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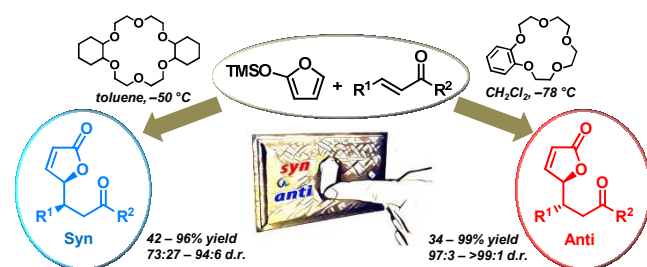
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ABSTRACT: The fluoride promoted vinylogous Mukaiyama-Michael reaction (VMMR) of 2-trimethylsilyloxyfuran with diverse α,β -unsaturated ketones is described. The TBAF catalyzed VMMR afforded high *anti*-diastereoselectivity irrespective of the solvents used. The KF/crown ethers catalytic systems proved to be highly efficient in terms of yields and resulted in a highly diastereoselective unprecedented solvent/catalyst switchable reaction. *Anti*-adducts were obtained as single diastereomers

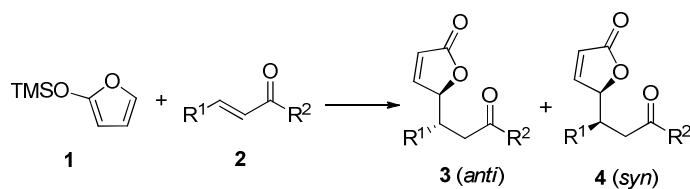
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3 or with excellent diastereoselectivities when benzo-15-crown-5 in CH₂Cl₂ was employed. On the other
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5 hand, high *syn*-diastereoselectivities (from 76:24 to 96:4) were achieved by employing dicyclohexane-
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7 18-crown-6 in toluene. Based on DFT calculations, the catalysts/solvents-dependent switchable
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9 diastereoselectivities are proposed to be the result of loose or tight cation-dienolate ion pairs.
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17 The γ -butenolide moiety is a powerful pharmacophore widely distributed in natural products
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19 and in an appreciable number of synthetic compounds.¹ The inclusion of this fragment in chiral
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21 intermediates expedites the synthesis of an ample variety of biologically active secondary metabolites.²
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23 Given the intrinsic value of this γ -lactone, much effort has been devoted to its stereoselective
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25 construction.²⁻⁴ One of the most efficient synthetic strategy is the vinylogous Michael reaction (VMR)
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27 with α,β -unsaturated ketones. This reaction enables the stereoselective introduction of a 3-oxoalkyl
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29 substituent in the butenolide γ -position.⁴ Despite the enormous potentials of this process, most of the
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31 methods reported to date involve the stereoselective γ -functionalization of deconjugated γ -substituted
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33 butenolides, affording γ,γ -disubstituted products.⁵ On the other hand, the stereoselective VMR of γ -
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35 unsubstituted 2(*5H*)-furanones and 2-silyloxyfurans with α,β -unsaturated ketones, leading to γ -
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37 monosubstituted products, has been much less investigated. Enantioenriched *syn* or *anti* products can
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39 be secured by efficient protocols employing chiral organocatalysts or ligands.⁶⁻¹¹ Unfortunately, these
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41 catalysts are often expensive or not commercially available. In addition, the *syn* adducts are accessible
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43 only in reactions with *trans*-chalcones.^{7b, 9}
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51 As the use of chiral catalysts is unnecessary for the development of a purely *syn/anti*-diastereoselective
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53 addition, the investigation of novel methods based on simple achiral and off-the-shelf catalysts has
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55 recently received appreciable attention. The few methodologies reported to date, are based on catalyzed
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57 vinylogous Mukaiyama-Michael reaction (VMMR) with 2-silyloxyfurans and lead prevalently to the
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anti-adducts (Scheme 1). Two efficient diastereoselective VMMRs of 2-(trimethylsilyloxy)furan (TMSOF, **1**) with α,β -unsaturated ketones (**2**) are catalyzed by I_2 ¹² or a *N*-heterocyclic carbene.¹³ They afford *anti*-adducts with good to excellent diastereoselectivities, starting from *trans*-chalcones, and with moderate to good selectivities, when aliphatic acceptors are employed in the reaction. VMMR with TMSOF and other 2-silyloxyfurans, catalyzed by different achiral catalysts, proved to be poorly *anti*-diastereoselective and limited in scope.¹⁴ High diastereoselectivities in the additions promoted by 1,1,3,3-tetrakis(trifluoromethanesulfonyl)propane were achieved only with 3-bromo-2-TESO-furan as the nucleophile.^{14c}



Scheme 1. VMMR of TMSOF and α,β -unsaturated ketones.

Given the small number of available purely diastereoselective TMSOF-based VMMRs in the presence of α,β -unsaturated ketones, and considering the growing impact of diastereodivergent processes,^{5b} we became interested in the design of a new methodology that, based on inexpensive and readily available catalysts, afforded in an efficient and convenient way both the *anti* and the *syn* diastereomers.

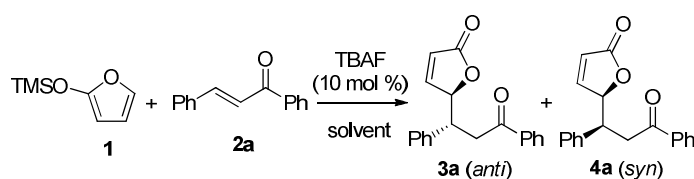
Although fluoride salts are known to promote the Mukaiyama-Michael reaction,¹⁵ their use has never been thoroughly investigated in the VMMR with 2-silyloxyfurans. The only example described is an *anti*-selective TBAF-catalyzed addition of TMSOF to a substituted *trans*-chalcone as a key step in the synthesis of mitomycins and antibiotic FR-900482, even if the diastereomeric ratio was not unambiguously determined.¹⁶ As a part of our ongoing research on phase transfer macrocycle-catalyzed reactions,¹⁷ we decided to extensively study the action of inorganic fluorides in the presence of crown

ethers as promoters of VMMR of TMSOF with α,β -unsaturated ketones, and compare their performances with tetrabutylammonium fluoride (TBAF).

RESULTS AND DISCUSSION

At the outset, we performed the addition of TMSOF (**1**) to *trans*-chalcone (**2a**), chosen as a model substrate, with catalytic amounts of TBAF (10 mol%) in different solvents (Table 1). The reactions were conducted at the lowest possible temperatures, compatibly with the different solvent freezing points, and were followed by treatment with an acidic aqueous solution to completely desilylate the adducts formed. In DMF, a complex mixture of products was obtained (Table 1, entry 1). In other solvents, the *anti*-product **3a** was favored. The best *anti*-diastereoselectivity was achieved in CH₂Cl₂ and CHCl₃ (98:2, entries 2 and 3). In toluene, a slightly lower diastereomeric ratio and a moderate yield were observed (entry 1). The longer reaction time are likely due to a less reactive fluoride ion, engaged in a tight ion pair.

Table 1. VMMR with chalcone **2a**, promoted by TBAF.^a

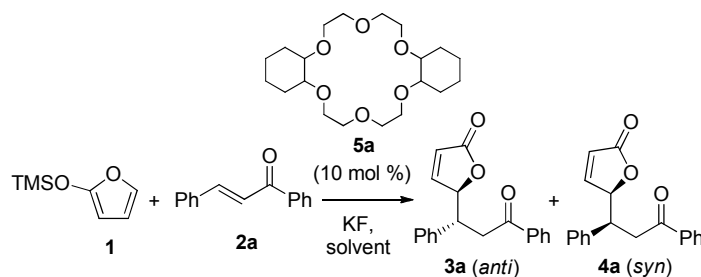


entry	Solvent	temp (°C)	time (h)	yield (%) ^b	<i>anti</i> / <i>syn</i> ^c
1	DMF	-60	5	–	–
2	CH ₂ Cl ₂	-78	20	78	98:2
3	CHCl ₃	-55	4	84	98:2
4	toluene	-78	40	57	93:7
5	THF	-78	20	79	83:17

^a Reaction conditions: **1** (0.24 mmol), **2a** (0.20 mmol), TBAF (1.0 M in THF, 0.020 mmol), solvent (1.0 mL). ^b Isolated yields. ^c Determined by ¹H NMR analysis of the crude product.

Interestingly, the use of KF in the presence of catalytic amount of dicyclohexane-18-crown-6 (**5a**) efficiently promoted the VMMR in a broader range of solvents, showing an intriguing solvent-dependent stereoselectivity (Table 2). In particular, a rough correlation between the solvent's dielectric constant (ϵ) and the *anti/syn* ratio was observed.¹⁸ Similarly to the TBAF-promoted addition, polar solvents (with an high dielectric constant) favored the *anti*-adducts (98:2 *anti/syn*, entries 1,2,4,5). However, the KF/**5a** system proved to be more efficient, giving Michael adduct in 98% yield in CH₂Cl₂ (ϵ 9.1) with an *anti*-diastereoselectivity as high as that achieved with TBAF (entry 1). The catalytic role played by crown ether **5a** was evident also in very polar solvents such as DMF (cf. entry 2 and 3) and CH₃CN (cf. entries 5 and 6), since in its absence incomplete conversion were observed even after prolonged reaction times and lower diastereoselectivities were achieved. Despite the high dielectric constant, a lower diastereoselectivity was observed in DCE (ϵ 10.45), probably due to the higher reaction temperature (entry 8). With a solvent of medium polarity, such as diethyl ether (ϵ 4.3), a very low *anti*-diastereoselectivity was observed (entry 9). Surprisingly, in the nonpolar toluene solvent (ϵ 2.38), the diastereoselectivity was reversed, with a marked preference for the *syn* product **4a** (7:93 *anti/syn*, entry 10). To the best of our knowledge, such a striking solvent-dependent inversion of diastereoselectivity is unprecedented in the synthesis of butenolides by VMMR.¹⁹ This finding appears to be of great synthetic interest, in that a single catalytic system can lead to both the *anti* and *syn* diastereomers just by choosing the appropriate solvent.

Table 2. VMMR with chalcone **2a**, promoted by KF/dicyclohexane-18-crown-6 (**5a**).^a



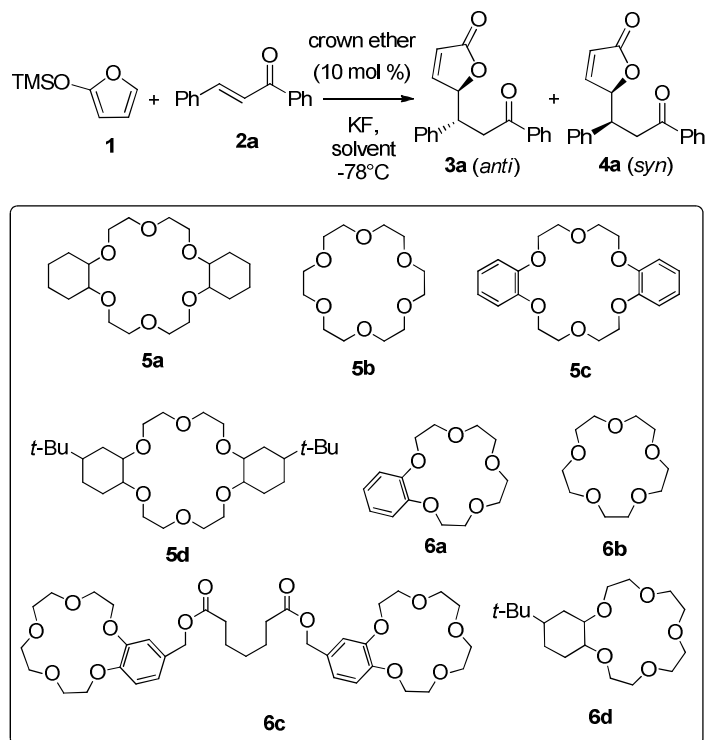
entry	Solvent	temp (°C)	time (h)	yield (%) ^b	anti/syn ^c
1	CH ₂ Cl ₂	-78	4	98	98:2
2	DMF	-60	2	74	98:2
3 ^d	DMF	-60	96	61	94:6
4	CHCl ₃	-55	20	87	98:2
5	CH ₃ CN	-40	20	72	98:2
6 ^d	CH ₃ CN	-40	96	29	90:10
7	THF	-78	20	83	93:7
8	DCE	-30	2	86	88:12
9	Et ₂ O	-78	20	32	57:43
10	toluene	-78	20	83	7:93

^a Reaction conditions: **1** (0.24 mmol), **2a** (0.20 mmol), KF (0.20 mmol), **5a** (0.020 mmol), solvent (1.0 mL). ^b Isolated yields. ^c Determined by ¹H NMR analysis of the crude product. ^d Reaction performed in absence of **5a**.

With the aim to further enhance the level of both *syn* and *anti*-diastereoselectivity, we screened different crown ethers (Table 3). The preference for the *syn* diastereomer **4a** in toluene was confirmed with four other commercially available 18-crown-6 ether derivatives **5b-d** (entries 2-4). However, **5a**, gave the best diastereomeric *ratio* (entry 1). The diastereoselectivity was slightly improved performing the reaction at -50 °C (entry 5), while the optimal catalyst loading was confirmed at 10 mol%.²⁰ 15-Crown-5 derivatives **6a-d** also catalyzed the reaction in toluene, albeit with lower yields (entries 6-9). Unexpectedly, the diastereoselectivity was reversed again, favouring the *anti*-isomer **3a**. The most efficient *anti*-selective crown catalyst proved to be benzo-15-crown-5 (**6a**), which afforded **4a** with

97:3 diastereomeric *ratio* and 76% yield. As expected, performing the reaction in more polar solvent such as CHCl_3 and CH_2Cl_2 , further increased the *anti*-selectivity: in both solvents exclusively the *anti*-isomer was formed with almost quantitative yields (entries 10 and 11).

Table 3. Screening of crown ethers in VMMR with **2a**.^a



entry	Catalyst	Solvent	time (h)	yield (%) ^b	<i>anti/syn</i> ^c
1	5a	toluene	20	83	7:93
2	5b	toluene	40	80	12:88
3	5c	toluene	40	90	8:92
4	5d	toluene	40	93	12:88
5 ^d	5a	toluene	4	96	6:94
6	6a	toluene	40	76	97:3
7	6b	toluene	40	53	62:38
8	6c	toluene	40	46	83:17

9	6d	toluene	40	57	50:50
10 ^e	6a	CHCl ₃	20	94	> 99:1
11	6a	CH ₂ Cl ₂	6	99	> 99:1

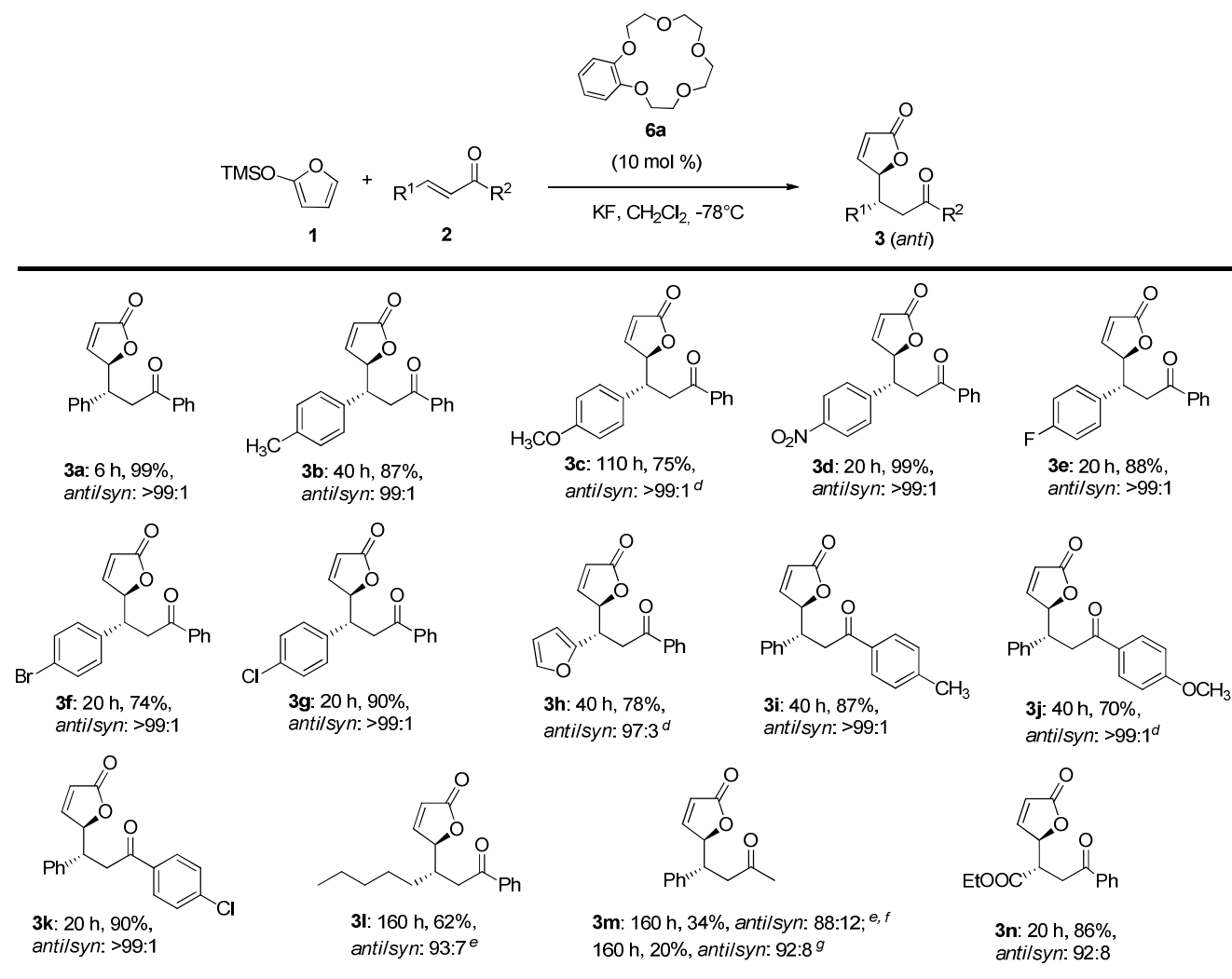
^a Reaction conditions: **1** (0.24 mmol), **2a** (0.20 mmol), KF (0.20 mmol), catalyst (0.020 mmol), solvent (1.0 mL). ^b Isolated yields. ^c Determined by ¹H NMR analysis of the crude product. ^d Reaction performed at -50 °C. ^e Reaction performed at -55 °C.

Having established the optimal conditions to obtain both the *anti* (conditions A: catalyst **6a** at -78 °C in CH₂Cl₂) and the *syn* isomers (conditions B: catalyst **5a** at -50 °C in toluene), we studied the scope of the reaction with several α,β -unsaturated ketones. To our delight, the addition to several *trans*-chalcones catalyzed by **6a** under conditions A (Table 4), afforded the *anti*-products as a single diastereomer in almost all cases except **3b** and **3h**, that were accompanied by small amounts of *syn* adducts. Electron-rich derivatives **2c,h,j** reacted with incomplete conversion. Improved yields were achieved by raising the reaction temperature to -50 °C without erosion of diastereoselectivity.²⁰ Replacement of aromatic with aliphatic groups in the substrate resulted in a sharp drop of reactivity. α,β -Unsaturated ketones **2l,m** required a -20 °C reaction temperature to furnish decent yields of **3l,m** with still high diastereoselectivities. In the case of product **3l**, lower temperature (-30 °C) led to a slight improvement of diastereoselectivity at the expense of yield. It is worth noting that TBAF gave poorer results even with these substrates.²⁰ The introduction of the electron-withdrawing carboxyl group on the β -carbon (ester **2n**) resulted in a high yield and excellent diastereomeric purity. As expected, a single regioisomer **3n** was obtained, arising from conjugated addition to the α,β -unsaturated ketone system.²¹ In the case of the reaction of TMSOF with an aliphatic substrate such as 3-octen-2-one, a complex mixture of products was isolated.

The VMRR of different α,β -unsaturated ketones catalyzed by **5a** under conditions B afforded invariably the *syn* adducts in good to high diastereoselectivities and with good yields (Table 5). As

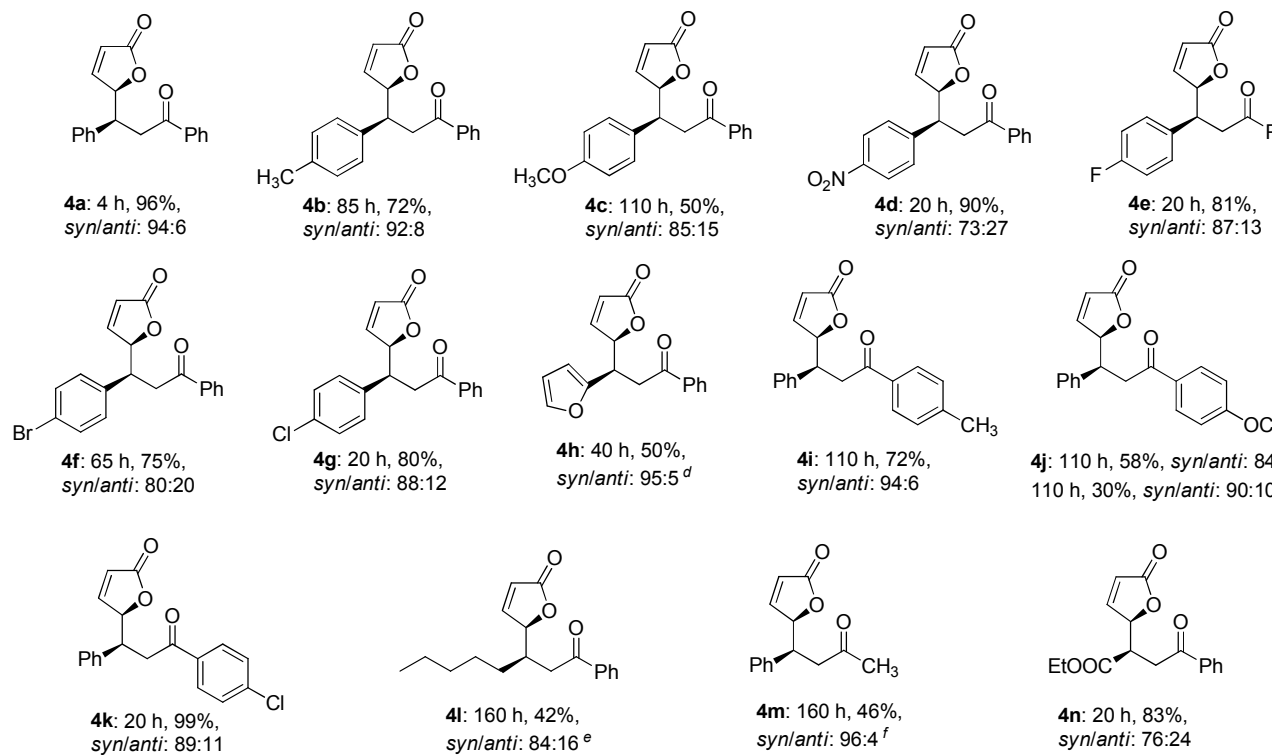
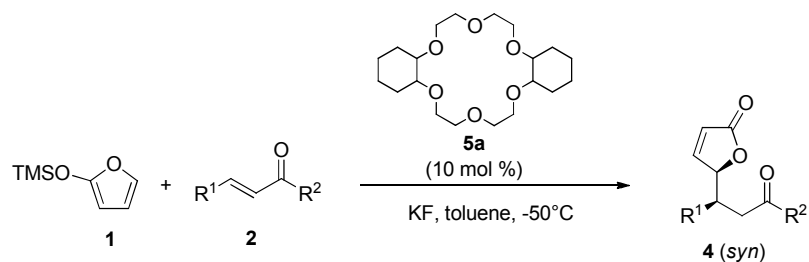
observed under conditions A, adjustments of reaction temperatures were required for the less reactive substrates (**2c,h,j,l,m**) and only moderate yields were obtained. Also under these conditions, the reaction with β -carboxy-substituted substrate **2n** afforded a single regioisomer **4n**.²¹

Table 4. *Anti*-diastereoselective VMMR (conditions A).^{a-c}



^a Reaction conditions: **1** (0.24 mmol), **2a** (0.20 mmol), KF (0.20 mmol), **6a** (0.020 mmol), CH_2Cl_2 (1.0 mL), $-78^\circ C$. ^b Isolated yields. ^c The diastereomeric ratios were determined by 1H NMR analysis of the crude product. ^d Reaction performed at $-50^\circ C$. ^e Reaction performed at $-20^\circ C$. ^f **1** (0.40 mmol) was used. ^g Reaction performed at $-30^\circ C$.

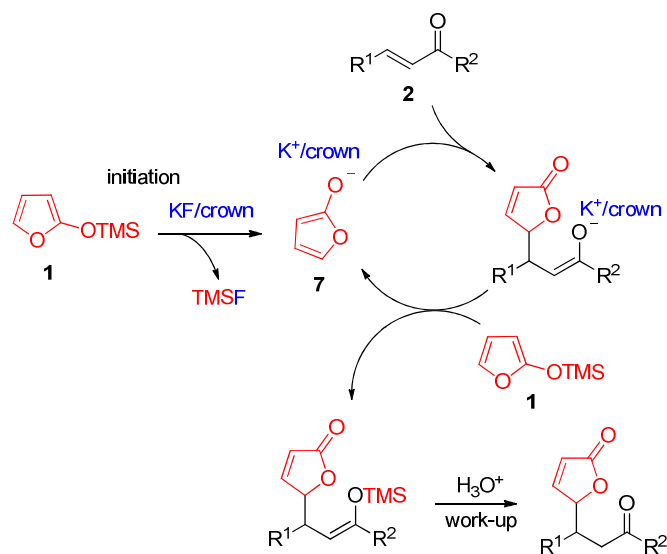
Table 5. *Syn*-diastereoselective VMMR (conditions B).^{a-c}



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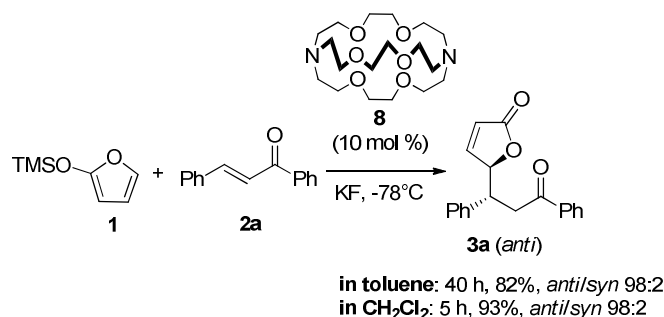
^a Reaction conditions: **1** (0.24 mmol), **2a** (0.20 mmol), KF (0.20 mmol), **5a** (0.020 mmol), toluene (1.0 mL), -50°C . ^b Isolated yields. ^c Determined by ^1H NMR analysis of the crude product. ^d Reaction performed at -78°C . ^e Reaction performed at -20°C . ^f Reaction performed at -30°C .

Considering that fluorides promote the reaction of enolsilanes through the generation of their corresponding enolates,²² we suggested the mechanism depicted in Scheme 2 for the VMMR of TMSOF, involving a complexed potassium dienolate **7**.



Scheme 2. Proposed mechanism of the fluoride promoted VMMR.

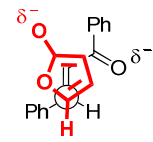
We believe that the switchable diastereoselectivity is determined by the intimacy of the ion pair **7** under different reaction conditions. In particular, conditions known to disassociate ion pairs, such as the presence of polar solvents or tetraalkylammonium cations,²³ preferentially lead to *anti* products. On the other side, the positive charge in K⁺/18-crown-6 complexes is more accessible for interaction with the enolate anion promoting, in nonpolar solvents such as toluene, the formation of *syn* products for the formation of tighter ion pairs.²³ 15-Crown-5 derivatives are known to form 2:1 “sandwich” complexes with K⁺,²⁴ in which presumably the cation is scarcely accessible to the anion, favoring a well separated ion pair that might explain the *anti*-selectivity, even in toluene. As a proof of concept, we performed the VMMR in presence of catalytic amounts (10 mol%) of [2.2.2]-cryptand (**8**), a ligand that fully sequesters alkali metal cations in the molecular cavity, resulting in a separated ion pair.²³ As expected on the basis of the aforementioned considerations, **8** favored the formation of the *anti*-product **3a** both in toluene and CH₂Cl₂ (Scheme 3).



14 **Scheme 3.** VMMR with **2a** promoted by [2.2.2]-cryptand (**8**).
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19 To rationalize the relationship between cation-anion separation and *syn-anti*
20 diastereoselectivity, DFT calculations were performed.²⁵ Both in presence or in absence of the cation,
21 Diels-Alder-like transition states were found to be favored over all the possible open transition states.²⁶
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23 With the “naked” dienolate anion involved as nucleophile in reaction with chalcone **2a** (to simulate
24 conditions in polar solvents or reactions catalyzed by TBAF, **8** or 15-crown-5 derivatives), our
25 calculations determined a preference for the *endo-TS-A* transition state, affording the *anti*-adduct **3a**
26 (Scheme 4, a), over the competing transition state *exo-TS-A*, 2.8 kcal/mol higher in energy. The
27 observed *endo* preference can be attributed to electrostatic repulsion between the nearby oxygen atoms
28 on the reactants which contributes to disfavor the *exo* transition state. On the other hand, when tight ion
29 pair **7** is involved as nucleophile (to simulate reactions catalyzed by KF/18-crown-6 derivatives in
30 toluene), we calculated the *exo-TS-B* transition state to be favored by 3.1 kcal/mol over the *endo-TS-B*
31 transition state (Scheme 4, b). This inversion of stability is due to the simultaneous coordination of the
32 two negatively charged oxygen atoms of the reactants to the cation, with the consequent formation of a
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a) Attack of the "naked" dienolate (conditions A):



endo-TS-A

(0.0 kcal/mol)

favored

leading to *anti*-product **3a**



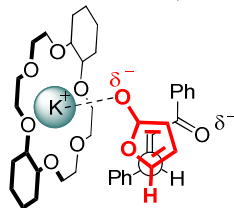
exo-TS-A

(+2.8 kcal/mol)

disfavored

leading to *syn*-product **4a**

b) Attack of the tight ion pair **7** (conditions B).

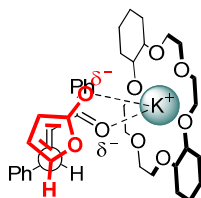


endo-TS-B

(+3.1 kcal/mol)

disfavored

leading to *anti*-product **3a**

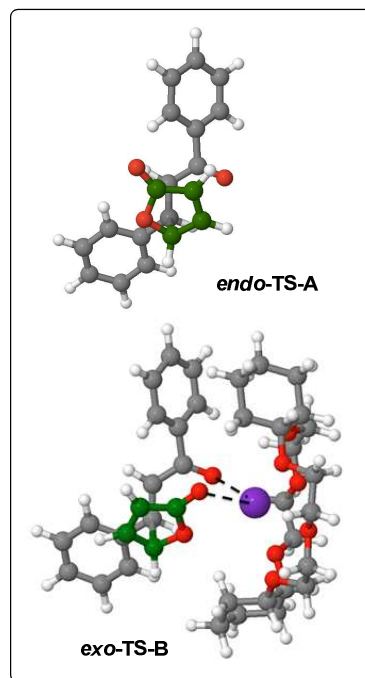


exo-TS-B

(0.0 kcal/mol)

favored

leading to *syn*-product **4a**



Scheme 4. DFT calculations of the transition state for the VMRR under conditions A and B, and 3D representation of the most stable transition states.

CONCLUSIONS

In conclusion, we have developed an efficient diastereoselective fluoride-promoted VMRR of TMSOF with aromatic α,β -unsaturated ketones catalyzed by inexpensive and off-the-shelf crown ethers. The present methodology is characterized by an unprecedented switchable *syn-anti* diastereoselectivity which allows to obtain both diastereomers in good to high yields and selectivities by choosing the appropriate solvent and macrocycle's size. Apart from showing better diastereoselectivities than other methods based on achiral catalysts, this new protocol enables the synthesis of *syn* adducts even from substrates other than chalcones. The origin of diastereo-divergence under different reaction conditions has been rationalized by DFT calculations.

Enantioselective variants of this method, employing chiral catalysts or Michael acceptors, are currently underway.

EXPERIMENTAL SECTION

General remarks. Starting materials and reagents purchased from commercial suppliers were generally used without purification unless otherwise mentioned. TBAF (1.0 M solution in THF), crown ethers **5a-d**, **6a-d**, [2.2.2]-cryptand (**7**), 2-(trimethylsilyloxy)furan (TMSOF, **1**) and α,β -unsaturated ketones **2a,c-e,g,m** were commercially available. Reaction solvents were purchased in anhydrous form, except for CH_2Cl_2 , diethyl ether and toluene, that were distilled over calcium hydride, and THF that was distilled over sodium/benzophenone. α,β -Unsaturated ketones **2b,f,h-k**,²⁷ **2l**²⁸ and **2n**²⁹ were prepared by methods reported in the literature. Reaction temperatures were measured externally. All reactions were conducted under inert atmosphere of nitrogen gas. Reactions were monitored by analytical thin layer chromatography (TLC) on precoated silica gel plates (0.25 mm) and visualized by UV light or by KMnO_4 /ethanol spray test and heating on a hot plate. Flash chromatography was performed on Silica Gel 60 (particle size: 0.040–0.063 mm) and the solvents employed were of analytical grade. ^1H NMR, ^{13}C NMR and 2D HMBC spectra were recorded on a 400 MHz spectrometer at room temperature in CDCl_3 as solvent. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak (CHCl_3 , $\delta = 7.26$ for proton spectra; $^{13}\text{CDCl}_3$, $\delta = 77.0$ for carbon spectra). The multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad singlet; bd, broad doublet. Coupling constants (J) are quoted in Hertz. High resolution mass spectra (HRMS) were recorded on a Fourier transform ion cyclotron resonance mass spectrometer (FTICR-MS) equipped with a 7T magnet, using electrospray ionization (ESI) or matrix-assisted laser desorption/ionization (MALDI).

General procedure for the TBAF-catalyzed VMMR. In a Schlenk tube, to a stirred solution of *trans*-chalcone **2a** (45.8 mg, 0.22 mmol) in CHCl_3 (1.1 mL) at $-55\text{ }^\circ\text{C}$, TBAF (1.0 M in THF, 0.022 mL, 0.022 mmol) and 2-(trimethylsilyloxy)furan **1** (41.3 mg, 0.26 mmol) were sequentially added. The

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3 mixture was stirred until disappearance of the starting material (TLC), and then treated with 1 M HCl
4 (1.0 mL) and THF (3.0 mL). The resulting solution was allowed to warm to room temperature, stirred
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6 for 2 h, and then was diluted with H₂O (1.2 mL) and extracted with CH₂Cl₂ (3 x 2 mL). The combined
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8 organic phases were washed with saturated NaHCO₃ solution (1.5 mL), dried over Na₂SO₄ and
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10 concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, petroleum
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12 ether – ethyl acetate, 8:2 to 6:4) affording **3a** (54.0 mg, 84% yield).
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20 **General procedure for the *anti*-diastereoselective VMMR catalyzed by KF/benzo-15-**
21 **crowns-5 (conditions A).** In a Schlenk tube, to a stirred solution of *trans*-chalcone **2a** (45.8 mg, 0.22
22 mmol) and benzo-15-crown-5 **6a** (5.9 mg, 0.022 mmol) in CH₂Cl₂ (1.1 mL) at –78 °C, KF (12.8 mg,
23 0.22 mmol) and 2-(trimethylsilyloxy)furan **1** (41.3 mg, 0.26 mmol) were added. The mixture was
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25 stirred until disappearance of the starting material (TLC), and then treated with 1 M HCl (1.0 mL) and
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27 THF (3.0 mL). The resulting solution was allowed to warm to room temperature, stirred for 2 h, and
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29 then was diluted with H₂O (1.2 mL) and extracted with CH₂Cl₂ (3 x 2 mL). The combined organic
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31 phases were washed with saturated NaHCO₃ solution (1.5 mL), dried over Na₂SO₄ and concentrated *in*
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33 *vacuo*. The crude product was purified by flash chromatography (silica gel, petroleum ether – ethyl
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35 acetate, 8:2 to 6:4) affording **3a** (63.7 mg, 99% yield).
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46 (*R*,R**)-5-(3-Oxo-1,3-diphenylpropyl)furan-2(5H)-one (**3a**). Obtained as a white solid (63.7 mg, 99%
47 yield), mp 83-85 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (m, 2H), 7.53 (m, 1H), 7.42 (m, 2H), 7.36–
48 7.20 (m, 6H), 6.06 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.26 (m, 1H), 3.70 (m, 1H), 3.56 (dd, *J* = 17.7, 5.0 Hz,
49 1H), 3.48 (dd, *J* = 17.7, 8.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 197.2, 172.5, 155.5, 139.5, 136.4,
50 133.2, 128.8, 128.5, 128.0, 127.8, 127.5, 121.8, 85.6, 44.2, 39.9; HRMS (MALDI) [M + H⁺] calcd for
51 C₁₉H₁₇O₃⁺ 293.1172, found 293.1170.
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(R,R*)-5-(1-(4-Methylphenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (3b)*. Obtained as a white solid (58.6 mg, 87% yield), mp 95-98 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (m, 2H), 7.54 (m, 1H), 7.43 (m, 2H), 7.28 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.07 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.24 (m, 1H), 3.64 (m, 1H), 3.57 (dd, *J* = 17.5, 4.8 Hz, 1H), 3.46 (dd, *J* = 17.5, 8.3 Hz, 1H), 2.31 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 197.4, 172.7, 155.6, 137.3, 136.6, 136.5, 133.3, 129.6, 128.6, 127.9 (2C), 121.9, 85.9, 44.1, 40.2, 21.0; HRMS (MALDI) [M + H⁺] calcd for C₂₀H₁₉O₃⁺ 307.1329, found 307.1329.

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(R,R*)-5-(1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (3c)*. Obtained as a yellow oil (53.2 mg, 75% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.87 (m, 2H), 7.53 (m, 1H), 7.42 (m, 2H), 7.30–7.18 (m, 3H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.06 (m, 1H), 5.22 (m, 1H), 3.76 (s, 3H), 3.63 (m, 1H), 3.53 (dd, *J* = 17.5, 5.0 Hz, 1H), 3.43 (dd, *J* = 17.5, 8.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 197.4, 172.7, 158.9, 155.6, 136.6, 133.3, 131.5, 129.1, 128.6, 127.9, 121.9, 114.2, 86.0, 55.2, 43.7, 40.3; HRMS (MALDI) [M + H⁺] calcd for C₂₀H₁₉O₄⁺ 323.1278, found 323.1277.

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(R,R*)-5-(1-(4-Nitrophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (3d)*. Obtained as a white solid (73.5 mg, 99% yield), mp 163-165 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 7.9 Hz, 2H), 7.63–7.52 (m, 3H), 7.44 (m, 2H), 7.34 (d, *J* = 5.6 Hz, 1H), 6.14 (m, 1H), 5.30 (m, 1H), 3.93 (m, 1H), 3.56–3.38 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 196.5, 172.1, 154.6, 147.4, 147.3, 136.0, 133.7, 129.3, 128.7, 127.9, 124.0, 122.7, 84.7, 43.5, 38.8; HRMS (MALDI) [M + H⁺] calcd for C₁₉H₁₆NO₅⁺ 338.1023, found 338.1024.

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(R,R*)-5-(1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (3e)*. Obtained as a white solid (60.1 mg, 88% yield), mp 102-105 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.86 (m, 2H), 7.54 (m, 1H), 7.42 (m, 2H), 7.36–7.25 (m, 3H), 7.00 (m, 2H), 6.08 (dd, *J* = 5.7, 1.9 Hz, 1H), 5.23 (m, 1H), 3.71 (m, 1H), 3.51 (dd, *J* = 17.8, 5.0 Hz, 1H), 3.42 (dd, *J* = 17.8, 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 197.1, 172.4, 161.9 (d, *J* = 246 Hz), 155.2, 136.3, 135.3 (d, *J* = 2 Hz), 133.4, 129.7 (d, *J* = 8 Hz), 128.6, 127.8,

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3 122.1, 115.7 (d, $J = 21$ Hz), 85.5, 43.3, 39.8; HRMS (MALDI) $[M + H^+]$ calcd for $C_{19}H_{16}FO_3^+$
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5 311.1078, found 311.1079.

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8 *(R*,R*)-5-(1-(4-Bromophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (3f)*. Obtained as a white solid
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10 (60.4 mg, 74% yield), mp 138-141 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 2H), 7.56 (m, 1H),
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12 7.49–7.36 (m, 4H), 7.32–7.18 (m, 3H), 6.10 (dd, $J = 5.8, 2.0$ Hz, 1H), 5.24 (m, 1H), 3.70 (m, 1H), 3.51
13
14 (dd, $J = 17.8, 5.1$ Hz, 1H), 3.41 (dd, $J = 17.8, 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0,
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16 172.4, 155.1, 138.7, 136.3, 133.5, 132.0, 129.9, 128.7, 127.9, 122.3, 121.6, 85.3, 43.6, 39.6; HRMS
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18 (ESI) $[M + Na^+]$ calcd for $C_{19}H_{15}BrNaO_3^+$ 393.0097/395.0076, found 393.0096/395.0075.

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22 *(R*,R*)-5-(1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (3g)*. Obtained as a white solid
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24 (64.7 mg, 90% yield), mp 111-113 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.54 (m, 1H), 7.42
25
26 (m, 2H), 7.34–7.24 (m, 5H), 6.08 (dd, $J = 5.6, 1.5$ Hz, 1H), 5.23 (m, 1H), 3.71 (m, 1H), 3.51 (dd, $J =$
27
28 17.8, 5.0 Hz, 1H), 3.42 (dd, $J = 17.8, 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 172.4, 155.2,
29
30 138.2, 136.3, 133.5, 133.4, 129.5, 129.0, 128.7, 127.9, 122.2, 85.4, 43.5, 39.6; HRMS (MALDI) $[M +$
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32 $H^+]$ calcd for $C_{19}H_{16}ClO_3^+$ 327.0783, found 327.0782.

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36 *(R*,R*)-5-(1-(2-Furanyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (3h)*. Obtained as a yellow solid
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38 (48.4 mg, 78% yield), mp 80-83 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.57 (m, 1H), 7.46
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40 (m, 2H), 7.40 (m, 1H), 7.32 (m, 1H), 6.30 (m, 1H), 6.22 (d, $J = 3.3$ Hz, 1H), 6.09 (dd, $J = 5.7, 1.9$ Hz,
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42 1H), 5.35 (m, 1H), 3.88 (m, 1H), 3.55 (dd, $J = 17.7, 7.8$ Hz, 1H), 3.45 (dd, $J = 17.7, 5.4$ Hz, 1H); ^{13}C
43
44 NMR (100 MHz, $CDCl_3$) δ 196.9, 172.4, 155.1, 152.2, 142.0, 136.4, 133.4, 128.7, 128.0, 122.0, 110.5,
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46 107.6, 83.7, 38.0, 37.7; HRMS (MALDI) $[M + H^+]$ calcd for $C_{17}H_{15}O_4^+$ 283.0965, found 283.0965.

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50 *(R*,R*)-5-(3-(4-Methylphenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one (3i)*. Obtained as a white solid
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52 (58.6 mg, 87% yield), mp 104-106 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, $J = 8.1$ Hz, 2H), 7.38–
53
54 7.11 (m, 8H), 6.06 (m, 1H), 5.26 (m, 1H), 3.71 (m, 1H), 3.53 (dd, $J = 17.6, 5.1$ Hz, 1H), 3.43 (dd, $J =$
55
56 17.6, 8.0 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 172.7, 155.6, 144.2, 139.7,
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3 134.1, 129.3, 128.9, 128.1, 128.0, 127.6, 121.9, 85.8, 44.3, 39.8, 21.6; HRMS (MALDI) $[M + H^+]$
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5 calcd for $C_{20}H_{19}O_3^+$ 307.1329, found 307.1329.
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8 *(R*,R*)-5-(3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one (3j)*. Obtained as a white solid
9
10 (49.6 mg, 70% yield), mp 139-141 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, $J = 8.6$ Hz, 2H), 7.37–
11
12 7.20 (m, 6H), 6.89 (d, $J = 8.6$ Hz, 2H), 6.05 (m, 1H), 5.26 (m, 1H), 3.84 (s, 3H), 3.70 (m, 1H), 3.50
13
14 (dd, $J = 17.4, 5.1$ Hz, 1H), 3.40 (dd, $J = 17.4, 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7,
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16 172.7, 163.6, 155.6, 139.8, 130.2, 129.7, 128.8, 128.1, 127.6, 121.9, 113.7, 85.8, 55.4, 44.3, 39.5;
17
18 HRMS (ESI) $[M + H^+]$ calcd for $C_{20}H_{19}O_4^+$ 323.1278, found 323.1278.
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22 *(R*,R*)-5-(3-(4-Chlorophenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one (3k)*. Obtained as a white solid
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24 (64.7 mg, 90% yield), mp 102-105 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.44–7.18 (m, 8H),
25
26 6.07 (m, 1H), 5.24 (m, 1H), 3.64 (m, 1H), 3.53 (dd, $J = 17.6, 4.8$ Hz, 1H), 3.44 (dd, $J = 17.6, 8.3$ Hz,
27
28 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 172.6, 155.5, 139.7, 139.4, 134.9, 129.4, 128.9 (2C), 128.0,
29
30 127.7, 122.0, 85.7, 44.5, 40.2; HRMS (ESI) $[M+Na^+]$ calcd for $C_{19}H_{15}ClNaO_3^+$ 349.0602, found
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32 349.0603.
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36 *(R*,S*)-5-(1-Oxo-1-phenyloctan-3-yl)furan-2(5H)-one (3l)*. Obtained as a white solid (39.1 mg, 62%
37
38 yield), mp 56-59 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.56 (m, 1H), 7.49–7.40 (m, 3H),
39
40 6.01 (dd, $J = 5.7, 1.6$ Hz, 1H), 5.24 (m, 1H), 2.86–2.78 (m, 2H), 2.71 (m, 1H), 1.70–1.19 (m, 8H), 0.87
41
42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 173.1, 156.2, 136.6, 133.3, 128.7, 127.9, 121.6, 84.8,
43
44 36.8, 36.2, 32.1, 31.7, 26.8, 22.5, 14.0; HRMS (MALDI) $[M+H^+]$ calcd for $C_{18}H_{23}O_3^+$ 287.1642, found
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46 287.1642.
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50 *(R*,R*)-5-(3-Oxo-1-phenylbutyl)furan-2(5H)-one (3m)*. Obtained as a white solid (17.2 mg, 34%
51
52 yield), mp 77-78 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.31–7.25 (m, 3H), 7.22 (m, 1H),
53
54 6.10 (m, 1H), 5.15 (m, 1H), 3.45 (m, 1H), 3.04 (dd, $J = 17.6, 5.2$ Hz, 1H), 2.91 (dd, $J = 17.6, 8.2$ Hz,
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56 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 172.7, 155.5, 139.3, 129.0, 128.0, 127.8,
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3 121.9, 85.7, 45.0, 44.2, 30.6; HRMS (MALDI) $[M+Na^+]$ calcd for $C_{14}H_{14}NaO_3^+$ 253.0835, found
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5 253.0835.
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7
8 *(R*,R*)-Ethyl 4-oxo-2-(5-oxo-2,5-dihydrofuran-2-yl)-4-phenylbutanoate (3n)*. Obtained as a colorless
9
10 oil (54.5 mg, 86% yield); 1H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.62–7.54 (m, 2H), 7.46 (m,
11
12 2H), 6.13 (m, 1H), 5.57 (m, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 3.63 (dd, $J = 18.2, 6.8$ Hz, 1H), 3.41 (m,
13
14 1H), 3.10 (dd, $J = 18.2, 4.9$ Hz, 1H), 1.26 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1,
15
16 172.1, 170.6, 155.1, 136.0, 133.6, 128.7, 128.0, 122.2, 81.9, 61.7, 43.2, 34.7, 14.0; HRMS (MALDI)
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18 $[M+Na^+]$ calcd for $C_{16}H_{16}NaO_5^+$ 311.0890, found 311.0889.
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24 **General procedure for the *syn*-diastereoselective VMMR catalyzed by KF/dicyclohexane-**
25
26 **18-crown-6 (conditions B)**. In a Schlenk tube, to a stirred solution of *trans*-chalcone **2a** (45.8 mg, 0.22
27
28 mmol) and dicyclohexane-18-crown-6 **5a** (8.2 mg, 0.022 mmol) in toluene (1.1 mL) at -50 °C, KF
29
30 (12.8 mg, 0.22 mmol) and 2-(trimethylsilyloxy)furan **1** (41.3 mg, 0.26 mmol) were added. The mixture
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32 was stirred until disappearance of the starting material (TLC), and then treated with 1 M HCl (1.0 mL)
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34 and THF (3.0 mL). The resulting solution was allowed to warm to room temperature, stirred for 2 h,
35
36 and then was diluted with H_2O (1.2 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic
37
38 phases were washed with saturated $NaHCO_3$ solution (1.5 mL), dried over Na_2SO_4 and concentrated *in*
39
40 *vacuo*. The crude product was purified by flash chromatography (silica gel, petroleum ether – ethyl
41
42 acetate, 8:2 to 6:4) affording **3a** (61.7 mg, 96% yield).
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51 *(R*,S*)-5-(3-Oxo-1,3-diphenylpropyl)furan-2(5H)-one (4a)*. Obtained as a white solid (61.7 mg, 96%
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53 yield), mp 97–100 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 7.36
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55 (m, 1H), 7.30–7.16 (m, 5H), 5.84 (dd, $J = 5.7, 1.9$ Hz, 1H), 5.45 (m, 1H), 3.96 (m, 1H), 3.81 (dd, $J =$
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57 18.0, 8.2 Hz, 1H), 3.45 (dd, $J = 18.0, 5.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 172.8, 155.3,
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3 137.1, 136.4, 133.4, 128.6, 128.5, 128.3, 127.9, 127.5, 121.9, 84.3, 42.8, 40.0; HRMS (MALDI) [M +
4 Na⁺] calcd for C₁₉H₁₆NaO₃⁺ 315.0992, found 315.0991.

7
8 (*R*,S**)-5-(1-(4-Methylphenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (**4b**). Obtained as a white solid
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10 (48.5 mg, 72% yield), mp 129-131 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.98 (m, 2H), 7.58 (m, 1H), 7.47
11 (m, 2H), 7.35 (m, 1H), 7.11–7.02 (m, 4H), 5.86 (m, 1H), 5.44 (m, 1H), 3.93 (m, 1H), 3.79 (dd, *J* =
12 18.0, 8.3 Hz, 1H), 3.43 (dd, *J* = 18.0, 5.7 Hz, 1H), 2.28 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 197.9,
13 172.9, 155.3, 137.3, 136.6, 134.1, 133.5, 129.3, 128.7, 128.2, 128.0, 122.1, 84.5, 42.5, 40.2, 21.0;
14
15 HRMS (MALDI) [M + H⁺] calcd for C₂₀H₁₉O₃⁺ 307.1329, found 307.1327.

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22 (*R*,S**)-5-(1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (**4c**). Obtained as a yellow oil
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24 (35.5 mg, 50% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.97 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 7.34
25 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 5.86 (m, 1H), 5.42 (m, 1H), 3.92 (m, 1H),
26
27 3.82–3.69 (m, 4H), 3.42 (dd, *J* = 17.9, 5.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 197.9, 172.9, 158.9,
28
29 155.4, 136.6, 133.5, 129.4, 129.1, 128.7, 128.0, 122.1, 113.9, 84.6, 55.2, 42.1, 40.4; HRMS (MALDI):
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31 [M + H⁺] calcd for C₂₀H₁₉O₄⁺ 323.1278, found 323.1277.

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36 (*R*,S**)-5-(1-(4-Nitrophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (**4d**). Obtained as a yellow oil
37
38 (66.8 mg, 90% yield); ¹H NMR (400 MHz, CDCl₃) δ 8.14 (m, 2H), 7.97 (m, 2H), 7.62–7.34 (m, 6H),
39
40 5.90 (m, 1H), 5.47 (m, 1H), 4.08 (m, 1H), 3.84 (dd, *J* = 18.3, 7.7 Hz, 1H), 3.56 (dd, *J* = 18.3, 6.1 Hz,
41
42 1H); ¹³C NMR (100 MHz, CDCl₃) δ 196.9, 172.1, 154.5, 147.4, 144.7, 136.1, 133.9, 129.5, 128.8,
43
44 128.0, 123.8, 122.8, 83.6, 42.9, 40.3; HRMS (MALDI) [M + H⁺] calcd for C₁₉H₁₆NO₅⁺ 338.1023,
45
46 found 338.1017.

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50 (*R*,S**)-5-(1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (**4e**). Obtained as a white solid
51
52 (55.3 mg, 81% yield), mp 106-109 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.96 (m, 2H), 7.57 (m, 1H), 7.46
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54 (m, 2H), 7.34 (m, 1H), 7.17 (m, 2H), 6.94 (m, 2H), 5.86 (m, 1H), 5.41 (m, 1H), 3.95 (m, 1H), 3.77 (dd,
55
56 *J* = 18.1, 8.0 Hz, 1H), 3.45 (dd, *J* = 18.1, 5.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 197.5, 172.6,
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3 162.0 (d, $J = 246$ Hz), 155.1, 136.4, 133.5, 132.8 (d, $J = 2$ Hz), 129.9 (d, $J = 8$ Hz), 128.7, 127.9, 122.2,
4
5 115.4 (d, $J = 21$ Hz), 84.2, 42.1, 40.4; HRMS (MALDI) $[M + H^+]$ calcd for $C_{19}H_{16}FO_3^+$ 311.1078,
6
7 found 311.1073.
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10 *(R*,S*)-5-(1-(4-Bromophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (4f)*. Obtained as a colorless oil
11
12 (61.3 mg, 75% yield); 1H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 7.38
13
14 (m, 2H), 7.33 (m, 1H), 7.09 (d, $J = 8.3$ Hz, 2H), 5.88 (m, 1H), 5.41 (m, 1H), 3.92 (m, 1H), 3.76 (dd, $J =$
15
16 18.0, 8.1 Hz, 1H), 3.45 (dd, $J = 18.0, 5.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 172.6, 155.0,
17
18 136.4, 136.2, 133.6, 131.7, 130.1, 128.7, 128.0, 122.4, 121.6, 84.0, 42.4, 40.2; HRMS (MALDI) $[M +$
19
20 $Na^+]$ calcd for $C_{19}H_{15}BrNaO_3^+$ 393.0097/395.0076, found 393.0096/395.0076.
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24 *(R*,S*)-5-(1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (4g)*. Obtained as a white solid
25
26 (57.5 mg, 80% yield), mp 115-118 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.59 (m, 1H), 7.48
27
28 (m, 2H), 7.34 (m, 1H), 7.24 (m, 2H), 7.15 (m, 2H), 5.88 (dd, $J = 5.7, 1.9$ Hz, 1H), 5.42 (m, 1H), 3.94
29
30 (m, 1H), 3.78 (dd, $J = 18.0, 8.0$ Hz, 1H), 3.46 (dd, $J = 18.0, 5.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)
31
32 δ 197.5, 172.6, 154.9, 136.4, 135.6, 133.6, 133.5, 129.7, 128.8, 128.7, 128.0, 122.4, 84.1, 42.3, 40.3;
33
34 HRMS (MALDI) $[M + H^+]$ calcd for $C_{19}H_{16}ClO_3^+$ 327.0783, found 327.0783.
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38 *(R*,S*)-5-(1-(2-Furanyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one (4h)*. Obtained as a yellow solid (31.1
39
40 mg, 50% yield), mp 91-93 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.59 (m, 1H), 7.53-7.44
41
42 (m, 3H), 7.27 (d, $J = 1.2$ Hz, 1H), 6.26 (m, 1H), 6.16 (d, $J = 3.0$ Hz, 1H), 6.00 (dd, $J = 5.7, 1.9$ Hz, 1H),
43
44 5.39 (m, 1H), 4.17 (m, 1H), 3.59 (dd, $J = 18.0, 7.3$ Hz, 1H), 3.42 (dd, $J = 18.0, 6.6$ Hz, 1H); ^{13}C NMR
45
46 (100 MHz, $CDCl_3$) δ 197.1, 172.6, 154.8, 151.3, 141.8, 136.3, 133.5, 128.7, 128.0, 122.1, 110.4, 107.8,
47
48 83.3, 38.0, 36.8; HRMS (MALDI) $[M + H^+]$ calcd for $C_{17}H_{14}NaO_4^+$ 305.0784, found 305.0784.
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52 *(R*,S*)-5-(3-(4-Methylphenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one (4i)*. Obtained as a white solid
53
54 (48.5 mg, 72% yield), mp 110-113 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, $J = 8.2$ Hz, 2H), 7.36
55
56 (m, 1H), 7.30-7.13 (m, 7H), 5.85 (dd, $J = 5.7, 2.0$ Hz, 1H), 5.45 (m, 1H), 3.96 (m, 1H), 3.79 (dd, $J =$
57
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59
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3 18.0, 8.4 Hz, 1H), 3.43 (dd, $J = 18.0, 5.5$ Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.4,
4
5 172.9, 155.3, 144.4, 137.3, 134.1, 129.4, 128.6, 128.4, 128.2, 127.6, 122.0, 84.4, 43.0, 40.0, 21.6;
6
7 HRMS (MALDI) $[\text{M} + \text{H}^+]$ calcd for $\text{C}_{20}\text{H}_{19}\text{O}_3^+$ 307.1329, found 307.1329.

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9
10 *(R*,S*)-5-(3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one (4j)*. Obtained as a white solid
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12 (41.1 mg, 58% yield), mp 149-152 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.97 (m, 2H), 7.39–7.17 (m, 6H),
13
14 6.94 (m, 2H), 5.84 (dd, $J = 5.7, 2.0$ Hz, 1H), 5.45 (m, 1H), 3.95 (m, 1H), 3.87 (s, 3H), 3.76 (dd, $J =$
15
16 17.7, 8.5 Hz, 1H), 3.39 (dd, $J = 17.7, 5.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.3, 172.8, 163.9,
17
18 155.3, 137.5, 130.4, 129.8, 128.6, 128.5, 127.6, 122.1, 113.9, 84.5, 55.5, 43.2, 39.8; HRMS (MALDI)
19
20 $[\text{M} + \text{H}^+]$ calcd for $\text{C}_{20}\text{H}_{19}\text{O}_4^+$ 323.1278, found 323.1278.

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24 *(R*,S*)-5-(3-(4-Chlorophenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one (4k)*. Obtained as a white solid
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26 (71.2 mg, 99% yield), mp 100-102 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (m, 2H), 7.44 (m, 2H), 7.34
27
28 (m, 1H), 7.30–7.15 (m, 5H), 5.85 (dd, $J = 5.7, 1.9$ Hz, 1H), 5.44 (m, 1H), 3.95 (m, 1H), 3.76 (dd, $J =$
29
30 18.0, 8.3 Hz, 1H), 3.43 (dd, $J = 18.0, 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.6, 172.7, 155.1,
31
32 140.0, 137.0, 134.8, 129.4, 129.0, 128.6, 128.3, 127.7, 122.1, 84.2, 42.9, 40.1; HRMS (MALDI) $[\text{M} +$
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34 $\text{Na}^+]$ calcd for $\text{C}_{19}\text{H}_{15}\text{ClNaO}_3^+$ 349.0602, found 349.0602.

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38 *(R*,R*)-5-(1-Oxo-1-phenyloctan-3-yl)furan-2(5H)-one (4l)*. Obtained as a yellow oil (26.5 mg, 42%
39
40 yield); ^1H NMR (400 MHz, CDCl_3) δ 7.96 (m, 2H), 7.58 (m, 1H), 7.51–7.43 (m, 3H), 6.16 (m, 1H),
41
42 5.25 (m, 1H), 3.25 (dd, $J = 17.7, 7.9$ Hz, 1H), 2.97 (dd, $J = 17.7, 5.1$ Hz, 1H), 2.65 (m, 1H), 1.42–1.11
43
44 (m, 8H), 0.85 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 199.0, 173.1, 155.4, 136.7, 133.4, 128.7, 128.0,
45
46 122.2, 85.2, 39.1, 36.3, 31.7, 28.0, 27.0, 22.4, 13.9; HRMS (MALDI) $[\text{M} + \text{H}^+]$ calcd for $\text{C}_{18}\text{H}_{23}\text{O}_3^+$
47
48 287.1642, found 287.1642.

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52 *(R*,S*)-5-(3-Oxo-1-phenylbutyl)furan-2(5H)-one (4m)*. Obtained as a colorless oil (23.3 mg, 46%
53
54 yield); ^1H NMR (400 MHz, CDCl_3) δ 7.36–7.18 (m, 4H), 7.12 (m, 2H), 5.84 (m, 1H), 5.34 (m, 1H),
55
56 3.74 (m, 1H), 3.24 (dd, $J = 18.2, 8.3$ Hz, 1H), 2.92 (dd, $J = 18.2, 5.8$ Hz, 1H), 2.17 (s, 3H); ^{13}C NMR
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(100 MHz, CDCl₃) δ 206.5, 172.8, 155.1, 137.0, 128.6, 128.2, 127.6, 122.0, 84.1, 44.7, 42.5, 30.5;

HRMS (MALDI) [M + Na⁺] calcd for C₁₄H₁₄NaO₃⁺ 253.0835, found 253.0834.

(*R*,S**)-Ethyl 4-oxo-2-(5-oxo-2,5-dihydrofuran-2-yl)-4-phenylbutanoate (**4n**). Obtained as a colorless oil (52.6 mg, 83% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.92 (m, 2H), 7.61–7.54 (m, 2H), 7.46 (m, 2H), 6.14 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.44 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.67 (m, 1H), 3.45 (dd, *J* = 18.2, 7.7 Hz, 1H), 3.22 (dd, *J* = 18.2, 5.1 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 197.0, 172.1, 170.2, 154.7, 136.0, 133.6, 128.7, 128.0, 122.0, 81.6, 61.5, 42.9, 35.2, 14.1; HRMS (MALDI) [M + H⁺] calcd for C₁₆H₁₇O₅⁺ 289.1070, found 289.1070.

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ASSOCIATED CONTENT:

Supporting Information. Optimization tables, computational details, copies of ¹H NMR and ¹³C NMR spectra of all the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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44 Solvent effects (toluene) were included with the SMD solvation model. Different geometries were
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46 analysed to find the best relative orientation of the reacting molecules. Further details are reported in
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