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α,β-Unsaturated δ-Lactones from Copper-Catalyzed Asymmetric Vinylogous Mukaiyama Reactions of Aldehydes: Scope and Mechanistic Insights

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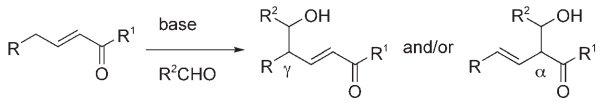
Abstract: A direct regio-, diastereo-, and enantiocontrolled access to α,β-unsaturated δ-lactones is described, based on the reaction of a silyl dienolate and an aldehyde in the presence of 10% of Carreira's catalyst. The scope and limitations of this reaction, as well as mechanistic insights concerning the reactivity of an allyl copper species, are discussed.

Keywords: aldol reaction · copper · lactones · mechanistic studies · vinylogous Mukaiyama reactions

Introduction

The vinylogous aldol reaction of an α,β-unsaturated ester (or ketone) (vinylogy is the transmission of electronic effects through a conjugated system) is an aldol reaction leading to a δ-hydroxy α,β-unsaturated carbonyl compound.[1] However, this reaction generally suffers from regioselectivity problems, affording an α,γ-mixture of aldol products (Scheme 1).[2] Due to this lack of regioselectivity, this methodology did not find synthetic success until the early 1970s. At that time, first Mukaiyama,[3] and then Paterson and Fleming,[4] described the use of silyl dienolates in the presence of Lewis acids at low temperatures, which led to the exclusive formation of the γ-aldol product.



Scheme 1. The vinylogous aldol reaction affording an α,γ-mixture of aldol products.

The synthetic potential of this reaction was rapidly recognized and the so-called vinylogous Mukaiyama reaction has found numerous synthetic applications, as illustrated, for example, in the total syntheses of lepicidin A, swhinolide A, ratjadone, and aurilide, as well as several synthetic approaches to natural products.[1d,5–8] Despite this great synthetic potential (an aldol product with an extra conjugated double bond, which can easily undergo further manipulation), catalytic and asymmetric vinylogous Mukaiyama reactions of α,β-unsaturated esters (ketones) have long remained an unexplored area.[1a,c] The development of regio- (α/γ), diastereo- (*E*/*Z*, *syn*/*anti*), and enantiocontrolled reactions is, notably in the context of the total synthesis of polypropionates of natural products, of great interest. In 1998, in the course of a project aimed at the total synthesis of octalactin A, we became interested in the development of catalytic and asymmetric vinylogous Mukaiyama reactions. More recently, impressive results have been obtained in Denmark's and Evans' groups using phosphoramidite-based Lewis bases and Cu–PyBox (PyBox = 2,6-bis[(4*S*)-isopropyl-2-oxazolin-2-yl]pyridine) Lewis acids, respectively.[9–12] In this paper, we wish to report our own efforts to develop catalytic and asymmetric vinylogous Mukaiyama (CAVM) reactions, which have opened a catalytic and asymmetric access to α,β-unsaturated δ-lactones.

Results and Discussion

By analogy with the structure of the octalactin side chain, we initiated our studies by carrying out the reaction of the α-substituted silyl dienolate **1** with aldehydes in the presence of various catalysts (Ti-binol (binol = 1,1′-binaphtha-

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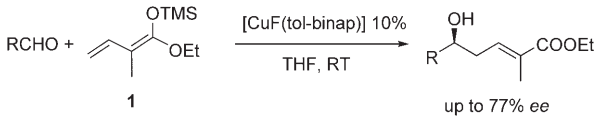
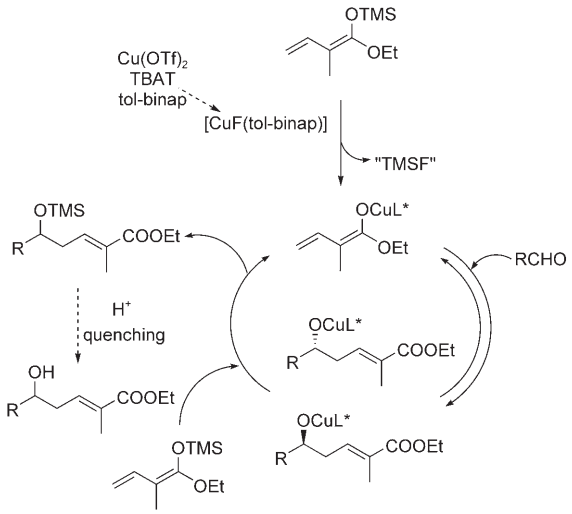
lene-2,2′-diol), Carreira's catalyst[13] [CuF(tol-binap)] (binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), and various chiral ammonium fluorides derived from cinchona alkaloids). Interesting results were obtained by using Carreira's catalyst, albeit with modest enantioselectivities (up to 77% *ee*) (Scheme 2).[14]



Scheme 2. CAVM reaction using Carreira's catalyst.

According to Carreira's mechanistic studies,[13] a catalytic cycle could be postulated involving the formation of a copper dienolate (Scheme 3). However, this catalytic cycle

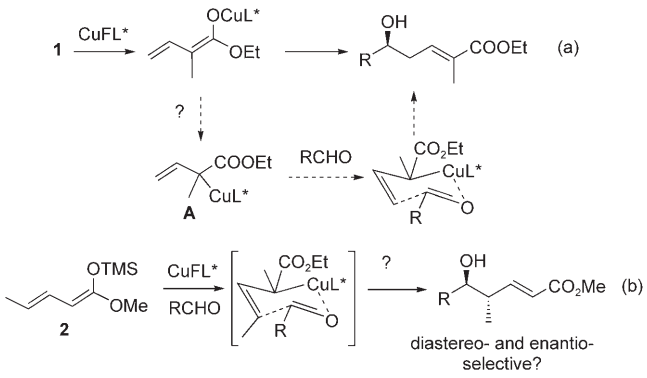


Scheme 3. A catalytic cycle involving the formation of a copper dienolate for a CAVM reaction using Carreira's catalyst. L* = tol-binap.

does not account for the origin of the enantioselectivity because the chiral copper center seems to be far away from the prochiral aldehyde.

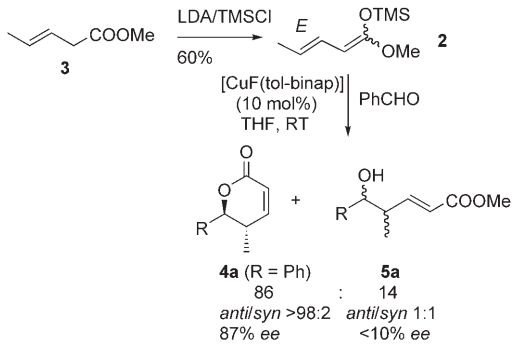
To explain the origin of the enantioselectivity, we first postulated that the activated species might be an α-copper enolate **A** (Scheme 4).[15] Thus, a six-membered transition state (Scheme 4, equation (a)), accounting for the origin of the enantioselectivity, was postulated.

According to this hypothesis and starting from a γ-substituted dienolate **2**, we thus anticipated to control, through a related six-membered transition state, both enantio- and diastereoselectivities (Scheme 4, equation (b)). Accordingly, γ-substituted dienolate **2** was synthesized from the commercially available ester **3** in 60% yield as an inseparable (3*E*,1*Z*/*E*) mixture. Its reactivity was first studied in the presence of Carreira's catalyst and benzaldehyde, which led



Scheme 4. Postulated reaction mechanism showing the activated α-copper enolate **A** species and a related six-membered transition state.L* = tol-binap.

to the formation of the expected "linear" vinylogous aldol product **5a** and the α,β-unsaturated lactone **4a** (Scheme 5). Interestingly, the linear product was obtained without any



Scheme 5. Reaction of **2** with Carreira's catalyst and benzaldehyde to give **5a** and **4a**.

selectivity (*syn*/*anti* 1:1; 8% *ee*), whereas the lactone was obtained as a single *anti* diastereoisomer with 87% *ee*.[16]

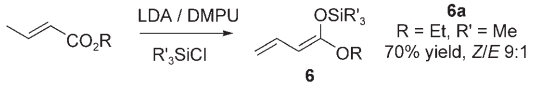
α,β-Unsaturated lactones are highly valuable intermediates present in a large number of natural products[17] possessing potent (mainly cytotoxic) biological activities. Examples include ratjadone,[6b] spicigerolide,[18] callystatin,[19] goniothalamin,[20] and fostriecin.[21] Furthermore, the unsaturated lactone moiety has been found to play a fundamental role in the biological activity of fostriecin.[21b] Accordingly, this methodology was applied to several other aliphatic, α,β-unsaturated, and aromatic aldehydes, as illustrated in Table 1. Diastereomerically pure *anti* lactones **4a–g** were obtained in moderate to good yields, with enantioselectivities ranging from 85% to 91%.

As the two dienolates **1** and **2** differ only in the position of the methyl group, it was intriguing to study the behavior of dienolate **6** (which bears no methyl group) under the same reaction conditions. Hence, dienolate **6a** was synthesized, starting from ethyl crotonate, in one step and 50–70% yield as a 9:1 *Z*/*E* mixture (Scheme 6).[22] However, both the

Table 1. Catalytic asymmetric vinylogous Mukaiyama reactions of silyl dienolate **2** with various aldehydes in the presence of [CuF{(*S*)-tol-binap}] (10%).

Entry	Aldehyde	Yield [%] (**4**+**5**)	Ratio[a] **4**/**5**	Lactones **4**	*anti*/*syn*[a]	*ee* [%]
1	benzaldehyde	85	86:14	**4a**	>98:2	87[b] (98)[c]
2	1-naphthaldehyde	95	80:20	**4b**	>98:2	85[d]
3	2,3-dimethoxybenzaldehyde	87	81:19	**4c**	>98:2	91[e]
4	furaldehyde	60	50:50	**4d**	>98:2	86[f]
5	cinnamaldehyde	60	70:30	**4e**	>98:2	82[g]
6	*i*PrCHO	65	64:36	**4f**	>98:2	91[h]
7	butyraldehyde	60	36:64	**4g**	>98:2	90[h]

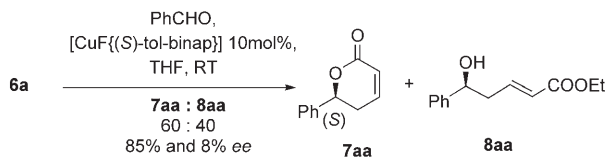
[a] Determined by ^{1}H NMR of the crude product. [b] HPLC DAICEL-OD, hexane-2-propanol, 95:5. [c] *ee* after recrystallization (heptane). [d] HPLC DAICEL-OJ, hexane/2-propanol, 82:18. [e] HPLC DAICEL-OJ, hexane/2-propanol, 95:5. [f] HPLC DAICEL-OJ, hexane/2-propanol, 95:5. [g] HPLC DAICEL-OJ, hexane/2-propanol, 90:10. [h] HPLC ChiralPAK AD, hexane/ethanol, 99:1.



Scheme 6. Synthesis of dienolate **6a** from ethyl crotonate. LDA = lithium diisopropylamide.

synthesis and purification (by kugelrohr distillation) of dienolate **6a** proved troublesome, particularly the removal of all of the residual 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU).[22b] Incidentally, all efforts to improve this protocol by using 2,2,6,6-tetramethylpiperidine (TMP), hexamethylphosphoramide (HMPA), phosphoric acid tripyrrolidine, or lithium bis(trimethylsilyl)amide (LiHMDS) proved unsuccessful in our hands.

The reaction of dienolate **6a** (R = Et, R′ = Me) with benzaldehyde in the presence of 10% of Carreira's catalyst, [CuF{(*S*)-tol-binap}], led to the formation of a 60:40 mixture of the α,β-unsaturated δ-lactone **7aa** and the linear vinylogous aldol product **8aa** (Scheme 7).



Scheme 7. Reaction of **6a** (R = Et, R′ = Me) with benzaldehyde in the presence of Carreira's catalyst to give **7aa** and **8aa**.

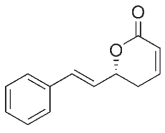
Purification by using flash chromatography led to the isolation of the lactone **7aa** in 50% yield and 85% *ee*, whereas the linear product **8aa** was isolated in 8% *ee*. The *S* configuration was assigned to the newly created stereogenic center by comparison with the previously described enantiomerically pure lactone.[23] As summarized in Table 2, the same reaction was carried out with various aromatic (entries 4 and 5), α,β-unsaturated (entry 7), and aliphatic aldehydes (entry 9), leading to the predominant formation of the lactones **7ab**–**ae** in good yields and with good enantioselectivities.

Table 2. Catalytic asymmetric vinylogous Mukaiyama reactions of silyl dienolate **6a** with various aldehydes in the presence of [CuF{(*S*)-tol-binap}] (10%).

Entry	Aldehyde	**6a** equiv [conc [M]]	Lactone	**7**:**8**[a]	Lactone (isolated yield [%])	*ee*[b] [%]
1	benzaldehyde	1.5 [0.05]	**7aa**	60:40	50	85
2		2 [0.05]		80:20	68	85
3		2 [0.1]		90:10	72	85
4	naphthaldehyde	1.5 [0.05]	**7ab**	90:10	80	75 (97)[c]
5	2,3-dimethoxy-benzaldehyde	1.5 [0.05]	**7ac**	60:40	64	82
6		2 [0.05]		90:10	85	82
7	cinnamaldehyde	1.5 [0.05]	**7ad**	70:30	60	60
8		2 [0.1]		75:25	65	60
9	isobutyraldehyde	1.5 [0.05]	**7ae**	60:40	40	85
10		2 [0.1]		75:25	65	85

[a] Determined by ^{1}H NMR of the crude product. [b] Determined by chiral HPLC. [c] *ee* after recrystallization from diethyl ether.

The first attempts to optimize the reaction (with benzaldehyde) showed the crucial importance of the amount of silyl dienolate **6a** on the lactone/linear product ratio (Table 2, entries 2 and 3). By simply conducting the reaction with two equivalents of silyl dienolate at a concentration of 0.1 M, the ratio could be increased to 90:10 without a decrease in the enantioselectivity (85% *ee*). These modified conditions also proved to be beneficial in the reactions with 2,3-dimethoxybenzaldehyde (Table 2, entry 6) and isobutyraldehyde (entry 10). The reaction with cinnamaldehyde (entry 8) provides a direct and one-step access (65% yield and 60% *ee*) to goniothalamin,[20] a known natural product that possesses interesting biological activities[20a,b] and for which a multistep synthesis has previously been described.[20c,d] However, all experiments aimed at increasing the enantioselectivity by changing the reaction conditions (ligand, dienolate structure) or by recrystallization proved unsuccessful (vide infra).


goniothalamin

Starting with these initial experiments, we set out to optimize this methodology and to gain insight into the reaction mechanism by modifying the various reaction parameters (precatalysts, dienolate structure, ligand, etc.) in a model reaction of silyl dienolates **6** with benzaldehyde.

Influence of the precatalyst: In the original procedure,[13] the precatalyst was made in situ by mixing $Cu(OTf)_2$ (10%; Tf = triflate), a nonhygroscopic source of fluoride, tetrabutylammonium triphenyldifluorosilicate (TBAT) (20%), and the ligand (11%) (Table 3, entry 1). The amount of precatalyst can be reduced to 5% with no deleterious effect on yield, *ee*, or lactone/linear product ratio (Table 3, entry 2). However, no reaction was observed with just 1% of precatalyst (Table 3, entry 3). In order to substitute the fluoride source, [Cu*t*BuO(tol-binap)] (from CuCl, NaO*t*Bu, and tol-binap) was successfully used, leading to the lactone/linear product mixture in a 60:40 ratio, with 87% *ee* for the lactone (Table 3, entry 6). Finally, under Riant's conditions in the presence of CuF_2 and tol-binap, no reaction was observed.[24]

Table 3. Influence of the copper precatalyst on the CAVM reaction of silyl dienolate **6a** with benzaldehyde.

Entry	Copper source	Base [%]	Tol-binap [%]	Lactone/linear ratio	Lactone + linear (combined yield) [%]	*ee* [%]
1	$Cu(OTf)_2$ 10%	TBAT (20)	11	90:10	85	87
2	$Cu(OTf)_2$ 5%	TBAT (10)	5	85:15	82	87
3	$Cu(OTf)_2$ 1%	TBAT (2)	1	no reaction	–	–
4	$Cu(OTf)_2$ 10%	TBAT (10)	11	no reaction	–	–
5	CuCl 10%	TBAT (20)	11	0:100	42	–
6	CuCl 10%	NaO*t*Bu (10)	11	60:40	70	87
7	CuCl 10%	NaO*t*Bu (10)	5	50:50	60	87
8	CuCl 1%	NaO*t*Bu (1)	1	no reaction	–	–
9	$Cu(OTf)_2$ 10%	NaO*t*Bu (10)	10	–	< 10 (α-product)	–
10	CuF_2 10%	–	10	no reaction	–	–

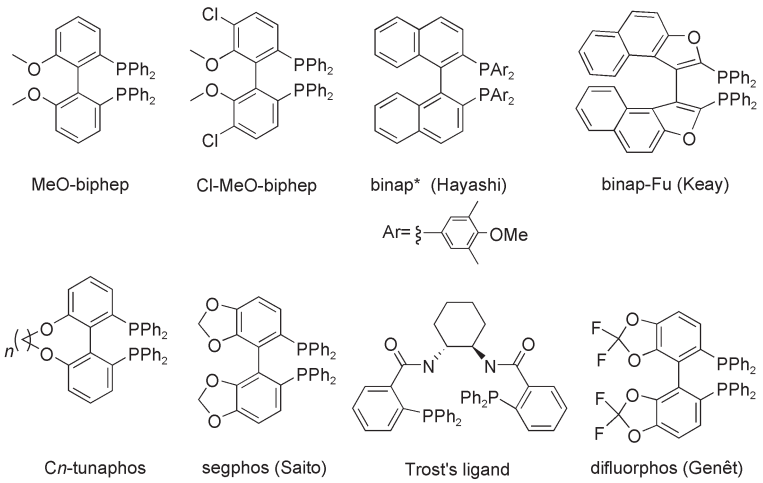
Dienolate structure: Modification of the silyl group was next investigated by using a *tert*-butyldimethylsilyl (TBDMS) group.[25] However, although a dramatic decrease in the lactone/linear ratio could be observed, the enantioselectivity remained unchanged (Table 4, entry 2). The ester group was found to have a greater influence on the enantioselectivity, as illustrated with dienolate **6d**, for which the enantioselectivity could be raised up to 99% *ee*, although to the detriment of the lactone/linear ratio (Table 4, entry 4).[26]

Table 4. Influence of the structure of the silyl dienolate **6** on the CAVM reaction with benzaldehyde.

Entry	R	Silyl group	Dienolate *Z*/*E* ratio	Lactone/linear ratio	Yield (lactone+linear) [%]	*ee* (lactone) [%]
1	Et	TMS	**6a** 90:10	90:10	85	85
2	Et	TBDMS	**6b** 90:10	30:70	43	81
3	Me	TMS	**6c** 90:10	85:15	80	80
4	*t*Bu	TMS	**6d** 80:20	15:85	78	99

Influence of the ligand: In order to optimize the enantioselectivity, a screening of several ligands was carried out (binap, binap*,[27] binap-Fu,[28] Cl-MeO-biphep, MeO-biphep, Trost's ligand, difluorphos,[29] C1-tunaphos,[30] segphos.[31])

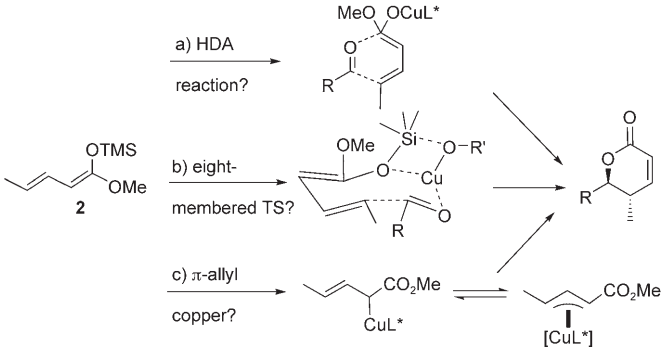
As previously observed by other groups,[29–31] there is a correlation between the dihedral angle and the enantioselectivity, but again to the detriment of the lactone/linear ratio (compare entries 3, 5, and 10 in Table 5). However, the best ligand in terms of enantioselectivity and lactone/linear ratio appears to be MeO-biphep, with which the lactone **7aa** was obtained in 62% isolated yield and 92% *ee* (Table 5, entry 5).



Mechanistic insights: As regards the reaction mechanism, several hypotheses may be envisaged at first glance (Scheme 8): a) a hetero-Diels–Alder (HDA)-type mechanism;[32–34] b) copper playing the role of Lewis acid in a clas-

Table 5. Ligand effects on the CAVM reaction of silyl dienolate **6a** with benzaldehyde.

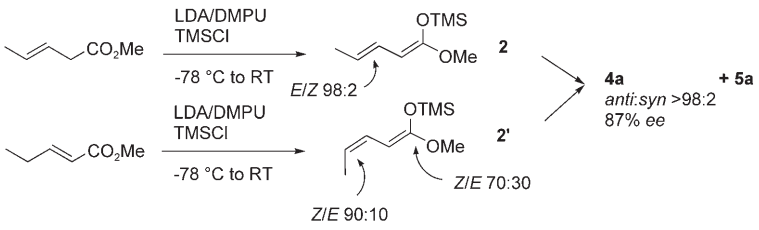
Entry	Ligand	Dihedral angle [°]	Lactone/linear **7aa**/**8aa** ratio	Isolated yield of **7aa** [%]	*ee* **7aa** [%]
1	tol-binap		90:10	75	85
2	binap*		80:20	68	75
3	binap	86.2	75:25	49	70
4	Cl-MeO-biphep		60:40	54	83
5	**MeO-biphep**	**72.3**	**78:22**	**62**	**92**
6	binap-Fu		65:35	49	60
7	Trost's ligand		0:100	–	–
8	difluorphos	67.6	50:50	40	94
9	segphos	67.2	60:40	51	96
10	C1-tunaphos	60.0	50:50	35	96



Scheme 8. Possible CAVM reaction mechanisms. L* = tol-binap.

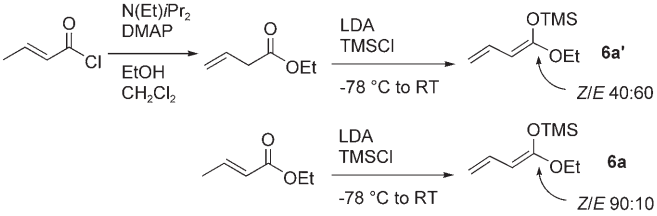
sical Mukaiyama reaction involving an eight-membered transition state;[35] c) reaction involving, as previously postulated (vide supra), the formation of an allyl–copper intermediate.

According to hypothesis (b), the *anti* diastereoselectivity may stem from the *E* stereochemistry of the terminal dienolate double bond. Consequently, starting from a *Z*-terminal double-bond dienolate, a *syn* diastereoselectivity outcome could be expected. In order to test this hypothesis, the 3*Z* dienolate **2′** was synthesized starting from the corresponding α,β-unsaturated ester (Scheme 9).[6a] However, when this dienolate **2′** was submitted to the vinylogous Mukaiyama reaction with benzaldehyde in the presence of Carreira's catalyst (10%), lactone **4a** was obtained with the same *anti* diastereoselectivity (*anti*/*syn* 98:2, 82–84% *ee*) as previously observed with dienolate **2**.



Scheme 9. Synthesis of 3*Z* dienolate **2′** from the corresponding α,β-unsaturated ester.

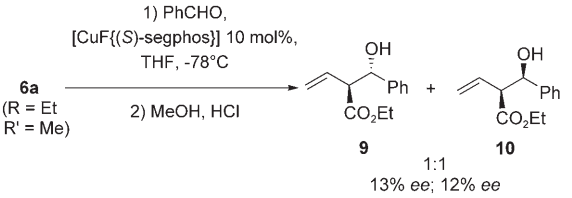
A similar situation was observed with the unsubstituted dienolate **6a** (Scheme 10). Starting from a 90:10 mixture of the *Z*/*E* dienolate **6a** (from ethyl crotonate) or from a 40:60



Scheme 10. Synthesis of **6a** and **6a′**.

Z/*E* dienolate **6a′** (obtained from the β,γ-unconjugated ester), the same lactone **4a** was obtained in similar yield and with similar enantioselectivity.

Consequently, a mechanism involving an eight-membered transition state (hypothesis (b), Scheme 8) can probably be ruled out. Among the other possibilities, we serendipitously obtained some mechanistic insights using the Segphos ligand. We observed that the CAVM reactions were faster in the presence of segphos[31] compared to those performed with tol-binap. Indeed, the CAVM reaction could be carried out at −78°C with segphos (no reaction occurs with tol-binap), leading to a 1:1 mixture of the two diastereoisomeric α-aldol products (Scheme 11). After purification on silica

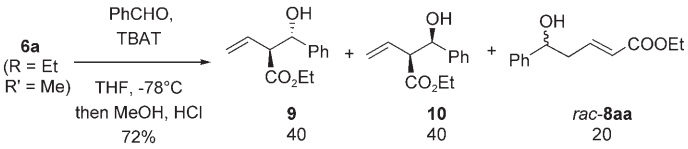


Scheme 11. The CAVM reaction with segphos as the catalyst ligand at −78°C.

gel, the two diastereoisomers **9** and **10** were isolated in a 1:1 ratio and with low enantiomeric excesses of 13% and 12% *ee*, respectively.

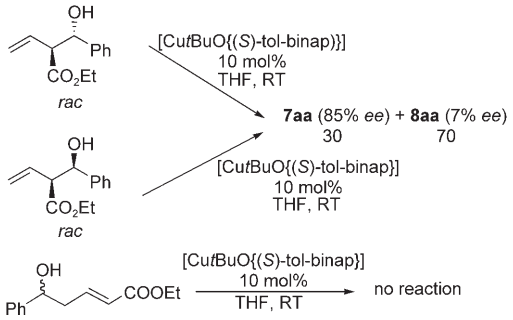
In order to monitor the evolution of these two α-aldol products under the reaction conditions at room temperature, these compounds were next independently synthesized[36] from silyl dienolate and benzaldehyde in the presence of TBAT at −78°C. This reaction yielded a 4:4:2 mixture of *anti*-α **9**, *syn*-α **10**, and racemic γ-aldol **8aa** (Scheme 12).

The three products were separated by using flash chromatography and, independently, were treated with a catalytic amount of the chiral copper catalyst. The two racemic α-compounds led to the same



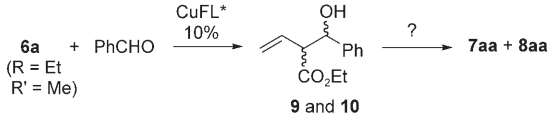
Scheme 12. Synthesis of *anti*-α **9**, *syn*-α **10**, and racemic γ-aldol **8aa**.

mixture of lactone and linear product, whereas linear **8aa** remained unchanged. Interestingly, the same lactone was isolated with the same enantiomeric excess (85% *ee*) from both the racemic *syn* and *anti* diastereoisomers (Scheme 13).



Scheme 13. Synthesis of **7aa** and **8aa** from both the racemic *syn* and *anti* diastereoisomers.

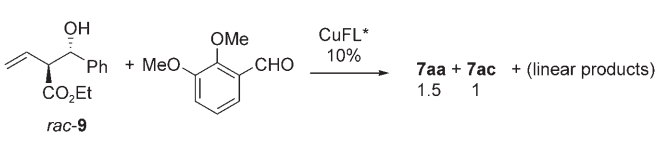
From these observations, the CAVM appears to proceed by two successive steps: first by a nonselective "regular" α-aldol reaction, followed by a rearrangement to give the enantio-enriched lactone **4a** (Scheme 14).



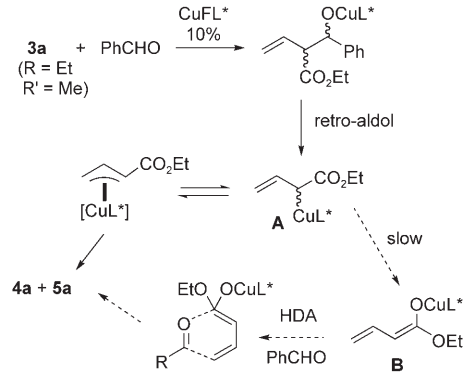
Scheme 14. The two steps of the CAVM reaction.

We have shown that this rearrangement is not an intramolecular reaction. Indeed, when the racemic α-aldol product **9** was treated with the copper catalyst in the presence of an another aldehyde (2,3-dimethoxybenzaldehyde), a 1.5:1 mixture of the two lactones **7aa** and **7ac** was obtained (Scheme 15).

To explain this rearrangement, we hypothesize a retro-aldol reaction leading to an allyl–copper species **A** (Scheme 16). The α-copper enolate may evolve into the O-enolate **B**, but such a process is known to be particularly slow and thus the HDA pathway may not be the predominant one.[15,37] We thus believe the allyl–copper to be the active species in the asymmetric transformation. Such species have also recently been invoked in some catalytic and asymmetric allylation reactions that take place in the presence of TBAT and a copper catalyst.[38] In conclusion, the CAVM might be viewed as a racemic "regular" α-aldol reaction, followed by an asymmetric allylation (Scheme 16).

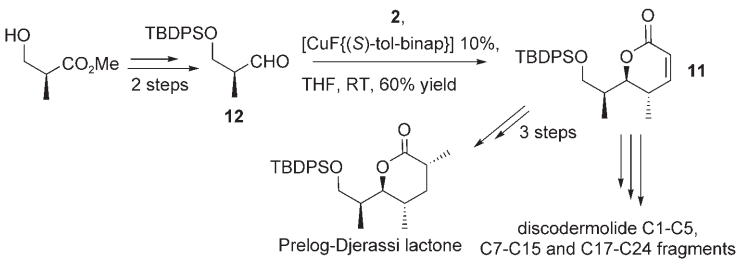


Scheme 15. Reaction of *rac*-**9** with 2,3-dimethoxybenzaldehyde in the presence of a copper catalyst to give lactones **7aa** and **7ac**.



Scheme 16. Proposed CAVM retro-aldol reaction mechanism leading to an allyl–copper species **A**. L* = tol-binap.

Synthetic applications: The synthetic potential of the CAVM reaction has been illustrated in the short accesses that it provides to the Prelog–Djerassi lactone,[16a] and the three main fragments of discodermolide[16b] starting from α,β-unsaturated lactone **11**. This lactone **11** was obtained as a single diastereoisomer in 60% isolated yield starting from chiral aldehyde **12** (obtained in two steps from the corresponding Roche ester). From this lactone intermediate, the Prelog–Djerassi lactone was then obtained in three steps and the three main fragments of discodermolide, C1–C5, C7–C15, and C17–C24, in two, five, and two steps, respectively (Scheme 17).



Scheme 17. Synthesis of the Prelog–Djerassi lactone and the three main fragments of discodermolide.

Conclusion

We have developed an efficient catalytic and asymmetric access to α,β-unsaturated lactones based on a one-step regio- (γ/α), diastereo- (*anti*/*syn*; *Z*/*E*), and enantioselective protocol. From a mechanistic point of view, the results are indicative of a mechanism involving a nonselective α-aldol reaction followed by an asymmetric allylation. Further developments and synthetic applications of this methodology are currently under investigation in our group.

Experimental Section

General: Unless otherwise specified, the reactions were carried out in oven-dried glassware under an argon atmosphere. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ as solvent; chemical shifts are given in ppm. Column chromatography was performed on 230–-400 mesh silica gel. THF was distilled from sodium/benzophenone. Dichloromethane, diisopropylamine, and chlorotrimethylsilane were distilled over CaH_2 prior to use. Elemental analyses were carried out by the "laboratoire de micro-analyse ICSN, Gif-sur-Yvette". IR spectra were recorded on an FTIR spectrometer. Mass spectra were recorded with a Navigator LC/MS (source AQA) in electrospray ionization mode. Optical rotations were determined operating at the sodium D line.

General procedure for the synthesis of silyl dienolates starting from α,β-unsaturated esters: *n*BuLi (7 mL, 11 mmol) was added dropwise to a solution of *N*,*N*′-diisopropylethylamine (DIPA; 1.5 mL, 11 mmol) in anhydrous THF (20 mL) at −50 °C. The mixture was stirred for 30 min, cooled to −78 °C, and then DMPU (1.4 mL, 11 mmol) was added dropwise. The resulting solution was stirred for 30 min and then the α,β-unsaturated ester (10 mmol) was added. This mixture was stirred for 30 min and then a solution of trimethylsilane chloride (TMSCl; 2 mL) in anhydrous THF (2 mL) was added over a period of 15 min. The resulting solution was allowed to warm to room temperature and stirred for 2 h. The solvent was removed under reduced pressure, the residue was taken up in pentane (50 mL), and this solution was filtered. The solvent was removed under reduced pressure and the crude material was distilled in a kugelrohr apparatus (45 °C, 1 mmHg) to furnish the respective silyl dienolate as an inseparable *Z*/*E* mixture.

General procedure for the synthesis of silyl dienolates starting from β,γ-unsaturated esters: The above general procedure was followed, but without the addition of DMPU.

General procedure for the CAVM reactions: A solution of $Cu(OTf)_2$ (dried at 100 °C over P_2O_5 prior to use) (18.4 mg, 0.05 mmol, 10 %) and (*R* or *S*)-tol-binap (38 mg, 0.055 mmol) in anhydrous THF (9 mL) was stirred for 30 min at room temperature (a clear yellow solution was obtained). A solution of TBAT (55.6 mg, 0.1 mmol) in anhydrous THF (1 mL) was then added and, after an additional 15 min, a bright yellow solution was obtained. Silyl dienolate (0.54 mmol) was added dropwise (the solution turned red-brown in color), followed by the aldehyde (0.27 mmol). The resulting mixture was stirred overnight at room temperature and then the solvent was removed under reduced pressure. The crude material was purified by using flash chromatography to provide the desired lactone. Whenever required (when lactone and linear products were obtained as an inseparable mixture), acetic anhydride (0.5 mL) and pyrdine (0.5 mL) were added to the crude mixture. After 1.5 h at room temperature, the mixture was diluted with toluene and the volatiles were evaporated in vacuo (three times). Flash chromatography on silica gel (heptane/EtOAc, 70:30) furnished the lactones.

(3*E*,1*Z*)-(1-Methoxypenta-1,3-dienyloxy)trimethylsilane (2):[39] According to the above-described general (DMPU-free) procedure, and starting from commercially available (*E*)-methyl pent-3-enoate, the silyl dienolate **2** was obtained after kugelrohr distillation (50 °C, 1 mmHg) in 60 % yield as an inseparable mixture (1*Z*/*E* 70:30, 3*E*/*Z* > 98:2). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.23 (s, 9H), 1.72 (dd, J = 1.4, 6.9 Hz, 3H), 3.56 (s, 3H), 4.41 (d, J = 10.3 Hz, 1H), 5.33 (dq, J = 14.9, 6.9 Hz, 1H), 6.10 ppm (m, 1H). Data are in accordance with those reported previously.[38]

(1*Z*/*E*,3*E*)-(1-Methoxypenta-1,3-dienyloxy)trimethylsilane (2′): According to the above-described general procedure, and starting from commercially available (*E*)-methyl pent-2-enoate, the silyl dienolate **2′** was obtained after kugelrohr distillation (50 °C, 1 mmHg) in 60 % yield as an inseparable mixture (1*Z*/*E* 70:30, 3*E*/*Z* 90:10). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.21 (s, 9H), 1.66 (dd, J = 1.6, 6.8 Hz, 3H), 3.59 (s, 3H), 4.54 (d, J = 10.8 Hz, 1H), 5.91 (m, 1H), 6.11 ppm (tq, J = 10.8, 1.7 Hz, 1H).

(1*Z*)-(1-Ethoxybuta-1,3-dienyloxy)trimethylsilane (6a):[36] According to the above-described general procedure and starting from ethyl crotonate, kugelrohr distillation of the crude mixture (45 °C, 1 mmHg) afforded **6a** (1.3 g, 70 % yield) as an inseparable mixture, *Z*/*E* 90:10. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.24 (s, 8.1H), 0.27 (s, 0.9H), 1.25 (t, J = 7.1 Hz, 0.3H), 1.31 (t, J = 7.0 Hz, 2.7H), 3.81 (q, J = 7.0 Hz, 1.8H), 3.92 (q, J = 7.1 Hz, 0.2H), 4.46 (d, J = 10.4 Hz, 0.9H), 4.54 (d, J = 10.4 Hz, 0.1H), 4.59 (dd, J = 1.8, 10.4 Hz, 1H), 4.83 (dd, J = 1.8, 17.2 Hz, 1H), 6.51 ppm (dt, J = 10.4, 17.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.0, 62.4, 80.4, 106.9, 131.7, 157.2 ppm. Data are in accordance with those reported previously.[36]

(5*S*)-Methyl-(6*S*)-phenyl-5,6-dihydropyran-2-one (4a): According to the above-described general procedure for the MVCA reaction, lactone **4a** was obtained in 60 % yield as a white powder. M.p. 66–68 °C; $[\alpha]_D^{20}$ = −39.8 (c = 0.67 in chloroform); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.02 (d, J = 7.2 Hz, 3H), 2.83 (m, 1H), 4.98 (d, J = 10.7 Hz, 1H), 6.10 (dd, J = 9.7, 2.5 Hz, 1H), 6.76 (dd, J = 9.7, 1.9 Hz, 1H), 7.39 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.8, 36.2, 86.0, 120.4, 127.4 (2C), 128.5 (2C), 128.9, 137.3, 151.1, 163.9 ppm; IR (KCl): $\tilde{\nu}$ = 3020, 1723, 1215 cm^{-1}; MS (EI): m/z (%): 188 (20) [M^+], 128 (20), 105 (15), 82 (100), 81 (42); elemental analysis calcd for $C_{12}H_{12}O_2$: C 76.57, H 6.43; found: C 76.36, H 6.82; HPLC (DAICEL-OD, hexane/2-propanol, 95:5): 87 % *ee*.

(5*S*)-Methyl-(6*S*)-naphthalen-2-yl-5,6-dihydropyran-2-one (4b): According to the above-described general procedure for the MVCA reaction, lactone **4b** was obtained in 68 % yield as a pale yellow powder. M.p. 107–110 °C; $[\alpha]_D^{20}$ = −37.3 (c = 0.3 in chloroform); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.01 (d, J = 7.2 Hz, 3H), 2.92 (m, 1H), 5.12 (d, J = 10.8 Hz, 1H), 6.1 (dd, J = 9.7, 2.5 Hz, 1H), 6.76 (dd, J = 9.7, 2.1 Hz, 1H), 7.51 (m, 3H), 7.84 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 16.0, 35.3, 86.3, 120.6, 124.5, 125.6, 126.7, 127.2, 127.8, 128.2, 128.7, 133.6, 134.7, 135.9, 151.4, 164.0 ppm; IR (KCl): $\tilde{\nu}$ = 3020, 1720, 1602 cm^{-1}; MS (EI): m/z (%): 238 (4) [M^+], 127 (15), 82 (78), 82 (100); HRMS (EI): m/z calcd for $C_{16}H_{14}O_2$: 238.0994; found: 238.0996; HPLC (DAICEL-OJ, hexane/2-propanol, 82:18): 85 % *ee*.

(5*S*)-Methyl-(6*S*)-(2,3-dimethoxyphenyl)-5,6-dihydropyran-2-one (4c): According to the above-described general procedure for the MVCA reaction, lactone **4b** was obtained in 61 % yield as a pale yellow powder. M.p. 92–94 °C; $[\alpha]_D^{20}$ = 8.5 (c = 0.27 in chloroform); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.97 (d, J = 7.3 Hz, 3H), 2.91 (m, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 5.40 (d, J = 10.9 Hz, 1H), 6.0 (dd, J = 9.7, 2.0 Hz, 1H), 6.70 (dd, J = 9.7, 2.6 Hz, 1H), 6.85–7.15 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.8, 34.8, 55.8, 61.3, 80.3, 112.7, 119.9, 120.3, 124.4, 131.2, 147.4, 151.8, 152.7, 164.4 ppm; IR (KCl): $\tilde{\nu}$ = 3022, 1724, 1521 cm^{-1}; MS (EI): m/z (%): 248 (100) [M^+], 166 (80), 82 (97), 77 (47); HRMS (EI): m/z calcd for $C_{14}H_{16}O_4$: 248.1049; found: 248.1045; HPLC (DAICEL-OJ, hexane/2-propanol, 95:5): 91 % *ee*.

(5*S*)-Methyl-(6*S*)-furan-2-yl-5,6-dihydropyran-2-one (4d): According to the above-described general procedure for the MVCA reaction, lactone **4d** was obtained in 28 % yield as a clear yellow oil. $[\alpha]_D^{20}$ = 7.3 (c = 0.74 in chloroform); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.01 (d, J = 7.2 Hz, 3H), 3.09 (m, 1H), 5.03 (d, J = 10.1 Hz, 1H), 6.0 (dd, J = 9.7, 2.4 Hz, 1H), 6.36 (dd, J = 3.2, 1.8 Hz, 1H), 6.41 (d, J = 3.2 Hz, 1H), 6.73 (dd, J = 9.8, 2.5 Hz, 1H), 7.36 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 16.2, 32.3, 78.3, 110.2, 110.5, 120.3, 143.3, 147.7, 150.9, 166.8 ppm; IR (KCl): $\tilde{\nu}$ = 3022, 2933, 1735, 1248 cm^{-1}; MS (EI): m/z (%): 178 (52) [M^+], 95 (25), 82 (100), 54 (34); HRMS (EI): m/z calcd for

$C_{10}H_{10}O_3$: 179.0708; found: 179.0686; HPLC (DAICEL-OJ, hexane/2-propanol, 95:5): 86% *ee*.

(5*S*)-Methyl-(6*R*)-styryl-5,6-dihydropyran-2-one (4e): According to the above-described general procedure for the MVCA reaction, lactone **4e** was obtained in 30% yield as a clear yellow oil. $[\alpha]_D^{20} = 4.4$ ($c = 0.5$ in chloroform); ^{1}H NMR (250 MHz, $CDCl_3$, 25°C): $\delta = 1.17$ (d, $J = 7.3$ Hz, 3H), 2.63 (m, 1H), 4.66 (m, 1H), 6.01 (dd, $J = 9.8$, 2.3 Hz, 1H), 6.22 (dd, $J = 15.9$, 7.4 Hz, 1H), 6.73 (m, 2H), 7.27–7.51 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.3$, 34.1, 84.5, 120.5, 126.9 (2C), 128.5, 128.8 (2C), 135.0, 151.0, 167.0 ppm; IR (KCl): $\tilde{\nu} = 2925$, 1720, 1217 cm^{-1}; MS (ES+): *m*/*z* (%): 253 (100) [*M*+K$^+$], 237 (65) [*M*+Na$^+$], 215 (30) [*M*+H$^+$]; HRMS (EI): *m*/*z* calcd for $C_{14}H_{14}O_2Na$: 237.0891; found: 237.0994; HPLC (DAICEL-OJ, hexane/2-propanol, 90:10): 82% *ee*.

(5*S*)-Methyl-(6*R*)-isopropyl-5,6-dihydropyran-2-one (4f): According to the above-described general procedure for the MVCA reaction, lactone **4f** was obtained in 35% as a clear yellow oil. $[\alpha]_D^{20} = 24.2$ ($c = 0.72$ in chloroform); ^{1}H NMR (250 MHz, $CDCl_3$, 25°C): $\delta = 0.94$ (d, $J = 6.8$ Hz, 3H), 1.05 (d, $J = 7.7$ Hz, 3H), 1.08 (d, $J = 7.5$ Hz, 3H), 1.95 (m, 1H), 2.56 (m, 1H), 3.09 (dd, $J = 9.8$, 3.1 Hz, 1H), 5.91 (dd, $J = 9.7$, 2.3 Hz, 1H), 6.62 ppm (dd, $J = 9.7$, 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 15.4$, 16.3, 19.6, 29.0, 30.9, 87.8, 120.1, 151.9, 164.5 ppm; IR (KCl): $\tilde{\nu} = 2968$, 1716, 1463, 1241 cm^{-1}; MS (EI): *m*/*z* (%): 154 (25) [*M*$^+$], 111 (35), 82 (100), 54 (51); HRMS (EI): *m*/*z* calcd for $C_9H_{14}O_2$: 154.0994; found: 154.0996; HPLC (ChiralPAK AD, hexane/ethanol, 99:1): 91% *ee*.

(5*S*)-Methyl-(6*R*)-butyl-5,6-dihydropyran-2-one (4g): According to the above-described general procedure for the MVCA reaction, lactone **4g** was obtained in 19% yield as a clear yellow oil. $[\alpha]_D^{20} = 15.3$ ($c = 0.5$ in chloroform); ^{1}H NMR (250 MHz, $CDCl_3$, 25°C): $\delta = 0.91$ (~t, $J = 6.89$ Hz, 3H), 1.08 (d, $J = 7.2$ Hz, 3H), 1.3–1.7 (m, 4H), 2.50 (m, 1H), 4.05 (m, 1H), 5.92 (dd, $J = 9.7$, 2.2 Hz, 1H), 6.61 ppm (dd, $J = 9.7$, 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 13.8$, 16.5, 17.9, 29.7, 34.9, 83.4, 120.1, 151.5, 166.5 ppm; MS (EI): *m*/*z* (%): 177 (30) [*M*+Na$^+$]; HPLC (ChiralPAK AD, hexane/ethanol, 99:1): 90% *ee*.

(*S*)-6-Phenyl-5,6-dihydropyran-2-one (7aa):[23] According to the above-described general procedure for the MVCA reaction, lactone **7aa** was obtained as a white solid in 72% yield. M.p. 84°C; $[\alpha]_D^{20} = -188$ ($c = 1.5$ in chloroform); ^{1}H NMR (250 MHz, $CDCl_3$, 25°C): $\delta = 2.36$–2.78 (m, 2H), 5.43 (dd, $J = 10.5$, 5.5 Hz, 1H), 6.12 (d, $J = 9.9$ Hz, 1H), 6.95 (m, 1H), 7.27–7.50 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 31.7$, 79.2, 121.7, 126.1 (3C), 128.6 (2C), 138.4, 144.8, 164.0 ppm; HPLC (DAICEL OD, hexane/2-propanol, 95:5): 85% *ee*. Data are in accordance with those reported previously.[23]

(*S*)-6-(Naphthalen-2-yl)-5,6-dihydropyran-2-one (7ab): According to the above-described general procedure for the MVCA reaction, lactone **7ab** was obtained as a white solid (80% yield). M.p. 157°C; $[\alpha]_D^{20} = -183$ ($c = 1$ in chloroform); ^{1}H NMR (250 MHz, $CDCl_3$, 25°C): $\delta = 2.58$–2.69 (m, 2H), 5.78 (dd, $J = 5.7$, 10.2 Hz, 1H), 6.2 (d, $J = 10.2$ Hz, 1H), 6.94–7.04 (m, 1H), 7.47–7.61 (m, 3H), 7.85–7.91 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 31.7$, 79.2, 121.7, 123.5, 125.1, 127.7, 128.0, 128.5, 133.0, 135.8, 144.8, 164.0 ppm; IR (KCl): $\tilde{\nu} = 3020$, 1215, 756 cm^{-1}; MS (EI): *m*/*z* (%): 154 (8) [*M*$^+$], 156.0 (59), 128 (100), 87.0 (59); elemental analysis calcd for $C_{15}H_{12}O_2$: C 80.34, H 5.39; found: C 79.79, H 5.43; HPLC (ChiralPAK OD, hexane/2-propanol, 70:30): 76% *ee* (97% *ee* for the lactone recrystallized from diethyl ether).

(*S*)-6-(2,3-Dimethoxyphenyl)-5,6-dihydropyran-2-one (7ac): According to the above-described general procedure for the MVCA reaction, lactone **7ac** was obtained as a white solid (80% yield). M.p. 104°C; $[\alpha]_D^{20} = -139.4$ ($c = 1$ in chloroform); ^{1}H NMR (250 MHz, $CDCl_3$, 25°C): $\delta = 2.57$–2.67 (m, 2H), 3.8 (s, 3H), 3.9 (s, 3H), 5.78 (dd, $J = 9.9$, 6.0 Hz, 1H), 6.14 (d, $J = 9.8$ Hz, 1H), 6.88–7.06 (m, 2H), 7.09–7.18 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 30.9$, 55.9, 61.0, 74.9, 112.6, 118.8, 121.4, 124.4, 132.4, 145.6, 146.0, 152.4, 164.5 ppm; IR (KCl): $\tilde{\nu} = 2931$, 1727, 1480 cm^{-1}; MS (EI): *m*/*z* (%): 234.0 (77) [*M*$^+$], 166.0 (100), 148.0 (44), 68.0 (61); elemental analysis calcd for $C_{13}H_{14}O_4$: C 66.66, H 6.02; found: C 66.73, H 6.45; HPLC (ChiralPAK OD, hexane/ethanol, 95:5): 92% *ee*.

(*S*)-6-Styryl-5,6-dihydropyran-2-one (7ad):[40] According to the above-described general procedure for the MVCA reaction, lactone **7ad** was obtained as a white solid (65% yield). M.p. 77°C (lit. 80°C); ^{1}H NMR (250 MHz, $CDCl_3$, 25°C): $\delta = 2.54$ (m, 2H), 5.1 (q, $J = 5.3$ Hz, 1H), 6.09 (d, $J = 9.8$ Hz, 1H), 6.28 (dd, $J = 15.9$, 6.3 Hz, 1H), 6.73 (d, $J = 15.9$ Hz, 1H), 6.90 (m, 1H), 7.28–7.43 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 30.0$, 121.7, 125.0, 126.9, 128.5, 128.8, 133.3, 135.9, 144.7, 164.0 ppm; HPLC (ChiralPAK AD, hexane/ethanol, 95:5): 60% *ee*. Data are in accordance with those reported previously.[40]

(*S*)-6-Isopropyl-5,6-dihydropyran-2-one (7ae):[41] According to the above-described general procedure for the MVCA reaction, lactone **7ae** was obtained as a yellow oil (65% yield). $[\alpha]_D^{20} = -49.6$ ($c = 1$ in chloroform); ^{1}H NMR (250 MHz, $CDCl_3$, 25°C): $\delta = 0.99$ (d, $J = 6.8$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 1.95 (m, 1H), 2.28–2.34 (m, 2H), 4.25 (m, 1H), 6.0 (d, $J = 9.6$ Hz, 1H), 6.87 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 18.2$ (2C), 26.8, 32.4, 82.9, 121.7, 145.6, 165.1 ppm. Data are in accordance with those reported previously.[41]

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