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Two Catalytic Methods of an Asymmetric Wittig [2,3]-Rearrangement

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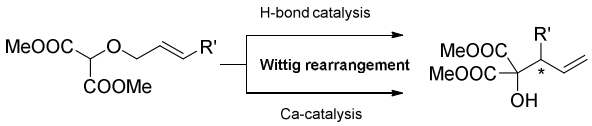
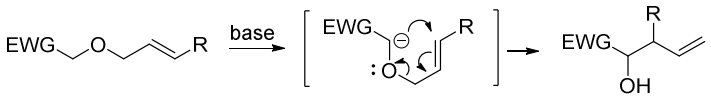
Abstract: Two different approaches for asymmetric catalytic Wittig [2,3]-rearrangement were developed. Allyloxymalonate derivatives were converted into homoallyl alcohols via organocatalytic or Ca^{2+}-catalyzed pathways in moderate to high enantioselectivities.



Introduction

Catalytic reactions are of fundamental importance in chemistry. Both metal-catalyzed and organocatalytic reactions are widely used in asymmetric synthesis. When a catalytic reaction is applied in a rearrangement reaction with a hundred percent atom efficiency, it leads to a highly efficient process. In this context, the development of an asymmetric catalytic rearrangement reaction remains challenging.

The sigmatropic Wittig [2,3]-rearrangement of allyl ethers affording sterically hindered homoallyl alcohols with a potential stereogenic center is an efficient tool for the formation of a C-C bond (Scheme 1).[1]



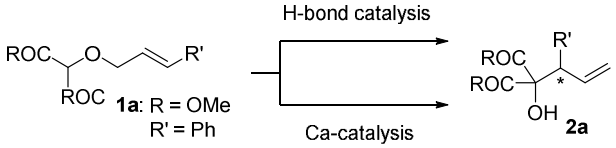
Scheme 1. Base induced Wittig [2,3]-rearrangement.

A great deal of effort has been invested in anion-promoted Wittig rearrangements. Usually strong Lewis bases, such as BuLi or *t*-BuLi are used to generate carbanion.[2] For enantioselective reactions, chiral ligands have been used.[3]

Examples of catalytic asymmetric Wittig rearrangements remain scarce. The pioneering organocatalytic paper in this field was published by Gaunt in 2006.[4] Only one example of an aminocatalytic asymmetric reaction was described and the obtained results remained moderate (*ee* 60%). Approximately 10 years later new approaches were simultaneously published by Denmark[5] and by us[6]. Denmark used phase-transfer catalysis for the rearrangement of allyloxyoxindole derivatives in moderate enantioselectivities (*ee* up to 54%). We used squaramide-catalyzed reactions on the same substrate, affording products in high enantiomeric purity (*ee* up to 97%) but the diastereoselectivity of the reaction was low (up to 2.7:1). Recently, Jacobsen *et al* published a conceptually new approach based on a synergistic ion-binding thiourea catalysis.[7] It was shown that in the transition state of [2,3]-sigmatropic rearrangements a set of noncovalent interactions involving hydrogen bondings by thiourea and simultaneous ion-bindings were responsible for the enantioselectivity of the reaction. High yields and enantioselectivities were obtained by applying this concept to allyloxymalonate derivatives (*ee* up to 93%). The following is complementary in terms of described methods and provides new information on the asymmetric Wittig rearrangement.

Results and Discussion

Herein we present two alternative methods for a Wittig [2,3]-sigmatropic rearrangement reaction of allyloxy-1,3-dicarbonyl compounds (Scheme 2).



Scheme 2. Two approaches to a Wittig [2,3]-rearrangement.

The organocatalytic method is based on our previous experience with an asymmetric Wittig [2,3]-rearrangement of oxindole derivatives.[6] An alternative method is a metal-catalyzed reaction in the presence of chiral ligands. Best to our knowledge, this is the first Lewis acid catalyzed asymmetric Wittig [2,3]-rearrangement.[8] For the past ten years calcium catalytic reactions have shown very high potency towards 1,3-carbonyl compounds. Calcium salts combined with chiral ligands can promote high enantioselective outcomes in various reactions.[9,10,11]

It is proposed that the formation of an anion in the substrate serves as a trigger for the rearrangement reaction. Therefore cinnamyloxymalonate **1a**, possessing an acidic proton, was chosen as a model compound.

Organocatalytic Wittig [2,3]-rearrangement

The set of organocatalysts used are depicted in Figure 1. Our first choice was bifunctional squaramide **I**, which showed high enantiodiscrimination in the case of allyloxy-oxindole derivatives. The second group of catalysts (compounds **II-VII**) is based on a cyclopropenimine scaffold. These highly basic compounds are comparable to the basicity of guanidines.[12] In addition to their high Lewis basicity they are also hydrogen bond donors (except catalysts **III and VII**). Monofunctional chiral guanidine **VIII** was the last choice.[13]

The results of screening experiments are presented in Table 1. Chiral squaramide **I** did not show any activity towards cinnamyloxymalonate **1a** even at a higher temperature and extended reaction time (Table 1, entry 1). When highly basic cyclopropenimine **II** was used

for the rearrangement, excellent reactivity and promising selectivity were achieved (Table 1, entry 2). Lowering the temperature of the reaction increased the enantioselectivity to 50%, while full conversion was reached with longer reaction time (Table 1, entry 3). Furthermore, a variety of catalyst **II** analogues were synthesized in order to improve the enantioselectivity of the reaction (Table 1, entries 4-8). Cyclopropenimine catalyst **II**-**VII** can be very easily prepared from amino-alcohols by a two-step procedure described by the Lambert group.[12] The instability of the cyclopropenimine catalysts as free bases should be noted. However, hydrochloric salts of the catalysts are stable at room temperature. Unfortunately, none of those analogues gave full conversion at reasonable reaction time and the selectivity in most cases was lower. Catalyst **III** and **VII** were exceptional with no hydrogen bond donor sites. Although almost full conversion was obtained at room temperature in the presence of catalyst **III,** the enantioselectivity of the reaction was very low (ee of **2a** 8%, Table 1, entry 4). Sterically more hindered catalyst **VII** was inactive, affording no conversion (Table 1, entry 8). The reaction catalyzed by guanidine **VIII** gave poorer results (Table 1, entry 9). Since full conversion is particularly important in terms of purification as compounds **1** and **2** are chromatographically inseparable, catalyst **II** was chosen for further screening, despite the fact that catalyst **IV** was to some extent more selective. Also, catalyst **II** is more stable than catalyst **IV**. Next, several typical solvents for hydrogen-bond mediated transformations were tested (Table 1, entries 10-13).. It is known that apolar solvents are preferred for the hydrogen bond catalyzed reactions. Hexane was excluded because of low solubility of reactants in this solvent. The reaction was faster in 1:1 mixture of hexane and chloroform than in $CDCl_3$ but the stereoselectivity was lower (Table 1, entries 3 and 10). Etheral solvents or toluene had no advantages over chloroform (Table 1, entries 12-14). As expected, racemic product was obtained in protonic solvent (Table 1, entry 15). The decrease of the amount of catalyst **II** led to only partial conversion after two days of the reaction (Table 1, entry 16).

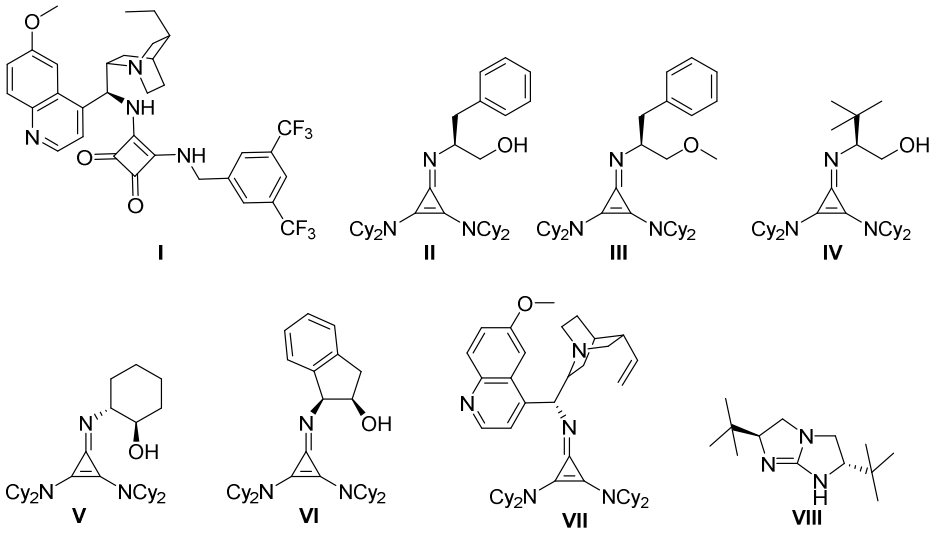
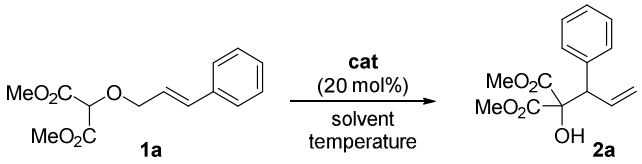


Figure 1. Catalysts screened for the organocatalytic Wittig [2,3]-rearrangement of cinnamyloxymalonates.

Table 1. Catalyst screening and optimization of the organocatalytic Wittig [2,3]-rearrangement of cinnamyloxymalonate 1a[a]



Entry	Catalyst	Solvent	Temp.	Time	Conv. (%)[b]	*ee* (%)[c]
1	**I**	$CDCl_3$	55 °C	96 h	0	-
2	**II**	$CDCl_3$	rt	2 h	100	33
3	**II**	$CDCl_3$	-20 °C	18 h	100	50
4	**III**	$CDCl_3$	rt	2 h	94	8
5	**IV**	$CDCl_3$	-20 °C	23 h	97	52
6	**V**	$CDCl_3$	-20 °C	18 h	88	-37
7	**VI**	$CDCl_3$	rt	18 h	45	*rac*

8	**VII**	$CDCl_3$	55 °C	72 h	0	-
9	**VIII**	$CDCl_3$	55 °C	72 h	90	-20
10	**II**	Hexane: $CDCl_3$[d]	-20 °C	5 h	100	45
11	**II**	EtOAc	rt	23 h	80	17
12	**II**	toluene	-20 °C	20 h	83	28
13	**II**	THF	-20 °C	20 h	74	23
14	**II**	Et_2O	-20 °C	18 h	78	31
15	**II**	MeOH	-20 °C	18 h	100	*rac*
16	**II**	$CDCl_3$	-20 °C	48 h[e]	57	-

[a] Reaction conditions: 0.1 mmol scale, 20 mol % of cat., solvent (0.5 mL). [b] Conversion determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by chiral HPLC analysis of the sample obtained by preparative TLC. [d] Mixture 1:1. [e] Reaction conditions: 0.1 mmol scale, 10 mol % of cat., solvent (0.25 mL).

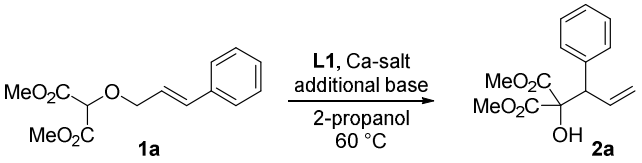
Ca^{2+}-catalyzed Wittig [2,3]-rearrangement reaction

Next, the results of a Ca-catalyzed Wittig [2,3]-sigmatropic rearrangement reaction of allyloxy-1,3-dicarbonyl compounds will be discussed.

In a metal-catalyzed reaction, several factors besides the chiral ligand (such as the source of metal, the solvent and the additional base) influence the stereoselectivity of the rearrangement. We limited the scope of ligands to bisoxazoline derivatives as most widely used in Ca^{2+}-catalysis[1415] although oxazolidines and bisoxazolidines have also been used in catalysis with other metals.[16] Also, the choice of solvent was 2-propanol as we have previously shown its superiority over other solvents for Ca^{2+}-bisoxazoline-catalyzed reactions.[17] (See Supporting Information for full optimization procedures).

Initially different calcium salts were screened in the presence or absence of imidazole as an additional base (Table 2, entries 1-6). The addition of imidazole in a calcium chloride/**L1** catalyzed reaction (Figure 2) was needed to yield higher conversion and enantioselectivity (Table 2, entries 1-2). The reaction with calcium iodide stopped after 6 hours, within 24 hours the reaction had not proceeded further. Calcium(II) bis(trifluoromethanesulfonimide) ($Ca(NTf_2)_2$) proved to be the superior of the Ca-salts (Table 2, entry 4), giving full conversion and enantiomeric excess of 75% in 24 hours. Next, other organic bases were evaluated (Table 2, entries 7-10), but still the addition of imidazole gave slightly higher enantioselectivity than with the other bases. The presence of cesium carbonate gave a racemic product in 6 hours, indicating that the inorganic base prevailed over the Ca-complex (Table 2, entry 11).

Table 2. Optimization of the reaction conditions of a Ca^{2+}-catalyzed rearrangement[a]



Entry	Ca-salt	Base	Time	Conv. (%)[b]	*ee* (%)[c]
1[d]	$CaCl_2$	–	3 d	58	39
2	$CaCl_2$	Imidazole	3 d	92	49
3	CaI_2	Imidazole	6 h[e]	36	64
4	$Ca(NTf_2)_2$	Imidazole	24 h	99	75
5	$Ca(HFIP)_2$[f]	Imidazole	1 h	99	*rac*
6	$Ca(HMDS)_2$[f]	Imidazole	1 h	99	*rac*
7	$Ca(NTf_2)_2$	Et_3N	24 h	79	68
8	$Ca(NTf_2)_2$	DIPEA[f]	24 h	97	70

9	$Ca(NTf_2)_2$	Morpholine	24 h	85	70
10	$Ca(NTf_2)_2$	Pyridine	3 d	40	52
11[g]	$Ca(NTf_2)_2$	Cs_2CO_3	6 h	99	*rac*

[a] Reaction conditions: **1a** (0.1 mmol), **L1** (5 mol%), Ca-salt (5 mol%) and base (5 mol%) in 2-propanol (1 mL) was stirred at 60 °C. [b] Conversion was determined by ^{1}H NMR of the crude product. [c] Enantiomeric excess was determined by chiral HPLC. [d] Reaction was carried out without additional base. [e] Reaction stopped after 6 h. [f] HFIP = hexafluoroisopropanyl, HMDS = hexamethyldisilazane, DIPEA = *N*,*N*-diisopropylethylamine. [g] Reaction was conducted at room temperature.

After the optimized conditions for the coordinative neutral ligand **L1** were determined (Table 3, entry 1), we screened other bisoxazoline ligands (Table 3, entries 2-6). Unexpectedly, all of the ligands were less active and produced products with either low enantioselectivity or racemic outcome. We also assessed the complex formation by NMR and ESI-MS, and found that the 1:1 complex between ligand **L1** and $Ca(NTf_2)_2$ formed immediately after mixing the two together (Figure S1 in SI), and was stable for at least up to 300 °C in ESI-MS (Figure S3 in SI).

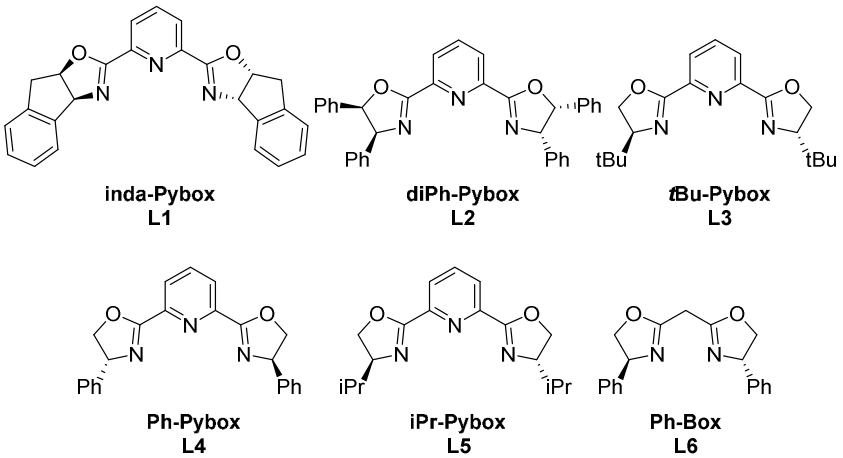
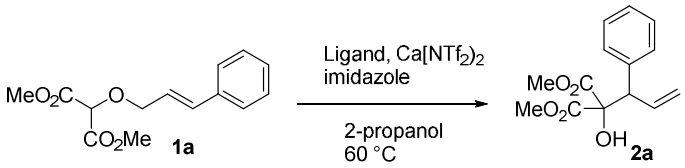


Figure 2. Bisoxazoline ligands used in the current study.

Table 3. Screening of different bisoxazoline ligands[a]



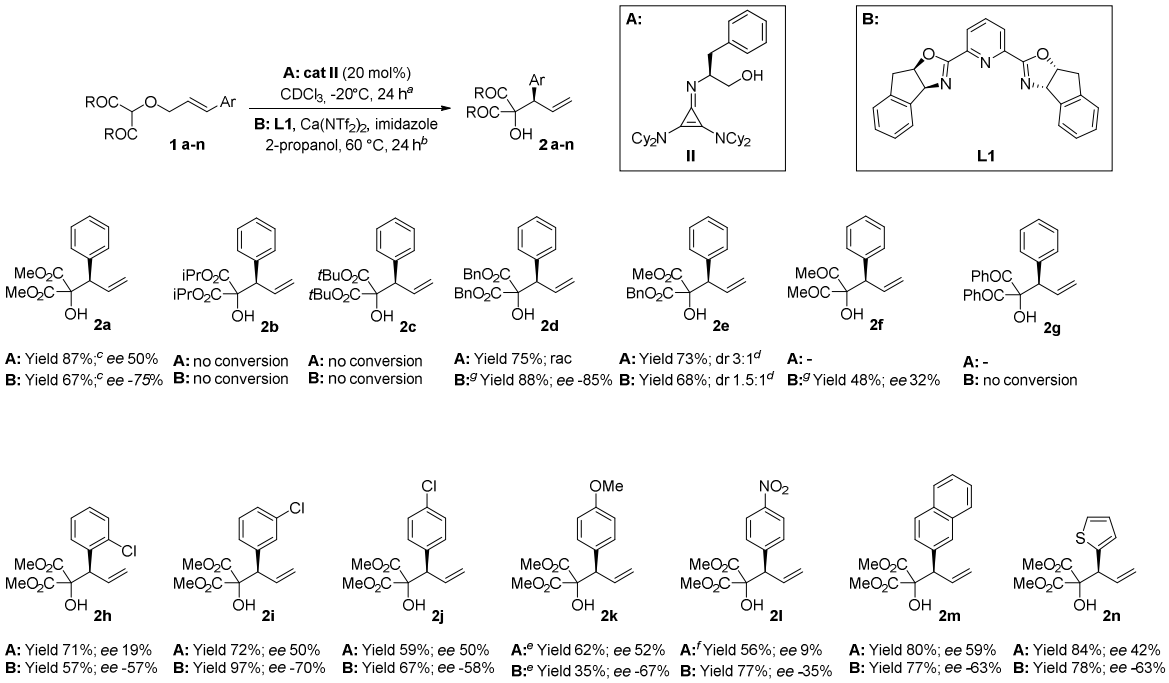
Entry	Ligand	Time	Conv. (%)[b]	*ee* (%)[c]
1	**L1**	24 h	99	75
2	**L2**	3 d	12	–
3	**L3**	24 h	44	-12
4	**L4**	24 h	29	*rac*
5	**L5**	24 h	43	*rac*
6	**L6**	24 h	54	*rac*

[a] Reaction conditions: 1a (0.1 mmol), ligand (5 mol%), $Ca(NTf_2)_2$ (5 mol%) and imidazole (5 mol%) in 2-propanol (1 mL) were stirred at 60 °C. [b] Conversion was determined by ^{1}H NMR of the crude product. [c] Enantiomeric excess was determined by chiral HPLC.

Scope of two alternative methods for a Wittig [2,3] rearrangement reaction

The scope of the reaction was evaluated by studying the effects of the substituents at the aromatic ring and at the carbonyl moiety. The two methods applied afforded comparable results in terms of yields and enantiomeric purities (Figure 3). The main difference was in the enantioselection. In organocatalytic reactions, the main enantiomer was in *R*-configuration; metal-catalyzed reactions afforded *S*-enantiomer as a major isomer. The absolute configuration was determined by a comparison of the optical rotation of compound **2a** with data published by Jacobsen.[7] Both methods are sensitive to steric hindrance and no products

were formed with isopropyl or *tert*-butyl derivatives **1b** and **1c**. Mixed ester **1e** was synthesized to explore the diastereoselectivity of the reaction. Unfortunately, the methods were characterized by low or moderate diastereoselectivity (for **2e** dr 1.5:1 and 3:1). Diketones **1f** and **1g** were poor starting materials for the rearrangement affording product with low yield or no conversion by Ca-catalyzed reactions (organocatalytic reactions were not applied on these compounds). The organocatalytic method showed higher sensitivity towards the steric hindrance. Previously we have found that only *E*-isomers of phenyl substituted allyloxy compounds were reactive in the case of organocatalytic rearrangement of oxindole derivatives.[6] The enantiomeric purity of the *o*-chlorophenyl derivative **2h** was lower in the case of the organocatalytic method compared with that obtained by metal-catalysis. *Meta*- and *para*-substitution did not affect the results substantially (compounds **2i** and **2j**). Electrondonating, electron withdrawing and heteroaromatic substituents were tolerated under the reaction conditions (**2k-n**). Surprisingly low enantiomeric excess was obtained with nitrophenyl derivative **2l** by the organocatalytic method. This might be due to the fact that the nitro group is a very strong H-bond acceptor and therefore the transition state could be completely different.



[a] Reaction conditions for the organocatalytic reaction **A**: 0.1 mmol scale, 20 mol % of cat. **II**, $CDCl_3$ (0.5 mL), -20°C, 24 h. Enantiomeric excess is determined by chiral HPLC analysis of the isolated product. [b] Reaction conditions for the Ca-catalyzed reaction **B**: **1a-n** (0.1 mmol), **L1** (5 mol%), $Ca(NTf_2)_2$ (5 mol%) and imidazole (5 mol%) in 2-propanol (1 mL) were stirred at 60 °C for 24 h. [c] Isolated yield. [d] Diastereoisomeric ratio is determined by ^1H NMR analysis of the crude mixture. [e] Reaction was stopped after 48 h. [f] Reaction was finished after 48 h. [g] Reaction was finished after 6 h.

Figure 3. Scope of the reaction (*R*-enantiomers obtained by organocatalytic method are depicted).

Based on the obtained results we propose transition state models for both methods.

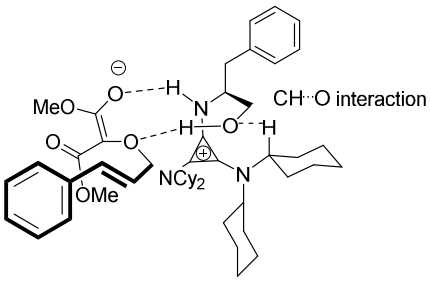


Figure 4. Model for the interaction of catalyst **II** with malonate derivative **1a** to account for the stereochemical outcome of the rearrangement.

In the organocatalytic reaction first the malonate derivative **1a** is deprotonated by a strongly basic catalyst affording an enolate anion and a cyclopropenium ion (Figure 4). It has been shown that a weak intramolecular CH···O interaction (0.5 kcal/mol) is responsible for the transition state organization in reactions catalyzed by chiral cyclopropenimines.[18] Our results indicate that the hydrogen bond donor capability of the catalyst is essential for achieving high stereoselectivity. Catalysts **II** and **III** differ from each other by their hydrogen bond donating properties. Methoxy-protected catalyst **III** has no hydrogen bond donors, by what lowering the stereoselectivity of the reaction drastically (compare entries 2 and 4 in Table 1). The same observation had been made by Lambert.[18] It is assumed that in the enantiodetermining rearrangement step, the conformation of the substrate is fixed with hydrogen bonds. The hydrogen bond between the OH group of catalyst **II** and the allylic oxygen promotes the rearrangement. A similar activation model has previously been proposed for the cycloaddition of azomethine ylides[19] and for a Mannich reaction.[20]

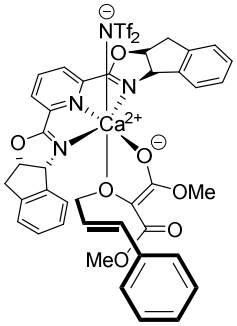


Figure 5. Model for the complexation of a Ca^{2+}/inda-Pybox complex with compound **1a** to account for the stereochemical outcome of the rearrangement.

Calcium^{2+}/Pybox complexes have been previously investigated by NMR [21] and X-ray crystallography[22]. Based on these publications, it is assumed that in the Ca^{2+}-catalytic reaction, the *N*,*N*,*N*-tridentate inda-Pybox ligand first forms a complex with $Ca(NTf_2)_2$, which is a strong Lewis acid. Then, calcium enolate is formed with substrate **1a** and the oxygen in the allyloxy group coordinates with calcium. Finally, the second trifluoromethanesulfonimide group is removed from calcium, giving the presented model (Figure 5).

Conclusions

We have developed two independent asymmetric catalytic methods for a Wittig [2,3]-rearrangement. In the organocatalytic pathway, a highly basic substituted cyclopropenimine catalyst was used. In the metal-catalyzed reaction, a Ca^{2+}/bisoxazoline complex was employed. Our ongoing investigations are focused on mechanistic models in order to increase so far modest selectivities.

Experimental Section

General remarks

Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a 400 MHz instrument. Residual solvent signals were used ($CDCl_3$ δ = 7.26 (^{1}H NMR), 77.16 (^{13}C NMR) and CD_3OD δ = 3.31 (^{1}H NMR), 49.00 (^{13}C NMR)) as internal standards. All peak assignments are confirmed by 2D experiments (^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC, ^{1}H-^{13}C HMBC). High resolution mass spectra were recorded by using an Q-TOF LC/MS spectrometer by using ESI ionization. Optical rotations were obtained at 20 °C in $CHCl_3$ and calibrated with pure solvent as a blank. Chiral HPLC was performed by using Chiralpak AD-H (250 x 4.6 mm), Chiralcel OJ-H (250 x 4.6 mm), Chiralcel OD-H (250 x 4.6 mm), Chiralpak AS-H (250 x 4.6 mm) or Lux 3u Amylose-2 (250 x 4.6 mm) columns. Precoated silica gel 60 F254 plates were used for TLC. Column chromatography was performed on a preparative purification system with silica gel Kieselgel 40-63 μm. The measured melting points are uncorrected. Purchased chemicals and solvents were used as received. DCM was distilled over phosphorous pentoxide. Petroleum ether has a boiling point of 40-60 °C. The reactions were performed under air atmosphere without additional moisture elimination unless stated otherwise.

Catalysts **I**[23], **VI**[24], and **VIII**[25] were prepared according to literature procedures and the analytical data matched with that of the literature. New catalysts **III**, **IV**, **V and VII** were prepared according to the analogous literature procedure.[26] Catalyst **II** is commercially available as an HCl salt.

Ligands **L5** and **L6** were purchased and used as received. Ligands **L1-L4** were prepared according to the literature procedures.[27,28,29,30]

Synthesis of catalysts III•HCl, IV•HCl, V•HCl , and VII

Dicyclohexylamine (6.0 equiv) was slowly added to a solution of tetrachlorocyclopropene (1.0 equiv) in DCM (0.1 M solution). A white precipitate formed as the reaction mixture was

stirred for a further four hours at room temperature. Next, primary amine (1.1 equiv) was added in one portion and the reaction mixture was stirred overnight. The crude reaction mixture was filtered through a celite plug, then washed with 1.0 M HCl (3 x), dried with anhydrous sodium sulfate and concentrated in vacuo to yield pure cyclopropenimine hydrochloride salt. The cyclopropenimine salt can be stored at room temperature without noticeable decomposition.

Free cyclopropenimine was obtained by dissolving the corresponding hydrochloride salt in DCM and washing the solution with 1.0 M aq NaOH, drying with anhydrous sodium sulfate and concentrating in vacuo.**(*S*)-*N*^{1},*N*^{1},*N*^{2},*N*^{2}-tetracyclohexyl-3-((1-methoxy-3-phenylpropan-2-yl)imino)cycloprop-1-ene-1,2-diamine hydrochloride salt III•HCl**

The synthesis was conducted with (*S*)-phenylalaninol methyl ether, affording compound **III** as a brown amorphous solid in 90% yield (131 mg). Optical rotation for **III**: $[\alpha]_D^{20}$ –31.9 (*c* 0.11, $CHCl_3$).

Spectra data for **III•HCl**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.33 – 7.20 (m, 5H, Ar), 3.96 (ddt, *J* = 9.5, 7.9, 4.6 Hz, 1H, NCH), 3.64 (dd, *J* = 9.5, 4.7 Hz, 1H, C*H*$_2$O), 3.54 (dd, *J* = 9.4, 8.2 Hz, 1H, C*H*$_2$O), 3.46 – 3.35 (m, 7H, CH_3 and NCyH), 3.04 (dd, *J* = 13.9, 4.4 Hz, 1H, C*H*$_2$Ph), 2.84 (dd, *J* = 13.9, 9.9 Hz, 1H, C*H*$_2$Ph), 1.95 – 1.18 (m, 40H, CyH). ^{13}C NMR (101 MHz, MeOD) δ 139.1, 130.4, 129.7, 127.9, 117.7, 115.9, 76.3, 61.4, 60.4, 59.6, 38.9, 33.3, 33.2, 26.71, 26.66, 25.7.

(*S*)-2-((2,3-Bis(dicyclohexylamino)cycloprop-2-en-1-ylidene)amino)-3,3-dimethylbutan-1-ol hydrochloride salt IV•HCl

The synthesis was conducted with (*S*)-*tert*-leucinol, affording compound **IV•HCl** as an off-white solid in 85% yield (490 mg). Optical rotation for **IV•HCl**: $[\alpha]_D^{20}$ –46.9 (*c* 0.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H, OH), 6.83 (d, *J* = 9.8 Hz, 1H, NH), 4.10 (dd, *J* = 11.9, 9.7 Hz, 1H, C*H*$_2$OH), 3.78 (dd, *J* = 12.0, 4.0 Hz, 1H, C*H*$_2$OH), 3.42 (td, *J* = 9.7, 4.0 Hz,

1H, CH*t*Bu), 3.32 (tt, *J* = 11.9, 3.4 Hz, 4H, NCyH), 2.05 – 1.10 (m, 40H, CyH), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 119.0, 68.4, 59.7, 59.5, 34.9, 32.7, 26.9, 25.9, 25.8, 25.02, 24.99, 24.93.

HRMS (ESI) calculated for $C_{33}H_{58}N_3O$, $[M + H]^+$: 512.4574, found 512.4569.

(1*R*,2*R*)-2-((2,3-Bis(dicyclohexylamino)cycloprop-2-en-1-ylidene)amino)cyclohexan-1-ol hydrochloride salt V•HCl

The synthesis was conducted with (1*R*,2*R*)-2-aminocyclohexanol, affording compound **V•HCl** was obtained as an off-white solid in 87% yield (475 mg). Optical rotation for **V•HCl**: $[\alpha]_D^{20}$ –14.8 (*c* 0.11, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H, OH), 7.80 (d, *J* = 7.5 Hz, 1H, NH), 4.20 – 3.99 (m, 1H, CyH), 3.51 – 3.22 (m, 5H, CyH), 3.15 – 2.95 (m, 1H, CyH), 2.29 – 2.02 (m, 3H, CyH), 2.00 – 1.06 (m, 44H, CyH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 117.2, 115.0, 70.5, 63.6, 59.6, 34.00, 33.98, 32.32, 32.29, 29.0, 28.9, 25.85, 25.82, 25.79, 24.90, 24.84, 24.80, 24.7, 24.4.

HRMS (ESI) calculated for $C_{33}H_{56}N_3O$, $[M + H]^+$: 510.4418, found 510.4412.

***N*^{1},*N*^{1},*N*^{2},*N*^{2}-tetracyclohexyl-3-(((*R*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)imino)cycloprop-1-ene-1,2-diamine VII**

The synthesis was conducted with (*R*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine, affording compound **VII** after purification by column chromatography on silica gel (5% NH_3/MeOH in DCM), as an off-white solid in 26% yield (75 mg). Optical rotation for **VII**: $[\alpha]_D^{20}$ +157.1 (*c* 0.09, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4.5 Hz, 1H, ArH), 8.00 (d, *J* = 9.2 Hz, 1H, ArH), 7.88 (s, 1H, ArH), 7.49 (d, *J* = 3.5 Hz, 1H, ArH), 7.38 (dd, *J* = 9.2, 2.6 Hz, 1H, ArH), 6.21 (ddd, *J* = 17.0, 10.2, 6.6 Hz, 1H, C*H*CH_2), 6.03 (d, *J* = 7.4 Hz, 1H, CHN), 5.23 – 5.10 (m, 2H, CHCH_2), 4.08 (s, 3H, OCH_3), 3.35 – 3.05 (m, 5H), 3.03 – 2.78 (m, 3H), 2.73 – 2.50 (m, 1H), 2.31 (q, *J* = 8.0 Hz, 1H), 2.00 – 0.52 (m, 45H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 147.9,

145.1, 140.1, 131.9, 128.3, 122.9, 115.7, 115.5, 113.8, 103.0, 58.7, 56.8, 49.2, 47.4, 39.6, 32.2, 31.9, 28.2, 25.2, 25.1, 24.6.

HRMS (ESI) calculated for $C_{47}H_{68}N_5O$, $[M + H]^+$: 718.5418, found 718.5414.

Synthesis of starting materials 1a-n

The synthesis of compounds **1a** and **1c** was described by Jacobsen.[7] We used a slightly modified procedure. The synthesis of allyloxy-1,3-dicarbonyl compounds **1a-n** was achieved as follows. 1,3-Dicarbonyl compounds were reacted with tosyl azide to produce diaza compounds, which were subjected to rhodium-catalyzed OH insertion reaction, affording the desired compounds **1**. A general procedure for the formation of **1a** is presented. In the synthesis of **1a** and **1h-n**, transesterification of malonyl ester occurred, to improve the yield, transesterification with *p*-TsOH in MeOH can be conducted. This procedure was performed only with compound **1a**.

Dimethyl 2-diazomalonate

To a solution of tosyl azide (1.735 g, 8.8 mmol) in acetonitrile (12 mL), triethylamine (1.227 ml, 8.8 mmol) and dimethyl malonate (0.916 mL, 8 mmol) was added at 0 °C. The reaction mixture was stirred overnight at room temperature. Then, solvent was evaporated under reduced pressure and the crude mixture purified by column chromatography on silica gel (10-20% EtOAc in petroleum ether/DCM 3/1 mixture), affording title compound as a colourless oil (1.227 g, 97%).

Dimethyl 2-(cinnamyloxy)malonate 1a

To a 10-mL flask was added cinnamyl alcohol (322 mg, 2.4 mmol) and rhodium(II) acetate dimer (4.4 mg, 0.01 mmol). The flask was flushed with Ar and DCM was added (5 mL). Dimethyl 2-diazomalonate (286 mg, 2 mmol) solution in DCM (5 mL) was added over 5 minutes at 0 °C. The reaction was stirred overnight at rt. After evaporating the solvent, the

crude mixture was purified by column chromatography on silica gel (3-10% EtOAc in petroleum ether/DCM 3/1 mixture), affording compound **1a** as a colourless oil. The impure fractions were dried under vacuum, dissolved in MeOH (10 mL), *p*-toluenesulfonic acid (30 mg) was added and the mixture was stirred at reflux overnight. After purification in the same conditions, the fractions were combined, affording compound **1a** as a colourless oil in 64% total yield (336 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 2H, 2×ArH), 7.35 – 7.29 (m, 2H, 2×ArH), 7.29 – 7.23 (m, 1H, ArH), 6.64 (d, *J* = 15.9 Hz, 1H, CHAr), 6.28 (dt, *J* = 15.9, 6.5 Hz, 1H, CH_2CH), 4.64 (s, 1H, CH), 4.34 (dd, *J* = 6.5, 1.2 Hz, 2H, CH_2), 3.81 (s, 6H, 2xCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 136.1, 134.9, 128.6, 128.1, 126.7, 123.7, 77.5, 71.8, 53.0.

HRMS (ESI) calculated for $C_{14}H_{16}NaO_5$, $[M + Na]^+$: 287.0890, found 287.0879.

Diisopropyl 2-(cinnamyloxy)malonate 1b

Compound **1b** was obtained as a colourless oil in 70% yield (112 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H, 2×ArH), 7.35 – 7.29 (m, 2H, 2×ArH), 7.28 – 7.25 (m, 1H, ArH), 6.63 (d, *J* = 16.0 Hz, 1H, CHAr), 6.30 (dt, *J* = 15.9, 6.5 Hz, 1H, CH_2CH), 5.12 (hept, *J* = 6.3 Hz, 2H, $CH(CH_3)_2$), 4.52 (s, 1H, CH), 4.34 (dd, *J* = 6.5, 1.1 Hz, 2H, CH_2), 1.27 (d, *J* = 6.2 Hz, 6H, 2xCH_3), 1.26 (d, *J* = 6.3 Hz, 6H, 2xCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 136.3, 134.7, 128.7, 128.2, 126.8, 124.3, 78.1, 71.7, 69.9, 21.8, 21.7.

HRMS (ESI) calculated for $C_{18}H_{24}NaO_5$, $[M + Na]^+$: 343.1516, found 343.1510.

Di-*tert*-butyl 2-(cinnamyloxy)malonate 1c

Compound **1c** was obtained as a white solid in 62% yield (255 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H, 2×ArH), 7.35 – 7.28 (m, 2H, 2×ArH), 7.28 – 7.22 (m, 1H, ArH), 6.63 (d, *J* = 15.9 Hz, 1H, CHAr), 6.30 (dt, *J* = 15.9, 6.4 Hz, 1H, CH_2CH), 4.37 (s, 1H, CH), 4.32 (dd, *J* = 6.4, 1.2 Hz, 2H, CH_2), 1.49 (s, 18H, 2x*t*Bu). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 166.0, 136.5, 134.3, 128.7, 128.1, 126.8, 124.6, 82.8, 79.0, 71.4, 28.1.

Dibenzyl 2-(cinnamyloxy)malonate 1d

Compound **1d** was obtained as a white solid in 56% yield (170 mg), mp 65-67 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.15 (m, 15H, 15xArH), 6.58 (d, *J* = 15.9 Hz, 1H, CHAr), 6.26 (dt, *J* = 15.9, 6.5 Hz, 1H, CH_2CH), 5.19 (s, 4H, CH_2Ph), 4.69 (s, 1H, CH), 4.34 (dd, *J* = 6.5, 1.1 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 136.2, 135.0, 128.7 (2C), 128.6, 128.5 (2C), 128.2, 126.8, 124.0, 77.7, 71.9, 67.7.

HRMS (ESI) calculated for $C_{26}H_{24}NaO_5$, $[M + Na]^+$: 439.1516, found 439.1505.

1-Benzyl 3-methyl 2-(cinnamyloxy)malonate 1e

Compound **1e** was obtained as a colourless oil in 59% yield (146 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.23 (m, 10H, 10xArH), 6.60 (d, *J* = 15.9 Hz, 1H, CHAr), 6.27 (dt, *J* = 16.0, 6.5 Hz, 1H, CH_2CH), 5.26 (d, *J* = 12.3 Hz, 1H, CH_2Ph), 5.22 (d, *J* = 12.2 Hz, 1H, CH_2Ph), 4.66 (s, 1H, CH), 4.33 (dd, *J* = 6.5, 1.0 Hz, 2H, CH_2), 3.76 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 166.6, 136.2, 135.0, 128.73 (2C), 128.67, 128.4, 128.3, 126.8 (2C), 123.9, 77.7, 71.9, 67.7, 53.0.

HRMS (ESI) calculated for $C_{20}H_{21}O_5$, $[M + H]^+$: 341.1384, found 341.1379.

3-(Cinnamyloxy)pentane-2,4-dione 1f

Compound **1f** was obtained in 3 hours at 5 °C, as a pale yellow oil, which solidifies in the freezer, in 62% yield (227 mg).

Spectra data for symmetric enol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.38 (s, 1H, OH), 7.44 – 7.39 (m, 2H, 2xArH), 7.37 – 7.31 (m, 2H, 2xArH), 7.30 – 7.26 (m, 1H, ArH), 6.68 (d, *J* = 15.9 Hz, 1H, CHAr), 6.36 (dt, *J* = 15.9, 6.1 Hz, 1H, CH_2CH), 4.31 (dd, *J* = 6.1, 1.3 Hz, 2H, CH_2), 2.20 (s, 6H, 2xCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.5, 136.4, 135.7, 133.6, 128.8, 128.3, 126.7, 124.3, 75.3, 21.0.

HRMS (ESI) calculated for $C_{14}H_{16}NaO_3$, $[M + Na]^+$: 255.0992, found 255.0986.

2-(Cinnamyloxy)-1,3-diphenylpropane-1,3-dione 1g

Compound **1g** was obtained as a yellow amorphous solid in 27% yield (87 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.92 (m, 2H, 2xArH), 7.58 – 7.49 (m, 1H, ArH), 7.47 – 7.28 (m, 12H, 12xArH), 6.59 (d, *J* = 15.9 Hz, 1H, CHAr), 6.23 (dt, *J* = 15.9, 6.4 Hz, 1H, CH_2CH), 5.66 (s, 1H, CH), 4.83 (dt, *J* = 6.4, 1.4 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3, 168.8, 135.8, 134.6, 133.7, 133.0, 130.8, 129.7, 129.1, 129.0, 128.9, 128.7, 128.4, 128.2, 126.8, 122.7, 66.4, 60.7.

HRMS (ESI) calculated for $C_{24}H_{20}NaO_3$, $[M + Na]^+$: 379.1305, found 379.1280.

Dimethyl (*E*)-2-((3-(2-chlorophenyl)allyl)oxy)malonate 1h

Compound **1h** was obtained as a white solid in 34% yield (91 mg), mp 53-55 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.3, 2.2 Hz, 1H, ArH), 7.35 (dd, *J* = 7.5, 1.8 Hz, 1H, ArH), 7.25 – 7.15 (m, 2H, 2xArH), 7.02 (d, *J* = 15.9 Hz, 1H, CHAr), 6.28 (dt, *J* = 15.9, 6.4 Hz, 1H, CH_2CH), 4.65 (s, 1H, CH), 4.38 (dd, *J* = 6.4, 1.1 Hz, 2H, CH_2), 3.82 (s, 6H, $2xCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 134.4, 133.4, 130.9, 129.9, 129.3, 127.2, 127.0, 126.9, 77.7, 71.9, 53.1.

HRMS (ESI) calculated for $C_{14}H_{15}ClNaO_5$, $[M + Na]^+$: 321.0500, found 321.0488.

Dimethyl (*E*)-2-((3-(3-chlorophenyl)allyl)oxy)malonate 1i

Compound **1i** was obtained as a colourless oil in 53% yield (149 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 1H, ArH), 7.29 – 7.20 (m, 3H, 3xArH), 6.59 (d, *J* = 15.9 Hz, 1H, CHAr), 6.30 (dt, *J* = 15.9, 6.3 Hz, 1H, CH_2CH), 4.62 (s, 1H, CH), 4.33 (dd, *J* = 6.3, 1.2 Hz, 2H, CH_2), 3.82 (s, 6H, $2xCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 138.1, 134.7, 133.2, 130.0, 128.2, 126.8, 125.6, 124.9, 77.8, 71.6, 53.1.

HRMS (ESI) calculated for $C_{14}H_{16}ClO_5$, $[M + H]^+$: 299.0681, found 299.0675.

Dimethyl (*E*)-2-((3-(4-chlorophenyl)allyl)oxy)malonate 1j

Compound **1j** was obtained as a white amorphous solid in 56% yield (159 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, 2H, 2xArH), 7.28 (d, *J* = 8.8 Hz, 2H, 2xArH), 6.59 (d, *J* = 16.0 Hz, 1H, CHAr), 6.26 (dt, *J* = 15.9, 6.4 Hz, 1H, CH_2CH), 4.62 (s, 1H, CH), 4.32 (dd, *J* = 6.4, 1.1 Hz, 2H, CH_2), 3.81 (s, 6H, 2xCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 134.7, 133.9, 133.5, 128.9, 128.0, 124.6, 77.8, 71.8, 53.1.

HRMS (ESI) calculated for $C_{14}H_{15}ClNaO_5$, $[M + Na]^+$: 321.0500, found 321.0487.

Dimethyl (*E*)-2-((3-(4-methoxyphenyl)allyl)oxy)malonate 1k

Compound **1k** was obtained as a colourless oil in 63% yield (166 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.7 Hz, 2H, 2xArH), 6.85 (d, *J* = 8.7 Hz, 2H, 2xArH), 6.57 (d, *J* = 15.9 Hz, 1H, CHAr), 6.14 (dt, *J* = 15.9, 6.7 Hz, 1H, CH_2CH), 4.63 (s, 1H, CH), 4.31 (dd, *J* = 6.7, 1.0 Hz, 2H, CH_3), 3.81 (s, 3H, OCH_3), 3.80 (s, 6H, 2xCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 159.8, 134.9, 128.9, 128.1, 121.5, 114.1, 77.4, 72.2, 55.4, 53.1.

HRMS (ESI) calculated for $C_{15}H_{18}NaO_6$, $[M + Na]^+$: 317.0996, found 317.0981.

Dimethyl (*E*)-2-((3-(4-nitrophenyl)allyl)oxy)malonate 1l

Compound **1l** was obtained as a yellow solid in 46% yield (147 mg), mp 58-60 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.7 Hz, 2H, 2xArH), 7.52 (d, *J* = 8.8 Hz, 2H, 2xArH), 6.74 (d, *J* = 16.0 Hz, 1H, CHAr), 6.47 (dt, *J* = 16.0, 5.9 Hz, 1H, CH_2CH), 4.63 (s, 1H, CH), 4.38 (dd, *J* = 5.9, 1.4 Hz, 2H, CH_2), 3.83 (s, 6H, 2xCH_3). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 166.8, 147.4, 142.7, 131.6, 129.1, 127.3, 124.2, 78.2, 71.3, 53.2.

HRMS (ESI) calculated for $C_{14}H_{15}NNaO_7$, $[M + Na]^+$: 332.0741, found 332.0732.

Dimethyl (*E*)-2-((3-(naphthalen-2-yl)allyl)oxy)malonate 1m

Compound **1m** was obtained as a pale yellow oil in 33% yield (97 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 3H, 3xArH), 7.75 (s, 1H, ArH), 7.60 (dd, *J* = 8.6, 1.7 Hz, 1H, ArH), 7.50 – 7.42 (m, 2H, 2xArH), 6.80 (d, *J* = 15.9 Hz, 1H, CH), 6.41 (dt, *J* = 15.9, 6.5 Hz, 1H, CH_2CH), 4.67 (s, 1H, CH), 4.39 (dd, *J* = 6.5, 1.2 Hz, 2H, CH_2), 3.82 (s,

6H, 2xCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 135.1, 133.7, 133.6, 133.4, 128.4, 128.2, 127.8, 127.1, 126.5, 126.3, 124.3, 123.6, 77.7, 72.1, 53.1.

HRMS (ESI) calculated for $C_{18}H_{18}NaO_5$, $[M + Na]^+$: 337.1046, found 337.1040.

Dimethyl (*E*)-2-((3-(thiophen-2-yl)allyl)oxy)malonate 1n

Compound **1n** was obtained as a yellow oil in 38% yield (102 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 4.9 Hz, 1H, ArH), 7.07 – 6.87 (m, 2H, 2xArH), 6.76 (d, *J* = 15.7 Hz, 1H, CHAr), 6.10 (dt, *J* = 15.7, 6.5 Hz, 1H, CH_2CH), 4.62 (s, 1H, CH), 4.29 (dd, *J* = 6.5, 1.2 Hz, 2H, CH_2), 3.81 (s, 6H, 2xCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 141.2, 128.1, 127.5, 126.7, 125.2, 123.3, 77.6, 71.6, 53.1.

HRMS (ESI) calculated for $C_{12}H_{14}NaO_5S$, $[M + Na]^+$: 293.0454, found 293.0447.

General procedure for organocatalytic Wittig [2,3] rearrangement of allyloxy-1,3-dicarbonyl compounds 1 (Method A)

A solution of allyloxy-1,3-dicarbonyl compound **1** (0.1 mmol) in $CDCl_3$ (0.25 mL) was added to a cooled solution of catalyst **II** (20 mol%) in $CDCl_3$ (0.25 mL). The reaction mixture was stirred at -20 °C for 24 hours. Upon completion of the reaction, the crude mixture was directly purified by flash chromatography on silica gel (0-10% EtOAc in petroleum ether/DCM 3/1 mixture), affording the desired product **2**. The enantioselectivity of the isolated product was determined by HPLC analysis, providing the product in (*R*)-configuration.

General procedure for Ca-catalyzed asymmetric Wittig [2,3] rearrangement of allyloxy 1,3-dicarbonyl compounds 1 (Method B)

To a solution of allyloxy 1,3-dicarbonyl compound **1** (0.1 mmol) in 2-propanol (1 mL), $Ca(NTf_2)_2$ (0.005 mmol), ligand **L1** (0.005 mmol) and imidazole (0.005 mmol) were added. The reaction mixture was stirred at 60 °C. Then, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (0-10% EtOAc in petroleum ether/DCM

3/1 mixture), affording the desired product **2**. The enantioselectivity of the isolated product was determined by HPLC analysis, providing the product in (*S*)-configuration.

Dimethyl (*R*)-2-hydroxy-2-(1-phenylallyl)malonate 2a

Compound **2a** was obtained as a white solid, for method A in 87% yield (23 mg) and for method B in 67% yield (18 mg), mp 86-88 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), **(*R*)-2a** 10.7 min and **(*S*)-2a** 9.6 min, enantiomeric excess for compound **2a** for method A was 50% and for method B was 75%. Optical rotation for **(*R*)-2a** (*ee* 50%): $[\alpha]_D^{20}$ –28.8 (*c* 0.11, $CHCl_3$). Analytic data were in agreement with the literature data.[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H, ArH), 7.31 – 7.20 (m, 3H, ArH), 6.18 (ddd, *J* = 17.1, 10.1, 9.1 Hz, 1H, C*H*CH_2), 5.23 – 5.13 (m, 2H, CH_2), 4.33 (d, *J* = 9.0 Hz, 1H, CHAr), 3.92 (s, 1H, OH), 3.84 (s, 3H, CH_3), 3.61 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.8, 138.1, 135.6, 129.3, 128.4, 127.5, 118.4, 82.7, 54.7, 53.8, 53.5.

HRMS (ESI) for $C_{14}H_{16}NaO_5$, calculated for $[M + Na]^+$: 287.0890, found: 287.0889.

Dibenzyl (*R*)-2-hydroxy-2-(1-phenylallyl)malonate 2d

Compound **2d** was obtained as a colorless oil, for method A in 75% yield (29 mg) and for method B in 88% yield (36 mg). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), **(*R*)-2d** 31.1 min and **(*S*)-2d** 25.3 min, enantiomeric excess for compound **2d** for method A was 0% and for method B was 85%. Optical rotation for **(*S*)-2d** (*ee* 85%): $[\alpha]_D^{20}$ – 15.6 (*c* 0.15, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 10H, ArH), 7.24 – 7.19 (m, 3H, ArH), 7.17 – 7.09 (m, 2H, ArH), 6.16 (ddd, *J* = 17.0, 10.3, 8.9 Hz, 1H, C*H*CH_2), 5.22 (s, 2H, CH_2Ar), 5.12 – 5.03 (m, 2H, CHCH_2), 4.98 (d, *J* = 12.2 Hz, 1H, CH_2Ar), 4.93 (d, *J* = 12.2 Hz, 1H, CH_2Ar), 4.34 (d, *J* = 8.8 Hz, 1H, CHAr), 3.98 (s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4,

169.1, 138.1, 135.6, 134.9, 134.6, 129.4, 128.73 (2C), 128.68, 128.63, 128.61, 128.5, 128.4, 127.4, 118.4, 82.6, 68.6, 68.4, 54.4.

HRMS (ESI) for $C_{26}H_{24}NaO_5$, calculated for $[M + Na]^+$: 439.1516, found: 439.1519.

1-Benzyl 3-methyl 2-hydroxy-2-((*R*)-1-phenylallyl)malonate 2e

Compound **2e** was obtained as a colorless oil, for method A in 73% yield (24 mg) and for method B in 68% yield (23 mg).

NMR data for the main diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.19 (m, 10H, ArH), 6.22 – 6.09 (m, 1H, C*H*CH_2), 5.26 (s, 2H, CH_2Ar), 5.10 – 5.04 (m, 2H, CHC*H*$_2$), 4.33 (d, *J* = 8.9 Hz, 1H, CHAr), 3.93 (s, 1H, OH), 3.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 169.4, 138.2, 135.4, 135.0, 129.4, 128.8, 128.7, 128.6, 128.4, 127.5, 118.5, 82.6, 68.5, 54.5, 53.4.

HRMS (ESI) for $C_{20}H_{20}NaO_5$, calculated for $[M + Na]^+$: 363.1203, found: 363.1193.

3-Hydroxy-3-(1-phenylallyl)pentane-2,4-dione 2f

Compound **2f** was obtained as a yellow oil, for method B in 48% yield (11 mg). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 230 nm), major enantiomer 6.0 min, minor enantiomer 5.3 min, enantiomeric excess for compound **2f** for method B was 32%. Optical rotation for **2f** (*ee* 32%): $[\alpha]_D^{20}$ +2.7 (*c* 0.099, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H, ArH), 7.31 – 7.18 (m, 3H, ArH), 6.02 (ddd, *J* = 17.1, 10.2, 9.1 Hz, 1H, C*H*CH_2), 5.16 – 5.09 (m, 2H, CH_2), 4.95 (s, 1H, OH), 4.35 (d, *J* = 9.1 Hz, 1H, CHAr), 2.34 (s, 3H, CH_3), 1.99 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.9, 206.8, 138.1, 135.5, 129.1, 128.6, 127.5, 118.2, 94.0, 55.7, 26.4, 26.1.

HRMS (ESI) for $C_{14}H_{16}NaO_3$, calculated for $[M + Na]^+$: 255.0992, found: 255.0987.

Dimethyl (*R*)-2-(1-(2-chlorophenyl)allyl)-2-hydroxymalonate 2h

Compound **2h** was obtained as a white solid, for method A in 71% yield (20 mg) and for method B in 57% yield (17 mg), mp 35-37 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 99:1, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), **(*R*)-2h** 35.3 min and **(*S*)-2h** 39.6 min, enantiomeric excess for compound **2h** for method A was 19% and for method B was 57%. Optical rotation for **(*R*)-2h** (*ee* 19%): $[\alpha]_D^{20}$ –17.0 (*c* 0.11, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.8, 1.8 Hz, 1H, ArH), 7.35 (dd, *J* = 7.8, 1.5 Hz, 1H, ArH), 7.21 (td, *J* = 7.6, 1.5 Hz, 1H, ArH), 7.15 (td, *J* = 7.6, 1.8 Hz, 1H, ArH), 6.00 (ddd, *J* = 16.9, 10.4, 8.4 Hz, 1H, C*H*CH_2), 5.20 – 5.16 (m, 1H, CH_2), 5.15 (d, *J* = 0.9 Hz, 1H, CH_2), 5.06 (d, *J* = 8.4 Hz, 1H, CHAr), 4.05 (d, *J* = 0.9 Hz, 1H, OH), 3.87 (s, 3H, CH_3), 3.58 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.7, 136.1, 134.8, 134.2, 130.3, 129.7, 128.5, 127.1, 118.9, 82.3, 54.0, 53.5, 49.0.

HRMS (ESI) for $C_{14}H_{15}ClNaO_5$, calculated for $[M + Na]^+$: 321.0500, found: 321.0487.

Dimethyl (*R*)-2-(1-(3-chlorophenyl)allyl)-2-hydroxymalonate 2i

Compound **2i** was obtained as a white solid, for method A in 72% yield (21 mg) and for method B in 97% yield (29 mg), mp 43-45 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), **(*R*)-2i** 9.6 min and **(*S*)-2i** 8.5 min, enantiomeric excess for compound **2i** for method A was 50% and for method B was 70%. Optical rotation for **(*R*)-2i** (*ee* 50%): $[\alpha]_D^{20}$ –28.0 (*c* 0.07, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 1H, ArH), 7.30 – 7.24 (m, 1H, ArH), 7.23 – 7.18 (m, 2H, ArH), 6.16 – 6.06 (m, 1H, C*H*CH_2), 5.22 – 5.18 (m, 1H, CH_2), 5.16 (s, 1H, CH_2), 4.30 (d, *J* = 8.9 Hz, 1H, CHAr), 3.94 (s, 1H, OH), 3.84 (s, 3H, CH_3), 3.64 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 169.5, 140.2, 135.0, 134.1, 129.63, 129.60, 127.7, 127.6, 119.0, 82.5, 54.2, 53.9, 53.6.

HRMS (ESI) for $C_{14}H_{16}ClO_5$, calculated for $[M + H]^+$: 299.0681, found: 299.0670.

Dimethyl (*R*)-2-(1-(4-chlorophenyl)allyl)-2-hydroxymalonate 2j

Compound **2j** was obtained as a white solid, for method A in 59% yield (17 mg) and for method B in 67% yield (20 mg), mp 47-49 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), **(*R*)-2j** 16.9 min and **(*S*)-2j** 15.2 min, enantiomeric excess for compound **2j** for method A was 50% and for method B was 58%. Optical rotation for **(*R*)-2j** (*ee* 50%): $[\alpha]_D^{20}$ –27.2 (*c* 0.09, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.5 Hz, 2H, ArH), 7.25 (d, *J* = 8.7 Hz, 2H, ArH), 6.11 (ddd, *J* = 17.5, 9.8, 8.9 Hz, 1H, C*H*CH_2), 5.20 – 5.16 (m, 1H, CH_2), 5.16 – 5.13 (m, 1H, CH_2), 4.31 (d, *J* = 8.8 Hz, 1H, CHAr), 3.94 (s, 1H, OH), 3.84 (s, 3H, CH_3), 3.63 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 169.5, 136.7, 135.2, 133.4, 130.8, 128.6, 118.7, 82.5, 53.91, 53.89, 53.6.

HRMS (ESI) for $C_{14}H_{15}ClNaO_5$, calculated for $[M + Na]^+$: 321.0500, found: 321.0491.

Dimethyl (*R*)-2-hydroxy-2-(1-(4-methoxyphenyl)allyl)malonate 2k

Compound **2k** was obtained as a white solid, for method A in 62% yield (17 mg) and for method B in 35% yield (10 mg), mp 74-76 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:EtOH = 95:5, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), **(*R*)-2k** 39.0 min and **(*S*)-2k** 21.8 min, enantiomeric excess for compound **2k** for method A was 52% and for method B was 67%. Optical rotation for **(*R*)-2k** (*ee* 52%): $[\alpha]_D^{20}$ – 24.9 (*c* 0.09, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H, ArH), 6.81 (d, *J* = 8.7 Hz, 2H, ArH), 6.15 (ddd, *J* = 17.1, 10.2, 8.8 Hz, 1H, C*H*CH_2), 5.22 – 5.11 (m, 2H, CH_2), 4.28 (d, *J* = 8.8 Hz, 1H, CHAr), 3.90 (s, 1H, OH), 3.83 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 3.62 (s, 3H, CH_3). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 170.0, 169.8, 158.9, 135.8, 130.4, 130.1, 118.1, 113.8, 82.8, 55.3, 54.0, 53.7, 53.5.

HRMS (ESI) for $C_{15}H_{18}NaO_6$, calculated for $[M + Na]^+$: 317.0996, found: 317.0998.

Dimethyl (*R*)-2-hydroxy-2-(1-(4-nitrophenyl)allyl)malonate 2l

Compound **2l** was obtained as a yellow solid, for method A in 56% yield (16 mg) and for method B in 77% yield (24 mg), mp 99-101 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), **(*R*)-2l** 23.8 min and **(*S*)-2l** 19.5 min, enantiomeric excess for compound **2l** for method A was 9% and for method B was 35%. Optical rotation for **(*R*)-2l** (*ee* 9%): $[\alpha]_D^{20}$ –10.9 (*c* 0.13, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.6 Hz, 2H, ArH), 7.59 (d, *J* = 8.7 Hz, 2H, ArH), 6.11 (dt, *J* = 18.1, 9.2 Hz, 1H, C*H*CH_2), 5.22 (s, 1H, CH_2), 5.19 (d, *J* = 6.6 Hz, 1H, CH_2), 4.44 (d, *J* = 8.9 Hz, 1H, CHAr), 4.02 (s, 1H, OH), 3.86 (s, 3H, CH_3), 3.63 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 169.2, 147.3, 145.9, 134.4, 130.4, 123.5, 119.7, 82.2, 54.11, 54.07, 53.7.

HRMS (ESI) for $C_{14}H_{16}NO_7$, calculated for $[M + H]^+$: 310.0921, found: 310.0910.

Dimethyl (*R*)-2-hydroxy-2-(1-(naphthalen-2-yl)allyl)malonate 2m

Compound **2m** was obtained as a white solid, for method A in 80% yield (25 mg) and for method B in 77% yield (24 mg), mp 89-91 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), **(*R*)-2m** 24.9 min and **(*S*)-2m** 14.7 min, enantiomeric excess for compound **2m** for method A was 59% and for method B was 63%. Optical rotation for **(*R*)-2m** (*ee* 59%): $[\alpha]_D^{20}$ –48.9 (*c* 0.06, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H, ArH), 7.83 – 7.74 (m, 3H, ArH), 7.53 (dd, *J* = 8.5, 1.6 Hz, 1H, ArH), 7.48 – 7.42 (m, 2H, ArH), 6.28 (ddd, *J* = 17.1, 10.2, 8.9 Hz, 1H, C*H*CH_2),

5.26 – 5.17 (m, 2H, CH_2), 4.52 (d, J = 8.8 Hz, 1H, CHAr), 4.00 (s, 1H, OH), 3.87 (s, 3H, CH_3), 3.58 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.0, 169.7, 135.7, 135.6, 133.5, 132.8, 128.3, 128.1, 128.0, 127.7, 127.5, 126.05, 125.97, 118.6, 82.9, 54.8, 53.8, 53.5.

HRMS (ESI) for $C_{18}H_{18}NaO_5$, calculated for $[M + Na]^+$: 337.1046, found: 337.1039.

Dimethyl (*S*)-2-hydroxy-2-(1-(thiophen-2-yl)allyl)malonate 2n

Compound **2n** was obtained as a white solid, for method A in 84% yield (22 mg) and for method B in 78% yield (21 mg), mp 54-56 °C. The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), **(*R*)-2n** 12.7 min and **(*S*)-2n** 11.7 min, enantiomeric excess for compound **2n** for method A was 42% and for method B was 63%. Optical rotation for **(*R*)-2n** (*ee* 42%): $[\alpha]_D^{20}$ –35.5 (*c* 0.09, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (ddd, J = 5.1, 1.2, 0.5 Hz, 1H, ArH), 6.99 (ddd, J = 3.5, 1.2, 0.5 Hz, 1H, ArH), 6.93 (dd, J = 5.1, 3.5 Hz, 1H, ArH), 6.09 (ddd, J = 17.0, 10.1, 8.9 Hz, 1H, C*H*CH_2), 5.22 (ddd, J = 17.0, 1.4, 0.9 Hz, 1H, CH_2), 5.17 (ddd, J = 10.1, 1.5, 0.6 Hz, 1H, CH_2), 4.67 (d, J = 8.9 Hz, 1H, CHAr), 3.99 (d, J = 0.8 Hz, 1H, OH), 3.83 (s, 3H, CH_3), 3.70 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 169.5, 139.6, 135.3, 126.6, 126.5, 125.2, 118.7, 82.4, 53.79, 53.75, 50.5.

HRMS (ESI) for $C_{12}H_{14}NaO_5S$, calculated for $[M + Na]^+$: 293.0454, found: 293.0446.

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Notes

The authors declare no competing financial interest.

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Supporting Information

^{1}H and ^{13}C NMR spectra, HPLC data, additional optimization data of Ca-catalyzed reaction, NMR and HRMS study of Ca complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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