

# Continuous Photochemical Generation of Catalytically Active $[\text{CpRu}]^+$ Complexes from $\text{CpRu}(\eta^6\text{-C}_6\text{H}_6)\text{PF}_6$

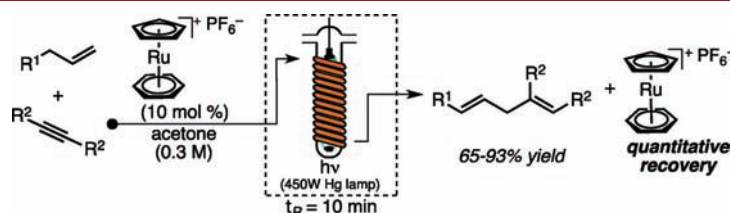
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## ABSTRACT

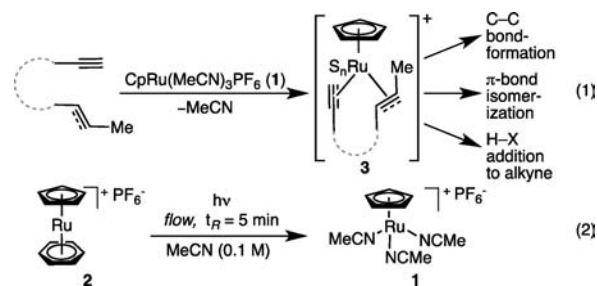


Inter- and intramolecular ene–yne coupling reactions catalyzed by a species generated *in situ* via photolysis of  $\text{CpRu}(\eta^6\text{-C}_6\text{H}_6)\text{PF}_6$ —an inexpensive, readily available, and shelf-stable complex—have been demonstrated under conditions of continuous flow. Importantly, the catalyst can be recovered quantitatively at the end of the reaction. Various functional groups are tolerated by the reaction, which affords skipped diene products in high yields.

We recently reported<sup>1</sup> a high-throughput continuous flow<sup>2,3</sup> preparation of  $\text{CpRu}(\text{MeCN})_3\text{PF}_6$  (**1**)<sup>4,5</sup> from complex **2**<sup>6</sup> under photolytic conditions (eq 2). Because the first step in reactions catalyzed by **1**<sup>7,8</sup> is believed to be

substitution of the labile acetonitrile ligands by solvent or substrate (**1** → **3**, eq 1), we reasoned that it might be possible to generate a catalytically active species by intercepting excited state intermediate **4**<sup>9</sup> during the photolysis itself (Scheme 1), thereby avoiding the isolation of **1** and enabling the use of sandwich complex **2** as a catalyst for a wide range of transformations. Herein we report an evaluation of this hypothesis.

- (1) Gutierrez, A. C.; Jamison, T. F. *J. Flow Chem.* **2011**, *1*, 24–27.  
 (2) For a recent review of continuous flow multistep organic synthesis, see: Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, 675–680.  
 (3) For contributions to this field from our laboratories, see: (a) Sniady, A.; Bedore, M. W.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 2155–2158. (b) Zaborenko, N.; Bedore, M. W.; Jamison, T. F.; Jensen, K. F. *Org. Process Res. Dev.* **2011**, *15*, 131–139. (c) Zhang, Y.; Jamison, T. F.; Patel, S. J.; Mainolfi, N. *Org. Lett.* **2010**, *13*, 280–283. (d) Bedore, M. W.; Zaborenko, N.; Jensen, K. F.; Jamison, T. F. *Org. Process Res. Dev.* **2010**, *14*, 432–440.  
 (4) Gill, T. P.; Mann, K. R. *Organometallics* **1982**, *1*, 485–488.  
 (5) Gill, T. P.; Mann, K. R. *Inorg. Chem.* **1984**, *23*, 2633–2640.  
 (6) Trost, B. M.; Older, C. M. *Organometallics* **2002**, *21*, 2544–2546.  
 (7)  $\text{CpRu}(\text{MeCN})_3\text{PF}_6$  (**1**) is a catalyst for numerous synthetically useful reactions, a field that was pioneered and developed by Trost and co-workers. References to and discussions about many of the seminal contributions in this area are included in the following reviews: (a) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630–6666. (b) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067–2096. (c) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705.  
 (8) For recent examples, see: (a) Austeri, M.; Rix, D.; Zeghida, W.; Lacour, J. *Org. Lett.* **2011**, *13*, 1394–1397. (b) Gutsulyak, D. V.; van der Est, A.; Nikonov, G. I. *Angew. Chem., Int. Ed.* **2011**, *50*, 1384–1387. (c) Austeri, M.; Linder, D.; Lacour, J. *Adv. Synth. Catal.* **2010**, *352*, 3339–3347. (d) Kiesewetter, M. K.; Waymouth, R. M. *Organometallics* **2010**, *29*, 6051–6056.

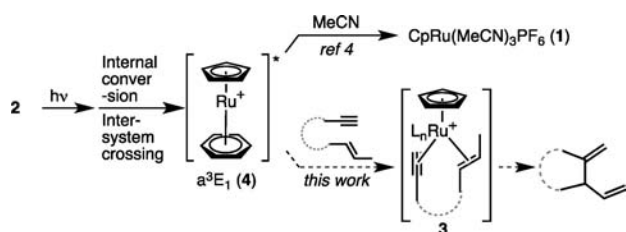


The photochemically induced arene dissociation from sandwich complex **2** in acetonitrile was thoroughly studied

- (9) This intermediate was characterized as a distorted  $a^3E_1$  LF state, which both is susceptible to nucleophilic attack and has a lengthened Ru–arene bond. For the original proposal of this mechanism and detailed spectroscopic studies, see: Schrenk, J. L.; McNair, A. M.; McCormick, F. B.; Mann, K. R. *Inorg. Chem.* **1986**, *25*, 3501–3504.

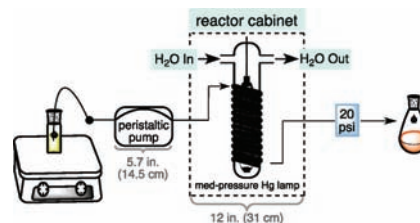
by Mann and co-workers in 1984.<sup>5</sup> The photoactive excited state was identified as the distorted  $a^3E_1$  ligand field state, characterized by an elongated ruthenium–arene bond and a hole in a low-lying d-orbital that make it susceptible to nucleophilic attack. Consistent with these data is a mechanism in which absorption followed by nonradiative decay and intersystem crossing afford the excited  $a^3E_1$  state (**4**, Scheme 1). The rate-limiting step is nucleophilic attack by a molecule of solvent or an anion in the first solvation sphere, in which the strength of the nucleophile is a crucial factor.

**Scheme 1.** Desired Reactivity: Intercepting Intermediate **4**



Prior to discussing additional details about our investigation, the operational aspects of the photochemical reaction deserve comment. Continuous flow micro- and macroreactors have significant benefits on the yield, reproducibility, efficiency, and throughput of many reactions, particularly photochemical.<sup>10–12</sup> In “batch” photochemistry, efficient irradiation of a given molecule in solution drops as its distance from the light source increases. The feasible substrate concentration is typically also compromised, to the significant detriment of the associated throughput ( $\text{mol L}^{-1} \text{min}^{-1}$ ). Taken together, these limitations make large-scale photochemical reactions especially challenging. In contrast, the relatively shallow fluidic channels of continuous flow reactors enhance light penetration, which increases both the efficiency and the homogeneity of the illumination per unit surface area.<sup>13</sup>

The photochemical apparatus constructed for our studies is depicted in Figure 1.<sup>14</sup> Flexible and chemically inert high purity perfluoro alkoxy alkane (HPFA) tubing<sup>15,16</sup> was wrapped around the quartz immersion well of a



**Figure 1.** Continuous flow photochemical reactor.

standard 450 W medium-pressure mercury lamp.<sup>17</sup> The reaction is pushed through the tubing by a peristaltic pump. The UV output was safely housed within an aluminum foil-lined container. The entire setup requires an area less than  $1 \times 0.3 \text{ m}^2$  and fits safely and conveniently inside a standard laboratory fume hood.

Of the multitude of reactions catalyzed by **1**,<sup>7,8</sup> we chose to examine an intramolecular ene–yne cycloisomerization.<sup>18,19</sup> Specifically, we began by examining the cycloisomerization of enyne **5** to diene **6** (Scheme 2). At the outset, acetone was used as a solvent for the cycloisomerization of enyne **5** to cyclopentene **6**. Under standard batch conditions, no conversion was observed in the presence of catalyst **2** (5 mol %).<sup>20</sup> However, under conditions of continuous flow, in the presence of catalyst **2** (5 mol %), complete conversion to the desired product (**6**) was rapidly obtained in a residence time ( $t_R$ ) of only 2 min. In order to probe flexibility in the type of solvent employed, a variety of solvents were examined with generous (10 mol %) catalyst loadings; no conversion to the desired diene was observed in ethyl acetate, dichloromethane, or in mixtures of dichloromethane and Lewis basic cosolvents such as DMF, ethyl acetate, or acetone.<sup>21</sup>

Having identified acetone as the solvent for the desired reaction,<sup>22</sup> we turned our attention toward optimization of other reaction parameters. We began with residence time ( $t_R$ ), which is easily examined by variation of the flow rate. Thus, decreasing the residence time to 30 s resulted in a

(17) The length of the reactor volume is defined herein as the length of the tubing in physical contact with the surface of the immersion well. Additional tubing (required to connect this volume to the rest of the reactor) extends out of the reactor cabinet, although this length is not counted as part of the formal reaction volume. See Supporting Information for details.

(18) For reviews on enyne cycloisomerizations, see: (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1–16. (b) Michelet, V.; Toullec, P. Y.; Genêt, J.–P. *Angew. Chem., Int. Ed.* **2008**, *47*, 426–4315.

(19) For studies on enyne cycloisomerizations catalyzed by **1**, see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 9728–9729. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2002**, *124*, 5025–5036. (c) Trost, B. M.; Gutierrez, A. C.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 9206–9218.

(20) Batch conditions were carried out in a quartz round-bottom flask, in the absence of a filter. No conversion was observed after exposure to the light source for 30 min (15 times longer than the exposure time required for full conversion in flow).

(21) The application of a Pyrex filter did not have any effect on the conversion in any of these cases.

(22) To verify that the reaction was indeed being catalyzed by the ruthenium complex and not by some other photochemical process, a control reaction was run in the absence of catalyst: no conversion was observed.

(10) Albini, A.; Germani, L. Photochemical Methods. In *Handbook of Synthetic Photochemistry*; Albini, A., Fagnoni, M., Eds.; Wiley-VCH: Weinheim, 2010; p 13 ff and references therein.

(11) For a review of photochemistry conducted in flow microreactors, see: Coyle, E. E.; Oelgemöller, M. *Photochem. Photobiol. Sci.* **2008**, *7*, 1313–1322.

(12) For an example of a photochemical reaction conducted under a continuous flow in a macroreactor, see: Hook, B. D.; Dohle, W.; Hirst, P. A.; Pickworth, M.; Berry, M. B.; Booker-Milburn, K. I. *J. Org. Chem.* **2005**, *70*, 7558–7564.

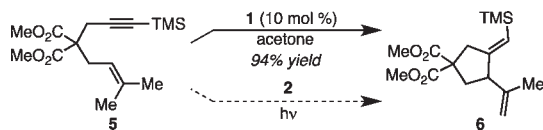
(13) Carofiglio, T.; Donnola, P.; Maggini, M.; Rossetto, M.; Rossi, E. *Adv. Synth. Catal.* **2008**, *350*, 2815–2822.

(14) A similar setup was reported by Hook and co-workers (ref 12).

(15) Idex Health & Science Materials and Tools, Chemical Compatibility. [http://www.idexhs.com/materials/chemical\\_compatibility.aspx](http://www.idexhs.com/materials/chemical_compatibility.aspx) (accessed Mar 1, 2011).

(16) In our initial studies, we used 0.762 mm (0.03 in.) i.d. tubing and a reactor volume of 250  $\mu\text{L}$  (tubing dimensions 1.59 mm o.d.  $\times$  0.762 mm i.d.  $\times$  54.8 cm).

## Scheme 2. Specific Reaction



concomitant decrease in conversion (Table 1, entry 1). Increasing the  $t_R$  to 45 s improved the conversion to 44% (entry 2). Further extension of the  $t_R$  to 90 s brought the reaction to 99% conversion (entry 4).

**Table 1.** Cycloisomerization Optimization<sup>a</sup>

entry	$t_R$ (min)	mol % <b>2</b>	tubing <sup>b</sup>	filter	conversion (%) <sup>c</sup>	<i>E/Z</i> <sup>c</sup>
1	0.50	5	HPFA	—	28	19:1
2	0.75	5	HPFA	—	44	16:1
3	0.75	5	HPFA <sup>d</sup>	—	48	15:1
4	1.5	5	HPFA	—	99	7:1
5	4.0	5	HPFA	—	100	1:1
6	8.0	5	HPFA	—	100	1:1
7	0.75	5	quartz	—	98	5:1
8	2.0	5	quartz	Pyrex	98	45:1
<b>9</b>	<b>2.5</b>	<b>5</b>	<b>quartz</b>	<b>Pyrex</b>	<b>100</b>	<b>22:1</b>
10	2.5	2.5	quartz	Pyrex	83	32:1

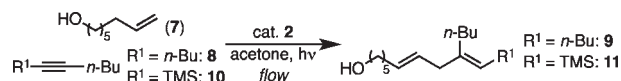
<sup>a</sup> Reactor volume was 250  $\mu$ L. Exposure to UV output without the application of any filter, unless otherwise indicated. <sup>b</sup> Inner diameter (i.d.) of HPFA tubing = 0.762 mm, unless otherwise noted. <sup>c</sup> Measured by GC analysis of the crude reaction. <sup>d</sup> Tubing i.d. = 1.58 mm.

At this juncture, the effect of the tubing material was examined. HPFA tubing is convenient because it is widely available, inexpensive, and easy to manipulate into various reactor volumes; however after repeated use, the photochemical reaction caused visible darkening of the inner tubing walls. Importantly, we found that the conversion rate was independent of the inner diameter of the tubing employed. Anticipating that the superior transparency of quartz should improve the efficiency of the reaction and that its chemical composition should render it more chemically inert than HPFA, tubing constructed of quartz was examined. A substantial increase in rate was in fact observed. A residence time of 45 s — which led to 50% conversion (entry 2) in HPFA tubing — was sufficient to convert 99% of the substrate to the desired product (entry 7).

(23) A previously purchased, commercially available Pyrex filter was used. Alternatively, the use of Pyrex tubing without a filter would be expected to be equally effective.

Interestingly, the degree of *E/Z*-isomerization of the product **6** (presumably facilitated by the silyl substituent) increased as the residence time was extended (entries 1–7). Use of a Pyrex filter<sup>23</sup> effectively suppressed the double-bond isomerization, while only moderately decreasing the rate of cyclization (entries 8–10).

**Table 2.** Intermolecular Enyne Coupling Optimization



entry	R <sup>1</sup>	filter	$t_R$ (min)	mol % <b>2</b>	conversion (%) <sup>a</sup>	<i>E/Z</i> <sup>a</sup>
1	<i>n</i> -Bu	—	5	6	12	—
2	<i>n</i> -Bu	—	10	6	49	—
3	<i>n</i> -Bu	—	15	8	100	—
4	<i>n</i> -Bu	—	10	8	67	—
<b>5</b>	<b><i>n</i>-Bu</b>	—	<b>10</b>	<b>10</b>	<b>100</b>	—
6	<i>n</i> -Bu	—	5	10	59	—
7	<i>n</i> -Bu	Pyrex	10	6	15	—
8	TMS	Pyrex	15	11	91	26:1
<b>9</b>	<b>TMS</b>	<b>Pyrex</b>	<b>20</b>	<b>11</b>	<b>100</b>	<b>17:1</b>

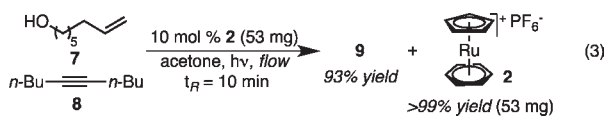
<sup>a</sup> Product obtained as a single geometric isomer unless otherwise indicated. Determined by GC analysis of the crude reaction mixture.

Lastly, the effect of catalyst loading was examined. Upon decreasing the amount of **2** from 5 to 2.5 mol %, the conversion fell to 83% (entry 9). The conditions described in entry 8 (2.5 mol % **2**,  $t_R$  = 2 min, quartz tubing, Pyrex filter), therefore, represent the optimized conditions for the cycloisomerization of enyne **5**, affording diene **6** in an excellent *E/Z* ratio of 22:1.

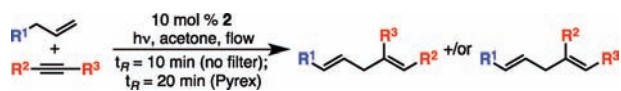
With parameters suitable for the intramolecular cycloisomerization in hand, we turned our attention to the intermolecular coupling of 7-octen-1-ol (**7**) and 5-decyne (**8**). Employing a  $t_R$  of 5 min and 6 mol % of **2**, 12% conversion to desired diene **9** was observed (Table 2, entry 1). In the presence of 8 mol % catalyst, complete conversion was observed in 15 min (entry 3) but fell when the  $t_R$  was decreased (entry 4). To obtain complete conversion in 10 min, a catalyst loading of 10 mol % was required (entries 4 and 5). As was observed for the intramolecular case, the rate of the intermolecular reaction was retarded in the presence of a Pyrex filter (entries 2 and 7), requiring 20 min for complete conversion (entries 8 and 9).

To demonstrate the excellent scalability of this synthetic methodology, the reaction was then conducted on a 1.33 mmol scale using the optimized conditions (Table 2, entry 5). Diene **9** was obtained in 93% isolated yield. *Moreover, complex 2 could also be recovered from the reaction, in quantitative yield (eq 3).* The recovered complex was then

reused in subsequent reactions, with no observable decrease in catalytic activity.



**Table 3.** Substrate Scope for Alkene–Alkyne Couplings<sup>a</sup>

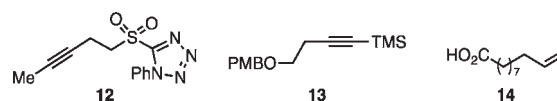


entry	filter	diene product	flow yield (%)	batch yield (%) <sup>b</sup>
1	–		93	90
2	–		60	66
3	Pyrex		62	93
4	Pyrex		70	50
5	Pyrex		85	89
6	Pyrex		65	85
7	–		86	82
			<i>r</i> = 1:1	1:1
8	Pyrex		58	86
			<i>r</i> = 1:1	1:1
9 <sup>c</sup>	Pyrex		90	94
			<i>E/Z</i> = 3:1	>99:1

<sup>a</sup> All yields are isolated yields. Product was obtained as a single regio- and geometric isomer in all cases unless stated otherwise. See text and Supporting Information for a detailed description of the reaction conditions. <sup>b</sup> Conditions (unoptimized) for batch reactions: CpRu(MeCN)<sub>3</sub>PF<sub>6</sub> (10 mol %), acetone, rt. <sup>c</sup> Optimized conditions for this substrate give 100% conversion and an *E/Z* ratio of >22:1 when a shorter *t*<sub>R</sub> of 2.5 min is employed (see Table 1, entry 8).

A number of coupling partners were then evaluated under the optimized conditions to determine reaction scope and catalyst generality (Table 3). In particular, we were interested in the functional group compatibility and the potential limitations the photochemical reaction might introduce. In addition to free alcohols (entry 1), aliphatic ketones containing  $\gamma$ -hydrogens were coupled successfully (entry 2).<sup>24</sup> Weinreb amides were also compatible (entry 3). Although under these conditions the coupling was still incomplete (70% conversion), from this crude reaction

mixture the corresponding diene was isolated in 62% yield (89% yield based on conversion). The intramolecular reaction of enyne **5** afforded the desired diene in 90% yield, although the extended time used in the optimized conditions for the intermolecular reaction decreased the *E/Z* ratio to 3:1 (entry 9). The limits of this reaction are illustrated in Figure 2. Although they afford the corresponding diene products in the batch reaction mediated by catalyst **1**, these substrates did not react under the photochemical conditions. Therefore, we recognize that substrates which absorb strongly in the UV spectrum are better suited for the batch conditions (using **1**).



**Figure 2.** Substrates incompatible with photolysis.

In conclusion, we have established that CpRu( $\eta^6$ -C<sub>6</sub>H<sub>6</sub>)-PF<sub>6</sub> (**2**), previously employed primarily as a stable synthetic intermediate en route to CpRu(MeCN)<sub>3</sub>PF<sub>6</sub> (**1**), is in fact a competent catalyst in reactions for which only **1** has been reported. Employing **2** avoids the preparation and isolation of trisacetonitrile catalyst **1**. Moreover, catalyst **2** is more robust and shelf-stable, is significantly less expensive than **1**, and can be fully recovered from reactions. While the use of this alternate procedure was demonstrated with ene–yne couplings, this account lays the groundwork for the development of new photocatalytic reactions, since in principle any reaction mediated by [CpRu]<sup>+</sup> should be equally accessible. Further investigation into the mechanism and scope of this reaction are ongoing.

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**Supporting Information Available.** Experimental procedures (including photographs and diagrams of the flow reactor) and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(24) Photoexcited carbonyl groups undergo facile intramolecular  $\gamma$ -hydrogen abstraction to form 1,4-biradicals. See: Wagner, P. J. Abstraction of  $\gamma$ -Hydrogens by Excited Carbonyls. In *Synthetic Organic Photochemistry*; Grisbeck, A. G., Mattay, J., Eds.; Marcel Dekker: New York, 2004; pp 11–40 and references therein.