Asymmetric Catalysis

DOI: 10.1002/ange.200602469

Highly Active Chiral Ruthenium Catalysts for Asymmetric Cross- and Ring-Opening Cross-Metathesis**

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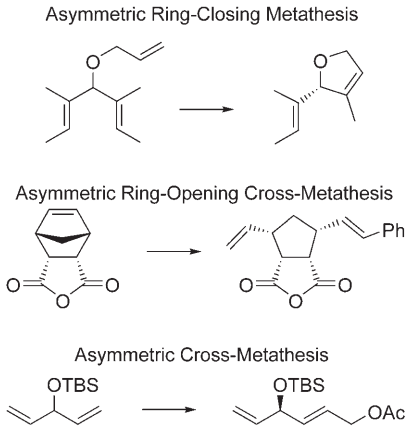
Olefin metathesis has found widespread application in small-molecule synthesis.[1] Its use can be subclassified into three transformations[1a]—ring-opening metathesis, ring-closing metathesis, and cross-metathesis—and one can readily envision an asymmetric variant of each of these reactions (Scheme 1). We report herein the use of highly active chiral ruthenium catalysts for asymmetric ring-opening cross-metathesis (AROCM) and the first example of an asymmetric cross-metathesis (ACM) reaction.



Scheme 1. Three classes of asymmetric metathesis. TBS = *tert*-butyldimethylsilyl.

Chiral molybdenum catalysts have been developed for asymmetric ring-closing metathesis (ARCM) and AROCM.[2–4] These catalysts lack extensive tolerance of functional groups and require rigorous exclusion of air and moisture. The use of more stable enantioselective ruthenium metathesis catalysts, which have a greater tolerance of

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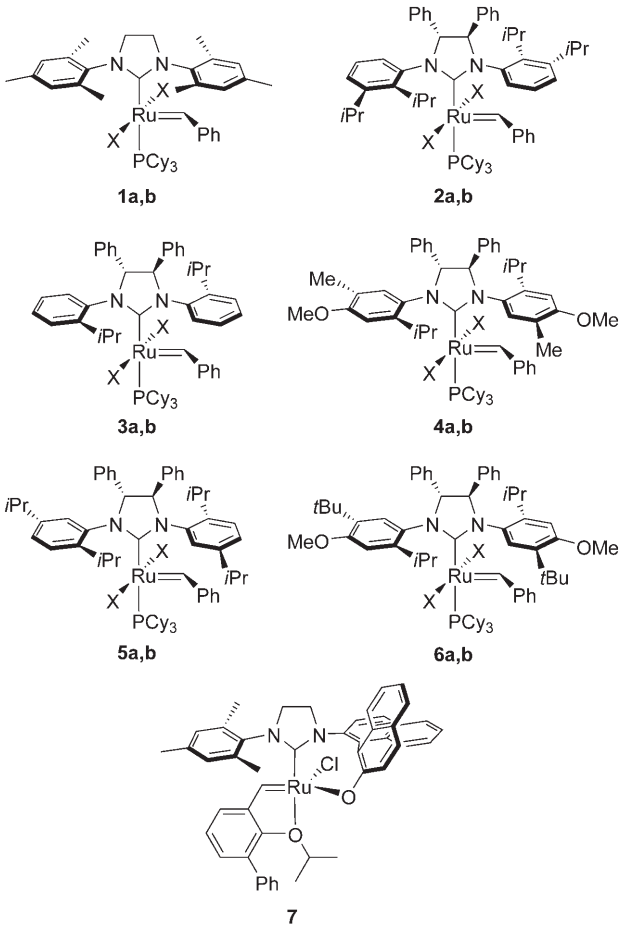
[**] We gratefully acknowledge Prof. F. D. Toste for early experimental work.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

functional groups, would dramatically expand the scope and utility of these transformations, as has been the case in other areas of olefin metathesis. We have recently prepared a series of highly active chiral ruthenium catalysts (Scheme 2, **2a**,**b**–**6a**,**b**).[5] The chirality in these catalysts is transferred from the

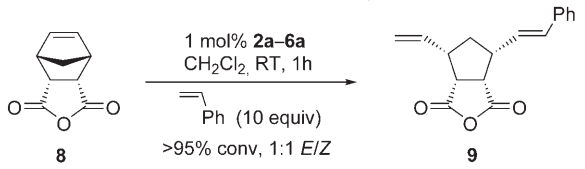


Scheme 2. Ruthenium–olefin metathesis catalysts (**a**: X = Cl, **b**: X = I). Cy = cyclohexyl.

backbone of the N-heterocyclic carbene (NHC) to the metal center through differentially substituted aryl rings on the NHC. The *ortho*-isopropyl groups lie on the opposite sides of the catalyst to the phenyl rings in the backbone of the NHC, thus creating a chiral C_2-symmetric environment around the metal center. Catalysts **2a**,**b**, **3a**,**b**, **5a**,**b**, and **6a**,**b** have been used in ARCM to form oxygen-containing heterocycles in good yields (64–98%) and with high *ee* values (76–92%).[6] These catalysts bearing monodentate chiral NHCs proved to be much more active and selective for ARCM than catalyst **7**, which possesses a bidentate chiral NHC and is stereogenic directly at the metal center.[7] We now report the application of our highly active catalysts to asymmetric ring-opening cross-metathesis and asymmetric cross-metathesis.

Encouraged by our results for ARCM, we turned our attention to AROCM. Catalyst **7** and related complexes have been successfully employed in AROCM for a number of norbornenes and related strained bicycles.[8] In our initial studies, anhydride **8** was treated with one mole percent of the catalysts **2a**, **3a**, **5a**, and **6a** in CH_2Cl_2 in the presence of ten equivalents of styrene (Table 1). Catalyst **6a** was the most selective of the dichloride catalysts, and no change in enantioselectivity was observed upon variation of the solvent

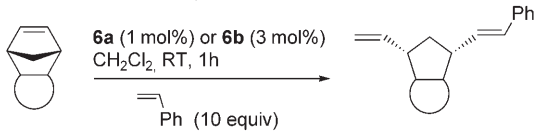
Table 1: AROCM with chiral ruthenium catalysts.

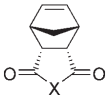
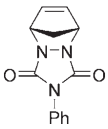
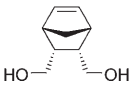
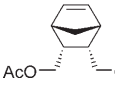


Catalyst	Product	*ee* [%]
2a	*ent*-**9**	47
3a	*ent*-**9**	29
5a	**9**	62
6a	**9**	76

(CH_2Cl_2, $CHCl_3$, THF, Et_2O, benzene, toluene, and with no solvent) or of the equivalents (1, 3, 5, and 10) of cross-partner. In our studies on ARCM, the diiodide catalysts **2b**–**6b** were found to be dramatically more enantioselective than the dichloride catalysts **2a**–**6a**.[6b] For AROCM, the use of diiodide catalyst **6b** in place of dichloride catalyst **6a** slightly improved the *ee* value to 80% and cooling the reaction to 0°C gave **9** in 82% *ee*. The diiodide catalysts are generally less reactive than the dichloride catalysts; therefore, the loading of **6b** was increased to 3 mol% to achieve activity similar to that observed with **6a**. Since catalysts **6a** and **6b** gave the highest *ee* value for substrate **8**, they were employed in studies to explore the substrate scope (Table 2). The *E*/*Z* ratio was close to 1:1 for all of the substrates examined, but we initially focused our attention on discovering trends within the *trans* series of products because in all cases the *ee* values of the *cis* products were lower than those of the *trans* products. Replacement of the anhydride oxygen atom with a *tert*-butylamine group to give **10** reduced the enantioselectivity to 57% for **6a** and 75% for **6b**, but both catalysts gave quantitative yields. Introducing heteroatoms into the norbornene skeleton **11** slightly reduced the *ee* value to 68%, and surprisingly catalysts **6a** and **6b** afforded products with the same *ee* value. When diols **12** and **13** were used, the yields were dramatically reduced to 30% and 10%, respectively. In these cases, substrate coordination to the catalyst may inhibit the reaction. In addition, the stereochemistry of the norbornene diols affected the *ee* values: the *endo* diol **13** gave 81% *ee* while the *exo* diol **12** gave only 33% *ee*. To prevent coordination to the catalyst, diol **13** was protected as a bisacetate **14**, which resulted in a decrease in the *ee* value to 60% accompanied by a large increase in the yield to 99%; the use of catalyst **6b** improved the *ee* value to 72%, but slightly reduced the yield to 78%. The *cis* series of products exhibited different trends in selectivity than the *trans* series (Table 2). The *ee* values for the *cis* products increased when those for the *trans* products decreased (**8** versus **10** with **6a**) and decreased when the *ee* values for *trans* products increased (**10**

Table 2: AROCM with catalysts **6a** and **6b**.



Substrate		Cat.[a,b]	*ee* [%] *E* (*Z*)	Yield [%] (*E*/*Z*)
	**8** X = O	**6a**	76 (4)	95 (1:1)
		6b	80 (n.d.)	96 (1:1)
	10 X = N-*t*Bu	**6a**	57 (33)	99 (1.4:1)
		6b	75 (50)	99 (1.2:1)
	**11**	**6a**	68 (15)	99 (1.2:1)
		6b	68 (10)	99 (1.2:1)
	**12**	**6a**	33 (29)	30 (1.1:1)
	**13**	**6a**	81 (20)	10 (n.d.)
	**14**	**6a**	60 (10)	99 (1.4:1)
		6b	72 (40)	78 (1.4:1)

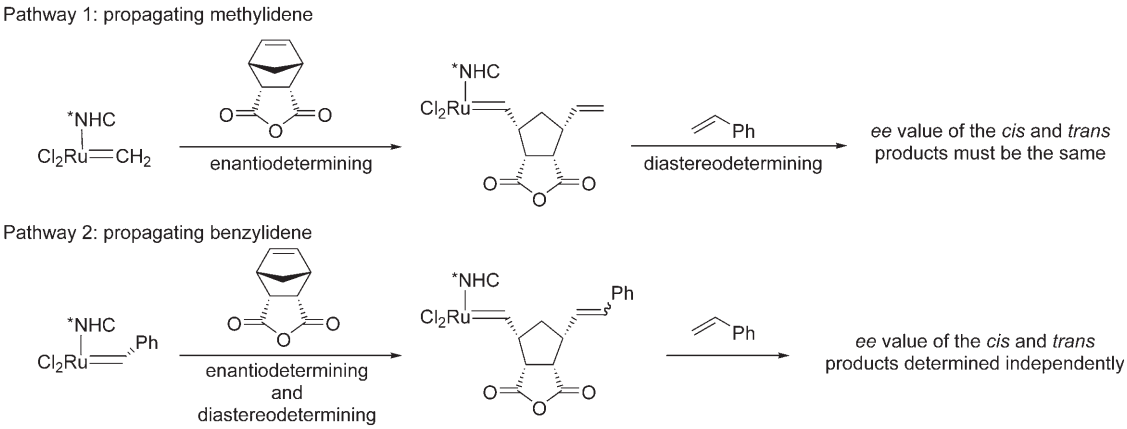
[a] Conditions for **6a**: 1 mol% catalyst, CH_2Cl_2, RT, 10 equiv styrene, 1 h. [b] Conditions for **6b**: 3 mol% **6a**, 1 equiv NaI, CH_2Cl_2, RT, 10 equiv styrene, 1 h. n.d. = not determined.

compared to **11** with **6a**). In addition, when catalysts **2a**,**b**–**5a**,**b** were examined with these substrates, catalysts **6a** and **6b** always gave the *trans* product with the highest *ee* value. However, catalysts **5a** and **5b** often gave the *cis* product with the highest *ee* value.

Careful evaluation of the data obtained thus far elucidates some aspects of the mechanism for AROCM and allows for a proposal as to the origin of enantioselectivity. No change in the *E*/*Z* ratio or *ee* value was observed on monitoring the reactions of **8** and **10** over 3 h. Moreover, the reactive terminal olefin in the products is never observed to undergo further cross-metathesis reactions at room temperature. These findings indicate that the products are not reactive towards secondary metathesis and therefore that the *ee* values and *E*/*Z* ratios observed are the direct result of a singular interaction with the catalysts. Of primary importance to the development of a mechanism for AROCM is to distinguish between the two possible ruthenium–alkylidene propagating species (Scheme 3). In pathway 1, the norbornene reacts with a ruthenium–methylidene intermediate and this ring-opening step determines the *ee* value of the products. Then in the cross-metathesis step the products are released, thereby determining the olefin geometry of the products and regenerating the ruthenium–methylidene species. This pathway requires that the *ee* value of both the *E* and *Z* products be identical. In pathway 2, the norbornene reacts with a ruthenium–benzylidene intermediate and both the *ee* value and olefin geometry of the products are determined concurrently in this ring-opening step. The products are then released in the cross-metathesis step that regenerates the ruthenium–benzylidene species. The *ee* values of the *E* and *Z* products are independent in this reaction pathway. Since the observed *ee* values of the *E* and *Z* products are significantly different, we propose that it is likely that the ruthenium–benzylidene is the propagating species in this system.

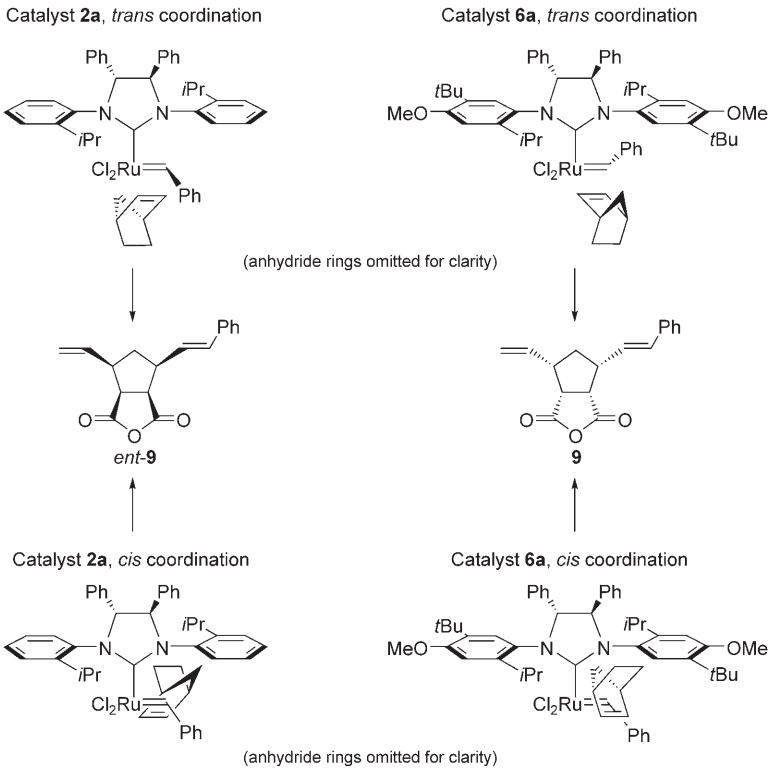
There has been a long-standing debate regarding the site of olefin coordination to the ruthenium catalyst that leads to metallocyclobutane formation. There is experimental evidence that supports olefin binding either *cis* or *trans* to the NHC.[9] In the most recent report on this issue,[9c] Romero and Piers provide compelling evidence for the observation of a 14-electron ruthenium species in which the metallocycle lies *trans* to the NHC. Computational studies also support olefin binding *trans* to the NHC;[10] in fact, calculations from a recent computational study of the use of catalyst **3b** in ARCM, showed olefin coordination *trans* to the NHC to be the lower energy pathway.[10a]

In our system, catalyst **2a** yields *ent*-**9**, and catalyst **6a** yields **9** as the major *trans* product.[11] Moreover, the propagating species is believed to be a benzylidene species, and norbornenes are well known to react preferentially on the *exo* face of the olefin.[12] With these caveats in mind, a *cis*-coordination pathway would require that the norbornene would approach catalyst **2a** from the face that is shielded by the *ortho*-isopropyl group, and catalyst **6a** from the face that



Scheme 3. Comparison of propagating species. *NHC = chiral N-heterocyclic carbene.

possesses the *meta-tert*-butyl group (Scheme 4). It is most likely that introducing a *tert*-butyl group in the *meta* position increases the steric bulk of that side of the ring. Therefore, the *cis*-coordination pathway seems unlikely as it requires the norbornene to approach both catalyst **2a** and **6a** from the more hindered side.

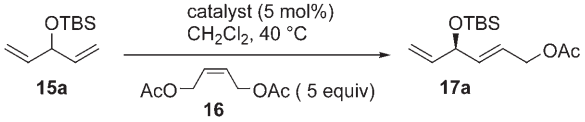


Scheme 4. Olefin approaches for **2a** and **6a** which afford the major *trans* enantiomer.

We propose that a *trans*-coordination pathway is more consistent with the observed data. This pathway would require that the benzylidene unit of catalyst **2a** sit under the unsubstituted side of the aryl ring and the benzylidene unit of catalyst **6a** sit under the side bearing an *ortho*-isopropyl group (Scheme 4). Thus, increasing the steric bulk of the *tert*-butyl side of the ring causes the benzylidene unit to move to the opposite side of the ring, thereby explaining the observed reversal of enantioselectivity between these two catalysts. We expect that our continued work on asymmetric metathesis will allow us to further develop this mechanistic insight.

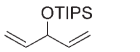
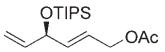
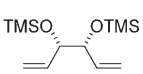
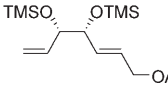
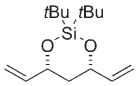
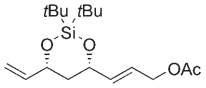
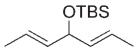
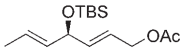
Catalyst **1a** has been used extensively in cross-metathesis,[13] and a chiral variant of this transformation would provide a powerful new synthetic tool for the construction of stereochemically complex targets. However, ACM is also the most challenging of the asymmetric metathesis transformations, as all three factors—the propagating species, its orientation, and enantiotopic olefin selection—must be controlled. In ARCM, there is only one possible propagating species which leads to productive metathesis, so only the orientation of that species and the selection of an enantiotopic olefin must be controlled. AROCM requires both control of the propagating species and its orientation, but facial selectivity of the enantiotopic olefin is easily controlled in the norbornene substrate. To address the enantiotopic olefin selection in ACM, we focused on *meso*-diene substrates which contained distinct small (H), medium (vinyl), and large (OR; for example, R = TBS) substituents at the allylic carbon atom. To address the nature of the propagating species, we employed the TBS-protected 1,4-pentadien-3-ol **15a** and *cis*-1,4-diacetoxy-2-butene (**16**) as substrates (Table 3). It was expected that the use of an excess of **16**, which is more active in metathesis than **15a**, would predominantly afford a ruthenium–acetoxyethylidene complex as the propagating species. This supposition was supported by the fact that the initial benzylidene unit of **2a** was observed to react exclusively with **16** to give cinnamyl acetate. Thus, we controlled the propagating species and achieved the first asymmetric olefin cross-metathesis reaction, although the results are certainly not optimized, with yields and *ee* values lower than expected. One systemic problem causing the low yield is that the terminal olefin present in the product is similar in reactivity to the starting material, thus resulting in consumption of the desired product and formation of a significant amount of symmetrical bis-cross-product (15%). Complexes **2a** and **5a** emerged as the most enantioselective catalysts for this reaction. For catalysts **3a**–**6a**, the enantioselectivity increased as the *meta* substitution increased in size from a proton through a methyl group to an isopropyl group, but a *tert*-butyl group proved to be too large and eroded the enantioselectivity. However, moving the isopropyl group to the opposite *meta* position to give **2a** proved to be equally as effective as **5a**. Since the use of catalyst **5a** gave slightly better yield than **2a**, we explored the use of **5a** with a number of other prochiral diene substrates (Table 4). Increasing the size of the protecting group by using the TIPS-protected 1,4-pentadien-3-ol **15b** (Table 4) resulted in a modest increase in the *ee* value from 44% to 52%. We also examined the use of the protected 1,2-diol **18** and the protected 1,3-diol **20**, which afforded *ee* values similar to those obtained with **15a**. In an attempt to improve the enantioselectivity of ACM we further reduced the reactivity of the diene substrate by preparing both 1,1- and 1,2-disubstituted olefins. Unfortunately, diene **22** proved to be unreactive under these conditions and diene **23** gave only 4% *ee*. The poor result for **23** could result from

Table 3: ACM with catalysts **2a**–**6a**.



Catalyst	*ee* [%]	Yield [%]
2a	44	20
3a	22	15
4a	34	20
5a	44	28
6a	37	12

Table 4: ACM with *cis*-1,4-diacetoxy-2-butene using catalyst **5a**.

Substrate	Product	*ee* [%]	Yield [%]
		52	54[a]
		40	17[b]
		37	48[c]
	–	n.r.	n.r.
		4	23[c]

[a] 5 mol% **5a**, 5 equiv of **15b** relative to **16**, no solvent, 40°C, 6 h. [b] 5 mol% **5a**, 5 equiv of **16**, no solvent, 40°C, 6 h. [c] 5 mol% **5a**, 5 equiv of **16**, 0.25 M in CH_2Cl_2, 40°C, 6 h. TIPS = triisopropylsilyl, TMS = trimethylsilyl, n.r. = no reaction.

the medium and large groups ($CHCHCH_3$ and OTBS, respectively) being too similar in size. This initial report into ACM sets the stage for future catalyst and substrate design to make this transformation synthetically useful.

In conclusion, we have reported an expansion in scope for asymmetric metathesis using highly active ruthenium catalysts with chiral monodentate NHCs. These catalysts showed excellent activity in ring-opening cross-metathesis reactions, and enantioselectivities ranged from 68% to 82%. These investigations allowed us to develop a working model for the mechanism of AROCM, from which we are working to design more-selective metathesis catalysts. We have achieved the first asymmetric cross-metathesis reactions, in which we obtained *ee* values ranging from 37% to 52%. These reactions represent an important proof of principle, and we are working to improve the yields and enantioselectivities for ACM.

Received: June 19, 2006
Published online: October 20, 2006

Keywords: asymmetric catalysis · carbenes · metathesis · reaction mechanisms · ruthenium

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[5] Catalysts **4a**,**b** have not been previously reported, but were prepared analogously to **2a**,**b**, **3a**,**b**, **5a**,**b**, and **6a**,**b**. For full experimental details, see the Supporting Information.

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