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Switchable Diastereoselectivity in the Fluoride-Promoted Vinylogous Mukaiyama–Michael Reaction of 2-[(Trimethylsilyl)oxy]furan Catalyzed by Crown Ethers

Giorgio Della Sala,*[,†] Marina Sicignano,[†] Rosaria Schettini,[†] Francesco De Riccardis,[†] Luigi Cavallo,*[,‡] Yury Minenkov,[‡] Chloé Batisse,[†,§] Gilles Hanquet,[§] Frédéric Leroux,[§] and Irene Izzo*[,†]

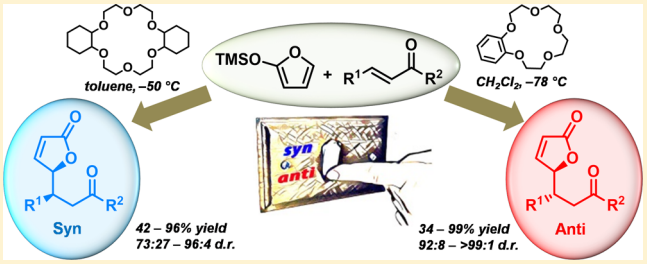
[†]Dipartimento di Chimica e Biologia "A. Zambelli", Università degli Studi di Salerno, Via Giovanni Paolo II 132, 84084 Fisciano, SA, Italy

[‡]Physical Sciences and Engineering Division, King Abdullah University of Science and Technology, KAUST Catalysis Center, Thuwal 23955-6900, Saudi Arabia

[§]CNRS, Laboratoire de Chimie Moléculaire UMR 7509 ECPM, Université de Strasbourg, 25 rue Becquerel, 67087 Strasbourg, France

Supporting Information

ABSTRACT: The fluoride-promoted vinylogous Mukaiyama–Michael reaction of 2-[(trimethylsilyl)oxy]furan 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 or with excellent diastereoselectivities when benzo-15-crown-5 in CH_2Cl_2 was employed. On the other hand, high *syn*-diastereoselectivities (from 73:27 to 96:4) were achieved by employing dicyclohexane-18-crown-6 in toluene. On the basis of DFT calculations, the catalysts/solvent-dependent switchable diastereoselectivities are proposed to be the result of loose or tight cation–dienolate ion pairs.

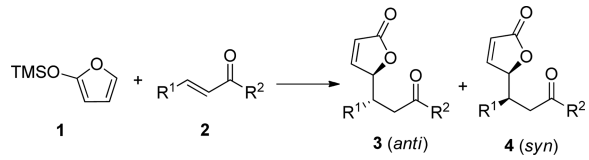


INTRODUCTION

The γ-butenolide moiety is a powerful pharmacophore widely distributed in natural products and in an appreciable number of synthetic compounds.[1] The inclusion of this fragment in chiral intermediates expedites the synthesis of an ample variety of biologically active secondary metabolites.[2] Given the intrinsic value of this γ-lactone, much effort has been devoted to its stereoselective construction.[2−4] One of the most efficient synthetic strategies is the vinylogous Michael reaction (VMR) with α,β-unsaturated ketones. This reaction enables the stereoselective introduction of a 3-oxoalkyl substituent in the butenolide γ-position.[4] Despite the enormous potential of this process, most of the methods reported to date involve the stereoselective γ-functionalization of deconjugated γ-substituted butenolides, affording γ,γ-disubstituted products.[5] On the contrary, the stereoselective VMR of γ-unsubstituted 2(5*H*)-furanones and 2-(silyloxy)furans with α,β-unsaturated ketones, leading to γ-monosubstituted products, has been much less investigated. Enantioenriched *syn*- or *anti*-products can be secured by efficient protocols employing chiral organocatalysts or ligands.[6−11] Unfortunately, these catalysts are often expensive or not commercially available. In addition, the *syn*-adducts are accessible only in reactions with *trans*-chalcones.[7b,9]

As the use of chiral catalysts is unnecessary for the development of a purely *syn*/*anti*-diastereoselective addition, the investigation of novel methods based on simple achiral and off-the-shelf catalysts has recently received appreciable attention. The few methodologies reported to date are based on catalyzed vinylogous Mukaiyama–Michael reaction (VMMR) with 2-(silyloxy)furans and lead prevalently to the *anti*-adducts (Scheme 1). Two efficient diastereoselective VMMRs of 2-[(trimethylsilyl)oxy]furan (TMSOF, **1**) with α,β-unsaturated ketones (**2**) are catalyzed by I_2[12] or an *N*-heterocyclic carbene.[13] They afford *anti*-adducts with good to excellent diastereoselectivities, starting from *trans*-chalcones,

Scheme 1. VMMR of TMSOF and α,β-Unsaturated Ketones



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and with moderate to good selectivities, when aliphatic acceptors are employed in the reaction. VMMR with TMSOF and other 2-(silyloxy)furans, 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]

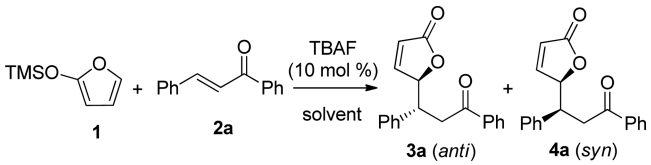
Given the small number of available purely diastereoselective TMSOF-based VMMRs in the presence of α,β-unsaturated ketones and considering the growing impact of diastereodivergent processes,[5b] we became interested in the design of a new methodology that, based on inexpensive and readily available catalysts, afforded an efficient and convenient path to 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-(silyloxy)furans. 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).

Table 1. VMMR with Chalcone 2a, Promoted by TBAF[a]



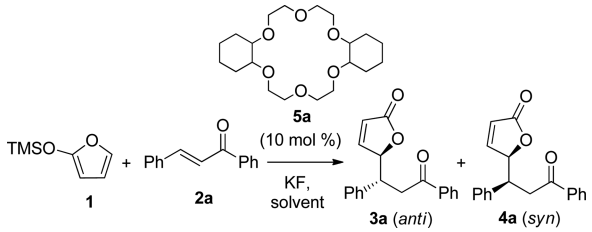
entry	solvent	temp (°C)	time (h)	yield[b] (%)	*anti*/*syn*[c]
1	DMF	−60	5		
2	CH_2Cl_2	−78	20	78	98:2
3	$CHCl_3$	−55	4	84	98:2
4	toluene	−78	40	57	93:7
5	THF	−78	20	79	83:17

[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 ^{1}H NMR analysis of the crude product.

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 CH_2Cl_2 and $CHCl_3$ (98:2, entries 2 and 3). In toluene, a slightly lower diastereomeric ratio and a moderate yield were observed (entry 1). The longer reaction times are likely due to a less reactive fluoride ion engaged in a tight ion pair.

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

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_2Cl_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_3CN	−40	20	72	98:2
6[d]	CH_3CN	−40	96	29	90:10
7	THF	−78	20	83	93:7
8	DCE	−30	2	86	88:12
9	Et_2O	−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 ^{1}H NMR analysis of the crude product. [d]Reaction performed in the absence of **5a**.

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, and 5). However, the KF/**5a** system proved to be more efficient, giving Michael adduct in 98% yield in CH_2Cl_2 (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. entries 2 and 3) and CH_3CN (cf. entries 5 and 6), since in its absence incomplete conversion was 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.

With the aim of further enhancing 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**

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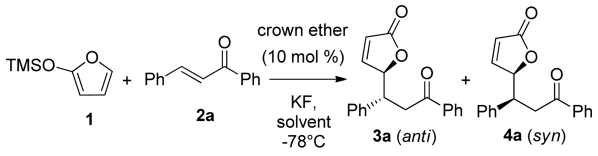
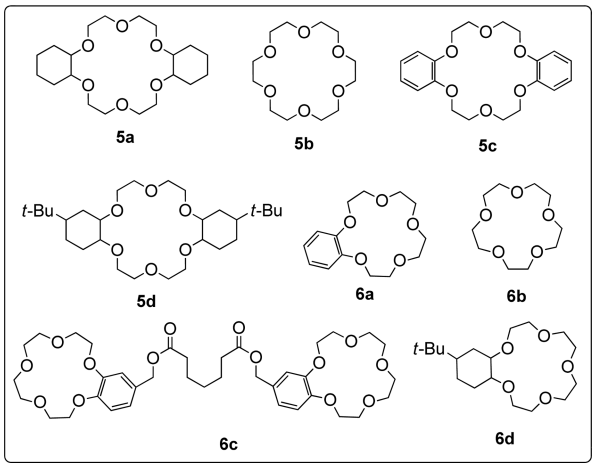
Table 3. Screening of Crown Ethers in VMMR with 2a[a]





entry	catalyst	solvent	time (h)	yield[b] (%)	*anti*/*syn*[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_2Cl_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 ^{1}H NMR analysis of the crude product. [d]Reaction performed at −50 °C. [e]Reaction performed at −55 °C.

gave the best diastereomeric ratio (entry 1). The diastereoselectivity was slightly improved when the reaction was performed 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, favoring 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 a more polar solvent such as $CHCl_3$ or 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).

Having established the optimal conditions to obtain both the *anti* (conditions A: catalyst **6a** at −78 °C in CH_2Cl_2) 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**, which 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**, a 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 VMMR 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]

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**.

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. Conversely, 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 the 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 CH_2Cl_2 (Scheme 3).

To rationalize the relationship between cation−anion separation and *syn*/*anti*-diastereoselectivity, DFT calculations were performed.[25] In both the presence or the absence of the cation, Diels−Alder-like transition states were found to be favored over all of the possible open transition states.[26] With the "naked" dienolate anion involved as nucleophile in reaction with chalcone **2a** (to simulate conditions in polar solvents or reactions catalyzed by TBAF, **8**, or 15-crown-5 derivatives), our calculations determined a preference for the ***endo*-TS-A** transition state, affording the *anti*-adduct **3a** (Scheme 4, a), over the competing transition state ***exo*-TS-A**, 2.8 kcal/mol higher in energy. The observed *endo* preference can be attributed to electrostatic repulsion between the nearby oxygen

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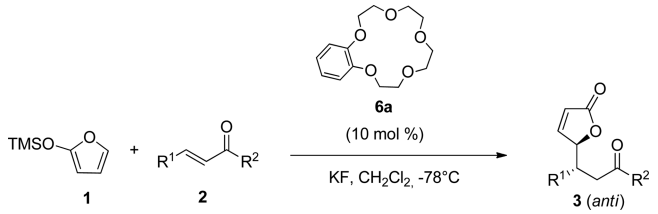
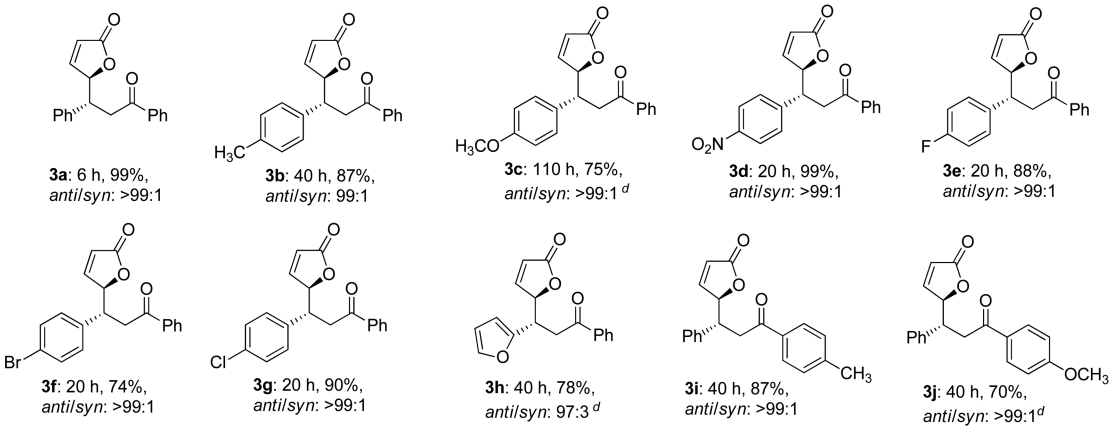
Table 4. *Anti*-Diastereoselective VMMR (Conditions A)[a−c]





[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 °C. [b]Isolated yields. [c]The diastereomeric ratios were determined by ^{1}H NMR analysis of the crude product. [d]Reaction performed at −50 °C. [e]Reaction performed at −20 °C. [f]**1** (0.40 mmol) was used. [g]Reaction performed at −30 °C.

atoms on the reactants, which contributes to disfavor the *exo* transition state. On the other hand, when tight ion pair **7** is involved as nucleophile (to simulate reactions catalyzed by KF/18-crown-6 derivatives in toluene), we calculated the ***exo*-TS-B** transition state to be favored by 3.1 kcal/mol over the ***endo*-TS-B** transition state (Scheme 4, b). This inversion of stability is due to the simultaneous coordination of the two negatively charged oxygen atoms of the reactants to the cation, with the consequent formation of a *syn*-product chelating the cation (Scheme 4, b).

CONCLUSIONS

In conclusion, we have developed an efficient diastereoselective fluoride-promoted VMMR 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 that allows both diastereomers to be obtained in good to high yields and selectivities by choosing the appropriate solvent and macrocycle 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 diastereodivergence 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** and **6a−d**, [2.2.2]cryptand (**8**), 2-[(trimethylsilyl)oxy]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 an inert atmosphere of nitrogen gas. Reactions were monitored by analytical thin-layer chromatography 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. ^{1}H 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 ($CHCl_3$, δ = 7.26 for proton spectra; $^{13}CDCl_3$, δ = 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 were recorded on a Fourier transform ion cyclotron resonance mass spectrometer equipped with a 7T magnet, using electrospray ionization or matrix-assisted laser desorption/ionization.

General Procedure for the TBAF-Catalyzed VMMR. In a Schlenk tube, to a stirred solution of *trans*-chalcone **2a** (45.8 mg, 0.22

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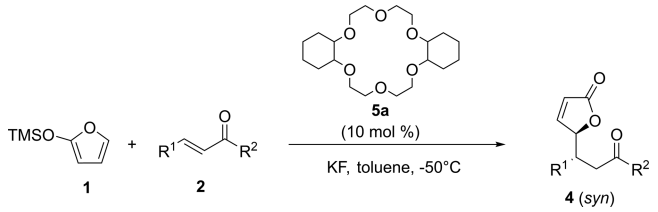
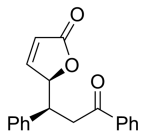
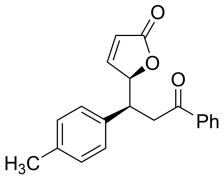
Table 5. *Syn*-Diastereoselective VMMR (Conditions B)[a,b,c]

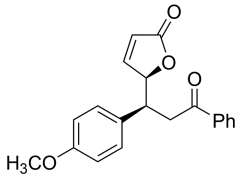




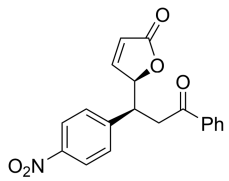
4a: 4 h, 96%, *syn*/*anti*: 94:6



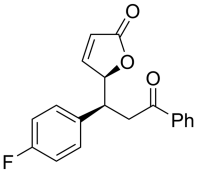
4b: 85 h, 72%, *syn*/*anti*: 92:8



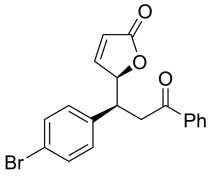
4c: 110 h, 50%, *syn*/*anti*: 85:15



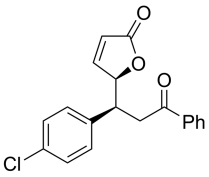
4d: 20 h, 90%, *syn*/*anti*: 73:27



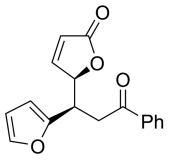
4e: 20 h, 81%, *syn*/*anti*: 87:13



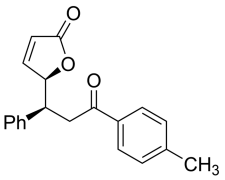
4f: 65 h, 75%, *syn*/*anti*: 80:20



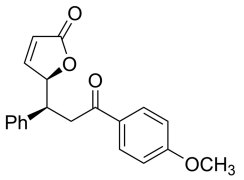
4g: 20 h, 80%, *syn*/*anti*: 88:12



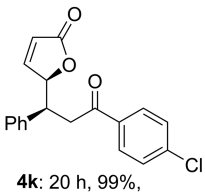
4h: 40 h, 50%, *syn*/*anti*: 95:5 [d]



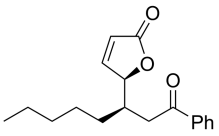
4i: 110 h, 72%, *syn*/*anti*: 94:6



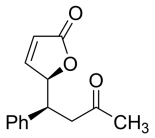
4j: 110 h, 58%, *syn*/*anti*: 84:16; [e] 110 h, 30%, *syn*/*anti*: 90:10



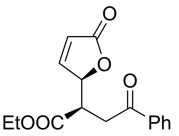
4k: 20 h, 99%, *syn*/*anti*: 89:11



4l: 160 h, 42%, *syn*/*anti*: 84:16 [e]



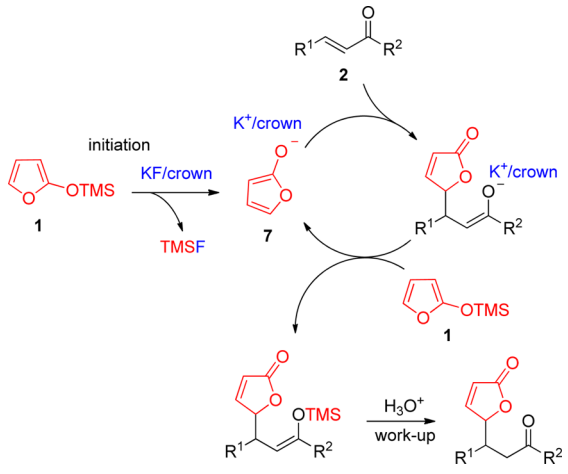
4m: 160 h, 46%, *syn*/*anti*: 96:4 [f]



4n: 20 h, 83%, *syn*/*anti*: 76:24

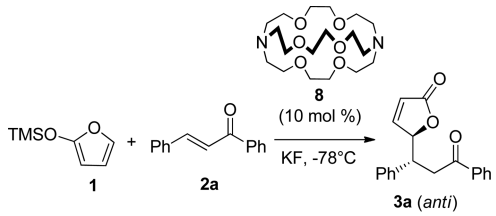
[a]Reaction conditions: **1** (0.24 mmol), **2a** (0.20 mmol), KF (0.20 mmol), **5a** (0.020 mmol), toluene (1.0 mL), −50 °C. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Reaction performed at −78 °C. [e]Reaction performed at −20 °C. [f]Reaction performed at −30 °C.

Scheme 2. Proposed Mechanism of the Fluoride-Promoted VMMR



mmol) in $CHCl_3$ (1.1 mL) at −55 °C were sequentially added TBAF (1.0 M in THF, 0.022 mL, 0.022 mmol) and 2-[(trimethylsilyl)oxy]-furan **1** (41.3 mg, 0.26 mmol). The mixture was stirred until disappearance of the starting material (TLC) and then treated with 1 M HCl (1.0 mL) and THF (3.0 mL). The resulting solution was allowed to warm to room temperature, stirred for 2 h, and then diluted

Scheme 3. VMMR with 2a Promoted by [2.2.2]-Cryptand (8)



in toluene: 40 h, 82%, *anti*/*syn* 98:2
in CH_2Cl_2: 5 h, 93%, *anti*/*syn* 98:2

with H_2O (1.2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (1.5 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether−ethyl acetate, 8:2 to 6:4) to afford **3a** (54.0 mg, 84% yield).

General Procedure for the *Anti*-Diastereoselective VMMR Catalyzed by KF/Benzo-15-crown-5 (Conditions A). In a Schlenk tube, to a stirred solution of *trans*-chalcone **2a** (45.8 mg, 0.22 mmol) and benzo-15-crown-5 **6a** (5.9 mg, 0.022 mmol) in CH_2Cl_2 (1.1 mL) at −78 °C were added KF (12.8 mg, 0.22 mmol) and 2-[(trimethylsilyl)oxy]furan **1** (41.3 mg, 0.26 mmol). The mixture was stirred until disappearance of the starting material (TLC) and then treated with 1 M HCl (1.0 mL) and THF (3.0 mL). The resulting

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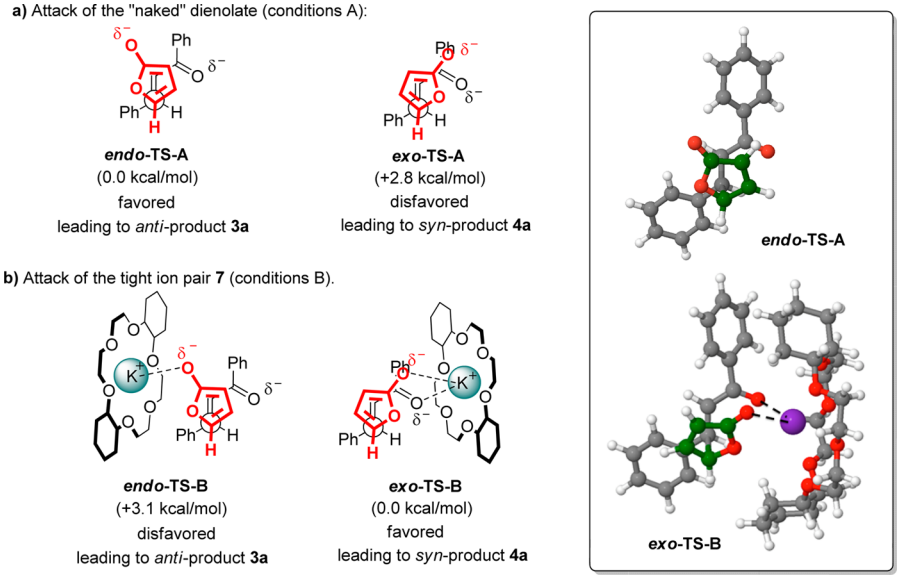
J. Org. Chem. 2017, 82, 6629−6637

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



solution was allowed to warm to room temperature, stirred for 2 h, and then diluted with H_2O (1.2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (1.5 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether−ethyl acetate, 8:2 to 6:4) to afford **3a** (63.7 mg, 99% yield).

(R,R*)-5-(3-Oxo-1,3-diphenylpropyl)furan-2(5H)-one* ***(3a)***. Obtained as a white solid (63.7 mg, 99% yield): mp 83−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, 2H), 7.53 (m, 1H), 7.42 (m, 2H), 7.36−7.20 (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, 1H), 3.48 (dd, J = 17.7, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 172.5, 155.5, 139.5, 136.4, 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 $C_{19}H_{17}O_3^+$ 293.1172, found 293.1170.

(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; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{19}O_3^+$ 307.1329, found 307.1329.

(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): ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{20}H_{19}O_4^+$ 323.1278, found 323.1277.

(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; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{19}H_{16}NO_5^+$ 338.1023, found 338.1024.

(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; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, 122.1, 115.7 (d, J = 21 Hz), 85.5, 43.3, 39.8; HRMS (MALDI) [M + H$^+$] calcd for $C_{19}H_{16}FO_3^+$ 311.1078, found 311.1079.

(R,R*)-5-(1-(4-Bromophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one* ***(3f)***. Obtained as a white solid (60.4 mg, 74% yield): mp 138−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 2H), 7.56 (m, 1H), 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 (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, 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 (ESI) [M + Na$^+$] calcd for $C_{19}H_{15}BrNaO_3^+$ 393.0097/395.0076, found 393.0096/395.0075.

(R,R*)-5-(1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one* ***(3g)***. Obtained as a white solid (64.7 mg, 90% yield): mp 111−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.54 (m, 1H), 7.42 (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 = 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, 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 + H$^+$] calcd for $C_{19}H_{16}ClO_3^+$ 327.0783, found 327.0782.

(R,R*)-5-(1-(2-Furanyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one* ***(3h)***. Obtained as a yellow solid (48.4 mg, 78% yield): mp 80−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.57 (m, 1H), 7.46 (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, 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 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, 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.

(R,R*)-5-(3-(4-Methylphenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one* ***(3i)***. Obtained as a white solid (58.6 mg, 87% yield): mp 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 2H), 7.38−7.11 (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 = 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, 134.1, 129.3, 128.9, 128.1, 128.0, 127.6, 121.9, 85.8, 44.3, 39.8,

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J. Org. Chem. 2017, 82, 6629−6637

21.6; HRMS (MALDI) [M + H^+] calcd for $C_{20}H_{19}O_3^+$ 307.1329, found 307.1329.

(R,R*)-5-(3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one* (**3j**). Obtained as a white solid (49.6 mg, 70% yield): mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.6 Hz, 2H), 7.37−7.20 (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 (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, 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; HRMS (ESI) [M + H^+] calcd for $C_{20}H_{19}O_4^+$ 323.1278, found 323.1278.

(R,R*)-5-(3-(4-Chlorophenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one* (**3k**). Obtained as a white solid (64.7 mg, 90% yield): mp 102−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.44−7.18 (m, 8H), 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, 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, 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 349.0603.

(R,S*)-5-(1-Oxo-1-phenyloctan-3-yl)furan-2(5H)-one* (**3l**). Obtained as a white solid (39.1 mg, 62% yield): mp 56−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.56 (m, 1H), 7.49−7.40 (m, 3H), 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 (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, 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 287.1642.

(R,R*)-5-(3-Oxo-1-phenylbutyl)furan-2(5H)-one* (**3m**). Obtained as a white solid (17.2 mg, 34% yield): mp 77−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.31−7.25 (m, 3H), 7.22 (m, 1H), 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, 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, 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 253.0835.

(R,R*)-Ethyl 4-Oxo-2-(5-oxo-2,5-dihydrofuran-2-yl)-4-phenylbutanoate* (**3n**). Obtained as a colorless oil (54.5 mg, 86% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.62−7.54 (m, 2H), 7.46 (m, 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, 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, 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) [M + Na^+] calcd for $C_{16}H_{16}NaO_5^+$ 311.0890, found 311.0889.

General Procedure for the *Syn*-Diastereoselective VMMR Catalyzed by KF/Dicyclohexane-18-crown-6 (Conditions B). In a Schlenk tube, to a stirred solution of *trans*-chalcone **2a** (45.8 mg, 0.22 mmol) and dicyclohexane-18-crown-6 **5a** (8.2 mg, 0.022 mmol) in toluene (1.1 mL) at −50 °C were added KF (12.8 mg, 0.22 mmol) and 2-[(trimethylsilyl)oxy]furan **1** (41.3 mg, 0.26 mmol). The mixture was stirred until disappearance of the starting material (TLC) and then treated with 1 M HCl (1.0 mL) and THF (3.0 mL). The resulting solution was allowed to warm to room temperature, stirred for 2 h, and then diluted with H_2O (1.2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (1.5 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether−ethyl acetate, 8:2−6:4) to afford **3a** (61.7 mg, 96% yield).

(R,S*)-5-(3-Oxo-1,3-diphenylpropyl)furan-2(5H)-one* (**4a**). Obtained as a white solid (61.7 mg, 96% yield): mp 97−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 7.36 (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 = 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, 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 + Na^+] calcd for $C_{19}H_{16}NaO_3^+$ 315.0992, found 315.0991.

(R,S*)-5-(1-(4-Methylphenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one* (**4b**). Obtained as a white solid (48.5 mg, 72% yield), mp 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.58 (m, 1H), 7.47 (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 = 18.0, 8.3 Hz, 1H), 3.43 (dd, J = 18.0, 5.7 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 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; HRMS (MALDI) [M + H^+] calcd for $C_{20}H_{19}O_3^+$ 307.1329, found 307.1327.

(R,S*)-5-(1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one* (**4c**). Obtained as a yellow oil (35.5 mg, 50% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 7.34 (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), 3.82−3.69 (m, 4H), 3.42 (dd, J = 17.9, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 172.9, 158.9, 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) [M + H^+] calcd for $C_{20}H_{19}O_4^+$ 323.1278, found 323.1277.

(R,S*)-5-(1-(4-Nitrophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one* (**4d**). Obtained as a yellow oil (66.8 mg, 90% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (m, 2H), 7.97 (m, 2H), 7.62−7.34 (m, 6H), 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, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 172.1, 154.5, 147.4, 144.7, 136.1, 133.9, 129.5, 128.8, 128.0, 123.8, 122.8, 83.6, 42.9, 40.3; HRMS (MALDI) [M + H^+] calcd for $C_{19}H_{16}NO_5^+$ 338.1023, found 338.1017.

(R,S*)-5-(1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one* (**4e**). Obtained as a white solid (55.3 mg, 81% yield): mp 106−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2H), 7.57 (m, 1H), 7.46 (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, J = 18.1, 8.0 Hz, 1H), 3.45 (dd, J = 18.1, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 172.6, 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, 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, found 311.1073.

(R,S*)-5-(1-(4-Bromophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one* (**4f**). Obtained as a colorless oil (61.3 mg, 75% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 7.38 (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 = 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, 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 + Na^+] calcd for $C_{19}H_{15}BrNaO_3^+$ 393.0097/395.0076, found 393.0096/395.0076.

(R,S*)-5-(1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one* (**4g**). Obtained as a white solid (57.5 mg, 80% yield): mp 115−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.59 (m, 1H), 7.48 (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 (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, $CDCl_3$) 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; HRMS (MALDI) [M + H^+] calcd for $C_{19}H_{16}ClO_3^+$ 327.0783, found 327.0783.

(R,S*)-5-(1-(2-Furanyl)-3-oxo-3-phenylpropyl)furan-2(5H)-one* (**4h**). Obtained as a yellow solid (31.1 mg, 50% yield): mp 91−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.59 (m, 1H), 7.53−7.44 (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), 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 (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, 83.3, 38.0, 36.8; HRMS (MALDI) [M + H^+] calcd for $C_{17}H_{14}NaO_4^+$ 305.0784, found 305.0784.

(R,S*)-5-(3-(4-Methylphenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one* (**4i**). Obtained as a white solid (48.5 mg, 72% yield): mp 110−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2 Hz, 2H), 7.36 (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 = 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, 172.9, 155.3, 144.4, 137.3, 134.1, 129.4, 128.6, 128.4, 128.2,

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J. Org. Chem. 2017, 82, 6629−6637

127.6, 122.0, 84.4, 43.0, 40.0, 21.6; HRMS (MALDI) [M + H$^+$] calcd for $C_{20}H_{19}O_3^+$ 307.1329, found 307.1329.

(R,S*)-5-(3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one* (**4j**). Obtained as a white solid (41.1 mg, 58% yield): mp 149−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.39−7.17 (m, 6H), 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 = 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, 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) [M + H$^+$] calcd for $C_{20}H_{19}O_4^+$ 323.1278, found 323.1278.

(R,S*)-5-(3-(4-Chlorophenyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one* (**4k**). Obtained as a white solid (71.2 mg, 99% yield): mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.44 (m, 2H), 7.34 (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 = 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, 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) [M + Na$^+$] calcd for $C_{19}H_{15}ClNaO_3^+$ 349.0602, found 349.0602.

(R,R*)-5-(1-Oxo-1-phenyloctan-3-yl)furan-2(5H)-one* (**4l**). Obtained as a yellow oil (26.5 mg, 42% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2H), 7.58 (m, 1H), 7.51−7.43 (m, 3H), 6.16 (m, 1H), 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 (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, 122.2, 85.2, 39.1, 36.3, 31.7, 28.0, 27.0, 22.4, 13.9; HRMS (MALDI) [M + H$^+$] calcd for $C_{18}H_{23}O_3^+$ 287.1642, found 287.1642.

(R,S*)-5-(3-Oxo-1-phenylbutyl)furan-2(5H)-one* (**4m**). Obtained as a colorless oil (23.3 mg, 46% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.18 (m, 4H), 7.12 (m, 2H), 5.84 (m, 1H), 5.34 (m, 1H), 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 (100 MHz, $CDCl_3$) 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 $C_{14}H_{14}NaO_3^+$ 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): ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{17}O_5^+$ 289.1070, found 289.1070.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00743.

Optimization tables, computational details, and ^{1}H NMR and ^{13}C NMR spectra of all products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: gdsala@unisa.it.
*E-mail: luigi.cavallo@kaust.edu.sa.
*E-mail: iizzo@unisa.it.

ORCID

Giorgio Della Sala: 0000-0001-5020-8502
Francesco De Riccardis: 0000-0002-8121-9463
Luigi Cavallo: 0000-0002-1398-338X
Frédéric Leroux: 0000-0001-8900-5753
Irene Izzo: 0000-0002-0369-0102

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426−9451. (b) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298−317. (c) Prassas, I.; Diamandis, E. P. *Nat. Rev. Drug Discovery* **2008**, *7*, 926−935. (d) Bermejo, A.; Figadère, B.; Zafra-Polo, M.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269−303. (e) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. (f) Rao, Y. R. *Chem. Rev.* **1976**, *76*, 625−694.

(2) (a) Barbosa, L. C. A.; Teixeira, R. R.; Amarante, G. W. *Curr. Org. Synth.* **2015**, *12*, 746−771. (b) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, *2009*, 1525−1542. (c) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109−118. (d) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, *1995*, 607−626. (e) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895−904. (f) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221−3242.

(3) (a) Zhang, Q.; Liu, X.; Feng, X. *Curr. Org. Synth.* **2013**, *10*, 764−785. (b) Ugurchieva, T. M.; Veselovsky, V. V. *Russ. Chem. Rev.* **2009**, *78*, 337−373. (c) Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001−1011. (d) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707−6738.

(4) (a) Jusseau, X.; Chabaud, L.; Guillou, C. *Tetrahedron* **2014**, *70*, 2595−2615. (b) Yan, L.; Wu, X.; Liu, H.; Xie, L.; Jiang, Z. *Mini-Rev. Med. Chem.* **2013**, *13*, 845−853.

(5) (a) Wang, Z.-H.; Wu, Z.-J.; Huang, X.-Q.; Yue, D.-F.; You, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Chem. Commun.* **2015**, *51*, 15835−15838. (b) Li, X.; Lu, M.; Dong, Y.; Wu, W.; Qian, Q.; Ye, J.; Dixon, D. J. *Nat. Commun.* **2014**, *5*, 4479. (c) Manna, M. S.; Mukherjee, S. *Chem. Sci.* **2014**, *5*, 1627−1633. (d) Yang, D.; Wang, L.; Zhao, D.; Han, F.; Zhang, B.; Wang, R. *Chem. - Eur. J.* **2013**, *19*, 4691−4694. (e) Das, U.; Chen, Y.-R.; Tsai, Y.-L.; Lin, W. *Chem. - Eur. J.* **2013**, *19*, 7713−7717. (f) Ji, J.; Lin, L.; Zhou, L.; Zhang, Y.; Liu, Y.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2013**, *355*, 2764−2768. (g) Zhang, W.; Tan, D.; Lee, R.; Tong, G.; Chen, W.; Qi, B.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 10069−10073.

(6) For an asymmetric example of *anti*-diastereoselective VMMR with different α,β-unsaturated ketones, see: Huang, H.; Yu, F.; Jin, Z.; Li, W.; Wu, W.; Liang, X.; Ye, J. *Chem. Commun.* **2010**, *46*, 5957−5959.

(7) For asymmetric examples of reaction with chalcones, see: (a) *Anti*-selective: Zhang, Q.; Xiao, X.; Lin, L.; Liu, X.; Feng, X. *Org. Biomol. Chem.* **2011**, *9*, 5748−5754. (b) *Syn*-selective: Zhang, Y.; Yu, C.; Ji, Y.; Wang, W. *Chem.—Asian J.* **2010**, *5*, 1303−1306.

(8) For asymmetric examples of *anti*-diastereoselective reaction with cyclic enones, see: (a) Jadhav, A. P.; Rao, V. U. B.; Singh, P.; Gonnade, R. G.; Singh, R. P. *Chem. Commun.* **2015**, *51*, 13941−13944. (b) Jusseau, X.; Retailleau, P.; Chabaud, L.; Guillou, C. *J. Org. Chem.* **2013**, *78*, 2289−2300.

(9) For an asymmetric example of *syn*-diastereoeselective reaction of 3,4-disubstituted 2(5*H*)-furanones with chalcones, see: Wang, J.; Qi, C.; Ge, Z.; Cheng, T.; Li, R. *Chem. Commun.* **2010**, *46*, 2124−2126.

DOI: 10.1021/acs.joc.7b00743
J. Org. Chem. 2017, 82, 6629−6637

(10) For an asymmetric example of *anti*-diastereoselective addition to α′-sulfonyl enones, see: Yang, H.; Kim, S. *Synlett* **2008**, *2008*, 555−560.
(11) In the literature, the stereodescriptors *syn* and *anti* were often attributed in a discordant manner. In this paper, the structures of *syn*- and *anti*-products are those reported in Scheme 1.
(12) Yadav, J. S.; Reddy, B. V. S.; Narasimhulu, G.; Reddy, N. S.; Reddy, P. J. *Tetrahedron Lett.* **2009**, *50*, 3760−3762. The authors stated that they obtained the *syn*-diastereoisomers as the major product, but the reported spectra are consistent with the *anti*-adduct.
(13) Wang, Y.; Du, G.-F.; Xing, F.; Huang, K.-W.; Dai, B.; He, L. *Asian J. Org. Chem.* **2015**, *4*, 1362−1365. The reported spectra are consistent with the *anti*-adduct, even if the structures in the article are incorrectly drawn.
(14) (a) Fraile, J. M.; García, N.; Herrerías, C. I.; Martín, M.; Mayoral, J. A. *ACS Catal.* **2012**, *2*, 56−64. (b) Chabaud, L.; Jousseaume, T.; Retailleau, P.; Guillou, C. *Eur. J. Org. Chem.* **2010**, *2010*, 5471−5481. (c) Takahashi, A.; Yanai, H.; Zhang, M.; Sonoda, T.; Mishima, M.; Taguchi, T. *J. Org. Chem.* **2010**, *75*, 1259−1265.
(15) (a) RajanBabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083−2089. (b) Gerlach, H.; Künzler, P. *Helv. Chim. Acta* **1978**, *61*, 2503−2509. (c) Boyer, J.; Corriu, R. J. P.; Perz, R.; Reye, C. *J. Organomet. Chem.* **1980**, *184*, 157−166.
(16) (a) Fukuyama, T.; Yang, L. *Tetrahedron Lett.* **1986**, *27*, 6299−6300. (b) Fukuyama, T.; Goto, S. *Tetrahedron Lett.* **1989**, *30*, 6491−6494.
(17) (a) Schettini, R.; De Riccardis, F.; Della Sala, G.; Izzo, I. *J. Org. Chem.* **2016**, *81*, 2494−2505. (b) Schettini, R.; Nardone, B.; De Riccardis, F.; Della Sala, G.; Izzo, I. *Eur. J. Org. Chem.* **2014**, *2014*, 7793−7797. (c) Schettini, R.; D'Amato, A.; De Riccardis, F.; Della Sala, G.; Izzo, I. *Synthesis* **2017**, *49*, 1319−1326. (d) Della Sala, G.; Nardone, B.; De Riccardis, F.; Izzo, I. *Org. Biomol. Chem.* **2013**, *11*, 726−731.
(18) The ε values are reported at 20°C: *Handbook of Organic Solvent Properties*; Smalwood, I. M., Ed.; Arnold: London, 1996.
(19) For an example of inversion of low *syn*/*anti*-diastereoselectivity by changing the solvent, see the *epi*-cupreine-catalyzed VMMR of angelica lactone with nitrostyrene: Sekikawa, T.; Kitaguchi, T.; Kitaura, H.; Minami, T.; Hatanaka, Y. *Org. Lett.* **2015**, *17*, 3026−3029.
(20) The optimization tables are reported in the Supporting Information.
(21) The structures of regioisomers **3n** and **4n** were confirmed by 2D HMBC spectra (see the Supporting Information).
(22) (a) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265−1267. (b) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598−1608. (c) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223−1225.
(23) (a) Landini, D.; Maia, A. In *Encyclopedia of Supramolecolar Chemistry*; Atwood, J. L., Steed, J. W., Eds.; Dekker: New York, 2004; Vol. 2, pp 939−949. (b) Maia, A.; Landini, D.; Petricci, S. *Supramol. Chem.* **2000**, *12*, 203−207.
(24) (a) *Cation Binding by Macrocycles: Complexation of Cationic Species by Crown Ethers*; Inoue, Y., Gokel, G. W., Eds.; Dekker: New York, 1990. (b) Ishii, Y.; Soeda, Y.; Kubo, Y. *Chem. Commun.* **2007**, 2953−2955. (c) Toupance, T.; Benoit, H.; Sarazin, D.; Simon, J. *J. Am. Chem. Soc.* **1997**, *119*, 9191−9197. (d) Boldea, A.; Levesque, I.; Leclerc, M. *J. Mater. Chem.* **1999**, *9*, 2133−2138. (e) Flink, S.; Boukamp, B. A.; van den Berg, A.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1998**, *120*, 4652−4657.
(25) (a) Molecular geometries were located using the PBE functional and a double-ζ plus polarization basis set. The reported free energies were obtained via single-point energy calculations using the M06 functional and a triple-ζ plus two polarizations basis set with the Gaussian 09 package. Solvent effects (toluene) were included with the SMD solvation model. Different geometries were analysed to find the best relative orientation of the reacting molecules. Further details are reported in the Supporting Information. (b) Some of the calculations were performed on the CRESCO/ENEA platform. Ponti, G.; Palombi, F.; Abate, D.; Ambrosino, F.; Aprea, G.; Bastianelli, T.; Beone, F.; Bertini, R.; Bracco, G.; Caporicci, M.; Calosso, B.; Chinnici, M.; Colavincenzo, A.; Cucurullo, A.; Dangelo, P.; De Rosa, M.; De Michele, P.; Funel, A.; Furini, G.; Giammattei, D.; Giusepponi, S.; Guadagni, R.; Guarnieri, G.; Italiano, A.; Magagnino, S.; Mariano, A.; Mencuccini, G.; Mercuri, C.; Migliori, S.; Ornelli, P.; Pecoraro, S.; Perozziello, A.; Pierattini, S.; Podda, S.; Poggi, F.; Quintiliani, A.; Rocchi, A.; Sciò, C.; Simoni, F.; Vita, A. *Proceedings of the 2014 International Conference on High Performance Computing and Simulation*; HPCS, 2014, Article No. 6903807, pp 1030−1033. (c) For an analogous DFT study of the aggregate proline/Li-glyme complex, involved in the proline catalyzed aldol reaction in presence of solvate ionic liquids, see: Obregon-Zuniga, A.; Milàn, M.; Juaristi, E. *Org. Lett.* **2017**, *19*, 1108−1111.
(26) For examples of *endo* Diels−Alder-like transition states in VMMR of 2-(silyloxy)furans, see also: (a) Reference 14c. (b) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881−7882.
(27) Kohler, E. P.; Chadwell, H. M. *Organic Sntheses*; Wiley, 1941; Collect. Vol. *1*, pp 78−79.
(28) Ni, C.; Zhang, L.; Hu, J. *J. Org. Chem.* **2008**, *73*, 5699−5713.
(29) Bhella, S. S.; Elango, M.; Ishar, M. P. S. *Tetrahedron* **2009**, *65*, 240−246.

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