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Diastereoselective Ru-Catalyzed Cross-Metathesis−Dihydroxylation Sequence. An Efficient Approach toward Enantiomerically Enriched *syn*-Diols

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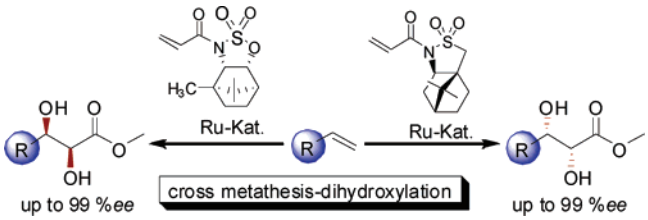

Sequential catalysis has evolved as a powerful concept within the past years and allows the more efficient use of catalytically active expensive transition metals in organic synthesis. In this paper we present the stereoselective cross-metathesis−dihydroxylation of various olefins with chiral auxiliary substituted acrylamides. The chiral information (i.e., the auxiliary) introduced in the metathesis reactions allows for a stereoselective subsequent RuO_4-catalyzed dihydroxylation. The sequence is concluded by an unusual kinetic resolution of the diastereomeric diols obtained in the oxidation reaction. As a consequence a variety of structurally diverse enantiomerically enriched diols are obtained. To the best of our knowledge the results summarized in this paper represent the first highly efficient diastereoselective RuO_4-catalyzed oxidation.

Introduction

Transiton-metal-catalyzed reactions belong to the most powerful transformations in modern organic chemistry. Despite the achievements that have been made in this field of chemistry, the number of transformations that managed to take the crossover from academic into industrial application is comparably low. Among others, the high price of the catalyst might account for these difficulties. Within the past years sequential catalysis has evolved as a probable solution for this dilemma.[1] In these reaction cascades a given catalyst is transformed in situ into a new catalytically active species once the first transformation of the sequence has been completed. The junction of two catalytic cycles by using one common metal catalyst allows for a more efficient use of the expensive catalyst and the avoidance of unnecessary purification procedures.

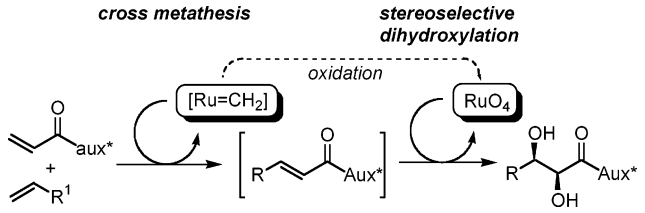

FIGURE 1. Stereoselective sequential catalysis as a means to obtain chiral *vic*-diols.

Due to the accessibility of eight different oxidation states, Ru-based catalysts are predestined for applications in sequential catalysis. Among the various catalytic reactions developed so far, the Ru-catalyzed olefin metathesis appears to be an interesting starting point for the development of these reaction

(1) (a) Müller, T. J. J. *Top. Organomet. Chem.* **2006**, *19*, 149. (b) Bruneau, C.; Derien, S.; Dixneuf, P. H. *Top. Organomet. Chem.* **2006**, *19*, 295.

(2) (a) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312. (b) Lee, B. T.; Schrader, T. O.; Martin-Matute, B.; Kauffman, C. R.; Zhang, P.; Snapper, M. L. *Tetrahedron* **2004**, *60*, 7391. (c) Tallarico, J. A.; Malnick, L. M.; Snapper, M. L. *J. Org. Chem.* **1999**, *64*, 344. (d) Schmidt, B.; Pohler, M. *J. Organomet. Chem.* **2005**, *690*, 5552. (e) Schmidt, B.; Pohler, M.; Costisella, B. *J. Org. Chem.* **2004**, *69*, 1421. (f) Finnegan, D.; Seigal, B. A.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 2603. (g) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390. (h) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672. (i) Schmidt, B. *Chem. Commun.* **2004**, 742. (j) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816. (k) Bielawski, C. W.; Louie, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 12872. (l) Schmidt, B.; Pohler, M. *Org. Biomol. Chem.* **2003**, *1*, 2512. (m) Kim, B. G.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 52.

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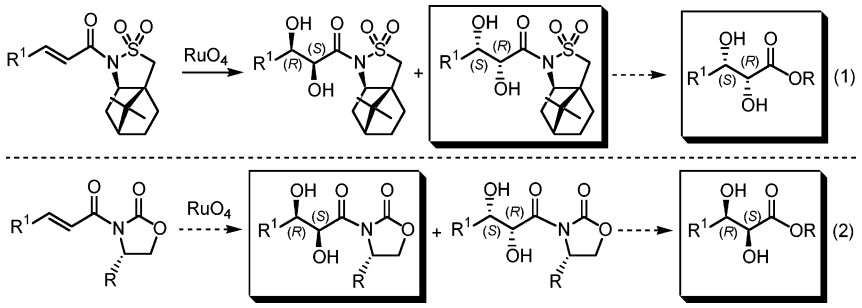


FIGURE 2. Auxiliary-induced asymmetric RuO_4-catalyzed dihydroxylation.

cascades.[2] Hence, it is not surprising that a variety of different catalytic sequences involving Ru-catalyzed metathesis have been developed within the past 5 years. However, to the best of our knowledge, the combination of different catalytic reactions with the aim of preparing enantiomerically enriched material has not yet been reported. In the present paper we report on our initial findings in the field of stereoselective sequential catalysis.

Our strategy is based on the experiences we gained in the field of RuO_4-catalyzed oxidations[3] of olefins within the past 5 years.[4] We envisioned such a reaction to be the final step in a catalytic sequence. Since no asymmetric RuO_4-catalyzed dihydroxylation has been reported so far, the combination of cross-metathesis between an olefin and a chiral auxiliary substituted acrylamide appears to be an interesting alternative to the classical introduction of chiral information by reacting a fully substituted carboxylic acid with the auxiliary.[5] By employing an enantiopure auxiliary substituted olefin in the cross-metathesis with a second olefin, two important issues are addressed: (1) A new C═C double bond is being formed, and (2) a chiral auxiliary is introduced. The subsequent in situ generation of RuO_4 sets the stage for a diastereoselective *syn*-dihydroxylation. See Figure 1.

Although at first sight the use of a chiral auxiliary appears to be less elegant, two main reasons make this method favorable; to date, all efforts to design chiral ligands for RuO_4 have met with failure. Since this metal oxide belongs to one of the strongest oxidants in organic synthesis and displays a low stability at pH > 7,[6] the use of the common ligand motifs (phosphines, amines, etc.) is not possible. At the moment, the use of a chiral auxiliary is the most promising way to obtain enantiomerically enriched products using RuO_4, and by using chiral auxiliaries, a stereochemical enrichment of the resulting diastereomeric products by crystallization, distillation, or chromatography is possible.[7]

In the present paper we report on the use of a cross-metathesis between different olefins and auxiliary substituted enantiopure acrylamides plus subsequent diastereoselective dihydroxylation. A new type of chiral auxiliary has been developed based upon a rational design that allows for the first time for an efficient diastereoselective RuO_4-catalyzed dihydroxylation of olefins in diastereomeric ratios up to 19:1. Moreover, an unusual kinetic resolution of the diastereomeric diols by methanolysis is reported, which allowed for the preparation of enantiomerically enriched *syn*-diols in either optical form with enantomeric excesses up to 99%.

Results and Discussion

Whereas OsO_4-catalyzed olefin dihydroxylations have been developed into one of the most powerful metal-catalyzed reactions in organic chemistry,[8] asymmetric oxidations involving catalytic amounts of RuO_4 have attracted considerably less attention. It is only recently that more sophisticated oxidation protocols for a selective oxygen transfer toward different functional groups have been developed.[4,9] We reported the rate acceleration in RuO_4-catalyzed dihydroxylation upon addition of catalytic amounts of Lewis acids (e.g., $CeCl_3$).[4c] Due to the formation of a redox-active cerium(IV)−periodato complex that acts as a redox mediator, a more efficient reoxidation of the primarily formed intermediate ruthenium(VI) ester was possible. The new protocol allowed for the selective dihydroxylation of olefins without the side reactions that were usually observed after prolonged reaction times (e.g., overoxidation, C−C bond scission, etc.).[10]

Our investigation started with the search for a suitable chiral auxiliary that can selectively direct the addition of RuO_4 on one of the diastereotopic faces of the double bond. Until now, only one report on an auxiliary-based asymmetric RuO_4-catalyzed dihydroxylation has appeared in the literature.[11] Oppolzer's camphorsultame[12] proved to induce moderate to good diastereoselectivities in the oxidation of various α,β-unsaturated carboxamides (eq 1, Figure 2). While this auxiliary allows for the preparation of one enantiomeric series of *syn*-

(3) Plietker B. *Synthesis* **2005**, 2453.

(4) Ru-catalyzed dihydroxylation: (a) Plietker, B.; Niggemann, M. *Org. Lett.* **2003**, *5*, 3353. (b) Plietker, B.; Niggemann, M.; Pollrich, A. *Org. Biomol. Chem.* **2004**, *2*, 1116. (c) Plietker, B.; Niggemann, M. *J. Org. Chem.* **2005**, *70*, 2402. RuO_4-catalyzed ketohydroxylation. (d) Plietker, B. *J. Org. Chem.* **2003**, *68*, 7123. (e) Plietker, B. *J. Org. Chem.* **2004**, *69*, 8287. (f) Plietker, B. *Eur. J. Org. Chem.* **2005**, 1919.

(5) While this work was in progress, two independent reports on the sequential cross-metathesis−dihydroxylation starting from methyl acrylate and various olefins appeared. However, the *syn*-diols were obtained as a racemate. (a) Beligny, S.; Eibauer, S.; Maechling, S.; Blechert, S. *Angew. Chem.* **2006**, *119*, 1933; *Angew. Chem., Int. Ed.* **2006**, *45*, 1900−1903. (b) Scholte, A. A.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 4759.

(6) (a) Griffith, W. P.; Suriaatmaja, M. *Can. J. Chem.* **2001**, *79*, 598. (b) Mills, A.; Holland, C. *J. Chem. Res.* **1997**, 368.

(7) Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899.

(8) (a) Schröder, M. *Chem. Rev.* **1980**, *80*, 187. (b) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2487. (c) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, Weinheim, 2000; p 357. (b) Bolm, C.; Hildebrand, J. P.; Muniz, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, Weinheim, 2000; p 399.

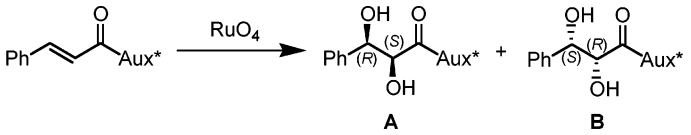
(9) (a) Roth, S.; Stark, C. B. W. *Angew. Chem.* **2006**, *118*, 6364; *Angew. Chem., Int. Ed.* **2006**, *45*, 6218−6221. (b) Roth, S.; Göhler, S.; Cheng, H.; Stark, C. B. W. *Eur. J. Org. Chem.* **2005**, 4109.

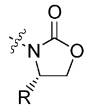
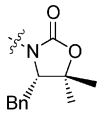
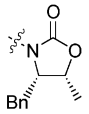
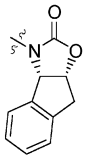
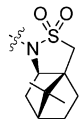
(10) This method was successfully applied in synthesis; for a prominent example see: Tiwari, P.; Misra, A. K. *J. Org. Chem.* **2006**, *71*, 2911.

(11) Lee, A. W. U.; Chen, W. H.; Yuen, W. H.; Xia, P. F.; Wang, W. Y. *Tetrahedron: Asymmetry* **1999**, *10*, 1421.

(12) Oppolzer, W.; Chapuis, C.; Bernadelli, G. *Helv. Chim. Acta* **1983**, *67*, 1397.

TABLE 1. Auxiliary Effects in Asymmetric RuO_4-Catalyzed Dihydroxylations



entry[a]	auxiliary	product	**A** : **B**[b]	yield [%][c]
1	 **1** (R = CH_3)	**2**	1.6 : 1.0	89
2	**3** (R = *i*-Pr)	**4**	2.6 : 1.0	75
3	**5** (R = *i*-Bu)	**6**	2.0 : 1.0	82
4	**7** (R = (*S*)-1-CH_3-Pr)	**8**	2.6 : 1.0	61
5	**9** (R = *t-Bu*)	**10**	3.7 : 1.0	61
6	**11** (R = *Ph*)	**12**	2.3 : 1.0	65
7	**13** (R = *Bn*)	**14**	1.6 : 1.0	67
8	**15** (R = *p*-NO_2PhCH_2)	**16**	2.1 : 1.0	53
9	 **17**	**18**	1.0 : 1.0	78
10	 **19**	**20**	1.6 : 1.0	81
11	 **21**	**22**	2.3 : 1.0	57
12	 **23**	**24**	1.0 : 4.6	83

[a] All reactions were performed on a 2 mmol scale using 1.0 mol % $RuCl_3$ (as a 0.1 M stock solution in water), 20 mol % $CeCl_3 \cdot 7H_2O$, and 1.5 equiv of $NaIO_4$ in a solvent mixture of CH_3CN/H_2O (6 mL/1 mL) at 0 °C and stopped after full conversion. [b] Determined by ^1H NMR integration. [c] Combined isolated yield.

diols, we wondered whether it was possible to identify another class of auxiliaries that would allow for the synthesis of the opposite enantiomeric series. Among the chiral auxiliaries that have been used in organic chemistry within the past 30 years, chiral oxazolidinones have attracted considerable attention.[13] On the basis of the simplified sketch shown in eq 2 (Figure 2), we speculated that this class of chiral auxiliary could induce the opposite sense of stereoinduction in the dihydroxylation reaction.

Hence, we started our investigation by analyzing the stereochemical course of the oxidation of cinnamic acid derived enantiopure oxazolidinones (Table 1).[14] The configuration of the main diastereomer was determined after methanolysis and comparison of the obtained mixture of enantiomers with an enantiopure sample obtained via asymmetric dihydroxylation of methyl cinnamate.

Indeed the use of oxazolidinones allowed for a reversal of the π-facial selectivity in the oxidation reaction (entries 1−11, Table 1). However, though the desired diols were obtained in good yields, the diastereoselectivities were only moderate and did not reach or surpass the selectivities obtained for the oxidation of camphorsultame-bound cinnamic acid **23** (entry 12, Table 1).

At this point we were wondering whether we could construct an auxiliary based on a rational design: a chiral compound possessing similar topological characteristics that could be referred to as a "pseudoenantiomeric camphorsultame". Our idea was guided by the following thoughts: The preferred formation of one rotamer, **I** (or **III**), plus the steric properties of the auxiliary build the base for a high degree of diastereoselectivity in the oxidation reaction. If we were able to stabilize the corresponding rotamer **II**, we would in principle be able to obtain a topologically similar auxiliary that should induce the opposite sense of stereoinduction starting from a unique enantiopure source (i.e., D-camphor) (Figure 3).

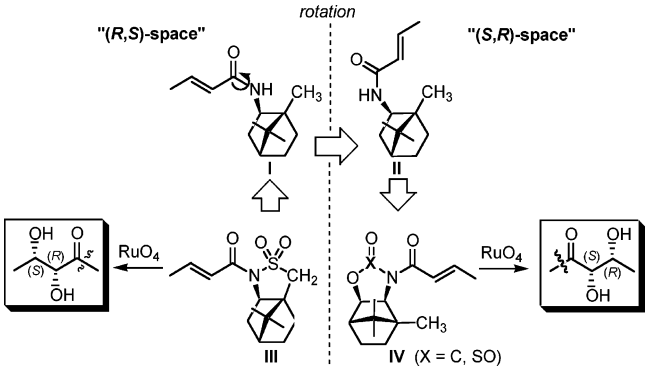
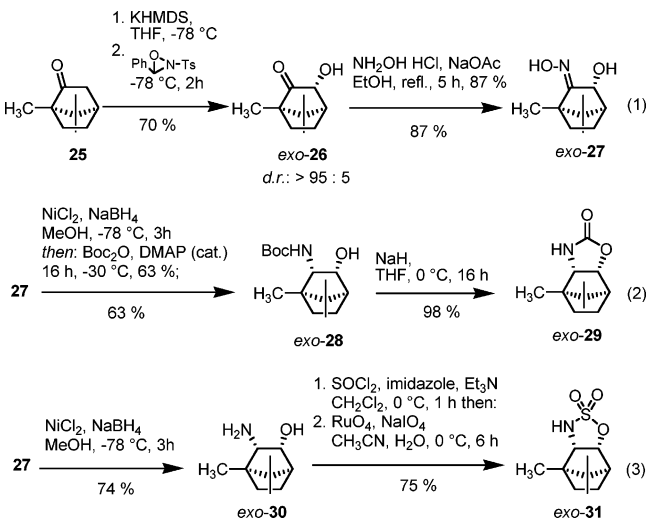


FIGURE 3. Rationale for the design of camphor-derived auxiliary **IV**.

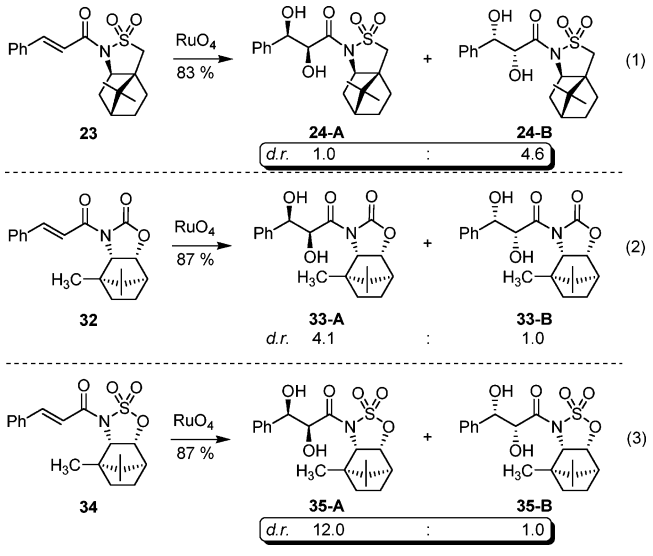
Hence, two chiral auxiliaries of type **IV** with two different linker groups were prepared in a straightforward manner starting from D-camphor. Diastereoselective α-hydroxylation was followed by oxime formation to give oxime *exo*-**27** as a key intermediate (eq 1, Scheme 1), whereas reduction, carbamate formation, and subsequent cyclization under basic conditions led to oxazolidinone *exo*-**29** (eq 2, Scheme 1). The corresponding sulfamidate *exo*-**31** was obtained upon treatment of *exo*-**30** with $SOCl_2$ and subsequent oxidation using RuO_4 (eq 3, Scheme 1).

SCHEME 1. Preparation of Oxazolidinone *exo*-29 and Sulfamidate *exo*-31



The auxiliaries were coupled to cinnamic acid and subsequently subjected to the RuO_4-catalyzed dihydroxlyation (Scheme 2). The first investigations concentrated on the use of oxazolidinone *exo*-**29** as the chiral auxiliary (eq 2, Scheme 2). Indeed the rationally designed camphor-derived oxazolidinone *exo*-**29** proved to induce a similar degree of stereoselectivity compared to the camphorsultame (eq 1 vs eq 2, Scheme 2). However, the corresponding sulfamidate *exo*-**31** proved to be an even more powerful chiral inductor (eq 3, Scheme 2). The simple exchange of the carbonyl group for SO_2 led to a significant increase in the diastereoselectivity from 4.1:1.0 to 12.0:1.0 (eqs 2 and 3, Scheme 2). Furthermore, the camphor-derived sulfamidate-based auxiliary induces the desired complementary sense of stereoselectivity and allows for the formation of two new stereocenters with opposite chirality compared to the camphorsultame (eq 1 vs eq 3, Scheme 2).

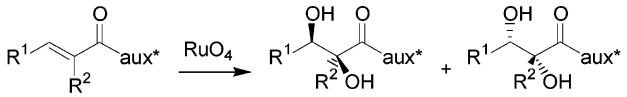
SCHEME 2. Diastereoselective Dihydroxylation Using Camphor-Derived Auxiliaries



(13) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23.

(14) The β-substituent was shown to significantly decrease the stereoselectivity in auxiliary-induced RuO_4-catalyzed dihydroxylations and was therefore chosen as a suitable model compound. See ref 11.

TABLE 2. Stereoselective RuO_4-Catalyzed Dihydroxylation



A **B**

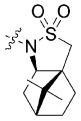
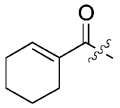
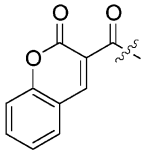
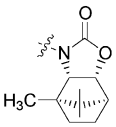
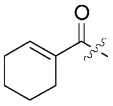
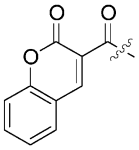
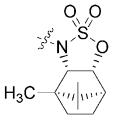
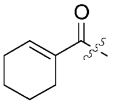
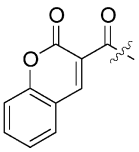
entry[a]	R^1,R^2	aux*	olefin	product	**A** : **B**[b]	yield [%][c]
1	R^1,R^2 = H		**36**	**37**	1.0 : 3.8	83
2	R^1 = *n*Pr R^2 = H		**38**	**39**	1.0 : 6.3	85
3	R^1 = C_6H_{11} R^2 = H		**40**	**41**	1.0 : 9.0	88
4	R^1 = Ph R^2 = H		**23**	**24**	1.0 : 4.6	83
5	R^1 = H R^2 = CH_3		**42**	**43**	1.0 : 1.4	87
6			**44**	**45**	1.0 : 1.4	90
7			**46**	**47**	10.1 : 1.0	74
8	R^1,R^2 = H		**48**	**49**	5.0 : 1.0	86
9	R^1 = *n*Pr R^2 = H		**50**	**51**	6.1 : 1.0	85
10	R^1 = C_6H_{11} R^2 = H		**52**	**53**	7.3 : 1.0	88
11	R^1 = Ph R^2 = H		**32**	**33**	4.1 : 1.0	87

Table 2. (Continued)

entry[a]	R^1,R^2	aux*	olefin	product	**A** : **B**[b]	yield [%][c]
12	R^1 = H R^2 = CH_3		**54**	**55**	8.1 : 1.0	87
13			**56**	**57**	4.9 : 1.0	68
14			**58**	**59**	1.0 : 10.1	74
15	R^1,R^2 = H		**60**	**61**	10.1 : 1.0	83
16	R^1 = *n*Pr R^2 = H		**62**	**63**	12.2 : 1.0	91
17	R^1 = C_6H_{11} R^2 = H		**64**	**65**	11.8 : 1.0	90
18	R^1 = Ph R^2 = H		**34**	**35**	12.0 : 1.0	87
19	R^1 = H R^2 = CH_3		**66**	**67**	2.2 : 1.0	85
20			**68**	**69**	2.7 : 1.0	90
21			**70**	**71**	1.0 : 19.0	79

[a] All reactions were performed on a 2 mmol scale using 1 mol % $RuCl_3$ (as a 0.1 M solution in water), 20 mol % $CeCl_3 \cdot 7H_2O$, and 1.5 equiv of $NaIO_4$ at 0 °C in a solvent mixture of acetonitrile/water (6 mL/1 mL). [b] Determined by ^{1}H NMR, GC, or HPLC integration. [c] Isolated yields.

Having in hand these powerful chiral auxiliaries, we investigated their potential in the dihydroxylation of various substituted olefins.

The new chiral auxiliaries proved to be broadly applicable. Depending on the substitution pattern, good to excellent diastereoselectivities were observed. In general, the sulfamidate-based auxiliary proved to induce the highest degree of stereoselectivity (entries 15−21, Table 2). Only in the case of a substituent at the α-position of the carboxylic acid moiety did the oxazolidinone-based auxiliary prove to be superior (entries 12 and 13 vs entries 19 and 20, Table 2). With regard to the diastereoselectivity trends, it appears indeed worthwhile to refer to the camphorsulfamidate as a pseudoenantiomeric camphorsultame: The trends for either diastereomer are comparable; however, the stereoinduction in the case of the sulfamidate auxiliary is significantly higher.

Having developed a new generation of auxiliaries that allow for the preparation of either enantiomeric series of diols, we

subsequently turned our attention toward the development of the sequential catalysis. Therefore, the initial cross-metathesis reaction was investigated in detail. Several catalysts were used in the present study (Figure 4).

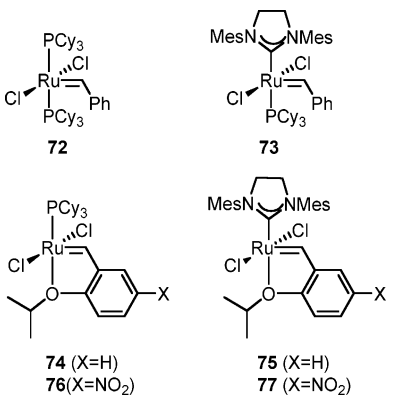
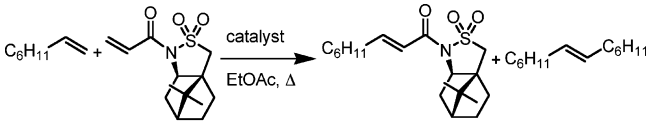


FIGURE 4. Catalysts employed in the present cross-metathesis study.

Apart from the nature of the catalyst, a strong focus was placed upon the use of exact stoichiometric amounts of either olefin employed in the reaction. Although the cross-metathesis between acrylic amides and olefins has been known for some time, in most cases the less electron rich olefin is used in excess to suppress undesired homocoupling between the electron rich olefins.[15] Since in our attempted sequential catalysis the less electron rich olefin is also enantiopure, we designed a special "dilution apparatus" that allowed for an exact stoichiometric cross-metathesis reaction between olefins of different electronic properties (Table 3).[16]

TABLE 3. Development of Cross-Metathesis: Influence of the Catalyst



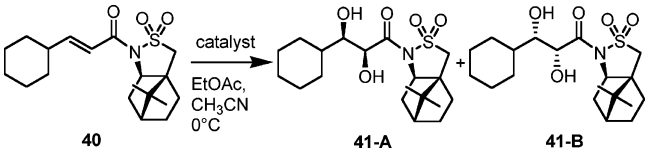
entry[a]	catalyst	time (h)	**40**:**79**[b]	yield[c] (%)
1	**72**	24	only **79**	nd
2	**73**	24	26:74	28
3	**74**	24	only **79**	nd
4	**75**	12	91:9	89
5	**76**	24	only **79**	nd
6	**77**	10	91:9	90

[a] All reactions were performed on a 1 mmol scale in ethyl acetate (1 mL) at reflux temperature using 2.5 mol % Ru catalyst. [b] Determined by GC integration. [c] Isolated yield.

As can be seen from Table 3 the Grubbs−Hoveyda complex **75**[17] and the Grela catalyst **77**[18] displayed the highest catalytic activity in the cross-metathesis (CM). Only minor amounts of the homocoupling products were obtained. With these results in hand, we turned our attention to the dihydroxylation (Table 4). Unfortunately, we found the most active CM catalyst **77** to be unreactive in the oxidation reaction.[19]

To destabilize the Ru−alkylidene complex **77**, we tried to perform an anion exchange using catalytic amounts of NH_4PF_6 prior to the addition of $NaIO_4$. The anion exchange was thought to facilitate the initial oxidation event in the dihydroxylation

TABLE 4. Dihydroxylation of Olefin 33: Influence of the Catalyst and Additive



entry[a]	catalyst	additive	time (min)	**41-A**:**41-B**[b]	yield[c] (%)
1	**77**		60		
2		NH_4PF_6 [e]	60	1.0:5.1	64
3	**75**		60	1.0:5.1	65
4		NH_4PF_6,[e] Bu_4NIO_4 [e]	30	1.0:5.1	73
5		$TBAIO_4$,[e] acetone[f]	15	1.0:5.1	85

[a] All reactions were performed on a 1 mmol scale using 2.5 mol % catalyst in a solvent mixture of CH_3CN/EtOAc/H_2O (1.5 mL/1.5 mL/0.5 mL). [b] Determined by ^1H NMR integration. [c] Combined isolated yield. [d] Determined by chiral HPLC. [e] A 1 equiv portion of additive based on the amount of catalyst was added. [f] A 1.5 mL volume of acetone was added.

(i.e., the reaction between the Ru−alkylidene complex and $NaIO_4$). Very much to our delight, the addition led to a significant increase in reactivity (entry 2, Table 4); the corresponding diol **41** was obtained as a mixture of diastereoiosmers in moderate yield. Catalytic amounts of complex **75** on the other hand furnished the oxidation product **41** in moderate yield in the absence of any additive (entry 3, Table 4). The addition of NH_4PF_6 led to a further increase in the yield (entry 4, Table 4). Exchanging the chloride ligand in the presence of catalytic amounts of Bu_4NIO_4 in acetone finally led to the formation of the oxidation product **41** in a good isolated yield and moderate diastereoselectivity (entry 5, Table 4).

Having found optimum conditions for the dihydroxylation, we set out to combine both processes in a sequential manner. We were delighted to find that the asymmetric cross-metathesis−dihydroxylation sequence proceeded equally well for camphorsultame-derived **36** and camphorsulfamidate-derived **60**. The *vic*-diols **41** and **65** were obtained in good yields and diastereoselectivities. However, within the subsequent methanolysis of the diastereomeric diol **41** or **65**, an unusual kinetic differentiation between the two stereoisomers was observed. As a result the *syn*-diol **80** was obtained in either enantiomeric form with more than 99% ee (Scheme 3). Moreover, the reaction stops at full conversion of the major diastereomer; a full set of signals for the minor isomer was observed in the crude ^1H NMR spectra. To the best of our knowledge, this is the first observation of an efficient kinetic separation within the cleavage of a chiral auxiliary.

With these results in hand, we subsequently investigated the reaction scope and were delighted to find this catalytic sequence to be broadly applicable (Table 5). The moderate to excellent selectivities obtained in the dihydroxylation improved signifi-

(15) (a) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem.* **2001**, *113*, 1317; *Angew. Chem., Int. Ed.* **2001**, *40*, 1277. (b) Hart, A. C.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 1094. (c) Phillips, A. J.; Hart, A. C.; Henderson, J. A. *Tetrahedron Lett.* **2006**, *47*, 3743.

(16) A figure of the apparatus is shown in the Supporting Information.

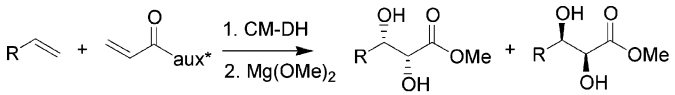
(17) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9073.

(18) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem.* **2002**, *114*, 4210; *Angew. Chem., Int. Ed.* **2002**, *41*, 4038.

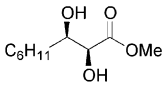
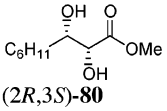
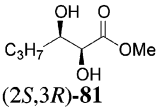
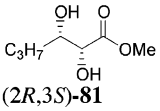
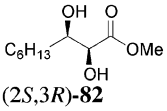
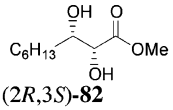
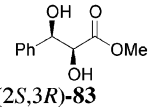
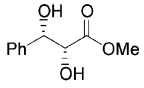
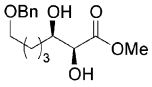
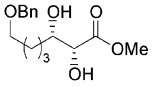
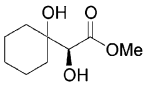
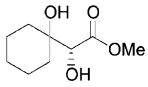
(19) The observed stability of Grela's catalyst underlines its reported extraordinary stability toward oxidation. See ref 18.

(20) Howe, N. R.; Sheikh, Y. M. *Science* **1975**, *189*, 386.

TABLE 5. Preparation of Enantiomerically Enriched *vic*-Diols

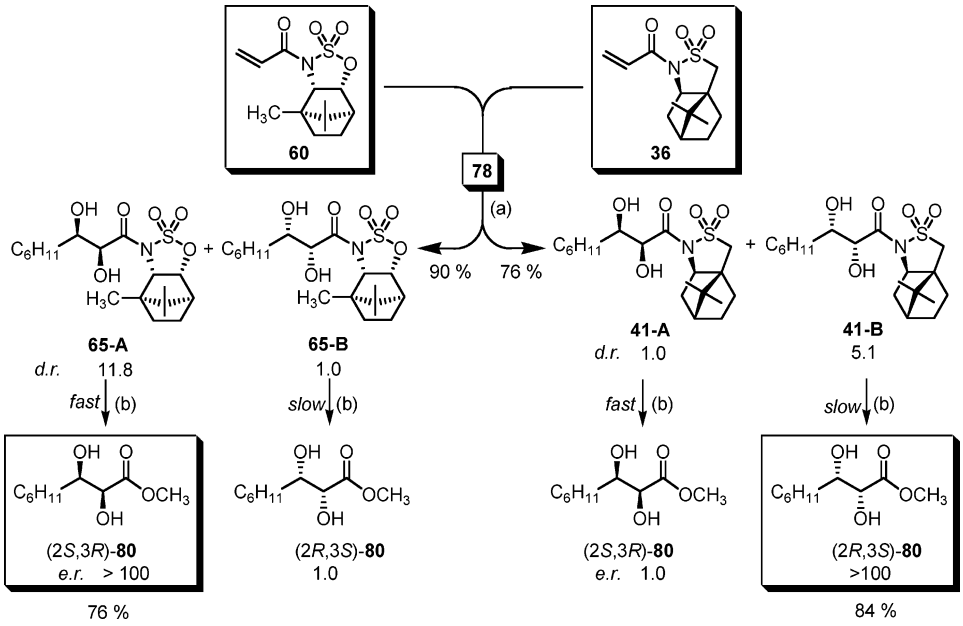


olefin I olefin II

entry[a]	olefin I	olefin II	product	*ee* [%][b]	yield [%][c,d]
1		**60**	 (2*S*,3*R*)-**80**	>99	63
2		**36**	 (2*R*,3*S*)-**80**	>99	75
3		**60**[e]	 (2*S*,3*R*)-**81**	84	61
4		**36**[e]	 (2*R*,3*S*)-**81**	>99	69
5		**60**	 (2*S*,3*R*)-**82**	91	52
6		**36**	 (2*R*,3*S*)-**82**	91	53
7		**60**	 (2*S*,3*R*)-**83**	94	63
8		**36**	 (2*R*,3*S*)-**83**	91	66
9		**60**	 (2*S*,3*R*)-**84**	90	55
10		**36**	 (2*R*,3*S*)-**84**	93	63
11		**60**[f]	 (2*S*)-**85**	90	29
12		**36**[f]	 (2*R*)-**85**	99	34

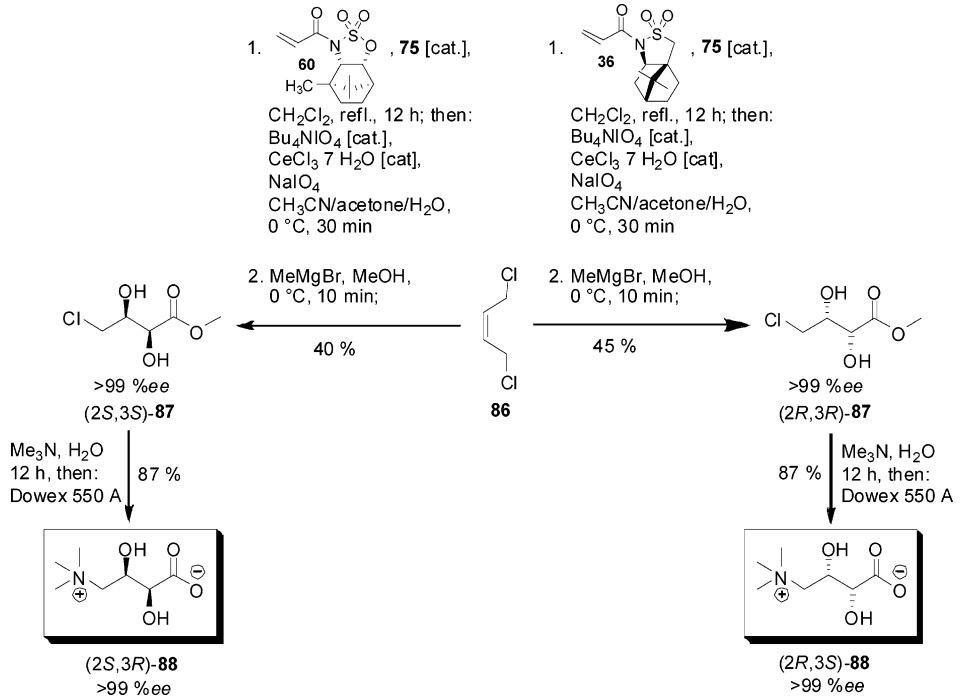
[a] All reactions were performed as indicated in Scheme 3. [b] Determined by chiral HPLC. [c] Combined isolated yield. [d] The auxiliary was recovered in good yield. [e] CM was performed with 3 equiv of olefin **I** in refluxing CH_2Cl_2 without the dilution apparatus. [f] CM was performed in refluxing CH_2Cl_2 with 3 equiv of olefin **I** without the dilution apparatus using 5 mol % catalyst **75** and 5 mol % MeI.

SCHEME 3. Cross-Metathesis Dihydroxylation of Olefin 78 and Amides 36 and 60[a]



[a] Reagents and conditions (1 mmol scale): (a) **75** (2.5 mol %), EtOAc (3 mL), reflux, 12 h, then Bu_4NIO_4 (5 mol %), $CeCl_3 \cdot 7H_2O$ (20 mol %), $NaIO_4$ (2 equiv), CH_3CN/acetone/H_2O (3 mL/3 mL/1 mL), 0 °C, 30 min; (b) MeMgBr (4.0 equiv), MeOH (3 mL), 0 °C, 10 min.

SCHEME 4. Two-Step Synthesis of Anthopleurine and *ent*-Anthopleurine 88



cantly within the methanolysis step. Various diols were obtained in high enantiomeric excesses ranging from 91% to 99%. A thorough control of the conversion is not necessary; the reaction stops at full conversion of the major stereoisomer. The kinetic resolution allowed for simple access to enantiomerically pure *vic*-diols in both enantiomeric forms. The methanolysis was performed on the crude mixture of diastereomeric alcohols obtained after the cross-metathesis−dihydroxylation reaction.

The catalytic sequence was finally applied to the total synthesis of anthopleurine **88**, a sea anemone alarm pheromone that was isolated in 1975 from the sea anemone *Anthopleura elegantissima* (Scheme 3).[20] This compound is a subunit of a larger polypeptidic structure and functions as an ion channel binder. With regard to its biological activity, our modular approach would allow the preparation of either enantiomer of anthopleurine in just three steps (Scheme 4). Indeed, applying the cross-metathesis−diastereoselective dihydroxylation conditions to sultame **36** or sulfamidate **60** in the presence of (*Z*)-1,4-dichlorobut-2-ene (**86**) followed by methanolysis yielded the enantiopure *vic*-diols (2*R*,3*R*)-**87** and (2*S*,3*S*)-**87** in good yields with excellent enantiopurity. Substitution of chloride by trimethylamine under standard conditions and saponification of

the methyl esters led to target compounds (2*S*,3*R*)-**88** and (2*R*,3*S*)-**88** in nearly quantitative yield (Scheme 4). A comparison of the optical rotations revealed the natural product to possess the (2*R*,3*S*)-configuration in accordance with Rappoport's earlier structural suggestion.[21]

Conclusion

Sequential catalysis has emerged as a powerful new concept which allows for the efficient use of one catalytically active metal for various transformations, avoiding unnecessary workup and purification procedures. In the present paper we summarize our results on the development of a diastereoselective cross-metathesis−dihydroxylation−methanolysis sequence. Within this development several problems were successfully addressed: (i) Two powerful camphor-based chiral auxiliaries have been identified, allowing for the first diastereoselective RuO_4-catalyzed dihydroxylation of olefins. (ii) An unusual kinetic separation of diastereomeric diols was observed, allowing for the selective methanolysis of the major diol formed within the oxidation event giving rise to *vic*-diols in either optical form and in good to excellent enantiomeric excess. (iii) Additives simplifying the in situ generation of RuO_4 from various metathesis catalysts were identified. (iv) The reaction scope was explored, and the catalytic sequence was applied toward the structural elucidation and determination of the absolute configuration of anthopleurine, a natural product.

Experimental Section

Total Synthesis of Anthopleurine 88 and *ent*-Anthopleurine *ent*-88. **Methyl 4-Chloro-2,3-dihydroxybutanoate (87).** In a 10 mL round-bottomed flask catalyst **75** (42 mg, 0.05 mmol, 5 mol %) was dissolved in dichloromethane (1.5 mL) under an argon atmosphere. CuCl (5 mg, 0.05 mmol, 5 mol %) and *o*-(isopropyloxy)styrene (8 mg, 0.05 mmol, 5 mol %) were added. The reaction mixture was stirred at 50 °C for 1 h until the solution turned deep green. The olefin **36** or **60** (1 mmol) was added followed by addition of (*Z*)-1,4-dichlorobutene (**86**) (187 mg, 1.5 mmol, 1.5 equiv). The mixture was heated to reflux and stirred until no more starting material could be detected (12 h). After complete conversion the slurry was cooled to room temperature and the solvent removed in vacuum. Bu_4NIO_4 (21.6 mg, 0.05 mmol, 5 mol %) and acetonitrile (1.5 mL) were added, and stirring was continued for 5 min. Meanwhile, $NaIO_4$ (427.8 mg, 2 mmol) and $CeCl_3 \cdot 7H_2O$ (74.5 mg, 0.2 mmol) were stirred in water (0.5 mL) in a 10 mL round-bottomed flask until the color of the suspension turned bright yellow. After the suspension was cooled to 0 °C, acetone (1.5 mL) and the metathesis reaction mixture were added. The resulting slurry was stirred at 0 °C until the oxidation was complete (10−30 min). Solid Na_2SO_4 and ethyl acetate were added, and the mixture was filtered through a plug of silica into a saturated aq Na_2SO_3 solution. The organic phase was separated, dried with Na_2SO_4, and concentrated in vacuum. The crude diol was then subjected to the standard methanolysis conditions: To a stirred solution of the diastereomeric diols (0.5 mmol) in a 1:1 mixture of CH_2Cl_2/MeOH (2 mL) was added a solution of MeMgBr (1.5 mmol, 500 μL, 3 M in THF) in 1 mL of MeOH (prepared at 0 °C prior to use). After the addition stirring was contiunued for 5−10 min at 0 °C. The reaction mixture was hydrolyzed by addition of a saturated aq $NaHSO_4$ solution (1 mL). The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuum. The crude diol was purified by column chromatography.

(2*S*,3*S*)-**87** was obtained in 40% yield (67 mg) starting from sulfamidate **60** and *cis*-1,4-dichlorobutene (**86**): $[\alpha]_D^{20}$ 16.9 (*c* 0.3, $CHCl_3$). (2*R*,3*R*)-**87** was obtained in 45% yield (76 mg) starting from sultame **36** and **86**: $[\alpha]_D^{20}$ −17.1 (*c* 0.25, $CHCl_3$); colorless solid; mp 31 °C; R_f 0.15 (1:1 isohexanes/ethyl acetate); enantiomeric excess determined by chiral HPLC (Chiralcel OJ, heptane/2-propanol (88:12), flow 0.9 mL/min, 215 nm), t_R(2*S*,3*S*) = 11.96 min, t_R(2*R*,3*R*) = 14.16 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (d, J = 1.5 Hz, 1H), 4.14 (ddd, J = 7.0, 1.5 Hz, 1H), 3.86 (s, 3H), 3.67 (dd, J = 11.0, 7.0, 1H), 3.64 (dd, J = 11.0, 7.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 72.3, 70.2, 53.1, 44.8 ppm; IR (KBr) ν 3427 (s), 1740 (s), 1440 (w), 1293 (w), 1254 (w), 1118 (m) cm^{-1}; HRMS (EI-HR) *m*/*z* calcd for $C_5H_9ClO_4$ 168.0166, found 168.0184.

2,3-Dihydroxy-4-(trimethylammonium)butanoate (88). Diol **87** (20 mg, 0.12 mmol) and NMe_3 (2 mL, 50% aq solution) were stirred in a 5 mL round-bottomed flask, heated to 45 °C, and stirred overnight. After the solution was cooled to room temperature, NMe_3 and H_2O were removed in vacuum. The residue was taken up in methanol (4 mL), and a basic ion exchanger (250 mg, Dowex 550 A (OH)) was added. The suspension was stirred at room temperature overnight. The ion-exchange resin was filtered off, and the solvent was evaporated to yield 18.3 mg (87%) of the desired betaine **88**: colorless solid; ^{1}H NMR (300 MHz, MeOH-d_4) δ 4.27 (dd, J = 9.6, 1.1 Hz, 1H), 3.72 (d, J = 3.4 Hz, 1H), 3.46 (dd, J = 13.5, 1.5 Hz, 1H), 3.33 (dd, J = 13.6, 9.7 Hz, 1H), 3.12 (s, 9H) ppm; ^{13}C NMR (100 MHz, MeOH-d_4) δ 177.5, 74.3, 70.6, 69.0, 54.8 ppm; IR (KBr) ν 3342 (s), 2945 (w), 2832 (w), 1606 (s), 1409 (w), 1198 (w), 1026 (w) cm^{-1}.

Data for anthopleurine (2*R*,3*S*)-88: optical rotations measured as a solution in 1 M HCl, $[\alpha]_D^{20}$ −25.0 (*c* 0.72, 1 M HCl); HRMS (ESI-HR) *m*/*z* calcd for $C_7H_{15}NNaO_4$ 200.0899, found 200.0896.

Data for *ent*-anthopleurine (2*S*,3*R*)-88: optical rotations measured as a solution in 1 M HCl, $[\alpha]_D^{20}$ 24.4 (*c* 0.25, 1 M HCl); HRMS (ESI-HR) *m*/*z* calcd for $C_7H_{15}NNaO_4$ 200.0899, found 200.0898.

Acknowledgment. We thank Prof. Dr. N. Krause for generous support. B.P. thanks the Fonds der Chemischen Industrie (Liebig fellowship) and the Deutsche Forschungsgemeinschaft (Emmy-Noether fellowship). Further financial support by the Dr.-Otto-Röhm-Gedächtnisstiftung is gratefully acknowledged. N.M.N. thanks Mrs. Sandra Hauler and cand.-chem. Johannes Klein for preparation of some starting materials.

Supporting Information Available: Experimental procedures for the preparation of all starting materials (α,β-unsaturated carboxylic acid derivatives) and the auxiliaries and ^{1}H NMR spectra of all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Musich, J. A.; Rapoport, H. *J. Am. Chem. Soc*. **1978**, *100*, 4865.

JO800145X