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Synthetic Methods

Catalytic, Asymmetric Synthesis of Phosphonic γ-(Hydroxyalkyl)butenolides with Contiguous Quaternary and Tertiary Stereogenic Centers

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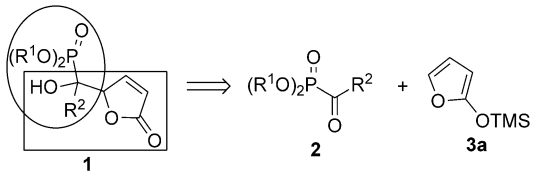
Abstract: A procedure that enables high yielding access to phosphonic γ-(hydroxyalkyl)butenolides with excellent regio-, diastereo- and enantiocontrol is reported. The simultaneous construction of up to two adjacent quaternary stereogenic centers by a catalytic asymmetric vinylogous Mukaiyama aldol reaction unites biologically and medicinally relevant entities, namely α-hydroxy phosphonates and γ-(hydroxyalkyl)butenolides. This is achieved by utilizing a readily available chiral copper-sulfoximine catalyst showing a broad functional group tolerance for both the electrophilic and nucleophilic reactants. A discussion about potential factors affecting the observed level of enantioselectivity, which stems from the enantiopure sulfoximine ligand, is also included.

Introduction

The ability to utilize phosphorus is one of the essential prerequisites for any known form of planetary life, and for a long time it was an accepted doctrine that all earthly organophosphorus molecules from natural sources consist of a fully oxidized phosphorus atom such as in phosphate esters. A turning point was marked by the discovery of the first phosphonic acid in a living organism.[1] Since this groundbreaking finding, plenty of related substances, in which the respective phosphorus atoms reside in lower oxidation states, have been located in microorganisms and higher life forms.[2] While large parts of their biosyntheses have not been completely understood yet, and many of the associated metabolic processes still appear enigmatic,[3] biogenic phosphonic acids became attractive targets for man-made syntheses.[4]

A particularly interesting subset within the numerous isolated natural organophosphorus compounds is based on α-hydroxy phosphonic acids or their derivatives.[5] Synthetic α-hydroxy phosphonates with their general structure depicted in Scheme 1 (circled) emerged as a sine qua non for modern biomedical and pharmaceutical research because of the spectacular array of diversified biological activities. For example, their physiological profiles range from activity against human immunodeficiency virus[6] (HIV) over herbicidal characteristics[7] to antioxidant properties.[8] As 1-hydroxy-1,1-bisphosphonates they embody a precious class of compounds for the therapeutic treatment of osteoporosis and similar bone diseases.[9,10] Besides, α-hydroxy phosphonates interfere with various metabolic pathways and inhibit a wide range of fundamentally important enzymes such as renin,[11] CD-45 tyrosine phosphatase,[12] tyrosine-specific protein kinases,[13] farnesyl transferase,[14] myo-inositol monophosphatase,[15] 5-enolpyruvoylshikimate-3-phosphate synthase,[16] or acetylcholinesterase.[17]



Scheme 1. Chiral α-hydroxy phosphonates (circled) and γ-(hydroxyalkyl)-butenolides (boxed) are connected in a single molecule **1** synthetically accessed from α-keto phosphonates **2** and silyloxy furan **3a**.

Two intrinsic properties help them to unfold their impressive biological potential: On the one hand, α-hydroxy phosphonic acids constitute close analogs of natural α-hydroxy carboxylic acids with the crucial difference that the geometry of the acid moiety is tetrahedral instead of trigonal planar—on the other hand, phosphonates are able to mimic metabolically regulating phosphate esters. This allows them to serve as bioisosteric and isopolar replacements.[18] Apart from these biochemically oriented applications, they also represent very useful precursors in the repertoire of organic chemists because α-hydroxy phosphonates can further be transformed into many α-functionalized derivatives.[19]

Other prominent structural motifs in the biota are butenolides and the allied saturated butyrolactones, respectively.[20]

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Quite commonly, the γ-position of the lactone core is accompanied by substituted alkyl fragments with secondary or tertiary alcohols (Scheme 1, boxed). Among these molecules, anti-HIV activity, anti-inflammatory or anti-proliferative properties are just a few of the discovered biological characteristics.[21]

With respect to the very potent structure–activity relationships of the aforementioned, independently in nature occurring entities, it is a logical step to fuse them on a molecular level to form chiral phosphonic γ-(hydroxyalkyl)butenolides **1** (Scheme 1). Given the fact that 1) most of the biogenic γ-(hydroxyalkyl)butenolides exist only as one stereoisomer and 2) in α-hydroxy phosphonates the vicinal stereogenic carbon center of the phosphorus is able to dictate the extent of biological activity,[11c,22] an enantioselective access towards the tertiary α-hydroxy phosphonates **1** is desirable. Synthetically challenging, these structures bear a quaternary stereogenic center adjacent to the tertiary one of the lactone core. In the past, the number of syntheses for optically active secondary α-hydroxy phosphonates increased continuously by means of chemical or enzymatic methods.[23,24] On the contrary, enantioenriched tertiary α-hydroxy phosphonates were untouched in literature until 2006. Zhao and Samanta pointed the way with a seminal work on asymmetric organocatalytic aldol additions of α-keto phosphonates **2** and acetone, and later others followed by synthesizing non-racemic tertiary α-hydroxyphosphono esters by asymmetric aldol, allylation, or hydrophosphonylation reactions.[25]

Results and Discussion

The search for novel lead structures with hopefully promising pharmacological qualities requires a reliable protocol to quickly build up complex molecules from a suitable library of precursors. To construct the framework of **1**, asymmetric vinylogous Mukaiyama aldol (VMA) reactions between readily available ketonic phosphonate derivatives **2** and 2-(trimethylsilyloxy)furan (**3a**) appeared an obvious solution.[26,27] Nevertheless, it must be emphasized that catalytic aldol additions to ketones with high levels of enantioselectivity are still rare and comparatively difficult to achieve.[28]

A recent publication of Miao, Chen and co-workers describes a copper-catalyzed diastereoselective VMA reaction between α-keto phosphonates **2** and dienol silane **3a** to give the racemic adducts **1** in variable yields from 46–89% and with diastereomeric ratios starting at 83:17.[29] Their work stimulated us to investigate a method for the *enantiocontrolled* preparation of phosphonic γ-(hydroxyalkyl)butenolides **1** that, at the outset of our studies, had not been reported, yet.[30] Based on our experience in the use of chiral C_1-symmetric sulfoximines as ligands in copper-catalyzed stereoselective Mukaiyama-type reactions,[31,32] we assumed that such hemilabile N,N′-chelators (Figure 1) could also be useful in catalytic asymmetric VMA reactions of ketonic phosphonates **2** and nucleophile **3a** to give the desired optically active aldol products **1**.

To test this hypothesis, we initially explored addition reactions of furan derivative **3a** to diethyl benzoylphosphonate (**2a**) in various solvents at room temperature (RT), which were

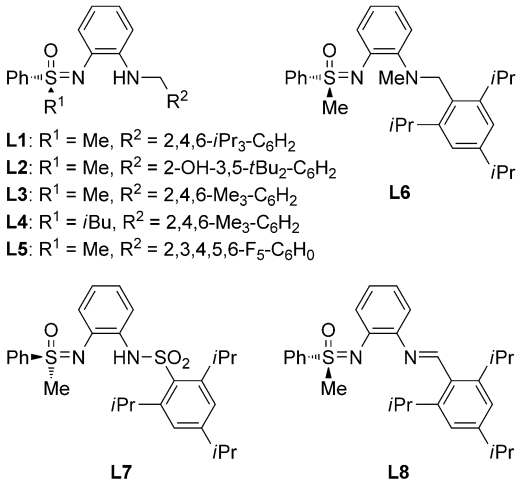
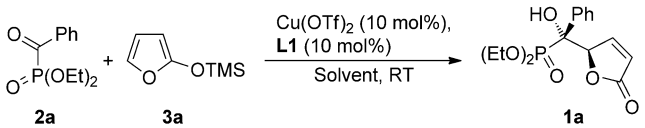


Figure 1. Chiral sulfoximines **L1**–**L8** probed as ligands in this study. **L1**–**L6** and **L8** bear (*S*) configuration at sulfur, **L7** is derived from a (*R*)-configured sulfoximine.

Table 1. Influence of solvents and additives on the enantioselective VMA reaction of α-keto phosphonate **2a** and dienol silane **3a**.[a]



2a **3a** **1a**

	Solvent	Additive	Yield [%][b]	*de* [%][c]	*ee* [%][d]
1	DCM	none	91	96	89
2	toluene	none	71	99	94
3	THF	none	62	98	93
4	1,4-dioxane	none	83	97	95
5	TBME	none	43	94	96
6	iPr_2O	none	69	98	94
7	Et_2O	none	79	97	95
8	1,4-dioxane	HFIP	74	97	96
9	1,4-dioxane	TFE	85	98	85
10	1,4-dioxane	*i*PrOH	80	89	68
11	Et_2O	HFIP	89	97	81
12[e]	Et_2O	TFE	92	98	98
13	Et_2O	*i*PrOH	91	99	91

[a] Additional reaction conditions: **2a** (0.20 mmol), additive (1.2 equiv), **3a** (1.1 equiv), solvent (2 mL), over night. Only the major stereoisomer of **1a** is displayed. [b] Total yield of unseparated diastereomers of **1a** after column chromatography. [c] The *de* values always refer to the *anti* product of **1a**. For details on its determination, see the Supporting Information. [d] The *ee* values always refer to (*S*,*R*)-**1a** as the major enantiomer. [e] Full conversion of **2a** within 30 min.

catalyzed by a complex derived from 10 mol% of $Cu(OTf)_2$ and enantiopure amino sulfoximine **L1** (Table 1, entries 1–7). Already the first experiment with dichloromethane (DCM) proceeded with promising stereocontrol, and the desired tertiary α-hydroxy phosphonate **1a** was formed in high yield (91%) with a diastereomeric excess (*de*) of 96% and an enantiomeric excess (*ee*) of 89% (entry 1). By switching the solvent to tolu-

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ene the major stereoisomer of **1a** could further be enriched (99% *de* and 94% *ee*), but unfortunately at the expense of a reduced yield of 71% (entry 2).

Next, various cyclic and linear ethers were applied. Fully aware of the fact that these solvents can interact with the chiral copper catalyst because of their ability to coordinate to the Lewis acid we anticipated finding a beneficial influence. With tetrahydrofuran (THF) the remarkable stereochemical differentiation could be maintained (98% *de* and 93% *ee*), yet **1a** was isolated only in a moderate yield of 62% (entry 3). As demonstrated by entry 4, the VMA reaction proceeded much better in 1,4-dioxane. With almost no decline in diastereoselectivity (97% *de*), **1a** was obtained in a satisfactory yield (83%) and the highest *ee* (95%) up to this point. Regarding the formation of **1a**, the series of linear ethers showed a clear trend (entries 5–7). From the results observed with *tert*-butyl methyl ether (TBME), diisopropyl ether and diethyl ether it can be seen that the extent of the yields of **1a** (43, 69, and 79%, respectively) diametrically depended on the decreasing steric demand of the ether's alkyl group. Apparently, the asymmetric induction (94–98% *de* and 94–96% *ee*) was not altered much by using these ethers. Although TBME furnished the best *ee*, it provided by far the lowest yield. Consequently, this solvent was considered to be not viable for the future study of the reaction.

To further optimize the conditions a few alcoholic additives were scrutinized, for they are known to be beneficial in metal-catalyzed Mukaiyama-type reactions.[29–31] Since 1,4-dioxane and diethyl ether proved equally well in terms of stereocontrol (Table 1, entries 4 and 7), the reactions were repeated with 1.2 equivalents of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), 2,2,2-trifluoroethanol (TFE) or isopropanol. Concerning the cyclic ether, no substantial improvement was found for HFIP (Table 1, entry 8). The *ee* of **1a** attained again the previous maximum of 96%, albeit to the detriment of a lower yield (74%). Interestingly, both the chiral catalyst's activity and its selectivity were reversed in the presence of TFE because **1a** was provided in a slightly better yield of 85%, but with a considerably decreased *ee* of 85% (Table 1, entry 9). As revealed by entry 10, the surprisingly strong decrease in enantioselectivity (68% *ee*) continued when isopropanol was added. Regarding the enantiocontrol in this dioxane-based system, the alcohol's acidity presumably takes precedence over steric or other factors of the additive. Furthermore, isopropanol caused an unexpectedly low diastereopreference (89% *de*), which was not observed when fluorinated additives were applied (97 or 98% *de* in Table 1, entries 8 and 9). In diethyl ether all three additives noticeably enlarged the yield of **1a** from 79% to a range of 89–92% (Table 1, entry 7 vs. 11–13). The original level of diastereoselectivity either remained intact (97% *de*) or could even be raised (98 or 99% *de*). Once again a strong, yet different relationship than before between each additive and the catalyst's asymmetric induction was evident. While especially HFIP and isopropanol decreased the *ee* of **1a** (81 and 91%, respectively), TFE supported the enantioselective pathway to a great extent, and its use culminated in an *ee* of 98% (Table 1, entry 12).[33]

Furthermore, another aspect of TFE, that has not been properly addressed in this discussion yet, has to be mentioned. For this additive, a very pronounced rate accelerating effect was observed in the solvents diethyl ether, toluene, and THF. Tracking the course of each reaction by thin layer chromatography (TLC) revealed that all three reactions were completed within 30 min and α-keto phosphonate **2a** was fully consumed. If no fluorinated alcohol was present, the catalysis proceeded slower and **2a** could still be detected by TLC a day later. Thus, the additive plays a dual role. Apart from facilitating the catalyst turnover and thus giving higher yields in shorter times, it is able to affect the asymmetric induction. Although we are still lacking a mechanistic model of our catalyst structure we propose that TFE coordinates to the chiral copper-sulfoximine complex generating a more stereoselective species, which could be explained by the concept of *Brønsted acid assisted Lewis acid catalysis*.[34,35] This might also be reflected by the fact that in each solvent the reaction mixture undergoes a very characteristic color change when the alcoholic additive is absent. Coordination of amino sulfoximine **L1** to $Cu(OTf)_2$ forms a green solution which, upon adding the reactants **2a**, TFE and **3a** in exactly the given order, keeps this color until the end. If the second step (the injection of the additive) is skipped, the green solution with the chiral catalyst and electrophile inside turns blackish blue within seconds after final addition of furan **3a**. Since diethyl ether and TFE worked best together in terms of yield and *ee*, these two parameters were fixed for the following experiments.

Subsequently, the chiral copper catalyst was varied by utilizing other copper salts or sulfoximines (Table 2). Entry 2 states that the asymmetric VMA reaction also worked with an analogous copper(I) precatalyst providing the α-hydroxy phospho-

Table 2. Exploration of copper salts and sulfoximines **L1**–**8** in the enantioselective VMA reaction of α-keto phosphonate **2a** and dienol silane **3a** to provide **1a**.[a]

	Copper salt	Ligand	Yield [%][b]	*de* [%][c]	*ee* [%][d]
1[e]	$Cu(OTf)_2$	**L1**	92	98	98
2	$(CuOTf)_2$·toluene	**L1**	75	98	96
3	$Cu(SbF_6)_2$[f]	**L1**	93	82	9
4	$Cu(ClO_4)_2 \cdot 6H_2O$	**L1**	83	98	93
5	$Cu(ClO_4)_2$[f]	**L1**	97	98	96
6	$Cu(OTf)_2$	**L2**	88	94	67
7	$Cu(OTf)_2$	**L3**	87	98	97
8	$Cu(OTf)_2$	**L4**	99	99	94
9	$Cu(OTf)_2$	**L5**	98	97	96
10	$Cu(OTf)_2$	**L6**	88	95	11
11	$Cu(OTf)_2$	**L7**	69	98	0
12	$Cu(OTf)_2$	**L8**	91	98	78
13[g]	$Cu(OTf)_2$	**L1**	98	>99	98
14[h]	$Cu(OTf)_2$	**L1**	99	>99	>99
15[i]	$Cu(OTf)_2$	**L1**	95	99	97

[a] Reaction conditions: **2a** (0.20 mmol), TFE (1.2 equiv), **3a** (1.1 equiv), copper salt (10 mol%), ligand (10 mol%), Et_2O (2 mL), RT, over night. [b–d] Same as in Table 1. [e] Identical with entry 12 of Table 1. [f] Prepared in situ from $CuCl_2$ and the respective silver salt. [g] Conducted at 10 °C. [h] Conducted at 0 °C. [i] Performed with 5 mol% of the copper-sulfoximine complex at 0 °C.

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nate under admirable stereocontrol (98% *de* and 96% *ee*). Compared to the result obtained with $Cu(OTf)_2$ the yield of **1a** decreased to 75% and it took significantly longer to fully consume the starting material **2a**. This could possibly indicate that copper(I) is not the active species in the catalytic cycle and that it needs to be transformed into a higher oxidation state before. $Cu(SbF_6)_2$ delivered **1a** in a high yield of 93% but largely reduced the diastereochemical differentiation (82% *de*). Above all, it rendered the enantioselective pathway almost void and gave the product with an *ee* of just 9% (entry 3). The commercially available hexahydrate of $Cu(ClO_4)_2$ served as basis for a catalyst with rather acceptable activity (83% yield) and good enantioselectivity (93% *ee*), but the corresponding anhydrous salt was more appropriate (Table 2, entries 4 and 5, respectively). Indeed, the yield reached a new peak (97%) with **1a** being isolated highly enantioenriched (96% *ee*). Besides, both types of $Cu(ClO_4)_2$ allowed the formation of the major diastereomer with excellent selectivity (98% *de*). Although the latter copper(II) source actually represents an attractive alternative to $Cu(OTf)_2$ we decided to renounce further optimization steps with anhydrous $Cu(ClO_4)_2$ because it required a tedious in situ preparation of the metal salt.

Next, applications of copper complexes with sulfoximine-based ligands **L2**–**L8**, which contain altered steric or electronic features, were tested. **L2** produced a less selective and reactive catalyst (Table 2, entry 6). Obviously, the higher steric demand of the two *tert*-butyl substituents and a competing additional coordination site for the copper ion which is offered by the phenyl ring's hydroxy function reduced both the stereocontrol (94% *de*, 67% *ee*) and the yield (88%). The three amino sulfoximines **L3**–**L5** (Table 2, entries 7–9) showed a better overall performance, giving phosphonate **1a** in good to almost quantitative yields (87–99%) and with excellent *de* values (97–99%). Although they were able to form the major enantiomer of **1a** with a respectable excess (94–97% *ee*), none of them was superior to **L1**.

Before the substrate scope of the reaction was investigated, another point was addressed. Bearing the generally high stereoselectivity in mind, which the amino sulfoximines **L1**–**L5** had exhibited under almost all conditions so far, we wondered which features of the ligand framework were responsible for this exceptional behavior. Compared to **L1** neither a branched alkyl chain next to sulfur in the "western part" (as in **L4**) nor a less bulky or strongly electron-deficient phenyl ring in the "eastern part" (as in **L3** or **L5**) significantly affected the enantioselection (vide supra). Thus, we hypothesized that major contributions would arise from the nitrogen atom of the amino function,[36] and that modifying this moiety should affect its ability to coordinate to the copper ion. Thus, sulfoximines **L6**–**L8** with variations of the advantageous core structure of **L1** were applied in the catalysis, and their effects on the stereochemical pathway towards product **1a** were studied. Exchange of the nitrogen's hydrogen atom with a methyl group in **L6** demonstrated that for very high asymmetric induction, a secondary amine was better than a tertiary (Table 2, entry 10 vs. 1). The enantioselectivity diminished when sulfoximine **L6** was applied and **1a** was isolated with a deteriorated *ee* of 11%. Interestingly, when the adjacent methylene unit of the secondary amine in **L1** was virtually substituted for a sulfone group the enantioregulatory pathway was negated. With the consequential sulfonamido sulfoximine **L7** butenolide **1a** was obtained as a racemate (Table 2, entry 11). However, ligand **L8** with constrained flexibility at the non-sulfonimidoyl nitrogen (which was realized by the rigid imine unit) turned out to be applicable affording **1a** with an *ee* of 78% (Table 2, entry 12).

These findings open room for discussion. The change from CH_2 to SO_2 in bidentate sulfoximines **L1** and **L7** obviously enforces an arrangement of the latter N,N′-ligand around the central metal atom, which leads to a completely unselective chiral copper-sulfoximine complex. The extreme difference between the *ee* values, which were achieved by **L1** (98% *ee* for **1a**) and **L7** (0% *ee* for **1a**) with secondary amino and sulfonamido groups, respectively, disproves the initial assumption that only an NH group was crucial for asymmetric induction. This is also supported by the fact that sulfoximine chelators **L6** (11% *ee* for **1a**) and **L8** (78% *ee* for **1a**), which possess no hydrogen at the second nitrogen coordination site, were able to accumulate one enantiomer of **1a**. Actually, the NH substitution pattern in the ligand backbone does not seem to be essential, but can be very supportive for an *efficient* asymmetric induction, depending on its chemical environment, though. Selectivity issues caused by neighboring groups like the CH_2 (as in **L1**) versus the bulkier SO_2 (as in **L7**) indicate that steric factors probably contribute. A comparison of the results coming from the NH (as in **L1**) versus the NMe (as in **L6**) substitution pattern supports this hypothesis. From another perspective, however, a proper electron density at the second nitrogen donor could be the major responsible factor. This would ultimately be reflected in the nitrogen's basicity towards the cupric Lewis acid. Indeed, sulfoximine ligands with donor sites of medium basicity (an aldimine in **L8**, a secondary amine in **L1**) deliver the product **1a** with good or excellent *ee* values whereas those with strong (a tertiary amine in **L6**) or very weak basicity (a sulfonamide in **L7**) fail to give reasonable enantiocontrol. Another test reaction with (*R*)-*N*-(2-aminophenyl)-*S*-methyl-*S*-phenylsulfoximine as ligand strengthens this assumption. This anilino sulfoximine, which lacks of any additional steric bulk at the primary amine and of which the basicity should be closer to the ones of **L1** and **L8** than of **L6** or **L7** furnished *ent*-**1a** with a moderate *ee* of 60%.

Finally, the effect of temperature was briefly scrutinized and the results are delineated in Table 2, entries 13 and 14. Apparently, 0 °C was found to be the optimal temperature. Virtually only one of the four possible stereoisomers of **1a** was selectively obtained in a yield of 99% and with both *de* and *ee* above 99% (Table 2, entry 14). If the catalyst loading was reduced to 5 mol%, the same efficiency could no longer be maintained at 0 °C (entry 15). Nevertheless, the general reactivity and stereoselectivity remained acceptable, and **1a** was isolated in 95% yield with a *de* of 99% and an *ee* of 97%.

Under the optimized conditions that comprised 10 mol% of a catalyst stemming from $Cu(OTf)_2$ and amino sulfoximine **L1** with TFE as additive in diethyl ether at 0 °C (Table 2, entry 14), we evaluated the scope of the transformation with respect to

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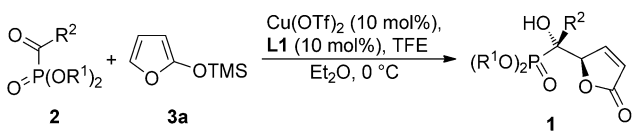
Table 3. Reactions of various α-keto phosphonates **2** with furan **3a**.[a]



2 **3a** **1**

	2	R^1	R^2	1	Yield [%][b]	*de* [%][c]	*ee* [%][d]
1[e]	**a**	Et	Ph	**a**	99	>99	>99
2	**b**	Me	Ph	**b**	50	96	>99
3	**c**	*i*Pr	Ph	**c**	99	>99	98
4	**d**	Et	2-Me-C_6H_5	**d**	83	>99	95
5	**e**	Et	3-Me-C_6H_5	**e**	90	98	>99
6	**f**	Et	4-Me-C_6H_5	**f**	93	99	>99
7	**g**	Et	4-Cl-C_6H_5	**g**	96	97	97
8	**h**	Et	4-MeO-C_6H_5	**h**	93	97	>99
9	**i**	Et	1-naphthyl	**i**	89	99	90
10	**j**	Et	2-naphthyl	**j**	86	99	99
11	**k**	Et	2-thienyl	**k**	81	93	94
12	**l**	Et	2-furyl	**l**	83	93	97
13	**m**	Me	Me	**m**	95	>99	99
14	**n**	Et	Me	**n**	98	>99	98
15	**o**	*i*Pr	Me	**o**	81	>99	99
16	**p**	Et	*i*Pr	**p**	90	>99	>99
17	**q**	Et	*n*Bu	**q**	89	>99	97
18	**r**	Et	cyclohexyl	**r**	88	97 (>99)[f]	>99
19	**s**	Et	Bn	**s**	62	98	90

[a] Reaction conditions: $Cu(OTf)_2$ (10 mol%), **L1** (10 mol%), **2** (0.20 mmol), TFE (1.2 equiv), **3a** (1.1 equiv), Et_2O (2 mL), 0 °C, overnight. [b–d] Same as in Table 1. [e] Identical with entry 14 of Table 2. [f] Before and after (in parentheses) column chromatography.

different α-keto phosphonates **2**. The results are described in Table 3. Firstly, the role of alkoxy substituents at phosphorus was examined for the up-coming series of aromatic ketones. Hence, two dialkyl benzoylphosphonates **2b** (R^1 = Me) and **2c** (R^1 = *i*Pr), which are of smaller or bigger size than **2a** (R^1 = Et) were tried. Indeed, the ester moieties of the electrophiles contributed significantly to the general success of the catalysis. Compared to the excellent yields (each 99%) and *de* values (each >99%) of the products **1a** and **c** with bulkier ethyl and isopropyl esters, respectively, dimethyl α-hydroxy phosphonate **1b** was obtained only with a barely tolerable yield of 50%, but a good *de* of 96% (entries 1–3). Interestingly, the enantioselective pathway for **1b** was not negatively affected furnishing an *ee* higher than 99%. Merely in case of diisopropyl benzoylphosphonate (**2c**) as substrate the *ee* of the corresponding product **1c** decreased negligibly (98%).

Taking into account that an ethyl ester group like in compound **2a** worked best, the scope was extended to a comprehensive spectrum of aromatic diethyl phosphonates. Entries 4–8 of Table 3 disclose that the developed catalytic system easily accepted various phenyl-substituted substrates **2d**–**h** to produce the VMA products **1d**–**h** in good to high yields (83–96%) with *de* values over 97%. The electronic nature of the substituents had only a subtle influence on the stereochemistry (Table 3, entries 6–8). Nevertheless, products **1f** and **h** with electron-donating 4-methyl or 4-methoxy groups at the phenyl ring were obtained with slightly better *ee* values (each >99%) than butenolide **1g** (97%), which bears an electron-withdrawing 4-chloro substituent. A more distinct effect concerning the enantioselectivity was found for the position of the substituent. As shown by entries 5 and 6, methyl groups in 3- or 4-position at the aromatic system allowed the formation of highly enantioenriched products **1e** and **f** (each >99% *ee*). In contrast, the analogous 2-methyl-substituted **1d** (entry 4) was produced less selectively and had an *ee* of 95%. Such a result can be explained by steric interactions of the methyl group in this position, which interfere with the chiral catalyst. This assumption was confirmed when the scope was expanded to α-keto phosphonates with fused aromatic rings (Table 3, entries 9 and 10). Reactants **2i** and **j** that possess either a 1- or 2-naphthyl rest adjacent to the carbonyl group reacted nearly equally well in terms of yield (89 and 86%) and both gave the major diastereomers of **1i** and **j** in almost complete manner (each 99% *de*). As expected, 1-naphthyl product **1i** had a comparably low *ee* of 90% while the 2-naphthyl derivative **1j** was isolated with an excellent *ee* of 99%. Indeed, these different enantioselectivities in the formation of **1i** and **j** are in full line with the previous data of entries 4 and 5 (Table 3).

Just recently it has been revealed that α-heteroaryl α-hydroxy phosphonates that possess a 2-furyl or 2-thienyl unit serve as precursors for compounds with certain plant-related biological activities.[37] All compounds, however, were prepared as racemates. In order to demonstrate the functional group tolerance of the chiral copper-sulfoximine catalyst and to establish a route to similar but enantioenriched heteroaromatic structures, thiophene- and furan-based α-keto phosphonates **2k** and **l** were utilized (Table 3, entries 11 and 12). These reactions proceeded quite flawlessly leading to the two corresponding products in acceptable yields (81 and 83%, respectively) and with an identical *de* of 93% for each. To our delight, a high level of enantioselectivity could be maintained in both experiments, providing butenolide **1k** with an *ee* of 94% and **1l** with an even better *ee* of 97%.

The recently ISO approved pesticide clacyfos,[38] derived from a (1-hydroxyethyl)phosphonate ester, served as stimulus to further elaborate the substrate scope with aliphatic α-keto phosphonates. Like before, the role of a methyl, ethyl and isopropyl group R^1 on the ester position of acetylphosphonates **2m**–**o** was studied first (Table 3, entries 13–15). In contrast to the analogous aromatic products **1b** and **1c**, the yield of the dimethyl phosphonate **1m** (95%) was much higher than the one of diisopropyl phosphonate **1o** (81%). Nonetheless, the best yield (98%) could again be obtained in case of the diethyl α-hydroxy phosphonate **1n**. Irrespective of the three sterically different alkoxy groups at phosphorus all stereoselectivities proved outstanding (>99% *de* for products **1m**–**o**, 98% *ee* for **1n** and 99% *ee* for **1m** and **o**, respectively). Based on the excellent performance of the ethyl ester group in substrate **2n** (Table 3, entry 14), a few other aliphatic diethyl α-keto phosphonates **2** were consequently applied with furan **3a**. In this context we found that the ketonic alkyl part R^2 could be prolonged from methyl to *n*-butyl as in **2q** without hampering the catalysis (Table 3, entry 17). Furthermore, it can also be sterically increased to isopropyl as in **2p** or cyclohexyl as in **2r**

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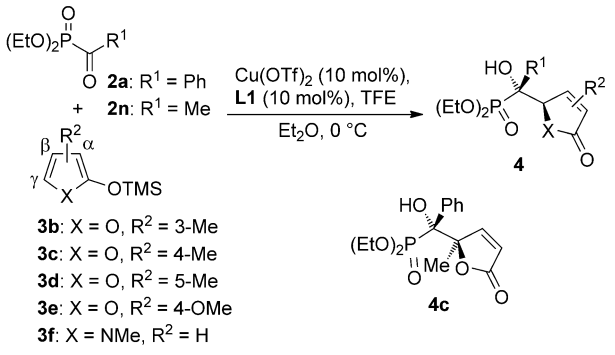
(Table 3, entries 16 and 18, respectively). Albeit the reactivities of the aliphatic electrophiles **2p**–**r** were somewhat lower compared to those of aromatic ones, they still afforded the corresponding tertiary α-hydroxy phosphonates **1p**–**r** with acceptable yields in a close range of 88–90%. Although no significant trend in diastereoselectivity seemed obvious (97–99% *de* for **1p**–**r**), increasing the steric bulk at the ketonic alkyl rest implied a better enantiocontrol during the catalysis (Table 3, entries 16 and 18 vs. entry 17). This was ultimately demonstrated by the salient *ee* values of over 99% for VMA products **1p** and **r** bearing isopropyl and cyclohexyl substituents, respectively. However, the *ee* (97%) of α-hydroxy phosphonate **1q**, which contained a linear C4 alkyl chain, was reasonably high as well. Unpleasantly, γ-(hydroxyalkyl)butenolide **1s** with a benzyl substituent was isolated in a rather low yield of 62% (Table 3, entry 19). Besides, the enantiofacial differentiation during the asymmetric catalysis was less efficient as indicated by an *ee* of 90%. The diastereoselectivity (98% *de*) was not affected, though. Finally, it is worth mentioning that under no circumstances, neither during the initial optimization process nor while exploring the substrate scope, α/γ-regioselectivity issues have occurred with silyloxy furan **3a**. All reactions were completely γ-selective and regioisomeric α-(hydroxyalkyl)butenolides have never been observed.[39]

Studies in the field of α-keto phosphonates **2** are usually focused only on these electrophiles themselves. Besides, often the reported scope is narrow and restricted to trivial or minor variation patterns of **2** while the applicable spectrum of their nucleophilic reaction partners is scarcely explored.[25] This is particularly true for heterocyclic silyloxy dienes in catalytic enantioselective aldol-type additions, which are mostly confined to the simple and unsubstituted 2-(trimethylsilyloxy)furan (**3a**).[27–29] By altering the steric or electronic demands of butenolide precursors **3** problems of selectivity and reactivity may arise, and an efficient catalyst must show its proficiency also under such conditions. Table 4 shows that the chiral copper-sulfoximine complex is largely able to deal with such issues.

As anticipated, the standard electrophile diethyl benzoylphosphonate (**2a**) reacted differently in catalyses with the silyloxy furans **3b**–**d**, which have a single methyl group as substituent R^2 at each possible position (Table 4, entries 1–3). These bulkier nucleophiles—compared to unsubstituted furan **3a** from entry 1 of Table 3—led to slightly declined yields of 70–88% for the products **4a**–**c**. While the diastereoselection remained unchanged, the enantiocontrol was noticeably influenced by the position of the methyl group in furan derivatives **3b**–**3d** (from α to β to γ, see Scheme of Table 4). The closer the methyl substituent was located to the newly connected γ-carbon in this series, the higher was the *ee* value of products **4a**–**c** (from 89 to 92 to 98%). The formation of two *vicinal quaternary* stereogenic centers with high asymmetric induction is still considered to be a tremendous challenge. Noteworthy, the chiral catalyst we are reporting here successfully accomplished this task yielding phosphorus butenolide **4c** with an excellent *ee* of 98%.

A comparison of entries 2 and 4 of Table 4 reveals how electronic factors in heterocycles **3** have to be taken into account.

Table 4. Applicability and scope of substituted nucleophiles **3**.[a]



	2	3	4	Yield [%][b]	*de* [%][c]	*ee* [%][d]
1	**a**	**b**	**a**	86	99	89
2	**a**	**c**	**b**	88	>99	92
3	**a**	**d**	**c**	70	99	98
4	**a**	**e**	**d**	77	99	71
5	**n**	**e**	**e**	61	85	82
6[e]	**n**	**f**	**f**	83	94 (>99)[f]	88

[a] Reaction conditions: **2** (0.20 mmol), TFE (1.2 equiv), **3** (1.1 equiv), Et_2O (2 mL). [b–d] Same as in Table 1. [e] Conducted at −20 °C. [f] Same as in Table 3.

These seem to be of higher relevance than just simple steric interactions. When benzoylphosphonate **2a** reacted with silyloxy furan **3e**, which bears the stronger electron-donating 4-methoxy substituent instead of the 4-methyl group (as in **3c**), the yield of product **4d** reached only 77%. Moreover, a pronounced regression of the *ee* down to 71% was detected for 4-methoxy butenolide **4d** (compared to the *ee* of 92% for 4-methyl butenolide **4b**). The entries 1–4 of Table 4 together with entry 1 of Table 3 unequivocally emphasize how the nucleophilicity at the γ-carbon atom in silyloxy furans **3a**–**e** affects the enantioselectivity of the catalysis. This can be rationalized as follows: The enantioselection improves in the same way as silyloxy furans **3** become less nucleophilic towards phosphonate **2a**. In turn, reduced nucleophilicity originates from a lower electron density at the respective γ-carbon of **3**, which is controlled by the nature and position of substituents R^2. Since the electron densities at the γ-carbon atoms of **3** directly correlate with their chemical shifts in nuclear magnetic resonance (NMR) spectra, a tendency is visible. The more the NMR signal of the γ-carbon atom in the sequence from **3e** to **c** to **a** moved into the downfield region of the spectrum (indicating a lower nucleophilic behavior), the higher were the *ee* values of corresponding VMA products.[40]

We also discovered that 4-methoxy silyloxy furan **3e** is more sensitive to its addition partners **2**. As delineated in entry 5 of Table 4, the VMA reaction of **3e** with acetylphosphonate **2n** gave product **4e**, but both yield (61%) and *de* (85%) were reduced. To our delight, the synthesis of aliphatic **4e** proceeded with higher enantioselectivity (82% *ee*) than the one for aromatic **4d**.[41] Decreasing the temperature from 0 °C to −30 °C was not helpful for the specific combination of substrates **2n** and **3e**. In this case product **4e** was obtained with the same

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yield and stereoselectivity as before (not shown in the Table). A nitrogen nucleophile could also be applied, confirming the functional group tolerance of the chiral catalyst (Table 4, entry 6). When acetylphosphonate **2n** reacted with *N*-methyl protected silyloxy pyrrole **3f**, γ-(hydroxyalkyl)lactam **4f** was formed in reasonable yield (83%) and with good stereocontrol (94% *de* and 88% *ee*).

Analyzing the X-ray crystal structures of compounds **1a** and **o** allowed the unambiguous determination of their relative and/or absolute configurations (Figure 2).[42] The stereochemically almost homogeneous product **1a** (>99% *de* and >99% *ee*) that was available by amino sulfoximine ligand (*S*)-**L1** displayed an *anti* relationship. In addition, the absolute configuration of *anti*-**1a** was established to be (*S*) for the quaternary stereogenic center at C1 and (*R*) for the tertiary stereogenic center at C2. For aliphatic product **1o** suitable crystals could be obtained within the context of its racemate synthesis (>99% *de*) with ligand *rac*-**L1**. Here, the relative configuration was confirmed to be *anti* again. Based on these data all other configurations for products **1** were assigned in analogy.

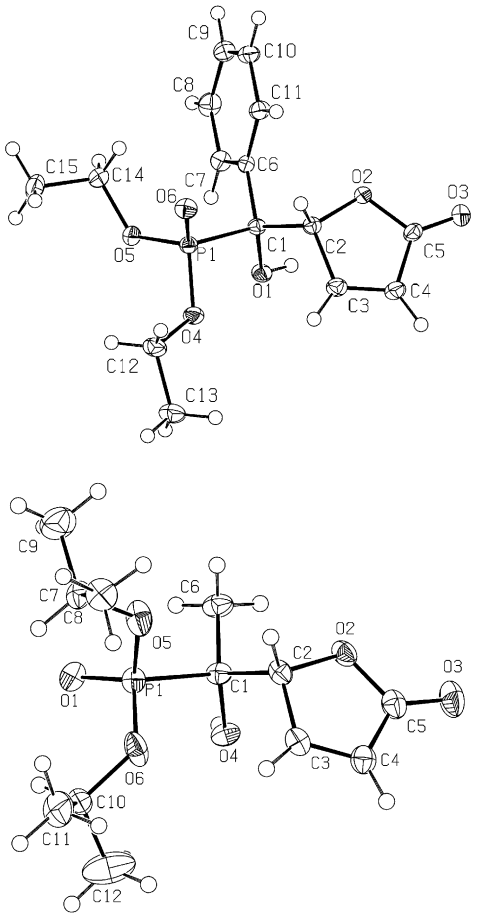


Figure 2. Figure ORTEP plots[43] of the X-ray crystal structures of (*S*,*R*)-**1a** (top) and *rac*,*anti*-**1o** (bottom). Ellipsoids are shown at 50% probability level.

Finally, the limitations of the reaction scope shall be discussed (Figure 3).[44] Electrophile **2t** failed to give its corresponding product with silyloxy furan **3a**. Presumably, this is due to the steric hindrance of the ketonic *tert*-butyl group, which prevented reactivity. With respect to heterocyclic patterns and their presence in electrophiles or nucleophiles, some unexpected reactivity issues were observed. The attempt to utilize phosphonate **2u** bearing the *N*-methyl pyrrole core was unsuccessful, and no conversion was observed with silyloxy furan **3a**. This was surprising because in reactions with **3f** as nucleophile this heterocyclic substituent was unproblematic. The pyrrole-2-carbonyl phosphonate **2u** was fully recovered, even when the reaction was conducted in diethyl ether at room temperature or in 1,4-dioxane at 100 °C. Interestingly, 2-(trimethylsilyloxy)thiophene (**3g**) did not act as nucleophile with benzoylphosphonate **2a**, although silyloxy thiophenes are prone to undergo Mukaiyama-type transformations and the thiophene moiety itself did not hamper the asymmetric catalysis when it was featured in phosphonate **2k**.[31e,45]

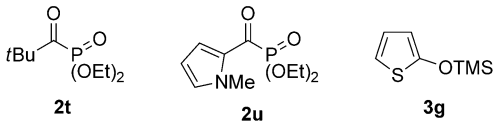
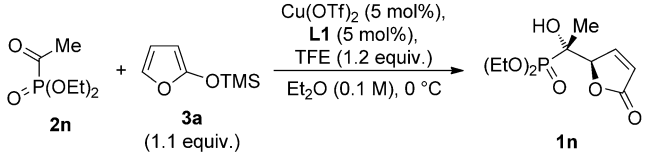


Figure 3. Phosphonates **2t** and **u** and silyl nucleophile **3g** failed to react.

In order to demonstrate the robustness and reliability of the catalytic system, an up-scaling experiment (from 0.2 mmol to 10 mmol) using acetylphosphonate **2n** and silyloxy furan **3a** to yield **1n** was performed (Scheme 2). Guided by the results presented in entry 15 of Table 2, the amount of $Cu(OTf)_2$ and amino sulfoximine **L1** was reduced to 5 mol%. Under those conditions, exactly the same stereoselectivities (99% *de* and 92% *ee*, respectively) were observed for both reactions. Worthy of note, the yield of **1n** was even higher on larger scale (94 vs. 83%). Besides, sulfoximine ligand **L1** could successfully be recovered with a yield of 72% in (stereo-)chemically homogenous manner as confirmed by NMR spectroscopy and analysis by high performance liquid chromatography on chiral stationary phase. Comparing the result of the small scale experiment with the one achieved by using 10 mol% of catalyst (entry 14 of Table 3), a slightly lower yield and *ee* of **1n** was observed.



Reaction on a scale of 0.2 mmol: 83% yield (44.1 mg), 99% *de*, 92% *ee*
Reaction on a scale of 10 mmol: 94% yield (2.472 g), 99% *de*, 92% *ee*

Scheme 2. Scale-up of the synthesis of **1n** with reduced catalyst loading.

Regarding the importance of the butyrolactone motif in naturally occurring compounds,[20] enantioenriched **1n** was transformed into the γ-(hydroxyalkyl)butanolide **5** (Scheme 3). Hydrogenation of the C–C double bond succeeded with full con-

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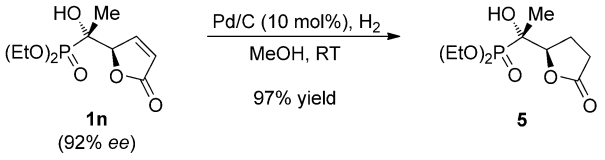

Scheme 3. Synthesis of butyrolactone **5** by hydrogenation of butenolide **1n**.

version of **1n**, and saturated lactone **5** could be isolated without chromatographic work-up in 97% yield.

Conclusion

A catalytic and highly stereoselective vinylogous Mukaiyama aldol reaction with substantial variations of α-keto phosphonates **2** and heterocyclic dienol silanes **3** has been developed to give products **1** of potential biomedical interest.[46,47] Noteworthy, an additional cleavage step to remove the TMS group under acidic conditions is not needed, and unprotected aldol products **1** are directly obtained. The catalyst derived from $Cu(OTf)_2$ and amino sulfoximine **L1**[48] overcomes commonly observed obstacles associated with such a process, namely the lower reactivity of ketonic substrates plus the control of regio-, diastereo- and enantioselectivity. Furthermore, possible key factors in the structure of C_1-symmetric sulfoximines are discussed being responsible for the high asymmetric induction.

Experimental Section

General procedure for the Cu-catalyzed VMA reaction

A Schlenk tube under argon atmosphere was charged with $Cu(OTf)_2$ (7.4 mg, 0.020 mmol) and amino sulfoximine **L1** (9.3 mg, 0.020 mmol). Et_2O (2.0 mL) was added, and the green solution was stirred at room temperature for 30 min. After cooling to 0 °C the corresponding α-keto phosphonate **2** (0.20 mmol), 2,2,2-trifluoroethanol (17 μL, 0.24 mmol) and heterocyclic dienol silane **3** (0.22 mmol) were added in the order given. The Schlenk tube was sealed with a rubber septum, and the reaction mixture was stirred until the electrophile was consumed as determined by TLC. The cold reaction mixture was directly subjected to flash column chromatography to give products **1**.

Synthesis of α-hydroxy phosphonate 1a

Prepared according to the general procedure from diethyl benzoylphosphonate (**2a**) and 2-(trimethylsilyloxy)furan (**3a**). The product was purified by flash column chromatography two times (first: *n*-pentane/acetone = 2:1; second: EtOAc) to give product **1a** as a white solid. Yield: 99%; $[\alpha] = 69.2$ ($c = 1.0$ in $CHCl_3$); m.p. 109–111 °C (racemate: 115–116 °C); de: >99%; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.65$ (dd, $J = 5.8$ Hz, 0.9 Hz, 1H), 7.62–7.59 (m, 2H), 7.36–7.33 (m, 2H), 7.31–7.27 (m, 1H), 6.05 (dd, $J = 5.8$ Hz, 1.7 Hz, 1H), 5.64 (dt, $J = 5.3$ Hz, 1.6 Hz, 1H), 4.33 (s br, 1H), 4.14–4.03 (m, 3H), 3.95 (ddq, $J = 14.3$ Hz, 10.1 Hz, 7.1 Hz, 1H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.23 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 172.80$, 153.77 (d, $J = 4.1$ Hz), 135.81, 128.43, 128.40 (d, $J = 2.1$ Hz), 126.26 (d, $J = 4.3$ Hz), 123.28, 85.39 (d, $J = 10.8$ Hz), 76.64 (d, $J = 160.9$ Hz), 64.51 (d, $J = 7.6$ Hz), 64.44 (d, $J = 7.6$ Hz), 16.49 (d, $J = 5.6$ Hz), 16.48 ppm (d, $J = 5.6$ Hz); ^{31}P NMR (243 MHz, $CDCl_3$): $\delta = 18.59$ ppm; IR (ATR): $\tilde{\nu} = 3195$, 2980, 2924, 1754, 1603, 1490, 1448, 1397, 1299, 1224, 1159, 1102, 1011, 888, 827, 696; MS (EI): *m/z* (%): 327 ($[M+H]^+$, 1), 308 (1), 243 (19), 151 (11), 121 (14), 111 (15), 105 (100), 93 (8), 83 (15), 77 (37), 65 (12), 55 (6), 51 (8); MS (CI): *m/z* (%): 355 ($[M+C_2H_5]^+$, 2), 327 ($[M+H]^+$, 63), 309 (14), 243 (97), 189 (21), 151 (17), 139 (100), 121 (22), 111 (45), 105 (44), 85 (56), 83 (13); elemental analysis calcd (%) for $C_{15}H_{19}O_6P$ (326.28): C 55.22, H 5.87; found: C 55.04, H 5.88; HPLC: $t_R = 24.3$ min [minor], 26.6 [major] (AD-H column, flow rate 0.7 mL min^{-1}, *n*-heptane/*i*PrOH = 93:7, $\lambda = 210$ nm, 20 °C); *ee*: >99%.

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Keywords: aldol reaction · asymmetric catalysis · butenolides · α-hydroxy phosphonates · sulfoximines

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[48] The (*R*)- and (*S*)-enantiomer of amino sulfoximine **L1** are commercially available, hence allowing easy access to both product enantiomers.

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