Olefination

Hydrazone and Oxime Olefination via Ruthenium Alkylidenes

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In memory of Robert H. Grubbs

Abstract: We describe the development of an efficient method for the olefination of hydrazones and oximes. The key design approach that enables this transformation is tuning of the energy/polarity of C=N π-bonds by employing heteroatom functionalities (NR$_2$, OR). The resulting hydrazones or oximes facilitate olefination with ruthenium alkylidenes. Through this approach, we show that air-stable, commercially available ruthenium alkylidenes provide access to functionalized alkenes (20 examples) in ring-closing reactions with yields up to 88 %.

Alkenes represent ubiquitous and desirable functional group handles found in chemical feedstocks,[1,2] pharmaceuticals,[3–5] and many natural products.[6,7] Synthetic methodologies to access highly functionalized alkenes either rely on carbonyl olefination strategies, including Wittig,[8,9] Julia,[10–12] Tebbe,[13,14] and Petasis[15,16] olefinations or olefin-olefin metathesis reactions (**1**) mediated by metal alkylidenes (Figure 1A).[17] Similar to olefin–olefin metathesis, carbonyl–olefin metathesis (**2**) and imine–olefin metathesis strategies (**3**) enable access to new alkene products, however these transformations are significantly less advanced. Despite recently developed organocatalytic[18] and Lewis acid-catalyzed approaches[19–21] for carbonyl–olefin metathesis, strategies based on metal alkylidenes remain limited.[19,22,23]

Although carbonyls are inherently not tunable, condensation with functionalized amines provides access to electronically diverse C=N π-bonds, potentially enabling a larger range of reactivity to allow for more productive interactions with metal alkylidenes.

Imine–olefin metathesis[24] (**3**) has been a targeted transformation since the early 1980s, however successful examples have been limited exclusively to imine-alkylidene cross metathesis (**4**).[24–28] Importantly, the formation of strong metal=heteroatom (M=E) bonds often provides the needed driving force for metathesis reactions with carbon=heteroatom (C=E) bonds.[24–27,29] Carbonyl–alkylidene and imine–alkylidene metathesis reactions are best facilitated by early transition metals that exhibit high oxophilicity (e.g. M=Ta, Nb, Mo, W; **5**, Figure 1B).[24–27,29,30] While these transformations would be highly desirable, their adoption in synthetic methodology has been limited[17] due to the high sensitivity to air, water, and reaction solvent that early transition

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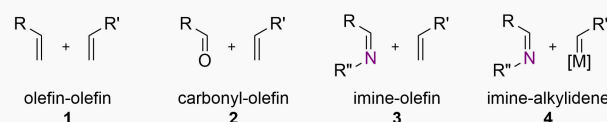corinnas@umich.edu

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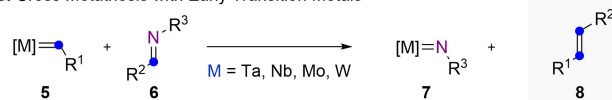
[+] These authors contributed equally to this work.

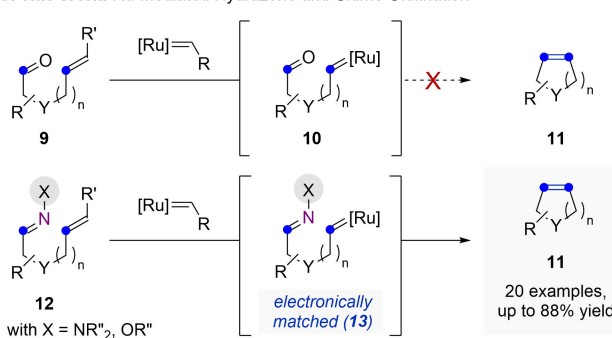[#] These authors contributed equally to this work.

Figure 1. A) Alkene formation via metal alkylidenes. B) Literature precedent for imine-alkylidene cross metathesis. C) Ruthenium-mediated olefination of hydrazones and oximes developed herein.

metals exhibit. As a result, these reactions have low/moderate functional group tolerance.[31] In contrast to early/mid-metal alkylidenes, the late metal variants (e.g. ruthenium alkylidenes) are air/water tolerant, and exhibit high functional group compatibility. Despite these advantages, successful carbonyl–olefin and imine–olefin metathesis reactions utilizing commercially available Grubbs-type ruthenium alkylidenes have not yet been developed.[22,23,29] Towards this goal, we developed a new strategy to enable hydrazone and oxime olefination (**12**) that employs air-stable, commercially available ruthenium alkylidenes (Figure 1C).[17] We anticipate this new methodology will complement existing olefin–olefin and carbonyl–olefin metathesis approaches to access functionalized alkene products. Specifically, Lewis acid-catalyzed carbonyl–olefin metathesis reactions are limited to nucleophilic alkenes while terminal alkenes remain inert.[19–21] Existing metal alkylidene-mediated carbonyl–olefin metathesis approaches are based on molybdenum alkylidenes, which are highly sensitive to air and water.[22] In comparison, olefin–olefin metathesis often necessitates the conversion of carbonyl precursors to alkene substrates in stoichiometric olefination protocols. The olefination of readily accessible hydrazones and oximes upon condensation of carbonyls as developed herein holds the potential of a valuable synthetic alternative to currently existing protocols.

We propose that the key challenge to adapt Grubbs-type ruthenium alkylidenes for the olefination of electronically

diverse C=N π-bonds is to match the polarity and energy of the π-bonds with the ruthenium alkylidene. The acceptor orbitals of late-metal alkylidenes are less polarized[30] and higher in energy than corresponding early-metals (Figure 2A).[32] Consequently, the inherent polarization and/or energy of the metal carbene double bond renders carbonyls and imines orbitally-matched with molybdenum alkylidenes but *mismatched* with ruthenium alkylidenes. Although recent analyses of NMR chemical shift tensors has shown electronic/magnetic similarities between molybdenum- and ruthenium alkylidenes, their reactivity profiles in the presence of heteroatoms are distinct.[30,33,34] We hypothesized that tuning the polarization of the carbon=heteroatom (C=E; E=O, NR) bond would enable productive interactions with metal alkylidene bonds that are otherwise inert to carbonyls or imines, such as ruthenium alkylidenes (Figure 2B).[30] Importantly, C=N bonds bearing adjacent π-donating substituents (e.g. hydrazones, oximes) exhibit a lower polarity and higher energy HOMO: factors we propose would facilitate productive interactions with metal alkylidenes (Figure 2D). Because the substrate, rather than the metal alkylidene is modified using this approach, olefin–olefin metathesis would also remain favorable, presenting an opportunity for a new class of ring-closing reactions. Preliminary experiments to probe this hypothesis were promising and showed unique reactivity: while no reactivity between an alkene and either carbonyls or aliphatic imines was observed, the desired products formed from hydrazones and oximes (see below).

Based on these initial results, we first investigated a variety of commercially available ruthenium alkylidenes to promote the reactions of alkenes with C=N π-bonds (Table 1). Tosyl hydrazone **14** was chosen as a readily
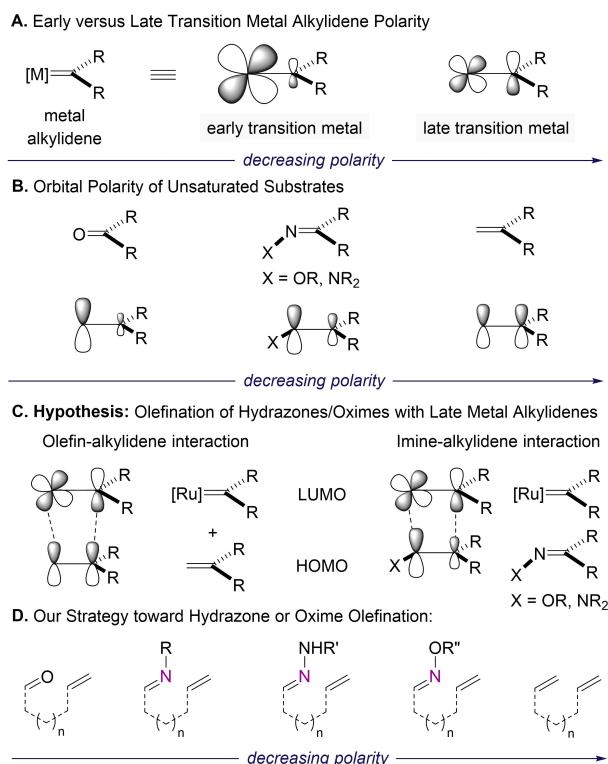
Figure 2. Design rationale for imine–olefin metathesis based on literature precedent in carbonyl–olefin metathesis relying on metal alkylidenes.

Table 1: Evaluation of ruthenium alkylidenes.[a]
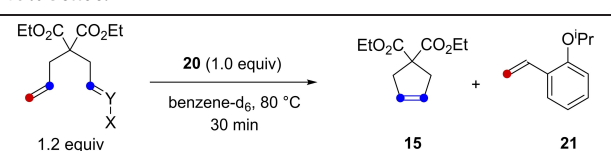
entry	[Ru]	temp. (°C)	yield **15** (%)[c]	yield **16** (%)[c]	[Ru] conversion (%)[c]
1	**17**	80	17	75	83
2	**18**	80	42	78	100
3	**19**	80	57	77	100
4	**20**	80	85	85	85
5	**20**[b]	25	66	69	77

[a] Conditions: [Ru] (0.01 mmol), **14** (1.2 equivalents), in benzene-d_6 (0.0145 M) at 80°C for 2 h in screw-top NMR tubes. [b] 25°C for 24 h. [c] Yield and conversion based on Ru alkylidene were determined by ^{1}H-NMR with phenyltrimethylsilane as the internal standard.

accessible substrate upon facile condensation of the corresponding aldehyde with tosyl hydrazine.[35] When one equiv of (PCy$_3$)$_2$RuCl$_2$(CHPh) (**17**) was treated with substrate **14** under air, 17 % of the ring-closing olefination product (**15**) was observed (Table 1, Entry 1). Changing to N-heterocyclic carbene (NHC) variant, **18**, afforded **15** in greater yield (42 %, Table 1, Entry 2). Productive ring-closing olefination was further amplified (57 %) by employing the fast-initiating variant,[36] **19**. Ultimately, the most thermally stable complex, **20**,[37,38] afforded the greatest yield of alkene product **15** (85 %, Table 1, Entry 5). Consistent with literature precedent, complexes **17–20** undergo initial reaction with the alkene moiety in **14** to form the corresponding ruthenium alkylidenes, which results in the concomitant formation of the styrene byproduct **16** in yields ranging from 75–85 %.[39] Interestingly, since we observed different amounts of olefination product **15** across all metal complexes evaluated, these results suggest that a step after initiation dictates the reaction efficiency.[40] After identification of **20** as the optimal alkylidene source for ruthenium-promoted ring-closing olefination of tosyl hydrazone **14**, we next explored electronically distinct C=N π-bond analogs differing in their nitrogen-substitution (Table 2).

Notably, although aldehyde **22** underwent precatalyst initiation to form styrene **21**, no formation of olefination product **15** was observed (Table 2, Entry 1). Similarly, aryl, alkyl, and sulfinyl-substituted imines **23–25** did not produce **15**, with styrene **21** being the only discernable product formed from precatalyst intitiation (Table 2, Entries 2–4). Analogous to aldehyde **22**, we attribute this lack of metathesis reactivity to the higher electrophilicity of the imine carbon, which renders them unproductive for olefination. In comparison, tosyl hydrazone **14** reacts readily with **20** to

form **15** in 85 % yield (Table 2, Entry 5). Benzoyl hydrazones and Boc-protected hydrazones (**26** and **27**) resulted in the desired product in 61 % and 68 % yields, respectively (Table 2, Entries 6 and 7) while the disubstituted *N,N*-dimethyl hydrazone **28** only led to trace amounts of the olefination product **15** (Table 2, Entry 8). Additionally, oximes were also productive substrates in ruthenium-promoted ring-closing olefinations. Specifically, methyl and benzyl substituted oximes **29** and **30** led to the desired product **15** in 50 % and 54 % yield, respectively (Table 2, Entries 9 and 10). More sterically encumbered oximes containing *tert*-butyl and adamantyl groups (**31**, **32**) resulted in increased yields of 66 % and 78 %, respectively (Table 2, Entries 11 and 12). The observed reactivity of oximes is consistent with our design rationale that reduced imine π-bond polarity enables olefination with ruthenium alkylidenes.

Subsequent optimization of reaction conditions focused on the evaluation of solvents for the olefination of hydrazones and oximes, using adamantyl oxime **32** as substrate (Table 3).[41] Conducting the reaction in aromatic solvents benzene and toluene, led to the highest yields of cyclopentene **15** observed in up to 87 % after 16 hours at 80 °C (Table 3, Entry 1). In comparison, chlorinated solvents such as chloroform and dichloromethane also enabled the formation of cyclopentene **15** in up to 72 % yield, albeit requiring longer reaction times of up to 40 hours (Table 3, Entries 3 and 4). Notably, the olefination of oximes also proceeds in more coordinating solvents including acetonitrile, tetrahydrofuran, acetone, and dimethylsulfoxide, albeit in overall lower yields ranging from 51 %

Table 2: Evaluation of substrates incorporating electronically diverse C=N π-bonds.[a]

EtO$_2$C CO$_2$Et → **20** (1.0 equiv), benzene-d$_6$, 80 °C, 30 min → EtO$_2$C CO$_2$Et (**15**) + O^{i}Pr (**21**)

1.2 equiv
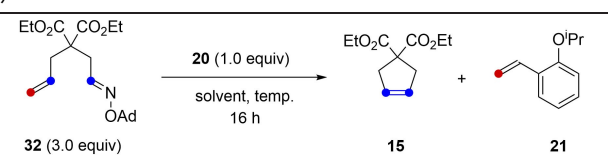
entry	substituent Y-X	ratio (*E:Z*)	conv. **20** (%)	yield **15** (%)	yield **21** (%)	
1	O (**22**)	-	0	0	14	
2	N-Ph (**23**)	> 20:1	72	0	52	imines
3	N-^{i}Pr (**24**)	> 20:1	76	0	76	imines
4	N-S(O)^{t}Bu (**25**)	> 20:1	89	0	72	imines
5	N-NHTs (**14**)	3:1	85	85	85	hydrazones
6	N-NHBz (**26**)	> 20:1	75	61	72	hydrazones
7	N-NHBoc (**27**)	> 20:1	98	68	75	hydrazones
8	N-NMe$_2$ (**28**)	> 1:20	83	5	79	hydrazones
9	N-OMe (**29**)	3:2	88	50	82	oximes
10	N-OBn (**30**)	3:2	77	54	64	oximes
11	N-O^{t}Bu (**31**)	2:1	79	66	74	oximes
12	N-OAd (**32**)	> 20:1	87	78	83	oximes

[a] Conditions: **20** (0.01 mmol), substrate (1.2 equivalents), (0.0145 M) in benzene-d$_6$ at 80 °C for 0.5 h in screw-top NMR tubes. Yield and conversion based on **20** were determined by ^{1}H-NMR with phenyltrimethylsilane as the internal standard.

Table 3: Solvent evaluation of the ruthenium-mediated olefination of hydrazones and oximes.[a]

EtO$_2$C CO$_2$Et → **20** (1.0 equiv), solvent, temp. 16 h → EtO$_2$C CO$_2$Et (**15**) + O^{i}Pr (**21**)

32 (3.0 equiv)

entry	solvent	temp. (°C)	yield **15** at 2h (%)[b]	yield **15** at 16h (%)[b]
1	benzene-d$_6$	80	79	87
2	toluene-d$_8$	80	75	85
3	CDCl$_3$	60	38	72
4	CD$_2$Cl$_2$	40	17	61[c]
5	acetonitrile-d$_3$	80	55	59
6	THF-d$_8$	60	64	66
7	acetone-d$_6$	60	50	74
8	DMSO-d$_6$	80	47	51
9	methanol-d$_4$	60	47	35[d]

[a] Conditions: **20** (0.01 mmol), **32** (3.0 equivalents), in deuterated solvent (0.0145 M) under N$_2$ atmosphere at various temperatures (40, 60, or 80 °C) for 0.5–16 h in screw-top NMR tubes. [b] Yield and conversion based on **20** were determined by ^{1}H-NMR with phenyltrimethylsilane as the internal standard. [c] 40 °C for 40 h. [d] Addition of MeOH to Grubbs-type Ru alkylidene catalysts leads to formation of Ru hydride species which isomerize the olefin product **15** resulting in lower yield at extended reaction times.[42,43]

to 74 % (Table 3, Entries 5–8). Productive olefination of adamantyl oxime **32** was also observed in methanol to form cyclopentene **15** in 47 % yield after 2 hours at 60 °C but resulted in lower yield of 35 % at 16 hours, presumably due to olefin isomerization (Table 3, Entry 9).[42,43]

With the optimized conditions for the olefination of hydrazones and oximes established, we next explored the substrate scope for this transformation to access a variety of structurally diverse alkene products (Table 4).[44] Specifically, we focused on the evaluation of benzoyl hydrazones differing in their overall substitution pattern. The products are typically used as benchmarks for the development of new metal alkylidene catalysts in olefin-olefin metathesis.

Hydrazone **26** forms cyclopentene **15** in 82 % yield, while its one-carbon homologue **33** results in the corresponding 6-membered olefination product **34** in 88 % yield (Table 4). In contrast to traditional olefin–olefin metathesis, the formation of cycloheptene **36**[45] was not observed when hydrazone **35** was converted under the optimal reaction conditions, suggesting that overcoming the increased entropy required for ring-closure is challenging. Notably, the optimized reaction conditions for the olefination of hydrazones and

oximes tolerated the presence of additional Lewis basic sites in the substrate such as Boc and Ts protected amines (**37** and **39**) forming the corresponding ring-closing products **38** and **40** in 41 % and 45 % yield, respectively (Table 4). Additionally, ether functionalities (**41** and **43**) are compatible, affording cyclic ethers **42** and **44** in 54 % and 63 % yield, respectively. Furthermore, aryl hydrazone **45** produced indene **46** in 40 % overall yield (Table 4). Next, the effect of distinct olefin substitution was investigated for the formation of cyclopentene **48**. Specifically, allyl substrate **47** bearing *t*Bu ester groups resulted in 45 % yield of the desired olefination product **48** while crotyl-derived substrate **49** formed cyclopentene **48** in diminished yields of 25 % (Table 4). Importantly, phenyl-bearing alkene **50** and the trisubstituted alkene **51** did not form the desired olefination product **48** and no initiation was observed, suggesting cross metathesis between the ruthenium alkylidene and alkene substrate is hampered. Interestingly, observations made in comparable olefin-olefin metathesis reactions reported that prenyl- and styrenyl-containing substrates are slow to initiate intermolecularly with ruthenium alkylidenes.[46] A variety of substitution patterns besides esters were also

Table 4: Substrate scope of the olefination of hydrazones and oximes as compared to classic substrates used in olefin–olefin metathesis.[a]
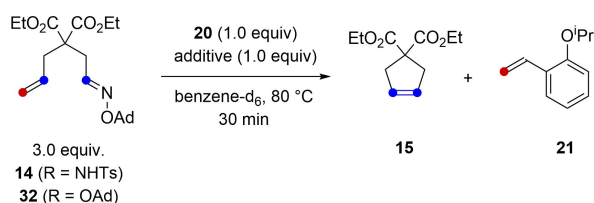

variation				heteroatoms		α to hydrazone
substrates	**26**	**33**	**35**	**37**	**39**	**41**	**43**	**45**
products	**15**	**34**	**36**	**38**	**40**	**42**	**44**	**46**
yield[b]	82%	88%	0%	41%	51%[c]	54%	63%	40%

variation	olefin variation		β to hydrazone	α to hydrazone		β to hydrazone		
substrates	**47** (R = H) **49** (R = Me) **50** (R = Ph)	**51**	**52**	**54**	**56** (R = H) **58** (R = Ph)	**60**	**62**	**64** (R = H) **66** (R = TBS)
products	**48**	**48**	**53**	**55**	**57** **59**	**61**	**63**	**65** **67**
yield[b]	45% (from **47**) 25% (from **49**) 0% (from **50**)	0%[d]	47%	47%	58%[e] (**57**, R = H) 0% (**59**, R = Ph)	38%	40%	0% (**65**, R = H) 36% (**67**, R = TBS)

[a] Conditions: **20** (0.01 mmol), substrate (1.2 equivalents) in benzene-d$_6$ (0.0145 M) at 80 °C for 2–16 h in screw-top NMR tubes. [b] Yield determined by ^{1}H-NMR using phenyltrimethylsilane as the internal standard. [c] Mixture of alkene isomers. [d] Does not initiate upon prolonged heating (7 d). [e] With **18** instead of **20**.

tolerated, including cyclohexane **52**, forming spirocycle **53** in 47 % yield. The methyl/phenyl substituted hydrazone **54** resulted in the desired olefination product **55** in 47 % yield (Table 4). Substitution in α-position to the hydrazone **56** was compatible affording cyclopentene **57** in 58 % yield. However, diphenyl hydrazone **58** failed to result in the formation of cyclopentene **59**, presumably due to increased steric hindrance close to the reactive site(s) (Table 4). Similarly, amide functionalities and halides are tolerated under the optimal conditions as demonstrated in the formation of **61** and **63** in 38 % and 40 %, respectively. Interestingly, a secondary hydroxyl-containing substrate **64** failed to undergo the desired transformation while the silyl-protected analog resulting in **67** in 36 % yield. Notably, conducting the transformation with equimolar amounts of ethanol (Figure 3) does not significantly inhibit the transformation, which suggests that the hydroxyl group in alcohol **64** may negatively impact reactivity. This is presumably due to a strong interaction between the hydroxyl group and the ruthenium center, forming a 5-membered ring chelate. These results demonstrate the robust nature of this method to access a variety of alkene products differing in their substitution in up to 88 % yield.

We subsequently evaluated the robustness[47] of the ruthenium alkylidene-mediated olefination of oximes and hydrazones by subjecting either hydrazone **14** or oxime **32** to the optimized reaction conditions in the presence of one equivalent of various additives (Figure 3). Notably, the addition of equimolar amounts of benzyl alcohol, chloroalkanes, nitriles, ethanol, and nitroalkanes resulted in cyclopentene **15** with less than 10 % decrease in overall yield, suggesting a high level of functional group tolerance. All reactions were carried out under air without the need for Schlenk technique, highlighting the synthetic simplicity of our system.

To showcase the synthetic potential of this new methodology, we examined a substrate (**68**) containing both carbonyl and oxime functional groups. Importantly, both moieties are found in many compounds of biological importance, and we hypothesized that the *type* of heteroatom could bias reactivity with a given metal alkylidene (Figure 4). We found that both the Schrock alkylidene (**72**) and Tebbe's reagent (**73**) react at the carbonyl in **68**, resulting in the selective formation of either the carbonyl-
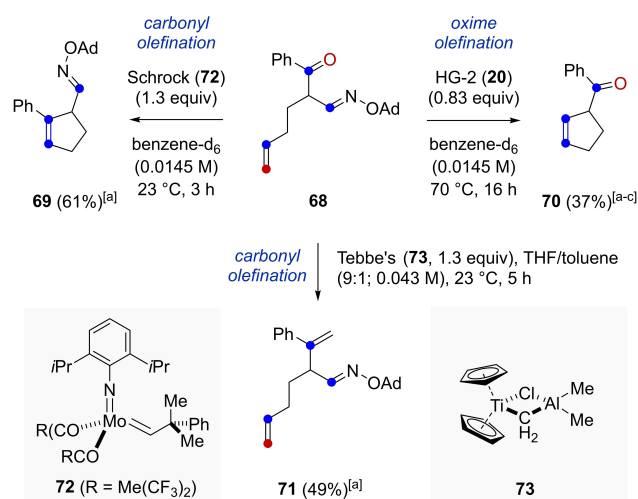

Figure 4. Divergent reactivity of carbonyls and oximes with Schrock's complex (**72**), HG-2 (**20**), and Tebbe's reagent (**73**) to enable selective carbonyl-olefin metathesis, oxime olefination, and carbonyl olefination. [a] Yield determined by ¹H-NMR using phenyltrimethylsilane as internal standard. [b] Yield relative to equivalents of HG-2 (**20**) used. [c] Isolated as mixture of alkene isomers.

olefin metathesis product **69** (61 % yield), or alternatively, the carbonyl olefination product **71** (49 % yield). In contrast, the reaction with HG-2 (**20**) afforded a unique outcome: *exclusive* formation of cyclopentene **70** in 37 % yield as the oxime olefination product (**69** and **71** not observed). This difference in the reaction selectivity as a function of the metal alkylidene highlights unique orthogonal reactivity pathways that are available. We anticipate that this distinct reactivity profile of hydrazine and oxime olefinations enabled when using HG-2 (**20**) will provide new and important avenues for the development of selective syntheses in complex settings.

To address the feasibility of a catalytic reaction protocol, we investigated the kinetic accessibility of ruthenium products towards derivatization. When hydrazone **26** is converted under optimal reaction conditions with Ru-alkylidene **19** followed by addition of excess 1,2-bis(diphenylphosphino)ethane (dppe), the desired olefination product **15** is isolated in 49 % yield together with equal amounts of *trans*-RuCl₂(dppe)₂ (Figure 5). This result suggests that the ruthenium-containing product can be rescued
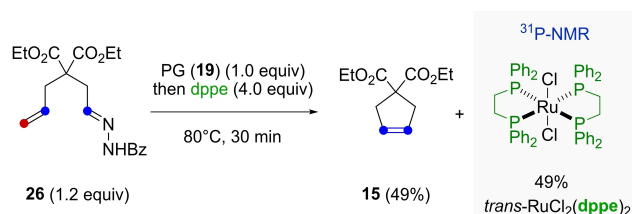

Yield of **15** starting from **14** with additive (1.0 equiv): BnOH (89%), dichloroethane (80%); acetonitrile (79%); ethanol (76%); MeNO₂ (82%); none (84%).

Yield of **15** starting from **32** with additive (1.0 equiv): BnOH (89%), dichloroethane (78%); acetonitrile (76%); ethanol (72%); MeNO₂ (70%); none (83%).

Figure 3. Robustness of the ruthenium-mediated olefination of hydrazones and oximes.

Figure 5. Isolation of a known ruthenium derivative following hydrazone olefination.

into a well-defined form post olefination reaction to be available for subsequent transformations.

In conclusion, we report the development of hydrazone and oxime olefinations in ring-closing reactions mediated by ruthenium alkylidenes. In comparison to literature reports of imine–metal alkylidene metathesis based on early transition metals, the method described herein is characterized by its operational simplicity and overall robustness. A variety of functional groups are tolerated affording the corresponding olefination products in up to 88 % yield. In comparison to established protocols for imine–metal alkylidene metathesis, our design principle for the direct olefination of hydrazones and oximes relies on the reduced polarity of C=N π-bonds to enable reactivity with ruthenium alkylidenes. Investigations into the mechanism for this reaction are currently ongoing.

Conflict of Interest

The authors declare no conflicts of interest.

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