ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

# C–C bond migration in the cycloisomerization of oxygen-tethered 1,6-enynes†

Cite this: *Chem. Commun.*, 2014, **50**, 5239

Received 30th September 2013,
Accepted 26th November 2013

DOI: 10.1039/c3cc47499b

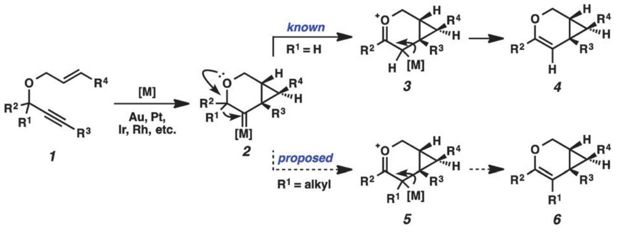
www.rsc.org/chemcomm

Susan M. Stevenson, Eric T. Newcomb and Eric M. Ferreira*

**A C–C bond migration event during the cycloisomerization of 1,6-enynes is described. Two different catalytic systems, iridium- or platinum-based, are able to induce this process. Alkyl migrations of larger rings and acyclic groups indicate that the reaction is not fully driven by the release of ring strain.**

Transformations initiated by the activation of alkynes have been extensively studied over the last decade. These reactions utilize the unique character of π-acidic metals (Au, Pt, Ir, Ga, *etc.*) to render alkynes electrophilic (*pull*) and, after attack of a nucleophile, generate an electron rich vinyl metal species which can attack various electrophiles (*push*).[1] Generally, transformations involving this *pull*/*push* type reactivity proceed through the intermediacy of a metal carbenoid.[2] Exploitation of such intermediates has allowed for a diverse array of pathways, including but not limited to: cyclopropanations,[3] oxidations,[4] C–H bond insertions,[5] and bond migrations (H, C, Si, S, *etc.*).[6] Of particular interest is the opportunity to generate new C–C bonds *via* the migration of alkyl groups. While migrations onto carbenes generated from the decomposition of diazo species have been widely explored,[7] migrations into Au and Pt carbenoids derived from alkynes are just beginning to be implemented into purposeful reaction design.

In accordance with our past research concerning the generation and reactions of Pt carbenoids in synthesis,[8] we recently described a highly enantiospecific cycloisomerization of oxygen-tethered 1,6-enynes to generate bicyclo[3.1.0]heptene derivatives.[9–11] Based on our observation of chirality transfer, we inferred that carbenoid formation occurs prior to 1,2-hydrogen migration (**1** → **3**, Scheme 1). This work further validated the generally accepted mechanism:[12] 1,2-hydrogen migration into the metal carbenoid leads to an oxocarbenium (**3**), which then undergoes demetalation to afford product **4**. Considering the relevancy of this substructure in pharmaceuticals,[13] we hoped to further utilize putative carbenoid intermediate **2** in hopes of accessing further molecular diversity. It was our hypothesis that other functional groups, such as alkyl moieties, may also migrate from a species akin to **2**. Specifically, we aimed to study the abilities and constraints of alkyl migration (**1** → **6**).[14] A recent report by Fensterbank and coworkers utilizing gold catalysis in the expansion of 4- and 5-membered rings[15] prompted us to disclose the current results of our study, wherein platinum and iridium complexes catalyze C–C bond migration events during the cycloisomerization of oxygen-tethered 1,6-enynes.[16]



Scheme 1 Proposed utilization of carbenoid intermediate.

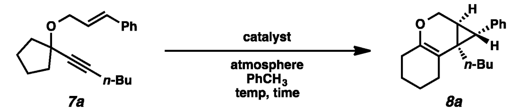
We initiated our studies on enyne **7a** with complexes that had previously been shown to catalyze 1,6-enyne cycloisomerizations. Both $PtCl_2$ and $(Ph_3P)Au(NTf_2)$ could catalyze this process, and the desired cycloisomerization product (**8a**) was generated in good yields (Table 1, entries 1, 2). We found Au catalysis afforded variable yields and the appearance of other rearrangement products, so we focused on Pt catalysis. More coordinatively saturated platinum complexes $(Ph_3P)_2PtCl_2$ and $(PhCN)_2PtCl_2$ both gave only trace amounts of product (entries 4 and 5), while performing the cycloisomerization with $PtCl_2$ at 60 °C gave product **8a** in a promising 54% yield (entry 1). An increase to 75% yield was observed when the reaction was run under an atmosphere of CO (entry 6). Using Zeise's dimer ($[(C_2H_4)PtCl_2]_2$) proved even better, and the tricycle was produced in 88% yield. Iridium-based catalysts were also proficient at achieving the desired reactivity. $[Ir(cod)Cl]_2$ at 110 °C catalyzed the cycloisomerization in 24% yield (entry 8). This increased to 37% yield when the $[Ir(cod)Cl]_2$ catalyst solution was purged with CO, and then the reaction run under an atmosphere of argon (entry 9). Under these same conditions, another iridium dimer, $[Ir(dbcot)Cl]_2$,[17]

---

*Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA. E-mail: emferr@mail.colostate.edu*

† Electronic supplementary information (ESI) available: Experimental details, characterization, spectroscopic, and crystallographic data. CCDC 963880. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc47499b

Table 1 Screening of catalytic conditions



| Entry | Catalyst (mol%) | Atmosphere | Temp (°C) | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | $PtCl_2$ (7) | Ar | 60 | 43 | 54 |
| 2 | $(Ph_3P)Au(NTf_2)$ (2.5) | Ar | 23 | 24 | 61 |
| 3 | $[Rh(CO)_2Cl]_2$ (2.5) | Ar | 110 | 16 | —[b] |
| 4 | $(Ph_3P)_2PtCl_2$ (2.5) | Ar | 60 | 72 | <5 |
| 5 | $(PhCN)_2PtCl_2$ (2.5) | Ar | 60 | 72 | <5 |
| 6 | $PtCl_2$ (7) | CO (1 atm) | 60 | 25 | 75 |
| 7 | $[(C_2H_4)PtCl_2]_2$ (2.5) | CO (1 atm) | 60 | 30 | 88 |
| 8 | $[Ir(cod)Cl]_2$ (2.5) | Ar | 110 | 60 | 24 |
| 9 | $[Ir(cod)Cl]_2$ (2.5) | CO, then Ar | 110 | 16 | 37 |
| 10 | $[Ir(dbcot)Cl]_2$ (2.5) | CO, then Ar | 110 | 3 | 68 |

[a] Isolated. [b] A complex mixture was observed.

gave product **8a** in 68% yield (entry 10). We decided to further investigate the substrate scope with both the Zeise's dimer and $[Ir(dbcot)Cl]_2$ catalytic systems, anticipating that the Pt and Ir catalysts may behave differently with specific substrates.

Utilizing these two sets of conditions, various substitution patterns were explored (Chart 1). Di- and tri-substituted alkenes were tolerated under either conditions. In general, phenyl-substituted alkenes ($R^2$ = Ph) gave higher yields of the cycloisomerization products than their alkyl-substituted counterparts. As shown in products **8k** and **8l**, electron rich and electron poor arene substituted alkynes are viable substrates under either set of conditions. Various alkene and alkyne substitutions were tolerated overall and yields were moderate to very good.

In order to further study the potential of alkyl migrations into metal carbenoids, we next examined the ring expansion of carbocycles larger and smaller than 5-membered. These results are shown in Chart 2. In 2004, Toste and coworkers discovered a gold-catalyzed cycloisomerization of carbon-tethered 1,5-enynes with ring expansion.[18] In a subsequent study,[19] substrates with larger rings (6- or 7-membered) underwent a C–H insertion process to give bis-cyclopropane containing products. With our oxygen-tethered 1,6-enyne substrates, however, no C–H insertion products were observed. These reactions generally proceeded in moderate to good yields.[20] We were surprised to find that even the expansion to produce an 11-membered ring product (**14**) was afforded in 42% yield.

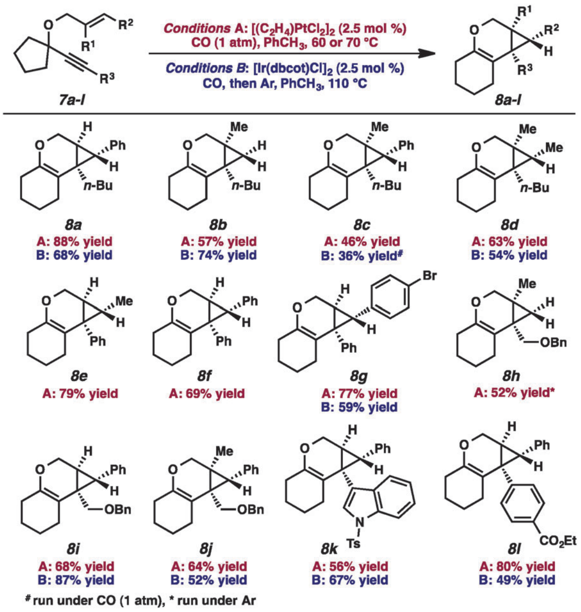


**Chart 1** Alkene and alkyne substitution evaluation.

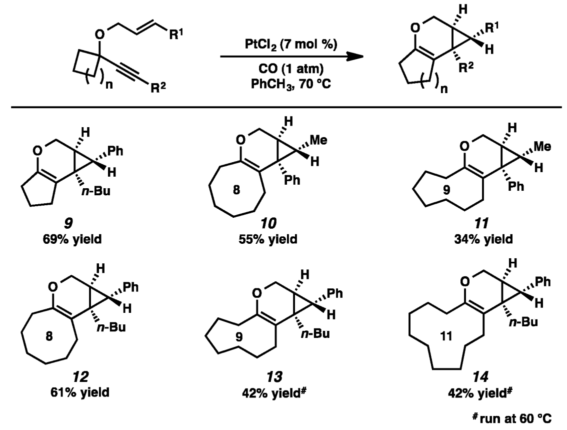
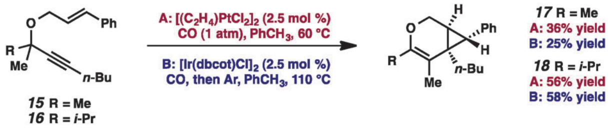


**Chart 2** Evaluation of ring expansion.

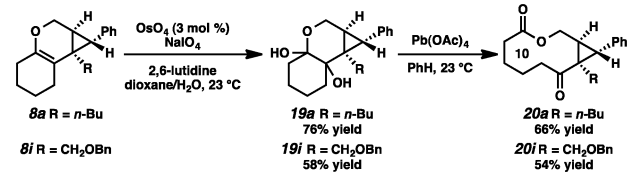
As a result of larger rings undergoing expansion under the reaction conditions, we hypothesized that strain release was not a singular driving force in our developed system. With this knowledge, the propensity of noncyclic alkyl groups to migrate into the putative carbenoid was tested. Indeed, methyl functionality was observed to shift, albeit in moderate yields (**15** → **17**, Scheme 2). When enyne **16** was subjected to Pt or Ir catalytic conditions, the smaller functional group (methyl) migrated exclusively in 56% yield and 58% yield, respectively.[21] These results highlight the ability of non-hydrogen functionalities to migrate without the thermodynamic gain of releasing ring strain.

As mentioned above, performing the Pt-catalyzed cycloisomerization under an atmosphere of CO generally increased the overall yields. Fürstner and coworkers observed an analogous effect in the $PtCl_2$-catalyzed formation of cyclobutenes.[22] They hypothesized that the π-accepting character of the CO ligand increases the electrophilicity of the Pt complex, resulting in a more facile reaction. In addition, recent computational evidence on 1,6-enynes supports that the Pt–CO complex favors mono-coordination of the alkyne over bis-coordination of both alkene and alkyne,[23] the former initiating the cycloisomerization. Both rationalizations could be applicable to our observed cycloisomerizations.

The effectiveness of our iridium systems is more curious to explain. We found that iridium dimers $[Ir(dbcot)Cl]_2$, $[Ir(cod)Cl]_2$, and $[Ir(coe)_2Cl]_2$ all afforded the desired cycloisomerization product when the reactions were run under CO, with $[Ir(dbcot)Cl]_2$ performing the best. Other iridium catalyst systems, including Vaska's



Scheme 2 Acyclic migration experiments.



Scheme 3 Oxidative cleavage to access macrolactones.

complex (IrCl(CO)(PPh$_3$)$_2$), which Shibata and coworkers had achieved success with in the cycloisomerizations of heteroatom-tethered 1,6-enynes,[10d] were much less effective in our studies.[24,25] Interestingly, bubbling CO through a solution of any of the three Ir dimers in toluene caused a dark blue precipitate to form, which dissolved upon heating. Similar observations were made by Roberto and coworkers[26] when they exposed [Ir(coe)$_2$Cl]$_2$ to CO: the metal complex changed from bright yellow to dark blue. Through IR experiments, this dark blue compound was determined to be an [Ir(CO)$_2$Cl]$_n$ polymeric complex. Based on these observations, we believe this [Ir(CO)$_2$Cl]$_n$ complex is the precatalyst generated in our cycloisomerization. The difference in reactivity of the three iridium dimers is unclear; competitive binding between the substrate and the alkene–diene precursor could be influential on reactivity. Alternatively, the [Ir(dbcot)Cl]$_2$ complex may be the most effective at generating the [Ir(CO)$_2$Cl]$_n$ precatalyst *via* the treatment with CO.

Because of the growing interest of macrocycles in the drug discovery community,[27] we envisioned that our products could easily be converted into macrolactones *via* oxidative cleavage of the cyclic enol ether. With this in mind, a two-step method to convert the tricyclic products into macrolactones was devised (Scheme 3). Reaction of tricycles **8a** and **8i** with catalytic OsO$_4$ gave diols **19a** and **19i** in 76% and 58% yield, respectively.[28] The resulting diols were then cleaved with Pb(OAc)$_4$ to give macrolactones **20a** and **20i**.

In conclusion, C–C bond migration into metal carbenoid intermediates generated through the cycloisomerization of oxygen-tethered 1,6-enynes has been described. A variety of alkene and alkyne substitutions were shown to be tolerated under Pt- and Ir-based catalytic systems. Additionally, ring expansions of up to an 11-membered ring as well as acyclic alkyl migrations were observed. The tricyclic enol ether products can be oxidatively cleaved to give macrolactones. Further investigations regarding the reactivity of these types of carbenoid intermediates are underway.

Colorado State University is acknowledged for support of this work. We acknowledge Prof. Louis Fensterbank for helpful discussions.

## Notes and references

1 (*a*) H. Schmidaur and A. Schier, *Organometallics*, 2010, **29**, 2–23; (*b*) A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410–3449; (*c*) D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395–403.

2 K. Ohe, *Bull. Korean Chem. Soc.*, 2007, **28**, 2153–2161.

3 For select examples, see: (*a*) M. J. Johansson, D. J. Gorin, S. T. Staben and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 18002–18003; (*b*) E. Mainetti, V. Mouriés, L. Fensterbank, M. Malacria and J. Marco-Contelles, *Angew. Chem., Int. Ed.*, 2002, **41**, 2132–2135; (*c*) K. Miki, K. Ohe and S. Uemura, *Tetrahedron*, 2003, **44**, 2019–2022.

4 J. Xiao and X. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 7226–7236.

5 T. de Haro and C. Nevado, *Synthesis*, 2011, 2530–2539.

6 (*a*) R. K. Shiroodi and V. Gevorgyan, *Chem. Soc. Rev.*, 2013, **42**, 4991–5001; (*b*) B. Crone and S. F. Kirsch, *Chem.–Eur. J.*, 2008, **14**, 3514–3522; (*c*) D. Garayalde and C. Nevado, *Beilstein J. Org. Chem.*, 2011, 7, 767–780.

7 M. P. Doyle, M. A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley-Interscience, New York, 1998.

8 (*a*) P. A. Allegretti and E. M. Ferreira, *Org. Lett.*, 2011, **13**, 5924–5927; (*b*) P. A. Allegretti and E. M. Ferreira, *Chem. Sci.*, 2013, **4**, 1053–1058; (*c*) P. A. Allegretti and E. M. Ferreira, *J. Am. Chem. Soc.*, 2013, **135**, 17266–17269.

9 E. T. Newcomb and E. M. Ferreira, *Org. Lett.*, 2013, **15**, 1772–1775.

10 For select examples of related cycloisomerizations, see: (*a*) J. Blum, H. Beer-Kraft and Y. Badrieh, *J. Org. Chem.*, 1995, **60**, 5567–5569; (*b*) A. Fürstner, F. Stelzer and H. Szillat, *J. Am. Chem. Soc.*, 2001, **123**, 11863–11869; (*c*) M. Méndez, M. P. Muñoz, C. Nevado, D. J. Cárdenas and A. M. Echavarren, *J. Am. Chem. Soc.*, 2001, **123**, 10511–10520; (*d*) T. Shibata, Y. Kobayashi, S. Maekawa, N. Toshida and K. Takagi, *Tetrahedron*, 2005, **61**, 9018–9024; (*e*) K. Ota, S. I. Lee, J.-M. Tang, M. Takachi, H. Nakai, T. Morimoto, H. Sakurai, K. Kataoka and N. Chatani, *J. Am. Chem. Soc.*, 2009, **131**, 15203–15211; (*f*) C.-M. Chao, D. Beltrami, P. Y. Toullec and V. Michelet, *Chem. Commun.*, 2009, 6988–6990; (*g*) H. Teller, M. Corbet, L. Mantilli, G. Gopakumar, R. Goddard, W. Thiel and A. Fürstner, *J. Am. Chem. Soc.*, 2012, **134**, 15331–15342.

11 For seminal examples of cycloisomerizations of oxygen-tethered enynes based on catalytic alkyne π-activation, see: (*a*) A. S. K. Hashmi, T. M. Frost and J. W. Bats, *J. Am. Chem. Soc.*, 2000, **122**, 11553–11554; (*b*) B. Martín-Matute, D. J. Cárdenas and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2001, **40**, 4754–4757.

12 E. Soriano, P. Ballesteros and J. Marco-Contelles, *J. Org. Chem.*, 2004, **69**, 8018–8023.

13 F. Micheli, *et al.*, *J. Med. Chem.*, 2010, **53**, 4989–5001.

14 For select recent examples and discussions of [1,2]-migrations onto similar metal carbenoid species, see: (*a*) T. Lauterbach, S. Gatzweiler, P. Nösel, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Adv. Synth. Catal.*, 2013, **355**, 2481–2487; (*b*) P. Nösel, L. Nunes dos Santos Comprido, T. Lauterbach, M. Rudolph, F. Rominger and A. S. K. Hashmi, *J. Am. Chem. Soc.*, 2013, **135**, 15662–15666; (*c*) A. S. K. Hashmi, I. Braun, M. Rudolph and F. Rominger, *Organometallics*, 2012, **31**, 644–661; (*d*) A. S. K. Hashmi, M. Wieteck, I. Braun, M. Rudolph and F. Rominger, *Angew. Chem., Int. Ed.*, 2012, **51**, 10633–10637; (*e*) A. S. Dudnik, Y. Xia, Y. Li and V. Gevorgyan, *J. Am. Chem. Soc.*, 2010, **132**, 7645–7655; (*f*) Y. Xia, A. S. Dudnik, Y. Li and V. Gevorgyan, *Org. Lett.*, 2010, **12**, 5538–5541.

15 A. Simonneau, Y. Harrak, L. Jeanne-Julien, G. Lemière, V. Mouriès-Mansuy, J.-P. Goddard, M. Malacria and L. Fensterbank, *ChemCatChem*, 2013, **5**, 1096–1099.

16 For an additional related example of alkyl migrations with these carbenoids, see: A. Tenaglia and S. Gaillard, *Angew. Chem., Int. Ed.*, 2008, **47**, 2454–2457.

17 dbcot: dibenzo[*a*,*e*]cyclooctatetraene.

18 M. R. Luzung, J. P. Markham and F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 10858–10859.

19 Y. Horino, T. Yamamoto, K. Uedo, S. Kuroda and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 2809–2811.

20 (a) PtCl$_2$ worked generally better for the different ring sizes than Zeise's dimer or [Ir(dbcot)Cl]$_2$. (b) Cyclohexane-containing substrates produced a complex mixture under our reaction conditions. (c) For the modest yielding reactions, the remaining mass balance appeared to be aldehyde derived from the alkene portion and other oligomeric material.

21 No product derived from migration of the i-Pr group was observed in the crude reaction mixture (determined by $^1$H NMR).

22 (*a*) A. Fürstner, P. W. Davies and T. Gress, *J. Am. Chem. Soc.*, 2005, **127**, 8244–8245; (*b*) For related work, see: A. Fürstner and C. Aissa, *J. Am. Chem. Soc.*, 2006, **128**, 6306–6307.

23 Y. Gimbert, L. Fensterbank, V. Gandon, J.-P. Goddard and D. Lesage, *Organometallics*, 2013, **32**, 374–376.

24 See the ESI† for further details.

25 No migrations were observed with *N*-tethered 1,6-enynes under our developed conditions.

26 D. Roberto, E. Cariati, R. Psaro and R. Ugo, *Organometallics*, 1994, **13**, 4227–4231.

27 E. M. Driggers, S. P. Hale, J. Lee and N. K. Terrett, *Nat. Rev. Drug Discovery*, 2008, **7**, 608–624.

28 Curiously, the use of NaIO$_4$ in the first step did not result in diol cleavage.