Appendix A

Synthesis of Additional Chiral Ruthenium Olefin Metathesis Catalysts

As described in Chapters 2–4, catalysts **2a,b**–**6a,b** have been prepared and applied to asymmetric ring-closing metathesis (ARCM), asymmetric ring-opening cross metathesis (AROCM), and asymmetric cross metathesis (ACM). For clarity of discussion in this section, the positions on the N-bound aryl rings have been labeled 1-6, as indicated for **3a,b**.

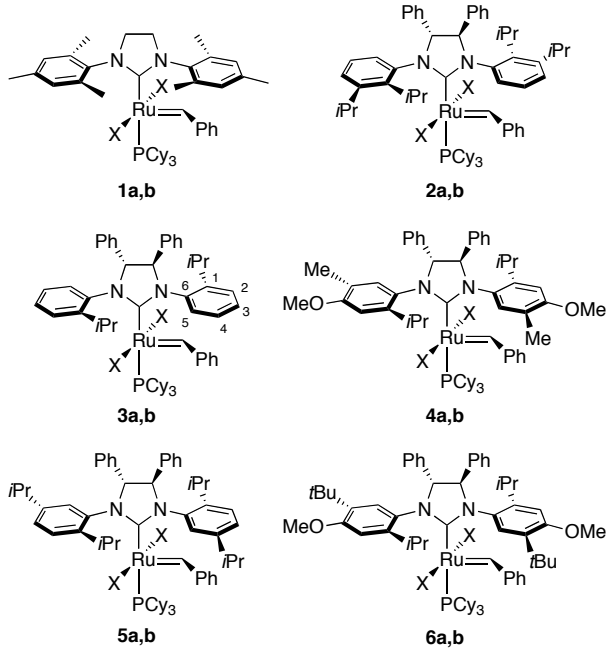
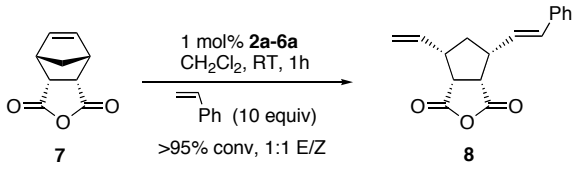


Figure A.1. Ruthenium olefin metathesis catalysts (a: X = Cl, b: X = I).

During the course of the work on AROCM, an inversion in the absolute stereochemistry of the products was observed that depended on the catalyst used for the transformation. For example, when the ring-opening of norbornene **7** to cyclopentane **8** was catalyzed by **2a**–**6a**, the two catalysts with only protons at the 4 positions, **2a** and **3a**, gave *ent*-**8**, while catalysts **5a** and **6a,** with substantial bulk at the 4 positions, gave **8** (Table A.1). From these reactions, it seemed that substituents at the 1 and 2 positions imparted selectivity for the opposite enantiomer of that which substituents at the 4 positions imparted selectivity. Substitution at the 4 positions seemed to have the largest contribution to the

final enantioselectivity of the reaction. Described in this appendix is the synthesis of four other catalysts with greater differences in the size of the substitution at the 1 and 4 positions. It was envisioned that increasing the difference in bulk between these positions would increase the enantioselectivity of AROCM by reducing the degree to which substitution at the 1 positions eroded the selectivity induced by substituting at the 4 positions (or vice versa).

Table A.1. AROCM with chiral ruthenium catalysts



Catalyst	Product	*ee*
2a	*ent*-**8**	47%
3a	*ent*-**8**	29%
5a	**8**	62%
6a	**8**	76%

One catalyst was prepared with a group larger than isopropyl at each 1 position and protons at the 4 positions. As described in Chapter 2, the attempted syntheses of catalysts with *tert*-butyl groups at the 1 positions were unsuccessful; thus an alternative group with intermediate steric requirements between an isopropyl group and a *tert*-butyl group was sought. It was determined that a cyclohexyl group would serve this purpose. Catalyst **10** was prepared with Dr. Steven Goldberg via the standard synthetic route (Figure A.2).

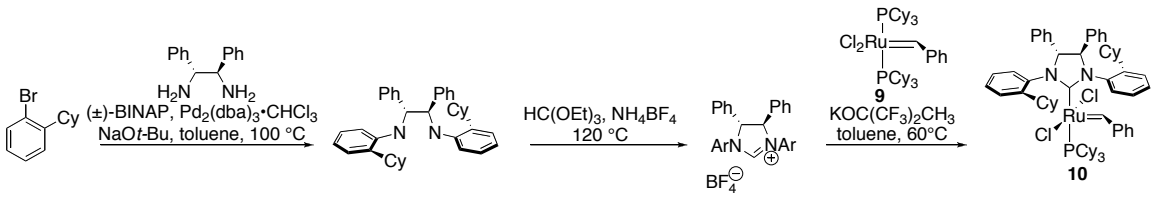


Figure A.2. Synthesis of catalyst **10**.

When used for the AROCM of **7**, catalyst **10** gave *ent*-**8** in 44% *ee*. While this was an improvement over the use of catalyst **3a** to obtain this absolute stereoisomer in this reaction, the enantioselectivity was inferior to when catalyst **2a** was employed. This catalyst was also examined for ARCM, and poor catalyst stability was observed.

Another approach to increasing the difference in bulk between positions 1 and 4 was realized in a catalyst with a smaller group (methyl) at each 1 position combined with *tert*-butyl groups at the 4 positions. Again following the standard synthetic approach, beginning from 4-*tert*-butyl-toluene, the phosphine version of this catalyst (**14**) and the chelating ether version (**16**) were each prepared in four steps (Figure A.2). Undergraduate Jane Wang worked with me on the preparation of these catalysts.

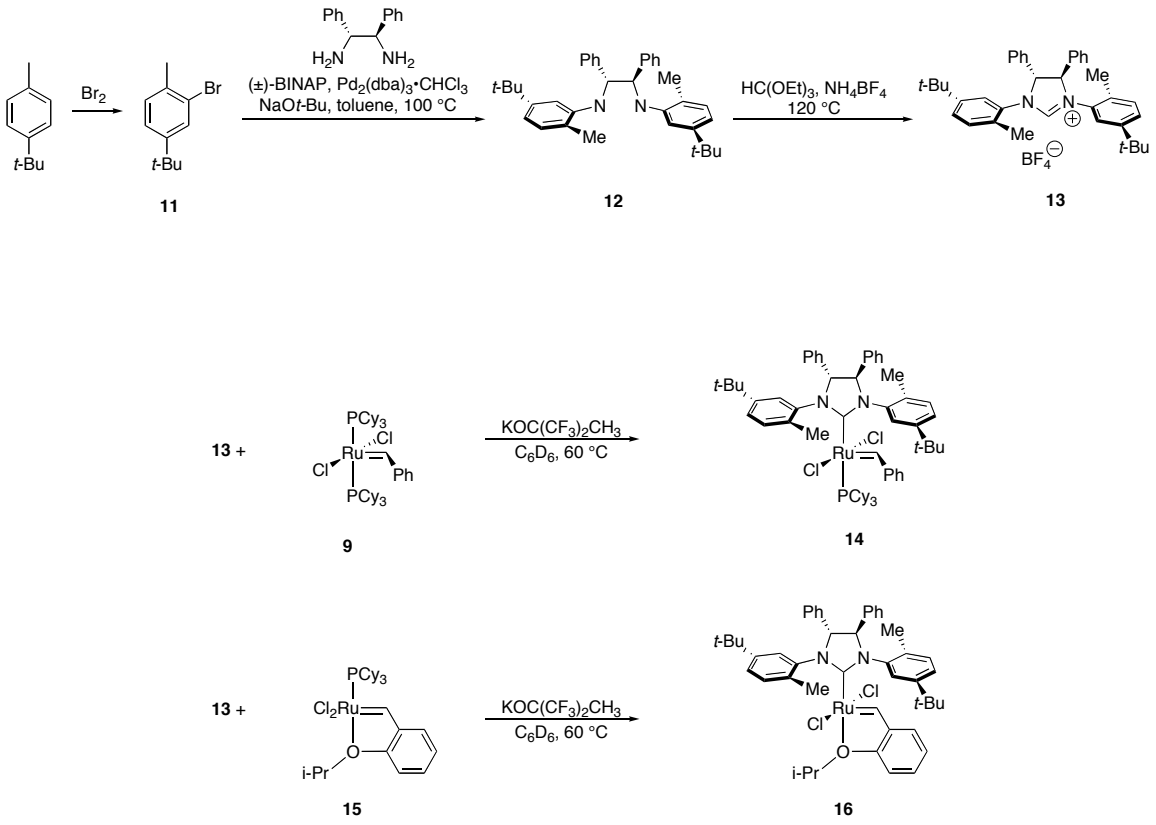
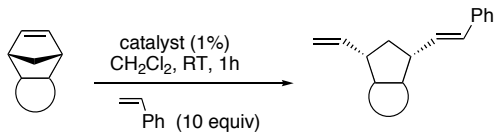
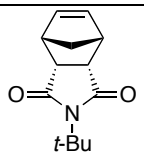
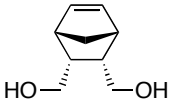


Figure A.3. Synthesis of catalysts **14** and **16**.

Catalysts **14** and **16** were found to give identical enantioselectivity as **6a** in the AROCM of **17**, and the use of catalyst**14** resulted in slightly reduced *ee* compared to the use of catalyst **6a** for the AROCM of **18** (Table A.2). There are two likely reasons for the lack of improvement in enantioselectivity in these cases. As described in Chapter 2, isopropyl groups at the 1 position lead to more effective catalyst gearing than methyl groups at the 1 positions. This decrease in gearing could offset any potential gains in selectivity from reduced bulk at the 1 positions. In addition, it is possible that the stereodefining interaction is between the substrate and only the 4 and 5 positions. In this model, substitution at the 1 position would influence the enantioselectivity only by changing, via ring-tilt, the spatial location of the *tert*-butyl groups at the 4 positions.

Table A.2. Performance of **14** and **16** in AROCM



Substrate	Catalyst[a]	*ee* [%]
 **17**	**6a**	57
	14	57
	16	57
 **18**	**6a**	81
	14	73

[a]Conditions: 1 mol%, CH_2Cl_2, RT, 10 equiv styrene, 1h.

Finally, a catalyst was examined with increased bulk (adamantyl groups) at the 4 positions and isopropyl groups at the 1 positions. This catalyst was prepared by the standard synthetic route (Figure A.4).

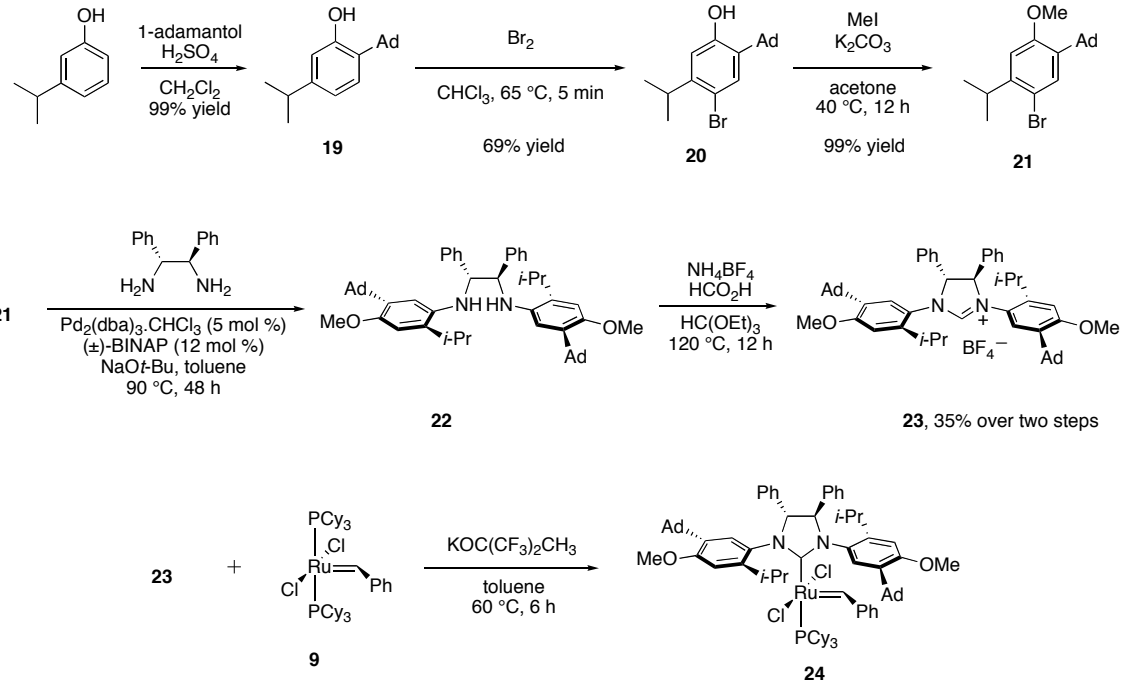
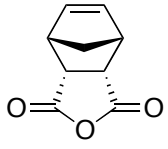
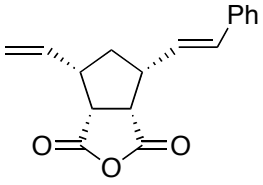
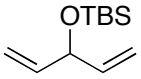
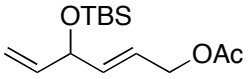
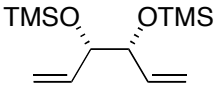
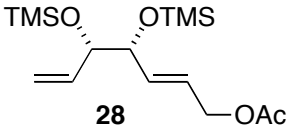


Figure A.4. Synthesis of adamantyl containing catalyst **24**.

Catalyst **24** was examined for its efficacy in AROCM and ACM (Table A.3). Unfortunately, catalyst **24** was poorly selective for AROCM and displayed poor activity and selectivity for ACM. It was hypothesized that the adamantyl group was so large that the gearing of the catalyst was disrupted. This was supported by the fact that two peaks are observed in the benzylidene region of the ^{1}H NMR, a large peak at 19.74 ppm and a small peak at 19.86 ppm. The small peak was assigned as a rotational isomer of the complex that corresponds to the larger benzylidene peak.

Table A.3. Enantioselective metathesis reactions using **24**

Substrate	Product	Catalyst	*ee* [%]
 **7**	 **8**	**6a**[a]	76
		24[a]	45
 **25**	 **26**	**5a**[b]	37
		24[c]	20
 **27**	 **28**	**5a**[b]	40
		24[c]	7[d]

[a] 1 mol%, CH_2Cl_2, rt, 1h.
[b] 5 mol%, 5 equiv of *cis*-diacetoxy-2-butene, neat, 40 °C, 6h.
[c] 20 mol%, 5 equiv of *cis*-diacetoxy-2-butene, neat, 40 °C, 6h.
[d] *ent*-**28** obtained.