

Appendix B

Additional Results in Asymmetric Metathesis

As described in Chapters 2–4 and Appendix A, catalysts **2–7** and their diiodide analogues have been prepared and applied to asymmetric ring-closing metathesis (ARCM), asymmetric ring-opening cross metathesis (AROCM), and asymmetric cross metathesis (ACM). Described in this appendix are the following: an attempt to employ these catalysts in ARCM to form nitrogen-containing heterocycles, an examination of the enantioselectivity of catalysts **2–6** for an expanded number of AROCM substrates, and efforts towards the kinetic resolution of racemic terminal olefin-containing molecules via ACM.

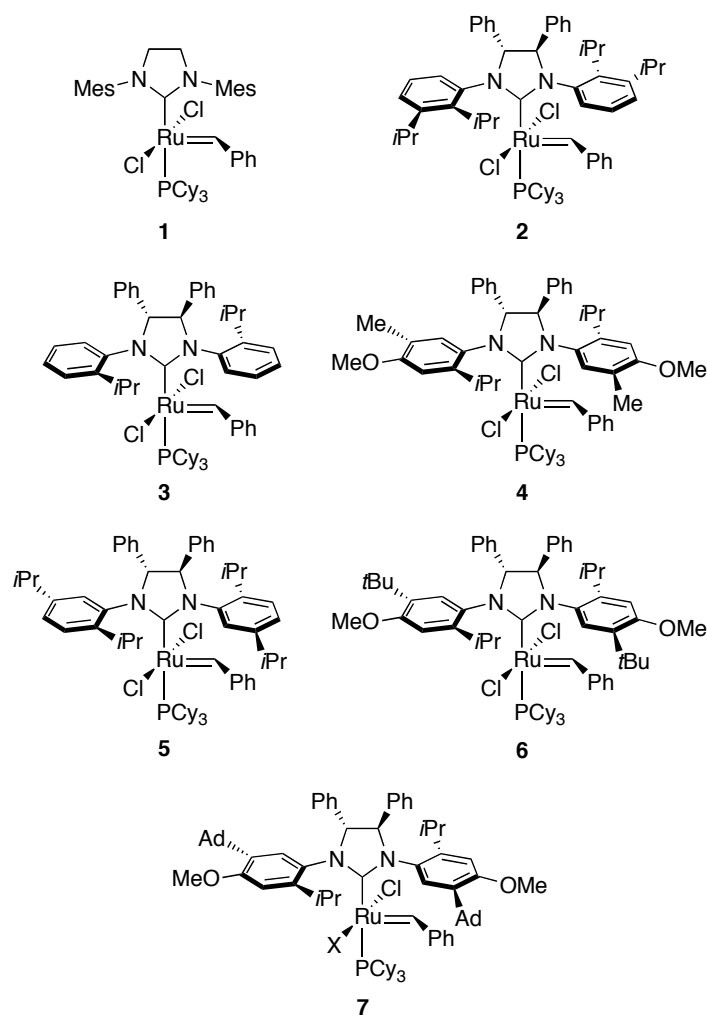
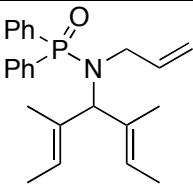
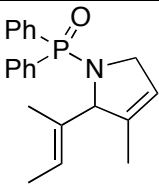
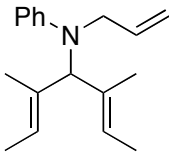
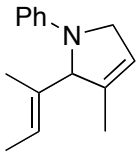


Figure B.1. Ruthenium olefin metathesis catalysts.

As described in Chapter 3, catalysts **2–6** have been successfully employed in ARCM to form oxygen-containing heterocycles. Given the biological importance of nitrogen-containing heterocycles, we sought to extend our ARCM methodology to their preparation. This work was done in collaboration with undergraduate Jane Wang. Two initial substrates were prepared. The nitrogen was protected as a phosphoramidate in one case and as an aniline in the other. It was envisioned that while the phosphoramidate might coordinate to the catalyst, the aniline would not. Unfortunately, neither substrate gave good enantioselectivity, and the use of the diiodide analogues of **2** and **3** resulted in no improvement in *ee* (Table B.1).

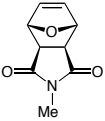
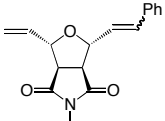

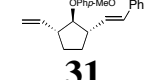
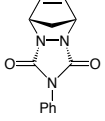
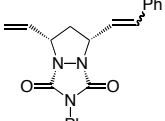
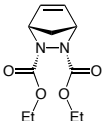
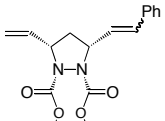
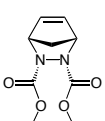
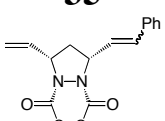
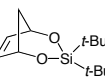
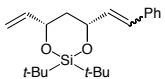
Table B.1. ARCM to form N-containing heterocycles

Substrate	Product	Catalyst	<i>ee</i> [%]
 <p>8</p>	 <p>9</p>	3	0
 <p>10</p>	 <p>11</p>	2	17
		3	10

In the course of the AROCM work reported in Chapter 4, a full study of the enantioselectivity of catalysts **2–6** was undertaken with a number of substrates. The complete results of those efforts are reported here (Table B.2).

Table B.2. Enantioselectivity of **2–6** for AROCM

Substrate	Product	Catalyst ^a	<i>ee</i> (E) [%]	<i>ee</i> (Z) [%] ^b
 12	 13	2	47 (<i>ent</i> - 13)	ND
		3	29 (<i>ent</i> - 13)	6 (<i>ent</i> - 13)
		5	62	ND
		6	76	40(<i>ent</i> - 13)
 14	 15	3	33(<i>ent</i> - 15)	5
		5	16	8 (<i>ent</i>)
		6	57	31
 16	 17	2	51(<i>ent</i> - 17)	30
		3	39(<i>ent</i> - 17)	17
		5	13(<i>ent</i> - 17)	44
		6	41	34
 18	 19	3	36(<i>ent</i> - 19)	14(<i>ent</i> - 19)
		6	33	29(<i>ent</i> - 19)
 20	 21	6	25	28(<i>ent</i> - 21)
 22	 23	3	23(<i>ent</i> - 23)	9(<i>ent</i> - 23)
		6	81	22(<i>ent</i> - 23)
 24	 25	3	41(<i>ent</i> - 25)	15(<i>ent</i> - 25)
		6	55	29(<i>ent</i> - 25)
 26	 27	6	60	ND

		3	31(<i>ent</i> - 29)	14
28	29	5	38(<i>ent</i> - 29)	33
		6	26	42
		3	24(<i>ent</i> - 31)	NA
30	31	5	6	NA
		6	46	NA
		3	30(<i>ent</i> - 33)	38
32	33	5	18	55
		6	67	16
		3	32(<i>ent</i> - 35)	28
34	35	5	8(<i>ent</i> - 35)	42
		6	20	21
		3	27(<i>ent</i> - 37)	31
36	37	5	8(<i>ent</i> - 37)	46
		6	22	8
		3	41	NA
38	39	5	36	NA
		6	30	NA

^aConditions: catalyst 1 mol%, substrate 0.1 mmol, styrene 1.0 mmol, CH₂Cl₂ 1.5 ml.

^bAbsolute stereochemistry known for **13**, **19**, **21**, **23**, **25**. *cis*-**15** obtained with **5** is enantiomeric to *cis*-**15** obtained with **3** and **6**.

ND = not determined. NA = not available, no Z product.

There are a few trends that emerge from this table:

- For most of the substrates, catalyst **6** gives the best *ee* for the E-isomer.
- For all of the substrates except **38**, catalysts **3** and **6** give opposite absolute stereoisomers of the Z-isomer products.
- For most of the substrates, catalyst **5** gives the best *ee* for the Z-isomer.
- For all substrates except **14**, only one stereoisomer of each Z-isomer is produced, regardless of the catalyst used.

- Catalyst **3** produced more consistent *ee*'s for the E-isomer products than the other catalysts.

Perhaps if another catalyst could be designed to continue the trend of improving enantioselectivity from catalyst **3** to **2**, a more general AROCM solution could be realized.

In Chapter 4, catalysts **2–6** were tested for the ACM of **38** with 1,4-*cis*-diacetoxy-2-butene (Table 4.3). Further results were only presented for catalyst **5**. In the interest of completeness, catalysts **3–7** were examined for ACM with a variety of substrates (Table B.3).

Table B.3. ACM with catalyst **3–7**

Substrate	Product	3	4	5	6	7 ^a
		13% <i>ee</i> , 38% yield	18% <i>ee</i> , 45% yield	22% <i>ee</i> , 26% yield	21% <i>ee</i> , 48% yield	16% <i>ee</i> , 55% yield
		22% <i>ee</i> , yield ND	34% <i>ee</i> , 20% yield	44% <i>ee</i> , 28% yield	37% <i>ee</i> , 12% yield	20% <i>ee</i> , 57% yield
		35% <i>ee</i> , 16% yield	--	52% <i>ee</i> , 8% yield	--	--
		23% <i>ee</i> , yield ND	26% <i>ee</i> , yield ND	40% <i>ee</i> , 17% yield	37% <i>ee</i> , yield ND	7% <i>ee</i> , <i>ent</i> - 19 yield ND
		29% <i>ee</i> , 46% yield	--	37% <i>ee</i> , 48% yield	--	--

^a 20 mol %

This work reinforces the work presented in Chapter 3 as catalyst **5** is the most enantioselective catalyst for ACM. Increasing the size of the silicon protecting group on 1,4-pentadiene-3-ol (**40**, **42**, **44**), increases the enantioselectivity of the transformation.

During these studies on the desymmetrization of meso dienes, it was discovered that these dienes are uniquely challenging substrates for the catalysts. The cross metathesis reaction of acetonide protected butene-3,4-diol (**50**) and ethyl acrylate proceeded in 81% isolated yield, while the cross metathesis of the analogous diene (**52**) and ethyl acrylate proceed in only 38% isolate yield (Figure B.2).

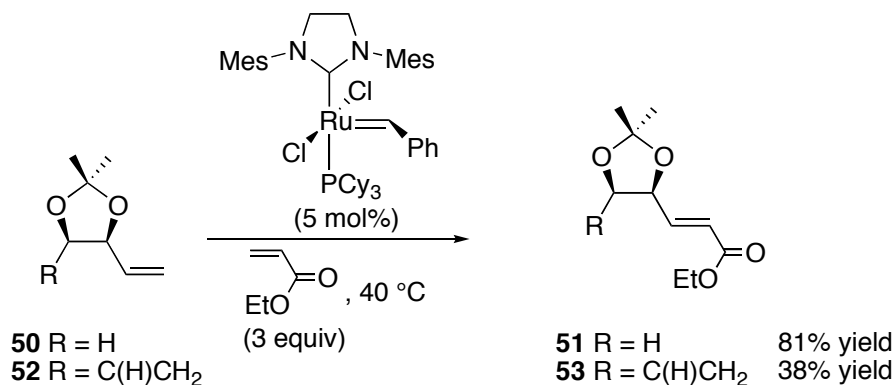


Figure B.2. Meso dienes give lower yields than alkene analogues.

Therefore, in an attempt to obtain better yields, the resolution, via ACM, of racemic compounds with terminal olefins was performed.

Studies were carried out on three resolution substrates (**54**, **56**, **58**) (Figure B.3). The design of substrate **54** followed from the strategy discussed in Chapter 4 of placing small (H), medium (OAc) and large (Ph) groups at the allylic position. It was necessary to protect the alcohol in **54** to avoid isomerization to ethyl, phenyl ketone. Substrate **56** was designed with this same motif, but with a bulkier large group (*tert*-butyl) and a smaller medium group (OH), while substrate **58** was prepared in an attempt to use a methyl group as the medium group along with an extremely bulky protecting group on the oxygen (OTBDPS). Only substrate **54** gave encouraging selectivity; however, to date no improvement in this resolution has been realized.

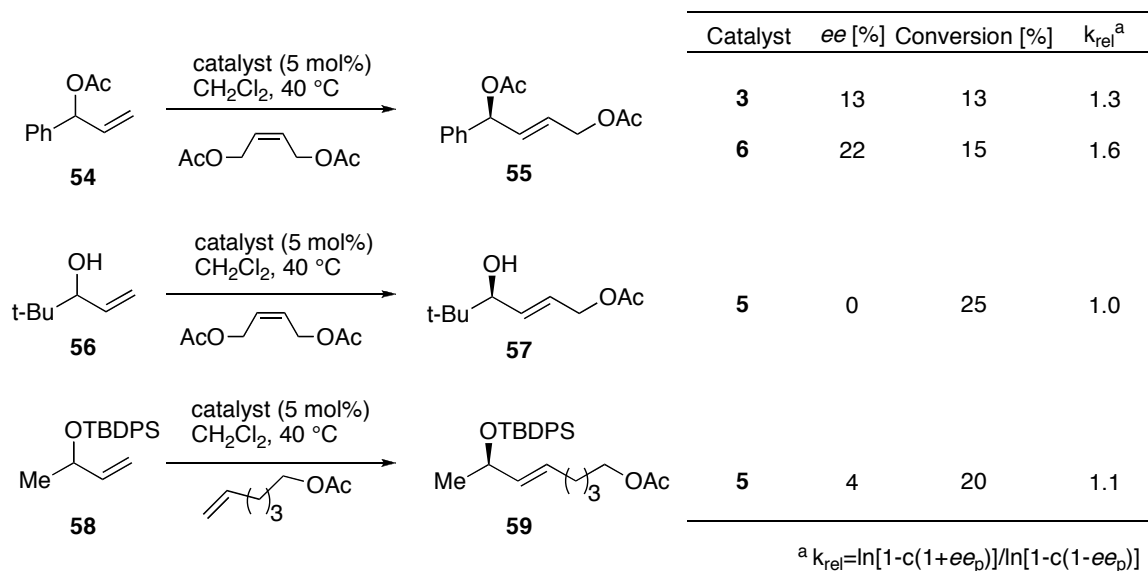


Figure B.3. Resolution studies.

HPLC Conditions

For **17**: Chiralcel AD-H, 5% IPA/Hex, 1ml/min. Retention times: Z-isomer 33.55 (minor), 39.28 (major); E-isomer 62.95 (major), 70.98 (minor).

For **29**: Chiralcel AD-H, 8% IPA/Hex, 1ml/min. Retention times: Z-isomer 14.13 (major), 18.38 (minor); E-isomer 48.63 (major), 56.67 (minor).

For **31**: Chiralcel AD-H, 0.2% IPA/Hex, 1ml/min. Retention times: 13.02 (minor), 15.12 (major).

For **35**: Chiralcel AD-H, 5% IPA/Hex, 1ml/min. Retention times: Z-isomer 19.66 (major), 23.40 (minor); E-isomer 27.20 (major), 43.72 (minor).

For **36**: Chiralcel OD-H, 2% IPA/Hex, 1ml/min. Retention times: Z-isomer 19.07 (major), 21.97 (minor), E-isomer 32.28 (minor), 53.88 (major).

For **39**: **39** was deprotected with TBAF and the resulting diol was analyzed using Chiralcel OD-H, 10% IPA/Hex, 1ml/min. Retention times: 14.69 (minor), 16.37 (major).

For **54**: Chiralcel AD-H, 2% EtOH/Hex, 1ml/min. Retention times: 5.41 (major), 5.85 (minor).

For **55**: Chiralcel AD-H, 3% IPA/Hex, 1ml/min. Retention times: 8.94, 9.64.