employment of toluene favored furan **27**, arising from silicon group migration (entry 1), whereas the use of THF favored the formation of furan **28**, originating from hydrogen migration (entry 2). Interestingly, we found that the conditions could be optimized in both directions to strongly favor a specific group migration while

(15) For studies of 1,2-Si migrations to carbene centers, see: (a) Creary, X.; Butchko, M. A. *J. Org. Chem.* **2002**, *67*, 112–118. (b) Creary, X.; Butchko, M. A. *J. Org. Chem.* **2001**, *66*, 1115–1121. (c) Creary, X.; Wang, Y. –X. *Tetrahedron Lett.* **1989**, *30*, 2493–2496.

minimizing the formation of desilylated furan **8**. Ultimately we discovered that conditions consisting of PtCl<sub>2</sub> in conjunction with 1-octene in toluene at 100 °C afforded furan **27** in 16:1 selectivity (entry 6), while PtCl<sub>2</sub> with ethyl vinyl ether in THF at 23 °C provided furan **28** in 8.5:1 selectivity (entry 12). To the best of our knowledge, this is the first example of manipulating the migratory selectivity of different groups to platinum carbene species.

**Table 3.** Si vs H Migration



entry	catalyst <sup>a</sup>	solvent, temp	additive (equiv)	time	ratio (27:28) <sup>b</sup>
1	[(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub> PtCl <sub>2</sub> ] <sub>2</sub>	PhCH <sub>3</sub> , 23 °C		1 h	1.5:1
2	[(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub> PtCl <sub>2</sub> ] <sub>2</sub>	THF, 23 °C		30 min	1:3.0
3	PtCl <sub>2</sub>	PhCH <sub>3</sub> , 23 °C	1-octene (1.0)	2 h	2.5:1
4	PtCl <sub>2</sub>	PhCH <sub>3</sub> , 23 °C	1-octene (1.0)	1.5 h	3.6:1
5	PtCl <sub>2</sub>	PhCH <sub>3</sub> , 60 °C	1-octene (1.0)	10 min	10:1
6	PtCl <sub>2</sub>	PhCH <sub>3</sub> , 100 °C	1-octene (1.0)	5 min	16:1 (92% <sup>c</sup> )
7	PtCl <sub>2</sub>	THF, 23 °C		70 h	1:3.0 <sup>d</sup>
8	PtCl <sub>2</sub>	THF, 50 °C		5 h	1:2.1 <sup>d</sup>
9	PtCl <sub>2</sub>	1,4-dioxane, 100 °C		5 min	6.0:1 <sup>d</sup>
10	PtCl <sub>2</sub>	THF, 23 °C	PPh <sub>3</sub> (0.05)	24 h	1:2.0 <sup>d</sup>
11	PtCl <sub>2</sub>	THF, 23 °C	1-octene (1.0)	2 h	1:9.4 <sup>d</sup>
12	PtCl <sub>2</sub>	THF, 23 °C	ethyl vinyl ether (1.0)	8 h	1:8.5 (83% <sup>c</sup> )

<sup>a</sup> 1.5 mol % [(C<sub>2</sub>H<sub>4</sub>)PtCl<sub>2</sub>]<sub>2</sub> or 5 mol % PtCl<sub>2</sub>. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Isolated yield. <sup>d</sup> 10–20% desilylated furan (i.e., **8**) was also observed.

We currently rationalize this set of outcomes based on the nature of the carbene metal center in each set of

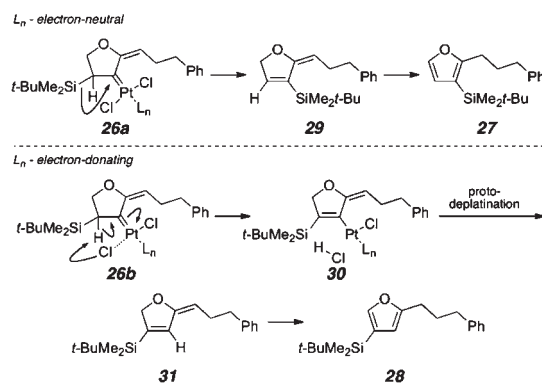
(16) For a review on the synthetic utility of silylfurans, see: Keay, B. A. *Chem. Soc. Rev.* **1999**, 28, 209–215.

(17) There is also a clear temperature effect in the silyl group migration. Although to a lesser degree, using an ethereal solvent such as 1,4-dioxane at 100 °C also favored silicon group migration (entry 9), illustrating a likely thermal barrier to this process.

(18) This hypothesis is consistent with DFT calculation studies evaluating the migratory processes of hydrogen and bromine in the gold-catalyzed synthesis of furans. See: Xia, Y.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. *J. Am. Chem. Soc.* **2008**, 130, 6940–6941.

conditions (Scheme 2). Gevorgyan and Li have shown that silicon groups will preferentially migrate over hydrogen when α to a gold carbene.<sup>4a</sup> The cases of predominant migration of the silicon group, using toluene at elevated temperatures, are consistent with this observation, strong evidence for the intermediacy of a carbene species. When the more Lewis basic THF is employed, however, the metal center is presumably more electron rich via solvent coordination.<sup>17</sup> Dissociation of the chloride counterion is thus facilitated, which can then assist in hydrogen removal.<sup>18</sup> Protodeplatination then occurs, resulting in a formal 1,2-hydrogen migration. Studies are currently underway to elucidate the variables that influence group migratory aptitudes.

**Scheme 2**



To summarize, homopropargylic alcohols bearing a suitable leaving group can be rearranged to form α, β-unsaturated carbenes. These intermediate species subsequently convert to polysubstituted furans in short reaction times with excellent overall yields. The required catalyst displays a notable ligand dependence, with olefin-based ligands, ethylene in particular, proving the most effective. The cycloisomerization conditions are significantly mild, without air or moisture sensitivity, and the reaction shows a wide array of functional group compatibility. We have observed an intriguing migration selectivity, where based simply on reaction conditions, hydrogen or silyl group migration is promoted. The migratory process offers strong evidence for the intermediacy of a carbene. We expect this mild entry into these interesting species will both enable further investigations and provide a platform for the development of synthetically useful transformations.

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**Supporting Information Available.** Experimental procedures, compound characterization data, and spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.