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A Rapid and Simple Cleanup Procedure for Metathesis Reactions

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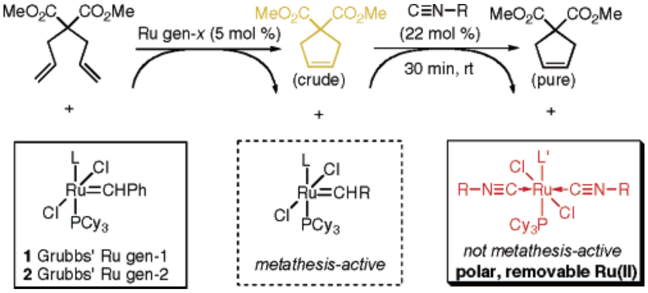
ABSTRACT

A new method for easy removal of ruthenium from metathesis reactions by using a polar isocyanide is reported. This protocol removed most ruthenium byproducts from a variety of synthetically useful metatheses. Moreover, the isocyanide-promoted carbene insertion results in rapid destruction of carbene reactivity, demonstrated in the commonly used first- and second-generation Grubbs' carbenes.

Olefin metathesis has become an important method for carbon−carbon double bond construction in organic synthesis.[1] Metathesis is widely employed in a variety of fields of chemistry, using the mild, functional group tolerant ruthenium carbenes discovered by Grubbs.[2] Metathesis has been used in large-scale reactions and continued use in pharmaceutical, small molecule, and parallel synthesis is immediately foreseeable. Despite the widespread use of metathesis procedures, a difficulty common to *all metathesis reactions* is the removal of the ruthenium at the end of the reaction. In this report, we detail a new procedure using a polar isocyanide that accomplishes the rapid quenching of carbene activity and leads to the ready removal of the resulting polar coordination complex (Scheme 1). This represents a practical, simple-to-use procedure for the removal of ruthenium in the purification of the organic products of metathesis. The protocol works efficiently for all commonly used carbene catalysts in a variety of alkene and enyne metathesis applications.

Several methods for the removal of ruthenium have been reported. First, Grubbs and Maynard described the use of a water-soluble phosphine for the removal of ruthenium in the first generation complex **1**.[3a] This requires 86 equiv of a water-soluble phosphine and extractive workup. The reported large-scale procedure used a 12 h treatment.[3b] Next, Georg et al.[3c] reported a mild oxidative procedure to convert **1** into a polar, undefined product that can be removed by chromatography after 24 h of treatment with 50 equiv of $Ph_3P{=}O$ or DMSO. This procedure is mild and is widely used. Third, Paquette et al.[3d] disclosed a rapid oxidative procedure using $Pb(OAc)_4$ that oxidizes the ruthenium carbene to polar, undefined products that are then removed by silica gel

Scheme 1. Isocyanide-Promoted Ligand Insertion: An Effective Cleanup Protocol



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(1) Grubbs, R. H., Ed. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003; Vols. 1−3.

(2) (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974−3975. Complex **1**: (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. Complex **2**: (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (d) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546−2558.

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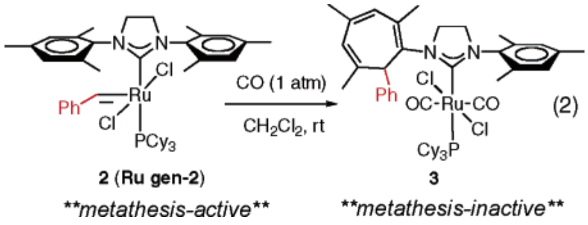
chromatography. During our investigation, Crudden et al.[3e] reported a mesoporous silicate for the removal of ruthenium applied to **1** and homogeneous catalysis by ruthenium hydrides. This requires a large excess of the silicate but is simple since only a filtration is required. For synthetic chemists, the most widely used procedure is that of Georg et al.,[3c] yet this suffers from lengthy reaction times.

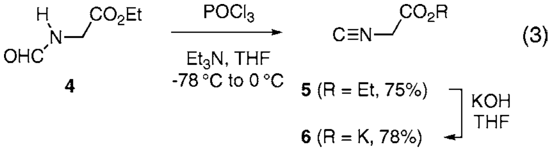
There are several shortcomings of the reported procedures. First, from an operational standpoint, they take too long: for a 1−4 h cross enyne metathesis, stirring 12−24 h with an oxidant is necessary. This slow oxidation has not been shown to immediately stop metatheses, which is essential for kinetic analysis[4] and to prevent unwanted, secondary metatheses.[5] Second, the oxidative procedures reported previously were shown to be effective for complexes **1** or **2**, but not all metathesis catalysts. For example, phosphine-free initiators, which are increasingly used in challenging applications, have not been evaluated in any cleanup protocol. Third, though the reported procedures remove ruthenium, the specific reaction is undefined. Recognizing some of the current trends in metathesis chemistry, we felt that a full range of cross metatheses should be evaluated. A new procedure would be desirable if it was fast, efficient for the range of carbene complexes used, applicable to a variety of metatheses, and proceeded by known chemistry.

We previously observed a unique ligand insertion promoted by carbon monoxide.[6] This reaction resulted in destruction of carbene activity and formed a moderately polar bis(carbonyl)ruthenium(II) complex. For carbene **2**, we observed Buchner product **3** arising from benzylidene insertion into a mesityl group (Scheme 2). We observed the same ligand insertion shown in eq 2 using aryl isocyanides. We reasoned that a polar isocyanide would rapidly quench the carbene through ligand insertion and confer polarity to the resulting ruthenium coordination complex. Polarity of the complex would then permit removal of ruthenium from the organic products of a typical metathesis reaction. This process represents a “well-defined” reaction of the no-longer-wanted carbene catalyst.

Scheme 2. Donor-Induced Ligand Insertion (Galan et al., Ref 6)



A polar isocyanide was prepared and used to quench a cross metathesis. We prepared the isocyanide salt **6**[7] and used it to evaluate the effectiveness of the quenching method (eq 3). Formation of the formamide and dehydration with $POCl_3$ gave high chemical yield of the ethyl ester **5**. Saponification with KOH (THF−water) and evaporation of the solvent mixture deposited an odorless[8] off-white amorphous solid (mp 164−165 °C) that was used for quenching. The solid was not hygroscopic and could be handled in the atmosphere during weighing. The effectiveness of the quench was evaluated in a cross enyne metathesis between 1-hexene and 1-benzoyloxy-2-propyne. At about 50% conversion, 44 mol % isocyanide **5** was added (8.8 equiv based on catalyst; solution in ca. 1 mL of toluene).[9] The reaction immediately changed yellow with complex **2**.[10] Further conversion was not observed, suggesting that catalysis was rapidly stopped.



The effectiveness of the isocyanide quench and optimization of the quenching procedure was evaluated in a typical ring-closing metathesis (RCM). Similar to previous investigations,[3] we chose an inductively coupled plasma (ICP) analytical method to quantitate ruthenium content in crude and purified metathesis samples.[11] These data were used to determine the efficiency of the cleanup procedure. The theoretical amount of ruthenium that should be left at the end of the reaction is 100 μg/5 mg of sample. We found an average of 97 μg/5 mg of sample after a 2 h reaction time using complex **2** (Table 1, entry 1). If the crude reaction was passed through silica gel, about half the ruthenium was removed (entry 2). In Table 1, the third column reports the concentration of ruthenium determined in the assay for a diluted sample. The last column accounts for the mass of the sample digested. In the previous literature, concentration of ruthenium is reported as “μg of Ru found per 5 mg of crude sample”. The effectiveness of the cleanup should be evident from the last column; comparisons to literature methods can also be made from these data.[12]

Next, the stoichiometry of the isocyanide addition was studied. It was expected that at least 2 equiv would be required based on ruthenium carbene. Each of these runs

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(3) (a) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137−4140. (b) Grubbs, R. H. *Org. React.* **2004**, *22*, 123−1234. (c) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411−1414. (d) Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Mendez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259−1261. (e) McEleney, K.; Allen, D. P.; Holliday, A. E.; Crudden, C. M. *Org. Lett.* **2006**, *8*, 2663−2666. Summary of methods: (f) Conrad, J. C.; Fogg, D. E. *Curr. Org. Chem.* **2006**, *10*, 185−202.

(4) For fast enyne metathesis, a rapid and irreversible quench is desirable. Kinetic studies in enyne metathesis led us to develop the technique described in this paper.

(5) If a small amount of active catalyst remains during solvent evaporation or during crude sample storage, the product can undergo carbene-promoted polymerization (e.g., for a RCM, the reverse reaction: ROMP).

(6) Galan, B.; Gembicky, M.; Dominiak, P. M.; Keister, J. B; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 15702−15703.

(7) Obrecht, R.; Hermann, R.; Ugi, I. *Synthesis* **1985**, 400−402.

(8) We typically run the metatheses *and* the treatment procedure in the fume hood. Because of its excellent ligand properties, the isocyanide **6** is assumed to be toxic. Due care should be used in handling the solid to avoid breathing any fine particulates.

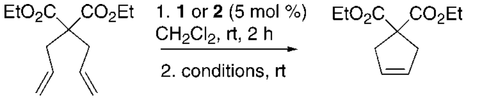
(9) IR was used to follow alkyne consumption, and methanolic solutions obscured the alkyne CH stretch. As a result, a toluene solution of ester **5** was used instead of carboxylate **6**.

(10) With the complex **1**, the solution turned blue-green.

(11) In this study, we quantitated total ruthenium content in the plasma and did not use MS to separate isotopes.

(12) 1 μg of Ru detected in a 5 mg sample corresponds to 200 ppm Ru.

Table 1. Removal of Ruthenium Byproducts from a Typical Ring-Closing Metathesis Reaction



(4)

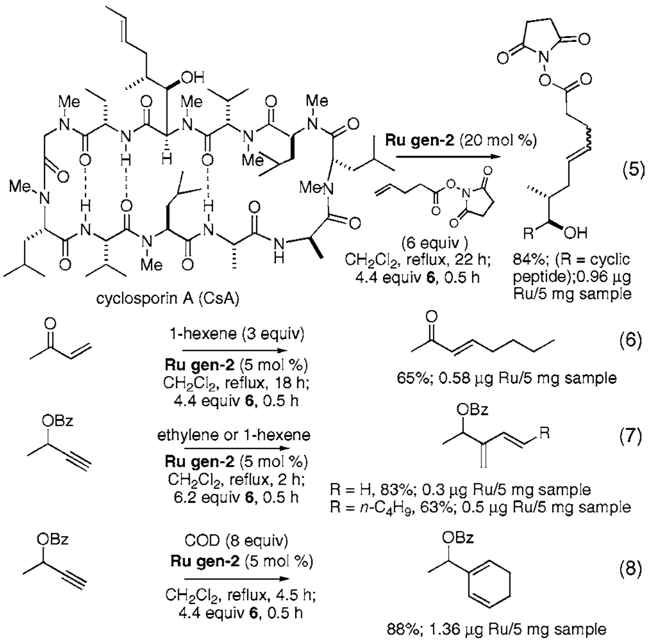
entry	treatment[a]	time/ h	concn [Ru]/ ppm	concn [Ru]/ μg/5 mg[b,c]
1	NT		16.1, 19.91	86.4, 108 (av = 97)
2	NT, chrom.		6.45, 6.25	44.0, 43.8 (av = 44)
3	2.2 equiv (11 mol %) **2**	0.5	2.21	16.2
4	4.4 equiv (22 mol %) **2**	0.5	1.35	8.31
5	4.4 equiv (22 mol %) **2**	1	1.15, 1.55	10.9, 10.3 (av = 10.6)
6	8.8 equiv (44 mol %) **2**	0.5	3.46	24.2
7	10 equiv (50 mol %) **2**	0.5	0.66, 0.69	4.61, 5.70
8[d]	4.4 equiv (22 mol %) **1**	0.5	0.67	4.87

[a] Treatment to the crude sample. Equivalents are based on ruthenium carbene used; mole percents are based on malonate reactant. [b] Ruthenium concentration in sample; all assayed values are 0.1−100 ppm in the analytical assay. [c] μg Ru/5 mg sample, calculated for the original sample from quantitation of ruthenium by ICP determination. [d] Complex **1** (Ru gen-1) was used in this run.

(entries 3−8) was performed by addition of the isocyanide after 2 h of reaction time and stirring for the time indicated, followed by plug filtration on silica gel. On addition of the isocyanide, the dark color of the reaction discharged. With a 0.5 h reaction time, 4.4−8.8 equiv of isocyanide proved effective. There was no advantage to longer quench periods. In the last entry, ruthenium in the first generation complex **1** was removed by the isocyanide treatment.

Next, the cleanup protocol[13] was examined for several different metatheses. Here we wanted to be sure the optimized procedure could be used reliably for typical metathesis reactions that are used by synthetic chemists. In the first case, a cross metathesis of the MeBMT side chain of cyclosporin and an alkene bearing an active ester was examined at high catalyst loading (eq 5, Scheme 3).[14] After treatment (4.4 equiv, 22 mol % of **6**; 30 min), the product was isolated in 84% yield with only 0.96 μg of Ru/5 mg of sample. This is noteworthy due to the potential of the cyclic undecapeptide to sequester the metal and because the side chain active ester withstands the quench procedure. The cleanup was effective for cross alkene and enyne metatheses, using the standard treatment of 4.4 equiv of **6** for 0.5 h (eqs 6−8). The enyne metathesis was performed with both ethylene and 1-hexene, and gave less than 1 μg of Ru/5 mg of sample in these cases after only 0.5 h of isocyanide treatment. Last, we investigated a methylene-free ring synthesis (eq 8) and found that the cleanup procedure was effective in this case. Yields in all cases were comparable to those previously reported. Overall, the crude products of intermolecular metatheses using the commonly used second generation Grubbs carbene complex **2** were effectively cleaned up by the isocyanide treatment just before routine purification. This quenches carbene activity (vide supra) and obviates the need for long waiting times before purification. This is an improvement in efficiency that should prove useful in practical and large-scale metathesis applications.

Scheme 3. Application of the Removal Method to Other Metathesis Reactions



The effectiveness of the isocyanide cleanup procedure was next evaluated for several commonly used metathesis catalysts (Table 2). These experiments were performed by using the RCM of diallyl malonate and quenched after 2 h. The isocyanide cleanup procedure was effective for metatheses conducted with the first generation Grubbs carbenes. In the first generation complexes, the ancilliary ligand is Cy$_3$P, which contains no aromatic moieties. In contrast, the aromatic mesityl groups are found in the second generation carbene complexes and account for the Buchner insertion chemistry described in eq 2.[6] There is still wide use of the first generation complex, both as the Grubbs benzylidene **1** and as the Hoveyda chelate **7**. We applied the cleanup procedure to these complexes and found that most of the ruthenium was removed (entries 1−5, Table 2). Though the details of this process are still unclear, it is presumed that a polar coordination complex is formed by application of the standard procedure.[15] Recently, the phosphine-free second generation carbene complexes **8**−**10** have become popular

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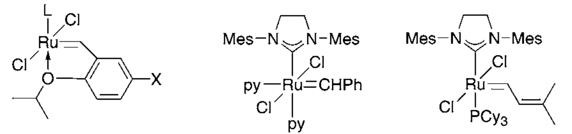
(13) Between 4.4 and 8.8 equiv of the isocyanide is used, based on ruthenium carbene (22−44 mol % based on unsaturated reactant). Representative Experimental Procedure (eq 7): Into an oven-dried 100 mL Schlenk flask were placed 177 mg (1.02 mmol) of butynyl benzoate in 5.0 mL of CH$_2$Cl$_2$, 0.8 mL (6.44 mmol, 6.2 equiv) of 1-hexene, and 43.3 mg of Grubbs' complex **2** (0.051 mmol, 5 mol %). The reaction was stirred at rt for 2 h. After this time, the mixture was treated with a solution of 38.8 mg of **6** (0.315 mmol, 31 mol % or 6.2 equiv based on **2**) in 1.0 mL of methanol. The color of the solution changed from purple to yellow within 5 min. The reaction mixture was stirred for 30 min at rt, concentrated in vacuo (rotary evaporator), and purified by column chromatography on approximately 10 g of silica gel (2.0 g of silica gel was used for every 0.01 mmol of catalyst used), using 1:8 ethyl acetate−hexanes as the eluent.

(14) Smulik, J. A.; Diver, S. T.; Pan, F.; Liu, J. *Org. Lett.* **2002**, *4*, 2051−2054.

(15) Further studies are in progress.

Table 2. Results of Isocyanide Cleanup Procedure Applied to RCM of Diethyl Diallylmalonate, Using Additional Metathesis Catalysts



7 (R=H, L=Cy$_3$P, Hoveyda gen-1)
8 (R=H, L=H$_2$IMes, Hoveyda gen-2)
9 (R=NO$_2$, L=H$_2$IMes, Grela gen-2)

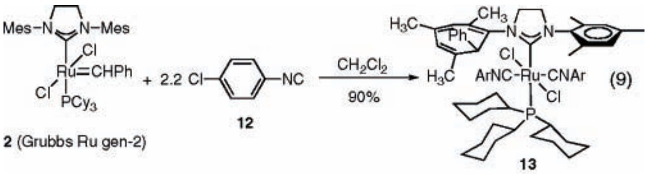
10 (Grubbs pyr solvate)

11 (Grubbs vinyl carbene)

entry^a	Ru carbene	isocyanide **6**^{b,c}	temp, time	concn [Ru]/ μg/5 mg^d
1	**1**, Ru gen-1	4.4 equiv	rt, 0.5 h	4.87
2	**1**, Ru gen-1	8.8 equiv	reflux, 0.5 h	0.8
3	**1**, Ru gen-1	8.8 equiv	6 h	1.2
4	**1**, Ru gen-1	8.8 equiv	12 h	1.1
5	**7**, Hov gen-1	4.4 equiv	0.5 h	2.05
6	**8**, Hov gen-2	4.4 equiv	0.5 h	1.16
7	**9**, Grela gen-2	8.8 equiv	0.5 h	0.8
8	**10**, Grubbs pyr solv	8.8 equiv	0.5 h	0.6
9	**11**, vinyl carbene	4.4 equiv	0.5 h	11

[a] RCM of eq 4, using carbene at 5 mol % loading. [b] Isocyanide **6** added as a solution in methanol. [c] Equivalents are based on the carbene complex, e.g., 4.4 equiv of **6** is 22 mol %. [d] Concentration expressed as μg/5 mg of organic product: e.g., 1.1 μg/5 mg of sample is 220 ppm.

choices for metathesis. As expected, the cleanup/quench protocol was effective for these other second generation carbene complexes (entries 6–8), including a vinyl carbene complex **11**.



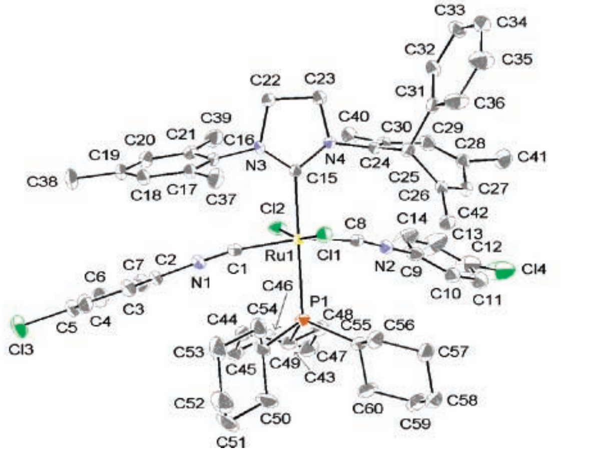


Figure 1. ORTEP drawing of isocyanide insertion complex **13**. Thermal ellipsoids are drawn at 50% probability. See the Supporting Information for bond angles and bond lengths.

The product resulting from a representative isocyanide-promoted ligand insertion was structurally identified. The second generation carbene complex **2** was reacted with 2.2 equiv of *p*-chlorophenyl isocyanide **12** to produce a crystalline complex **13**, eq 9. X-ray analysis revealed two molecules of isocyanide **12** had added to the ruthenium center and the benzylidene had formally inserted into one of the mesityl groups (Figure 1).[16] The observed chemistry is analogous to our earlier findings with carbon monoxide.[6] The cycloheptatrienyl protons of **13** were found as singlets at δ 5.61 and 5.41 ppm, with a benzylic methine appearing at 5.04. The ^{31}P NMR showed a single resonance at δ 13.9 ppm. With this structural data in hand, we wanted to know if the same insertion was triggered by the polar isocyanide **6**. The resulting complex did not provide X-ray quality crystals. Solution NMR studies were performed on the triphenylphosphine complex, (H$_2$IMes)(Ph$_3$P)Cl$_2$Ru═CHPh, reacted with 2.7 equiv of the polar carboxylate **6** (1:1 v/v CD$_2$Cl$_2$–CD$_3$OD). Proton resonances were observed at δ 5.80, 5.79 ppm, and a benzylic methine appeared at δ 4.91 ppm, supporting the cycloheptatrienyl substructure. The ^{31}P NMR spectrum showed a single resonance at δ 36.3 ppm.[17] The similar spectroscopic properties support the conclusion that the polar isocyanide promotes a ligand insertion as observed in complex **13**. In terms of the cleanup protocol, the polar isocyanide ligands confer greater polarity to the hexacoordinate ruthenium complex, facilitating its removal from the organic products of metathesis. The ligand insertion of eq 9 also results in loss of the metal carbene fragment, which switches off the catalyst's metathesis activity.

In conclusion, we have demonstrated a useful cleanup procedure for metathesis reactions. The isocyanide addition to a crude metathesis reaction mixture results in "quench" of the metal carbene by triggering a bond insertion into the mesityl group. We demonstrated that the quench is effective for a variety of metatheses and for all of the commonly used Grubbs' carbene complexes. The carboxylate salt of isocyanide **6** is an odorless solid that is easily obtained and easily handled. Further study of the insertion processes promoted by strongly coordinating ligands is under active study in our group.

Acknowledgment. The authors thank the Petroleum Research Fund (PRF AC-44202) and the NSF (CHE-601206) for financial support of this work. We also thank Dr. Cara L. Nygren (SUNY at Buffalo) for obtaining the solid-state structure of **13** and Materia (Pasadena, CA) and Boeringher-Ingelheim for their generous catalyst support.

Supporting Information Available: Detailed experimental procedures and structure determination for **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) X-ray diffraction data were collected on a Bruker SMART APEX2 diffractometer with Mo Kα (λ = 0.71073 Å) radiation, using a colorless crystal with the dimensions of 0.40 × 0.13 × 0.13 mm^3. Intensity data were integrated with SAINTPLUS program. The crystal structure was solved by direct methods with SHELXTL NT version 6.14, and refined by full matrix least-squares against F^2. Non-hydrogen atoms were refined anisotropically. Positions of hydrogen atoms were found by difference electron density Fourier synthesis. Crystal data for **13**: $C_{60}H_{73}N_4Cl_4PRu(CH_2Cl_2)_4$, mp 152–154 °C, M = 1457.83, triclinic, space group $P\bar{1}$, a = 12.6750(3) Å, b = 14.9214(4) Å, c = 19.4499(5) Å, V = 3504.87(15) Å^3, Z = 2, T = 90(1) K, D_c = 1.381 g·cm^{-3}, $2\theta_{max}$ = 26.4°, $R(F)$ = 3.6% for 62709 reflections with $F_o > 2\sigma(F_o)$ and $Rw(F^2)$ = 0.263 for all 17343 independent reflections, 802 parameters. GOF(F^2) = 1.02.

(17) The same experiment was performed on the Cy$_3$P complex of **2** (Grubbs' Ru gen-2), see the Supporting Information for details.