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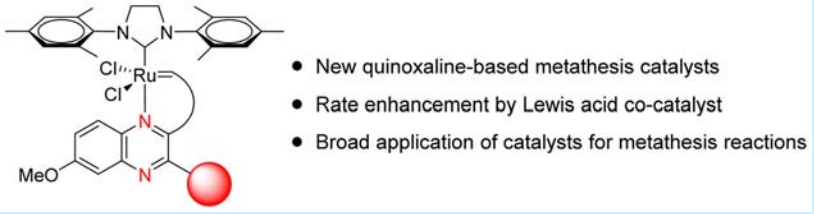
The Discovery of Quinoxaline-Based Metathesis Catalysts from Synthesis of Grazoprevir (MK-5172)

Michael J. Williams,* Jongrock Kong,* Cheol K. Chung, Andrew Brunskill, Louis-Charles Campeau, and Mark McLaughlin

Department of Process and Analytical Chemistry, Merck Research Laboratories, Rahway, New Jersey 07065, United States

Supporting Information

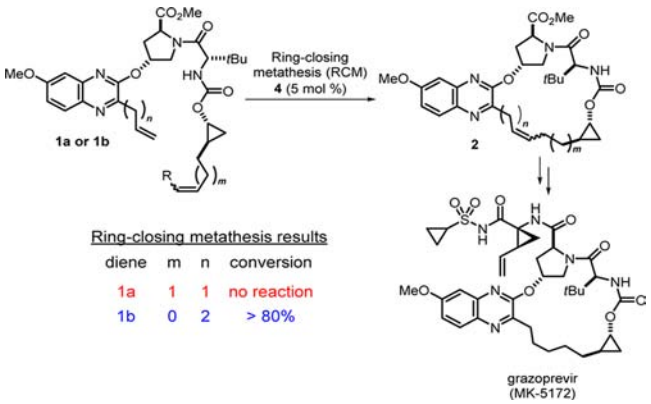


ABSTRACT: Olefin metathesis (OM) is a reliable and practical synthetic methodology for challenging carbon−carbon bond formations. While existing catalysts can effect many of these transformations, the synthesis and development of new catalysts is essential to increase the application breadth of OM and to achieve improved catalyst activity. The unexpected initial discovery of a novel olefin metathesis catalyst derived from synthetic efforts toward the HCV therapeutic agent grazoprevir (MK-5172) is described. This initial finding has evolved into a class of tunable, shelf-stable ruthenium OM catalysts that are easily prepared and exhibit unique catalytic activity.

Olefin metathesis (OM) has emerged as a powerful carbon−carbon bond forming methodology with applications encompassing natural product total syntheses[1] and industrial processes (e.g., chemical,[2] polymer,[3] and pharmaceutical[4]). In order to increase the application breadth of OM, catalyst properties are continually optimized to their peak performances (e.g., yield, selectivity, turnover-number, functional group compatibility), often by the introduction of new ligand frameworks.[5] We envisioned olefin metathesis as the key bond-forming reaction to establish the macrocyclic backbone of the HCV NS3/4a protease inhibitor grazoprevir (MK-5172).[6] During these efforts, we identified the intermediacy of a novel, isolable ruthenium complex. Herein, we present the evolution of this finding into a new class of metathesis catalysts and demonstrate its unique properties.

Discovery of the ligand framework emerged from a collection of unexpected experimental findings. Initial studies on the ring closing metathesis (RCM) of substrates **1a** and **1b** revealed that the yield of macrocyclization depended greatly on the relative length of both olefin side chains (Scheme 1). Notably, exposure of allyl quinoxaline substrate **1a** to RCM conditions failed to afford any desired product while use of homoallyl **1b** led to a high yield of macrocycle **2**.[7] Similarly, attempts to perform the intermolecular homodimerization of intermediate **3** only generated trace product, but the system readily underwent cross metathesis (CM) with the addition of an exogenous donor olefin.[8] These observations led us to hypothesize that homoallyl substrate **3** undergoes initial alkylidene formation, but does not complete the catalytic cycle to form a dimer and regenerate the catalyst, instead persisting as complex **5**, a stable six-membered chelate.[9]

Scheme 1. RCM Approach toward Grazoprevir (MK-5172)



Competition experiments using ^{1}H NMR spectroscopy supported this hypothesis, revealing that the stoichiometric treatment of substrate **3** with a Hoveyda−Grubbs second generation catalyst (**4**) did indeed result in the appearance of a new alkylidene triplet at 18.6 ppm vs the benzylidene singlet at 16.5 ppm in the starting material. After aging the sample overnight, the triplet/singlet ratio was approximately 5:1 showing favorable equilibrium toward the alkylidene formation

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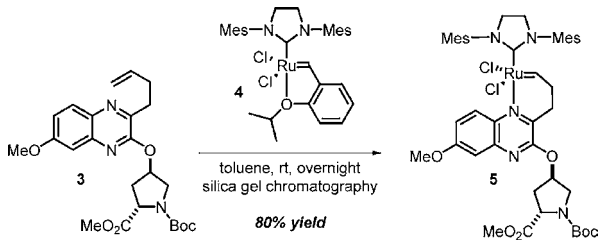
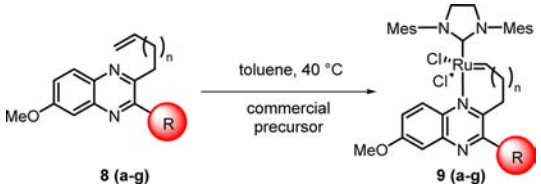
over the benzylidene. Complex **5** was isolated from the reaction mixture in 80% yield after silica gel chromatography (Scheme 2).

Scheme 2. Initial Discovery and Isolation of Quinoxaline Based Complexes



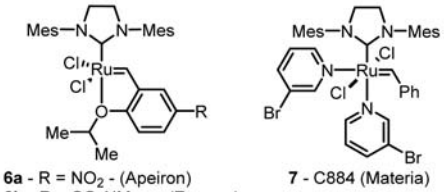
With complex **5** as the basis of our catalyst design, we sought to pursue an accessible, simplified version with greater modularity. We prepared a set of complexes that probed the structure–activity relationship around the chelating quinoxaline ligand by replacing the proline moiety with alternative substituents (Table 1). Compounds were easily synthesized featuring electron-donating and -withdrawing substituents (**9a**–**9f**), and two alkylidene chain lengths (**9a** and **9g**), highlighting the quinoxaline ligand's modularity. Under optimized conditions, all the complexes described could be isolated via crystallization directly from the relevant reaction mixtures in good to excellent yields.[10] These complexes are strikingly stable, as demonstrated by a series of solution phase and solid-state experiments.[11] In particular, complex **9a** was observed to not undergo *trans* → *cis* rearrangement during handling.[12] We suggest this stability is attributable to (1) the formation of a strong steric repulsion between the quinoxaline moiety and the mesitylene rings of the *N*-heterocyclic carbene (NHC) if the ligand were to adopt the *cis*-configuration (Figure 1) and (2) electronic factors.[12e]

Table 1. Synthesis of Quinoxaline Complexes (9a–9g)



8 (a-g) 9 (a-g)

entry	quinoxaline (8)	R	n	commercial precursor	yield 9 (%)[a]
1	8a	O*i*Pr	1	6a	82
2	8a	O*i*Pr	1	6b	98
3	8b	SMe	1	6b	97
4	8c	NMe_2	1	6b	98
5	8d	OMe	1	6b	99
6	8e	S*i*Pr	1	6a	80
7	8f	SO_2*i*Pr	1	6a	85
8	8g	O*i*Pr	0	6a	91
9	8g	O*i*Pr	0	6b	91
10	8g	O*i*Pr	0	7	77



6a - R = NO_2 - (Apeiron)
6b - R = SO_2NMe_2 - (Zannon)
7 - C884 (Materia)

[a]Isolated yields.

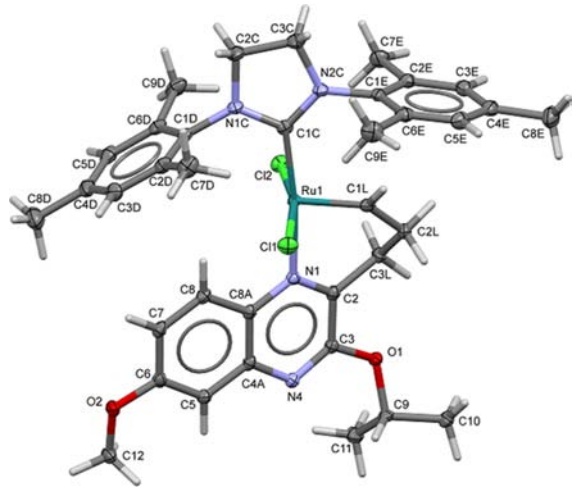


Figure 1. Crystal structure of complex **9a** with thermal ellipsoids drawn at the 50% probability level. Selected bond distances (Å) and angles (deg): Ru1–Cl1 = 2.381, Ru1–Cl2 = 2.378, Ru1–N1 = 2.158, Ru1–C1C = 2.039, Ru1–C1L = 1.814; Cl1–Ru1–Cl2 = 166.53°, C1L–Ru1–N1 = 89.42°, C1C–Ru1–N1 = 172.77°.

We examined the metathesis activity of our new catalysts using the heterocyclic precursor, *tert*-butyl diallylcarbamate (**10**, eq 1), as an RCM substrate (Figure 2). Initial observations revealed competent metathesis activity with faster kinetic profiles using catalysts featuring an electron-withdrawing substituent (cf. complex **9f** vs complexes **9a** and **9c**).[13] Much like the analogous observation with macrocycle **1a**, little to no metathesis activity was observed when the alkylidene chain length was shortened from homoallyl to allyl: complex **9g** promoted <1% conversion of compound **10** to the desired RCM product **11** when treated under the same conditions.

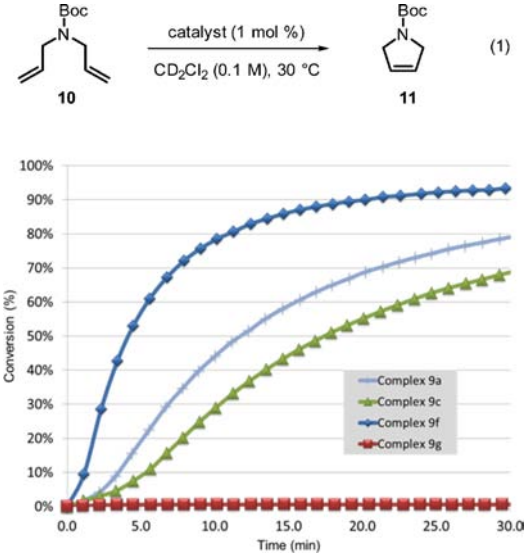


Figure 2. RCM of *tert*-butyl diallylcarbamate **10** with complexes **9a**, **9c**, **9f**, and **9g**. Conditions: **10** (0.1 M), catalyst (1 mol %; 0.001 M), in CD_2Cl_2 at 30 °C. Conversion was measured by ^{1}H NMR spectroscopy.

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Given that electron-deficient catalysts were more active in the RCM reaction, we envisioned that the reaction kinetics could be accelerated by protonation of the quinoxaline ligand with an acid co-catalyst. Protonation should create a more electron-deficient ligand and concomitantly decrease the Ru−N bond strength.[14] We were pleased to find that the addition of catalytic Brønsted acid (5 mol % benzenesulfonic acid, BSA) to a mixture of complex **9a** (1 mol %) and diethyl diallylmalonate (**12**) resulted in a significant enhancement of the reaction rate (Figure 3).

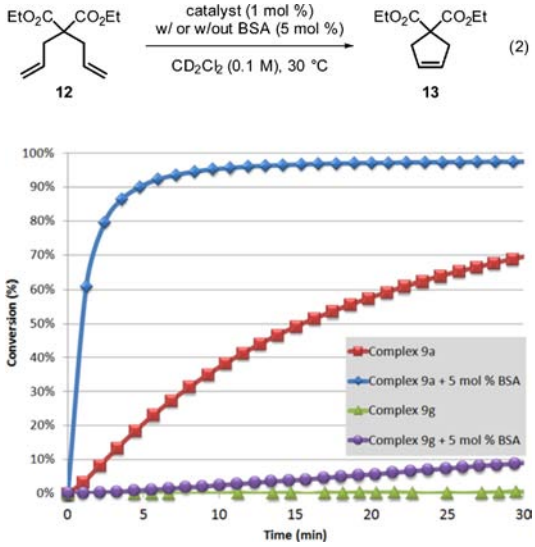


Figure 3. RCM of diene **12** with catalysts **9a** and **9f** in the presence and absence benzenesulfonic acid (5 mol %); Conditions: CD_2Cl_2 (0.1 M), catalyst loading (0.005 M), at 30 °C. Conversion was measured by ^1H NMR spectroscopy. BSA = benzenesulfonic acid.

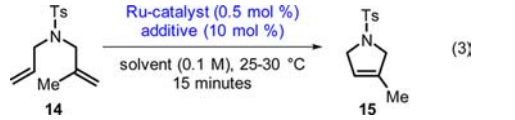
When BSA was added to a mixture of previously inactive complex **9g** and malonate **12**, metathesis activity was then observed (~10% conversion over 0.5 h). Despite achieving only a modest level of conversion under these conditions, the ability to initiate metathesis in the presence of BSA demonstrated the potential latent utility of these complexes.

Encouraged by the positive result of using BSA as an activator, we pursued a high-throughput experimentation (HTE) approach to define an optimal co-catalyst. An array of Brønsted and Lewis acids, along with three Ru complexes, were screened in the RCM of diene **14** to form dihydropyrrole **15**. This screen revealed that $AlCl_3$, BSA, and HBF_4 were found to have the greatest benefit to the reaction rate relative to control reactions (Table 2).

The reactivity of catalyst **9a** was fully evaluated in the presence and absence of catalytic $AlCl_3$ for metathesis reactions (Table 3).[15] The RCM reactions with precursors **14** and **16** proceeded in excellent yields in the absence of co-catalyst (91.9−98.7%, entries 3−4 and 7−8) in both DCM and toluene. However, both reactions, when treated with catalytic $AlCl_3$, proceeded to completion in 0.5 h versus 6 h without (94.5−99.8% yield, entries 1−2 and 5−6). The ring opening metathesis polymerization (ROMP) of cyclooctadiene (**18**) was shown to proceed in excellent conversion in the presence and absence of catalytic $AlCl_3$ in CD_2Cl_2 (95.6−99.1% conversion, entries 5 and 6). The CM of 1-hexene (**20**) also proceeded to high conversion (97−99%, entries 11 and 12) in the presence and absence of catalytic $AlCl_3$.

Having demonstrated the broad applicability of complex **9a**, we then determined whether the less reactive complex **9g** was

Table 2. Thermal Plot from Lewis and Brønsted Acid Co-catalysts HTE Screening



solvent	complex	HOAc	BSA	HCl[a]	HBF_4	TFA	TFMSA	CSA	TCA	HI	$ZnCl_2$[b]	$AlCl_3$[c]	control
DCE	9a	9	80	87	87	87	51	87	87	75	6	88	18
	9c	31	94	84	97	75	45	65	75	62	11	96	29
	9g	0	6	0	2	0	1	0	0	0	0	5	0
toluene	9a	59	86	78	93	89	44	87	86	69	18	92	59
	9c	70	94	76	97	83	33	73	79	82	31	95	73
	9g	0	2	0	1	0	1	0	0	0	0	0	0

[a]HCl in dioxane. [b]$ZnCl_2$ in THF (0.5 M). [c]$AlCl_3$ in THF (0.5 M). Conditions: **14** (0.1 M), 100 μL solvent, and 0.5 mol % of complex with 10 mol % of additive. Chart numbers represent solution yield (%) as measured by UPLC-MS analysis, and colors indicate yield (highest yield = green; lowest yield = red). See the Supporting Information for complete details. HOAc = acetic acid, BSA = benzenesulfonic acid, TFA = trifluoroacetic acid, TFMSA = trifluoromethanesulfonic acid, CSA = camphorsulfonic acid, TCA = trichloroacetic acid; DCE = 1,2-dichloroethane.

Table 3. Metathesis Reactions Using Complex 9a

entry	substrate	product	time (h)	$AlCl_3$ (mol %)	solvent	conv % (yield %)
1[a]	NTs (16)	N−Ts (17)	0.5	20	DCM	100 (99.8)
2[a]			0.5	20	tol	100 (94.5)
3[b]			6	0	DCM	99 (98.6)
4[b]			6	0	tol	100 (98.7)
5[a]	Me, NTs (14)	Me, N−Ts (15)	0.5	20	DCM	97 (94.2)
6[a]			0.5	20	tol	100 (95.0)
7[b]			6	0	DCM	93 (91.9)
8[b]			6	0	tol	100 (95[e])
9[c]	(18)	n (19)	1	2	CD_2Cl_2	99 (-)
10[c]			1	0	CD_2Cl_2	96 (-)
11[d]	2 (20)	2, 2 (21)	16	20	tol - d_8	99 (-)
12[d]			16	0	tol - d_8	97 (-)

[a]Conditions: **14** or **16** (0.1 M) in DCM or tol, 1 mol % **9a**, $AlCl_3$·THF complex (0.5 M in THF, 20 mol %), 30 °C. [b]Conditions: **14** or **16** (0.1 M) in DCM or tol, 1 mol % **9a**, 30 °C. [c]Conditions: **18** (0.1 M) in CD_2Cl_2, 0.1 mol % **9a**, 0 or 2 mol % $AlCl_3$·THF complex (0.5 M in THF), 30 °C; conversion based upon ^1H NMR analysis. [d]Conditions: **20** (0.1 M) in tol-d_8, 1 mol % **9a**, 0 or 20 mol % $AlCl_3$·THF complex (0.5 M in THF), 23 °C; conversion based upon ^1H NMR analysis. [e]Isolated yield. See the Supporting Information for details. Ts = *para*-toluenesulfonyl, DCM = dichloromethane, tol = toluene.

capable of inducing efficient latent catalysis.[16] Consistent with the results from Table 2, we observed only marginal effects using acidic activation for the CM of 1-hexene (**20**) to 5-decene (**21**) but were delighted to find that thermal activation indeed led to the desired latency effect (Table 4). Less than 5% conversion was observed after 24 h at ambient temperature, and only 8% conversion at 50 °C, but 90% conversion to the desired product was observed upon increasing the temperature to 95 °C. This

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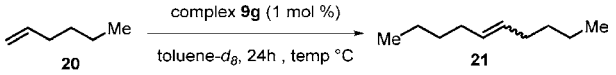
Table 4. CM of 1-Hexene (20) in the Presence of Complex 9g



entry[a]	temp (°C)	conversion (%)[b]
1	23	<5
2	50	8
3	75	27
4	95	90

[a]Conditions: The concentration of 1-hexene (**20**) in toluene-d_8 was 0.5 M, and the reactions were carried out in a sealed tube under a nitrogen atmosphere. [b]Conversion was determined via ^{1}H NMR spectroscopy where product was cleanly observed.

experiment highlights one of the unique properties of this catalyst in its ability to modulate reactivity based on reaction temperature.

In summary, we have transformed a serendipitous discovery of an intermediate Ru-complex derived from our work on the synthesis of grazoprevir (MK-5172) into a highly tunable metathesis catalyst class. The ruthenium complexes are isolated in good to excellent yields, are shelf- and solution-stable for extended periods, and exhibit wide-ranging metathesis activities including active to latent catalysis. Furthermore, we have successfully designed and explored a strategy for modulating metathesis reactivity using acids as competent co-catalysts or by modulating the reaction temperature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00070.

Crystallographic data (CIF)

Experimental details, characterization data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: michael.williams222@icloud.com.

*E-mail: jongrock.kong@merck.com.

Notes

The authors declare no competing financial interest.

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(5) For representative reviews on ligand classes, see corresponding chapters in ref 2a.

(6) See: Kuethe, J.; Zhong, Y.-L.; Yasuda, N.; Beutner, G.; Linn, K.; Kim, M.; Marcune, B.; Dreher, S. D.; Humphrey, G.; Pei, T. *Org. Lett.* **2013**, *15*, 4174 and references therein.

(7) The manuscript related to this subject matter is currently in preparation and will be reported in due time.

(8) The reaction proceeded to 100% conversion over 1 h with 5 equiv of 1,4-diacetoxy-cis-2-butene at 80 °C.

(9) The serendipitous discovery of novel OM complexes has occurred previously. See: (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (b) Tallarico, J. A.; Bonitatebus, P. J., Jr.; Snapper, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 7157.

(10) A variety of commercial *N*-heterocyclic carbene (NHC)-containing OM catalysts were utilized as the starting material.

(11) Complex **9a** demonstrated solution stability up to 30 days in CD_2Cl_2 at room temperature under nitrongen, and the solid material showed shelf stability up to 6 months.

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