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Enantioselective Organocatalytic Addition of Azlactones to Maleimides: A Highly Stereocontrolled Entry to 2,2-Disubstituted-2*H*-oxazol-5-ones

Andrea-Nekane R. Alba,[a] Guillem Valero,[a] Teresa Calbet,[b] Mercé Font-Bardía,[b] Albert Moyano,*[a] and Ramon Rios*[a]

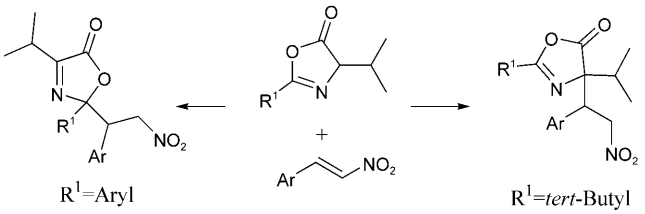
Dedicated to Professor José Barluenga on the occasion of his 70th birthday

Abstract: The first highly diastereo- and enantioselective organocatalytic synthesis of 2,2-disubstituted-2*H*-oxazol-5-ones is described. The addition of oxazolones to maleimides is promoted by bifunctional thiourea catalysts, which afford the corresponding 2,2-disubstituted-2*H*-oxazol-5-ones with total regio- and stereocontrol.

Keywords: maleimides · Michael addition · organocatalysis · oxazolones

Introduction

The enantioselective construction of quaternary stereocenters is a challenging goal in organic synthesis and this topic has received considerable attention from the synthetic community.[1] In this context, the alkylation of azlactones (4*H*-oxazol-5-ones) has emerged as one of the most useful ways to build quaternary stereocenters, due to their high reactivity and easy transformation into quaternary α-substituted α-amino acid derivatives.[2] In 2008, Jørgensen and co-workers reported the first asymmetric oxazolone addition to α,β-unsaturated aldehydes, catalyzed by chiral secondary amines, with excellent results.[3] Subsequently, Jørgensen and co-workers[4] and ourselves[5] almost simultaneously disclosed the tertiary-amine-catalyzed azlactone addition to nitrostyrenes, which proceeded with high diastereoselectivities. One of the most interesting points to emerge from both papers was the regioselectivity of the reaction, which was dependent on the substitution pattern of the azlactone. When 2-aryl-substituted azlactones were used only C-2 addition was observed, whereas the use of 2-*tert*-butylazlactones exclusively afforded the C-4-substituted regioisomer (Scheme 1).



Scheme 1. Regioselectivity of the addition of azlactones to nitrostyrenes.

However, it should be highlighted that the nature of the electrophile also plays an important role in the regiochemistry of the addition. As first demonstrated by Steglich et al.,[6] in several cases the regiochemistry is totally directed by the nature of electrophile. Thus, α,β-unsaturated aldehydes appear to give C-4-substituted azlactones independent of the nature of C-2 substituent.[3] Very recently, we have found that the addition of azlactones to 1,1-bis(phenylsulfonyl)ethene also takes place with complete C-4 regioselectivity (Scheme 2).[7]

With these results in mind, and in the context of a research program devoted to the development of new asymmetric methodologies based on organocatalysis,[8] we decided to study the behavior of azlactones towards other electrophiles, such as maleimides. Maleimides have been used extensively in metal-mediated asymmetric synthesis as dieno-

[a] A.-N. R. Alba, G. Valero, Prof. Dr. A. Moyano, Dr. R. Rios[+]
Department of Organic Chemistry, Universitat de Barcelona
Martí i Franqués 1-11, 08028 Barcelona (Spain)
Fax: (+34) 933397878
E-mail: amoyano@ub.edu
rios.ramon@icrea.cat

[b] T. Calbet, M. Font-Bardía
Departament de Cristalografia, Mineralogia i Dipòsits Minerals
Universitat de Barcelona, Martí i Franqués s/n
08028 Barcelona (Spain)

[+] ICREA Researcher at UB

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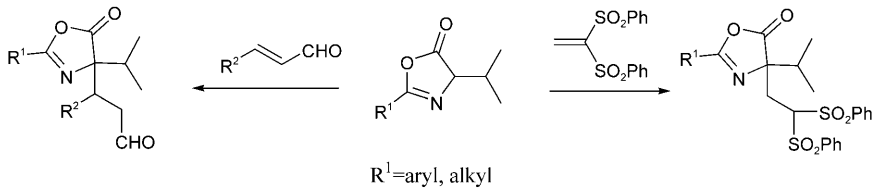
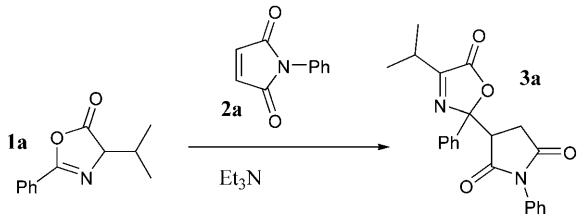


Scheme 2. Regioselectivity of the addition of azlactones to α,β-unsaturated aldehydes and vinyl sulfones.

philes[9] or dipolarophiles[10] in cycloadditions, or as Michael acceptors.[11] Following the landmark 1989 paper of Riant and Kagan,[12] maleimides have been employed in enantioselective Diels–Alder cycloadditions with anthrones[13] and, more recently, in asymmetric Michael reactions with 1,3-dicarbonyl compounds,[14] aldehydes,[15] and 2-mercaptobenzaldehydes.[16] Their use in vinylogous Michael reactions with α,α-dicyanoolefins has also been reported.[17] To the best of our knowledge, the asymmetric conjugate addition of azlactones to maleimides had not yet been studied and should provide a practical route to synthetically and biologically important chiral α-succinimidates.[18]

Results and Discussion

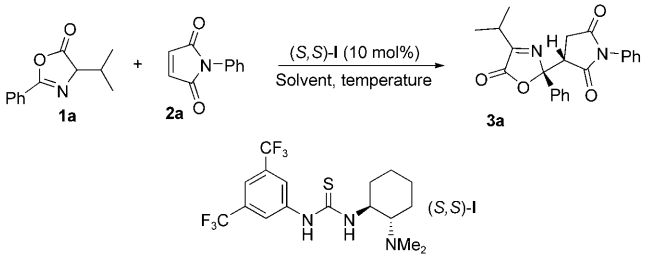
Our initial investigations revealed that 4*H*-oxazol-5-one **1a** underwent a Et_3N-catalyzed Michael addition to *N*-phenylmaleimide (**2a**) in toluene at room temperature (Scheme 3) to afford compound **3a** as mixture of diastereomers (2.4:1 diastereomeric ratio (d.r.)) in 92% isolated yield, with complete C-2 regioselectivity.



Scheme 3. Addition of azlactone **1a** to *N*-phenylmaleimide (**2a**).

We turned our attention to an asymmetric version of the same reaction. To this end, we tested Takemoto's thiourea catalyst (*S*,*S*)-**I**[19] in different solvents, with the intention to take advantage of the bifunctional nature of the catalyst to improve the diastereoselectivity of the process[7] (Table 1). To our delight, the reaction afforded optically active adduct **3a** (84:16 enantiomeric ratio (e.r.)) when run in toluene at room temperature, with excellent diastereoselectivity (20:1 d.r.) and total conversion after 1 h (Table 1, entry 1). When the reaction was performed at −20 °C both the diastereoselectivity (25:1 d.r.) and the enantioselectivity (94:6 e.r.) increased, although the reaction rate was appreciably reduced (Table 1, entry 7). When the reaction was run in ethyl acetate (Table 1, entry 3) both the diastereoselectivity and the enantioselectivity were reduced, whereas chloroform (Table 1, entry 2) provided results only marginally inferior to those obtained with toluene. When polar solvents ethanol and DMF were used, no reaction was observed (Table 1, entries 4 and 5).

Table 1. Optimization of reaction conditions with Takemoto's thiourea.[a]



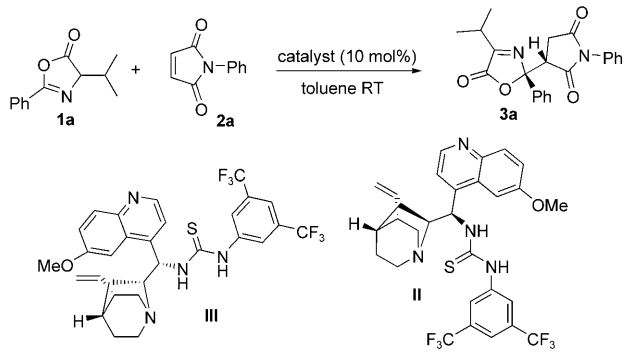
Entry	Solvent	Conversion (1 h) [%][b]	*T* [°C]	d.r.[b]	e.r.[c]
1	toluene	100	RT	20:1	84:16
2	$CHCl_3$	100	RT	18:1	82:12
3	AcOEt	100	RT	13:1	71:29
4	EtOH	–	RT	–	–
5	DMF	–	RT	–	–
6	toluene	100	4	25:1	87:13
7	toluene	20	−20	25:1	94:6

[a] Maleimide **2a** (1 equiv) was added to a mixture of **1a** (1.2 equiv) and catalyst **I** (10 mol%). [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Major diastereomer e.r., determined by chiral HPLC.

Next, we screened catalysts other than (*S*,*S*)-**I**, which included chiral thioureas and bases derived from *Cinchona* alkaloids, in toluene at room temperature (Table 2). The reaction was efficiently catalyzed by quinidine-derived thiourea **II**, although with reduced enantioselectivity (Table 2, entry 2 versus 1). Quinine-derived thiourea **III** also catalyzed the addition but, surprisingly, with a very low reaction rate (Table 2, entry 3). When chiral bases quinine (**VII**), quinidine (**VIII**), and Sharpless' ligands **IV**–**VI** were used no reaction was observed (Table 2, entries 4–8). This shows that the hydrogen-bond-donating thiourea moiety is crucial in the catalysis of this new reaction (see Scheme 5 below).

Once the reaction conditions were optimized with respect to catalyst (Takemoto's thiourea **I**) and solvent (toluene), we performed a screening of substituted azlactones. The scope of the reaction with C-2-substituted valine-derived azlactones **1a**–**d** is summarized in Table 3. As previously noticed by Jørgensen and co-workers[3] and ourselves,[7] when fluorine atoms were located in positions 2,4 on the phenyl ring the enantioselectivities increased up to 95:5 e.r. in relation to entry 1, Table 3. It should be noted that when 2-alkyl-substituted oxazolones were treated with maleimides in the presence of catalyst **I**, a 3.5:1 regioisomeric mixture of C-4 and C-2 adducts was obtained. The major C-4 ad-

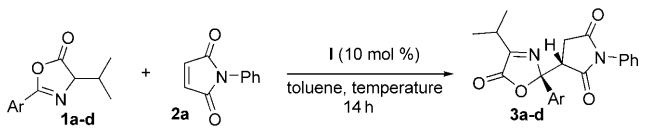
Table 2. Catalyst screening.[a]



Entry	Catalyst	Conversion (14 h) [%][b]	d.r.[b]	e.r.[c]
1	(*S*,*S*)-**I**	100	20:1	84:16
2	**II**	100	20:1	68:32
3	**III**	<10	n.d.[e]	n.d.
4	$(DHQD)_2AQN$[f] (**IV**)	0	–	–
5	$(DHQD)_2PHAL$[g] (**V**)	0	–	–
6	$(DHQD)_2PYR$[h] (**VI**)	0	–	–
7	**VII**	0	–	–
8	**VIII**	0	–	–

[a] Maleimide **2a** (1 equiv) was added to a mixture of **1a** (1.2 equiv) and catalyst **I** (10 mol%) in toluene at RT [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Major diastereomer e.r., determined by chiral HPLC. [d] After 24 h, traces of the product were detected by NMR analysis. [e] n.d. = none detected. [f] $(DHQD)_2AQN$ = hydroquinidine(anthraquinone-1,4-diyl) diether. [g] $(DHQD)_2PHAL$ = 1,4-bis-(dihydroquinidinyl)-phthalazine. [h] $(DHQD)_2PYR$ = hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether.

Table 3. C-2 substituent screening: Addition of 2-aryl-4-isopropylazlactones to *N*-phenylmaleimide.[a]



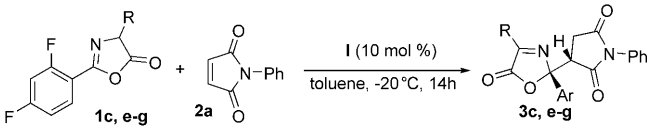
Entry	Ar	Compound	Yield [%][b]	*T* [°C]	d.r.[c]	e.r.[d]
1	Ph	**3a**	76	−20	20:1	94:6
2	2,6-$F_2C_6H_3$	**3b**	76	−20	20:1	92:8
3	2,4-$F_2C_6H_3$	**3c**	99	4	25:1	95:5
4	2-FC_6H_4	**3d**	85	RT	20:1	84:16

[a] Maleimide **2a** (1 equiv) was added to a mixture of **1** (1.2 equiv) and catalyst **I** in toluene. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Major diastereomer e.r., determined by chiral HPLC.

ducts were produced with low diastereoselectivities and with moderate enantioselectivities.[20]

We retained the 2-(2,4-difluorophenyl) substituent in azlactones **1e–g** to investigate the effect of the C-4 alkyl substituent (Table 4). Both the yields and the enantiomeric purities were good in all instances. The diastereoselectivity of the process was clearly dependent on the α-branching degree of the C-4 alkyl substituent and increased along the series methyl < isobutyl < isopropyl < *tert*-butyl (Table 4, entries 1–4, respectively). This last example (reaction with *tert*-leucine-derived azlactone **1e**) was remarkable in that, after

Table 4. C-4 substituent screening: Addition of 2-(2,4-difluorophenyl)-azlactones to *N*-phenylmaleimide.[a]



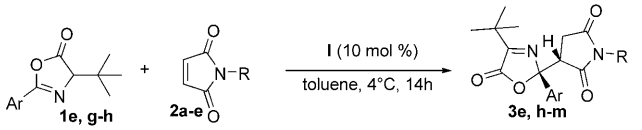
Entry	R	Compound	Yield [%][b]	d.r.[c]	e.r.[d]
1	Me	**3g**	73	4.4:1	95:5
2	*i*Bu	**3f**	87	8:1	96:4
3	*i*Pr	**3c**	99	25:1	95:5
4	*t*Bu	**3e**	99	>25:1	99.5:0.5

[a] Maleimide **2a** (1 equiv) was added to a mixture of **1** (1.2 equiv) and catalyst **I** (10 mol%) in toluene and stirred for 14 h at −20 °C. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Major diastereomer e.r., determined by chiral HPLC.

chromatographic purification, the essentially stereoisomerically pure adduct **3e** (>25:1 d.r. and 99.5:0.5 e.r.) was obtained in 99% yield.

Finally, we studied the scope of the reaction with maleimides **2a–e** with azlactones derived from *tert*-leucine (Table 5). In all cases, the reactions were very stereoselec-

Table 5. Reaction scope: Addition of 2-aryl-4-*tert*-butylazlactones to *N*-aryl maleimides.[a]

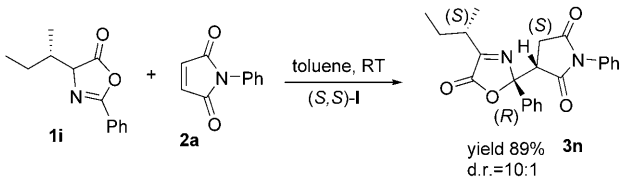


Entry	Ar	R	**3**	Yield [%][b]	d.r.[c]	e.r.[d]
1[e]	2,4-$F_2C_6H_3$	Ph	**3e**	99	>25:1	99.5:0.5
2	2,4-$F_2C_6H_3$	4-$MeOC_6H_4$	**3h**	84	>25:1	97.5:2.5
3[f]	2-FC_6H_4	Ph	**3i**	85	>25:1	96:4
4	2,4-$F_2C_6H_3$	3-ClC_6H_4	**3j**	62	>25:1	96:4
5	2,4-$F_2C_6H_3$	4-$CF_3C_6H_4$	**3k**	92	>25:1	97:3
6	2,4-$F_2C_6H_3$	6-ClC_6H_4	**3l**	94	>25:1	98:2
7	Ph	Ph	**3m**	95	>25:1	96:4

[a] Maleimide **2** (1 equiv) was added to a mixture of **1** (1.2 equiv) and catalyst **I** (10 mol%) in toluene and stirred for 14 h at 4 °C. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Major diastereomer e.r., determined by chiral HPLC. [e] Reaction run at −20 °C. [f] Reaction run at RT.

tive and afforded diastereomerically pure (>25:1 d.r.) 2-aryl-2-(3-succinimidyl)-2*H*-oxazol-5-ones of high enantiomeric purity (>96:4 e.r.). It should be noted that product **3e** precipitated from the solution in toluene and as a result could be isolated in enantiopure form (only one enantiomer detected by HPLC) and in 99% yield by simple filtration of the reaction mixture.

The relative and absolute configuration of compound **3n**, obtained from the reaction of azlactone **1i** (derived from (*S*)-isoleucine) with *N*-phenylmaleimide (**2a**) (Scheme 4), were ascertained by X-ray diffraction analysis of a single crystal of the major diastereomer (Figure 1).



Scheme 4. Reaction of azlactone **1i** with maleimide **2a**.

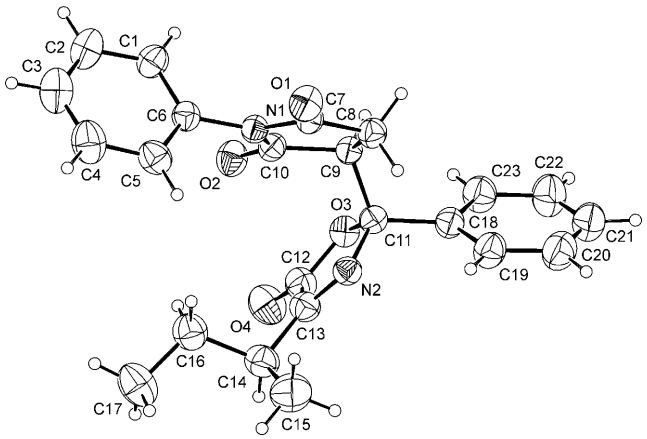
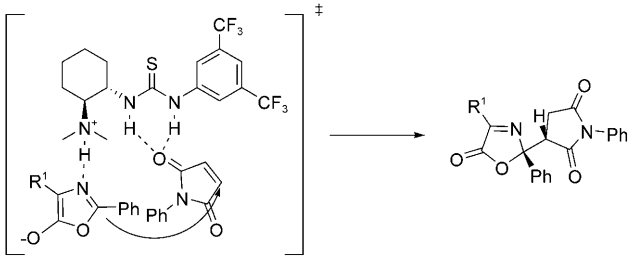


Figure 1. X-ray structure of **3n**.[21]

Based on these data, we tentatively propose a bifunctional transition state in which the tertiary amine of the catalyst deprotonates the azlactone and the thiourea moiety activates the maleimide, as shown in Scheme 5.



Scheme 5. Proposed transition state for azlactone addition to maleimides.

Conclusion

We have reported a new, organocatalytic, easily executed, and highly enantioselective entry to 2*H*-oxazol-5-ones with quaternary stereocenters. The addition of 4-alkyl-azlactones **1** to maleimides **2** is efficiently catalyzed by bifunctional thiourea–amine **I** (both enantiomers of which are commercially available) with complete C-2 regioselectivity and with good to excellent diastereoselectivity. The resulting adducts are obtained with good yields and enantioselectivities. The procedure presented herein has distinct advantages in terms of operational simplicity, environmentally friendly conditions, and suitability for large-scale reactions for practical industrial preparations.[22]

Experimental Section

General procedure for azlactone addition to maleimides: In a small flask, oxazolone **1a–i** (0.30 mmol, 1.2 equiv), maleimide **2a–e** (0.25 mmol, 1.0 equiv), and catalyst **I** (0.025 mmol, 0.1 equiv) in toluene (1 mL) were stirred at the temperature described in Tables 3–5 or Scheme 4. The crude products **3a–n** were purified by flash column chromatography.

*Compound **3a***: The reaction was run with (*R*,*R*)-**I**. Colorless oil, 88% enantiomeric excess (*ee*). $[\alpha]_D^{25} = -20.5$ ($c = 0.7$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): $\delta = 7.61$–7.56 (m, 2H), 7.47–7.42 (m, 5H), 7.41–7.36 (m, 1H), 7.20–7.15 (m, 2H), 3.89 (dd, $J = 9.7$, 5.4 Hz, 1H), 3.02 (h, $J = 6.8$ Hz, 1H), 2.93 (dd, $J = 18.6$, 5.4 Hz, 1H), 2.75 (dd, $J = 18.6$, 9.7 Hz, 1H), 1.30 (d, $J = 6.8$ Hz, 3H), 1.24 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.5$, 172.7, 171.6, 163.2, 136.4, 131.3, 130.0, 129.3, 129.2, 129.1, 129.0, 128.9, 126.4, 126.2, 125.9, 104.7, 47.6, 31.7, 29.7, 28.3, 19.3, 19.1 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{21}N_2O_4$: 377.1496 $[M+H]^+$; found: 377.1487; HPLC (Chiralpak IC, 1 mL min^{-1}, hexane/*i*PrOH 80:20, 254 nm): retention times (t_R) for major diastereomer = 17.8, 28.7 min.

*Compound **3b***: The reaction was run with (*S*,*S*)-**I**. Colorless oil, 84% *ee*. $[\alpha]_D^{25} = +10.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): $\delta =$ 7.48–7.38 (m, 4H), 7.23–7.20 (m, 2H), 7.02–6.96 (m, 2H), 4.41 (dd, $J =$ 8.9, 6.0 Hz, 1H), 3.03 (h, $J = 6.7$ Hz, 1H), 2.97 (dd, $J = 18.5$, 9.7 Hz, 1H), 2.89 (dd, $J = 9.5$, 7.2 Hz, 1H), 1.29 (d, $J = 6.9$ Hz, 3H), 1.23 ppm (d, $J =$ 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.3$, 172.6, 171.0, 163.4, 161.7 (d, $J = 6.5$ Hz), 159.2 (d, $J = 7.3$ Hz), 132.3, 132.2, 132.0, 131.3, 129.3, 129.2, 128.9, 128.9, 126.6, 126.2, 113.3 (d, $J = 3.4$ Hz), 113.0 (d, $J = 2.7$ Hz), 45.5, 31.5, 28.1, 19.1, 18.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -105.3$ (m), -107.3 ppm (m); HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{19}F_2N_2O_4$: 413.1307 $[M+H]^+$; found: 413.1305; HPLC (Chiralpak IC, 1 mL min^{-1}, hexane/*i*PrOH 80:20, 254 nm): t_R for major diastereomer = 18.2, 30.0 min.

*Compound **3c***: The reaction was run with (*R*,*R*)-**I**. Colorless oil, 90% *ee*. $[\alpha]_D^{25} = -17.0$ ($c = 2.1$, $CHCl_3$); ^{1}H NMR (300 MHz. $CDCl_3$, TMS_{int}): $\delta =$ 7.47–7.35 (m, 4H), 7.20–7.16 (m, 2H), 6.99–6.89 (m, 2H), 4.28 (dd, $J =$ 9.7, 5.6 Hz, 1H), 3.05 (h, $J = 6.8$ Hz, 1H), 2.86 (dd, $J = 18.4$, 9.7 Hz, 1H), 2.72 (dd, $J = 18.4$, 5.6 Hz, 1H), 1.31 (d, $J = 6.8$ Hz, 3H), 1.24 ppm (d, $J =$ 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.3$, 172.8, 172.5, 165.2 (d, $J = 11.9$ Hz), 163.0, 162.7 (d, $J = 12.3$ Hz), 161.8 (d, $J = 12.7$ Hz), 159.3 (d, $J = 11.9$ Hz), 131.2, 129.6 (dd, $J = 10.0$, 4.2 Hz), 129.2, 128.9, 126.2, 111.6 (dd, $J = 21.1$, 21.2 Hz), 105.8, 105.5, 105.3, 102.5 (d, $J = 3.8$ Hz), 44.9 (d, $J = 4.6$ Hz), 31.5, 28.4, 19.3, 19.0 ppm; ^{19}F NMR (376 MHz. $CDCl_3$): $\delta = -105.3$ (m), -106.9 ppm (m); HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{19}F_2N_2O_4$: 413.1307 $[M+H]^+$; found: 413.1304; HPLC (Chiralpak IC, 1 mL min^{-1}, hexane/*i*PrOH 75:25, 254 nm): t_R major diastereomer = 13.3, 19.5 min.

*Compound **3d***: The reaction was run with (*S*,*S*)-**I**. Colorless oil, 67% *ee*. $[\alpha]_D^{25} = -10.5$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): $\delta =$ 7.47–7.56 (m, 5H), 7.26–7.17 (m, 4H), 4.35 (dd, $J = 9.4$, 5.9 Hz, 1H), 3.06 (h, $J = 6.9$ Hz, 1H), 2.85 (dd, $J = 18.6$, 9.7 Hz, 1H), 2.79 (dd, $J = 18.2$, 5.6 Hz, 1H), 1.32 (d, $J = 6.9$ Hz, 3H), 1.24 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.4$, 172.9, 172.3, 163.1, 161.4, 158.9, 135.4 (d, $J = 9.9$ Hz), 132.1 (d, $J = 8.8$ Hz), 129.2, 128.9, 128.4 (d, $J =$ 2.7 Hz), 126.5, 126.2, 124.5 (d, $J = 4.2$ Hz), 123.7 (d, $J = 11.9$ Hz), 116.9 (d, $J = 116.9$ Hz), 102.9 (d, $J = 3.4$ Hz), 44.9 (d, $J = 4.9$ Hz), 31.7, 28.4, 19.3, 19.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -111.4$ ppm (t, $J = 16.0$ Hz); HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{19}FN_2NaO_4$: 417.1221 $[M+Na]^+$; found: 417.1222; HPLC (Chiralpak IA, 1 mL min^{-1}, hexane/*i*PrOH 90:10, 254 nm): t_R major diastereomer = 67.7, 70.5 min.

*Compound **3e***: The reaction was run with (*R*,*R*)-**I**. Colorless oil, 99% *ee*. $[\alpha]_D^{25} = -13.8$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): $\delta =$ 7.48–7.37 (m, 4H), 7.21–7.19 (m, 2H), 6.99–6.91 (m, 2H), 4.27 (dd, $J =$ 9.7, 5.5 Hz, 1H), 2.85 (dd, $J = 18.3$, 9.7 Hz, 1H), 2.73 (dd, $J = 18.4$, 5.6 Hz, 1H), 1.34 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.8$, 173.3,

172.7, 165.2 (d, J=11.2 Hz), 162.7 (d, J=11.9 Hz), 161.9, 159.3 (d, J=11.9 Hz), 134.2, 131.2, 129.6 (dd, J=9.9, 4.2 Hz), 129.2, 129.1, 128.9, 126.4, 126.2, 111.6 (dd, J=21.1, 3.5 Hz), 105.1 (dd, J=25.3, 25.4 Hz), 101.2 (d, J=4.2 Hz), 44.9 (d, J=5.0 Hz), 35.0, 31.5, 26.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−106.3 (m), −107.8 ppm (m); HRMS (ESI): m/z: calcd for $C_{23}H_{24}F_2N_3O_4$: 444.1729 $[M+NH_4]^+$; found: 444.1731; HPLC (Chiralpak IB, 1 mL min^{-1}, hexane/*i*PrOH 80:20, 254 nm): t_R major diastereomer = 26.7, 28.6 min.

Compound ***3f***: The reaction was run with (*S*,*S*)-**I**. Colorless foam, 92% *ee*. $[\alpha]_D^{25}$=+9.5 (c=1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=7.50–7.35 (m, 4H), 7.21–7.16 (m, 2H), 7.00–6.89 (m, 2H), 4.29 (dd, J=9.7, 5.8 Hz, 1H), 2.86 (dd, J=18.3, 9.7 Hz, 1H), 2.73 (dd, J=18.3, 5.8 Hz, 1H), 2.59–2.54 (m, 2H), 2.21 (h, J=6.7 Hz, 1H), 0.99 (d, J=6.7 Hz, 3H), 0.96 ppm (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.1, 172.8, 167.7, 165.2 (d, J=11.9 Hz), 163.7, 162.8, 162.6, 161.7 (d, J=12.3 Hz), 159.2 (d, J=12.3 Hz), 134.2, 131.2, 129.5 (dd, J=4.2, 10.0 Hz), 129.2, 129.1, 128.9, 128.8, 127.9, 126.4, 126.2, 126.0, 111.7 (dd, J=21.5, 3.4 Hz), 105.8, 105.5, 105.3, 103.0 (d, J=3.8 Hz), 44.9 (d, J=4.2 Hz), 36.8, 31.4, 26.0, 22.6, 22.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−105.4 (m, 1F), −106.8 ppm (m, 1F); HRMS (ESI): m/z: calcd for $C_{23}H_{21}F_2N_2O_4$: 427.1464 $[M+H]^+$; found: 427.1464; HPLC (Chiralpak IA, 1 mL min^{-1}, hexane/*i*PrOH 90:10, 254 nm): t_R major diastereomer = 25.8, 27.3 min.

Compound ***3g***: The reaction was run with (*R*,*R*)-**I**. Colorless foam, 90% *ee*. $[\alpha]_D^{25}$=−12.4 (c=1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=7.48–7.36 (m, 4H), 7.21–7.15 (m, 2H), 7.00–6.88 (m, 2H), 4.27 (dd, J=9.7, 5.6 Hz, 1H), 2.86 (dd, J=18.3, 9.7 Hz, 1H), 2.67 (dd, J=18.3, 5.6 Hz, 1H), 2.37 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.1, 165.1, 163.7, 162.8, 161.8, 159.2, 131.2, 129.7, 129.2, 128.9, 126.2, 119.8, 111.8, 105.5, 45.0, 31.4, 14.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−105.4 (m), −107.1 ppm (m); HRMS (ESI): m/z: calcd for $C_{20}H_{14}F_2KN_2O_4$: 423.0553 $[M+K]^+$; found: 423.0553; HPLC (Chiralpak IA, 1 mL min^{-1}, hexane/*i*PrOH 80:20, 254 nm): t_R major diastereomer = 16.1, 17.6 min.

Compound ***3h***: The reaction was run with (*R*,*R*)-**I**. Yellow oil, 95% *ee*. $[\alpha]_D^{25}$=−12.0 (c=1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=7.42–7.36 (m, 1H), 7.12–7.08 (m, 2H), 6.99–6.91 (m, 4H), 4.26 (dd, J=9.7, 5.6 Hz, 1H), 3.81 (s, 3H), 2.84 (dd, J=18.4, 9.7 Hz, 1H), 2.71 (dd, J=18.4, 5.4 Hz, 1H), 1.34 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.8, 173.6, 173.0, 165.6 (d, J=11.6 Hz), 162.0, 159.7, 158.9 (d, J=11.8 Hz), 129.5 (dd, J=10.1, 4.5 Hz), 127.4, 123.8, 120.1 (dd, J=12.1, 4.0 Hz), 114.6, 111.6 (dd, J=21.1, 3.8 Hz), 105.5 (dd, J=25.9, 26.0 Hz), 101.2 (d, J=4.0 Hz), 55.5, 44.9 (d, J=4.5 Hz), 35.0, 31.4, 26.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−106.3 (m), −107.8 ppm (m); HRMS (ESI): m/z: calcd for $C_{24}H_{26}F_2N_3O_5$: 474.1835 $[M+NH_4]^+$; found: 474.1837; HPLC (Chiralpak IA, 1 mL min^{-1}, hexane/*i*PrOH 90:10, 254 nm): t_R major diastereomer = 29.0, 36.4 min.

Compound ***3i***: The reaction was run with (*R*,*R*)-**I**. Colorless oil, 84% *ee*. $[\alpha]_D^{25}$=−20.1 (c=1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=7.47–7.37 (m, 5H), 7.23–7.17 (m, 4H), 4.33 (dd, J=9.3 Hz, 5.8 Hz, 1H), 2.85 (dd, J=18.3, 9.3 Hz, 1H), 2.78 (dd, J=18.7, 5.9 Hz, 1H), 1.35 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.6, 173.5, 172.9, 162.0, 161.4, 158.9, 132.1 (d, J=9.9 Hz), 131.3, 129.2, 128.8, 128.4 (d, J=2.3 Hz), 126.5, 125.2, 124.5 (d, J=3.4 Hz), 123.7 (d, J=11.5 Hz), 116.9 (d, J=21.8 Hz), 101.7 (d, J=3.4 Hz), 44.9 (d, J=4.9 Hz), 34.9, 31.7, 26.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−111.5 ppm (m); HRMS (ESI): m/z: calcd for $C_{23}H_{22}FN_2O_4$: 409.1558 $[M+H]^+$; found: 409.1564; HPLC (Chiralpak IA, 1 mL min^{-1}, hexane/*i*PrOH 95:5, 254 nm): t_R major diastereomer = 65.5, 69.6 min.

Compound ***3j***: The reaction was run with (*R*,*R*)-**I**. Colorless oil, 92% *ee*. $[\alpha]_D^{25}$=−7.5 (c=0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=7.41–7.36 (m, 3H), 7.25–7.24 (m, 1H), 7.14–7.12 (m, 1H), 6.99–6.91 (m, 2H), 4.28 (dd, J=9.7, 5.6 Hz, 1H), 2.86 (dd, J=18.5, 9.8 Hz, 1H), 2.73 (dd, J=18.5, 5.5 Hz, 1H), 1.35 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.9, 173.6, 172.8, 172.5, 172.3, 161.8, 134.7, 132.2, 130.2, 129.5 (dd, J=8.4, 4.2 Hz), 129.2 (d, J=5.6 Hz), 129.1, 126.5, 124.3, 111.7 (d, J=21 Hz), 105.6 (dd, J=26.6, 26.7 Hz), 101.1 (d, J=8 Hz), 44.9, 35.0, 31.4, 26.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−105.4 (m), −107.1 ppm (m); HRMS (ESI): m/z: calcd for $C_{23}H_{20}ClF_2N_2O_4$: 461.1074 $[M+H]^+$; found: 461.1073; HPLC (Chiralpak IB, 1 mL min^{-1}, hexane/*i*PrOH 80:20, 254 nm): t_R major diastereomer = 11.7, 12.2 min.

Compound ***3k***: The reaction was run with (*R*,*R*)-**I**. Colorless oil, 94% *ee*. $[\alpha]_D^{25}$=−6.6 (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=7.75–7.70 (m, 2H), 7.42–7.35 (m, 3H), 7.00–6.90 (m, 2H), 4.30 (dd, J=9.7, 5.5 Hz, 1H), 2.89 (dd, J=18.5, 9.7 Hz, 1H), 2.74 (dd, J=18.5, 5.5 Hz, 1H), 1.33 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.9, 172.7, 172.3, 165.3 (d, J=11.9 Hz), 162.8 (d, J=11.9 Hz), 161.9, 161.9, 159.3, 134.3, 130.7 (d, J=33.7 Hz), 129.5 (dd, J=9.5, 3.4 Hz), 126.4, 126.3, 120.0, 111.75 (dd, J=21.1, 2.7 Hz), 105.8, 105.6, 105.3, 101.1 (d, J=3.1 Hz), 45.0 (d, J=4.2 Hz), 35.0, 31.5, 26.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−62.4 (s, 3F), −105.2 (m, 1F), −107.3 ppm (m, 1F); HRMS (ESI): m/z: calcd for $C_{24}H_{20}F_5N_2O_4$: 495.1338 $[M+H]^+$; found: 495.1337; HPLC (Chiralpak IB, 1 mL min^{-1}, hexane/*i*PrOH 80:20, 254 nm): t_R major diastereomer = 8.7, 14.7 min.

Compound ***3l***: The reaction was run with (*R*,*R*)-**I**. Colorless oil, 96% *ee*. $[\alpha]_D^{25}$=−8.6 (c=1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=7.45–7.35 (m, 3H), 7.20–7.14 (m, 2H), 7.00–6.90 (m, 2H), 4.27 (dd, J=9.7, 5.6 Hz, 1H), 2.86 (dd, J=18.5, 9.7 Hz, 1H), 2.71 (dd, J=18.5, 5.6 Hz, 1H), 1.33 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.9, 173.0, 172.5, 165.3 (d, J=11.9 Hz), 162.7 (d, J=12.7 Hz), 161.0, 159.3 (d, J=12.3 Hz), 134.7, 129.4, 127.4, 119.9 (d, J=11.1 Hz), 111.8, 111.6, 105.8, 105.6, 105.3, 101.2, 44.9, 35.0, 31.5, 26.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−105.3 (m), −107.0 ppm (m); HRMS (ESI): m/z: calcd for $C_{23}H_{20}ClF_2N_2O_4$: 461.1074 $[M+H]^+$; found: 461.1072; HPLC (Chiralpak IB, 1 mL min^{-1}, hexane/*i*PrOH 80:20, 254 nm): t_R major diastereomer = 9.2, 17.2 min.

Compound ***3m***: The reaction was run with (*R*,*R*)-**I**. Colorless foam, 92% *ee*. $[\alpha]_D^{25}$=−12.6 (c=0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ=7.61–7.56 (m, 2H), 7.50–7.38 (m, 6H), 7.21–7.14 (m, 2H), 3.87 (dd, J=9.7, 5.2 Hz, 1H), 2.93 (dd, J=18.6, 5.3 Hz, 1H), 2.74 (dd, J=18.6, 9.7 Hz, 1H), 1.33 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.5, 172.9, 172.7, 162.1, 136.5, 134.0, 129.9, 129.2, 129.0, 128.8, 126.4, 103.5, 47.6, 34.9, 31.7, 26.9 ppm; HRMS (ESI): m/z: calcd for $C_{23}H_{23}N_2O_4$: 391.1652 $[M+H]^+$; found: 391.1653; HPLC (Chiralpak IB, 1 mL min^{-1}, hexane/*i*PrOH 80:20, 254 nm): t_R major diastereomer = 9.9, 26.4 min.

Compound ***3n***: The reaction was run with (*S*,*S*)-**I**. White solid, 10:1 d.r. $[\alpha]_D^{25}$=+24.4 (c=1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ=7.60–7.55 (m, 2H), 7.46–7.41 (m, 5H), 7.40–7.35 (m, 1H), 7.19–7.15 (m, 2H), 3.91 (dd, J=9.7, 5.5 Hz, 1H), 2.93 (dd, J=18.5, 5.5 Hz, 1H), 2.87–2.10 (m, 1H), 2.75 (dd, J=18.5, 9.7 Hz, 1H), 1.89–1.77 (m, 1H), 1.55–1.45 (m, 1H), 1.26 (d, J=6.9 Hz, 3H), 0.89 ppm (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.5, 172.7, 170.9, 163.3, 136.5, 131.3, 129.8, 129.1, 129.0, 128.8, 126.4, 126.2, 104.8, 47.4, 35.0, 31.7, 26.6, 16.5, 11.6 ppm; HRMS (ESI): m/z: calcd for $C_{23}H_{23}N_2O_4$: 391.1652 $[M+H]^+$; found: 391.1651.

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[1] For reviews on the asymmetric construction of quaternary stereocenters, see a) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363 and references therein; b) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688; c) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402; *Angew. Chem. Int. Ed.* **1998**, *37*, 388.

[2] R. A. Mosey, J. S. Fisk, J. J. Tepe, *Tetrahedron: Asymmetry* **2008**, *19*, 2755.

[3] a) S. Cabrera, E. Reyes, J. Alemán, A. Milelli, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2008**, *130*, 12031; b) for a very elegant three-component reaction based on this concept, see: J. Jiang, J. Qing, L.-Z. Gong, *Chem. Eur. J.* **2009**, *15*, 7031.

[4] J. Alemán, A. Milelli, S. Cabrera, E. Reyes, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 10958.

[5] A.-N. Balaguer, X. Companyó, T. Calvet, M. Font-Bardía, A. Moyano, R. Rios, *Eur. J. Org. Chem.* **2009**, 199.

[6] W. Steglich, P. Grüber, G. Höfle, W. König, *Angew. Chem.* **1971**, *83*, 725–726; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 653–655.

[7] A.-N. R. Alba, X. Companyó, G. Valero, A. Moyano, R. Rios, *Chem. Eur. J.* **2010**, *16*, 5354.

[8] a) G. Valero, A.-N. Balaguer, A. Moyano, R. Rios, *Tetrahedron Lett.* **2008**, *49*, 6559; b) G. Valero, J. Schimer, I. Cisarova, J. Vesely, A. Moyano, R. Rios, *Tetrahedron Lett.* **2009**, *50*, 1943; c) X. Companyó, G. Valero, L. Crovetto, A. Moyano, R. Rios, *Chem. Eur. J.* **2009**, *15*, 6564; d) X. Companyó, M. Hejnová, M. Kamlar, J. Vesely, A. Moyano, R. Rios, *Tetrahedron Lett.* **2009**, *50*, 5021; e) X. Companyó, A.-N. Balaguer, F. Cárdenas, A. Moyano, R. Rios, *Eur. J. Org. Chem.* **2009**, 3075; f) A.-N. Alba, X. Companyó, A. Moyano, R. Rios, *Chem. Eur. J.* **2009**, *15*, 11098; g) A.-N. Alba, X. Companyó, A. Moyano, R. Rios, *Chem. Eur. J.* **2009**, *15*, 7035; h) N. El-Hamdouni, X. Companyó, R. Rios, A. Moyano, *Chem. Eur. J.* **2010**, *16*, 1142.

[9] a) S. W. Baldwin, P. Greenspan, C. Alaimo, A. T. McPhail, *Tetrahedron Lett.* **1991**, *32*, 5877; b) Y. Arai, T. Kontani, T. Koizumi, *J. Chem. Soc. Perkin Trans. 1* **1994**, 15; c) E. J. Corey, M. A. Letavic, *J. Am. Chem. Soc.* **1995**, *117*, 9616; d) O. Kitagawa, H. Izawa, K. Sato, A. Dobashi, A. Taguchi, M. Shiro, *J. Org. Chem.* **1998**, *63*, 2634.

[10] a) S. Cabrera, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2005**, *127*, 16394; b) D. J. Aldous, M. G. B. Drew, W. N. Draffin, E. M.-N. Hamelin, L. M. Harwood, S. Thurairatnam, *Synthesis* **2005**, 3271; c) O. Dogan, H. Koyuncu, P. Garner, A. Bulut, W. J. Youngs, *Org. Lett.* **2006**, *8*, 4687; d) C. Nájera, M. de Gracia Retamosa, J. M. Sansano, *Org. Lett.* **2007**, *9*, 4025; e) S. Fukuzawa, H. Oki, *Org. Lett.* **2008**, *10*, 1747; f) C. Nájera, M. de Gracia Retamosa, J. M. Sansano, *Angew. Chem.* **2008**, *120*, 6144; *Angew. Chem. Int. Ed.* **2008**, *47*, 6055; g) C. Nájera, M. de Gracia Retamosa, J. M. Sansano, A. de Cozar, F. P. Cossío, *Tetrahedron: Asymmetry* **2008**, *19*, 621; h) S.-B. Yu, X.-P. Hu, J. Deng, D.-Y. Wang, Z.-C. Duan, Z. Zheng, *Tetrahedron: Asymmetry* **2009**, *20*, 621.

[11] a) R. Shintani, W.-L. Duan, T. Nagano, A. Okada, T. Hayashi, *Angew. Chem.* **2005**, *117*, 4687; *Angew. Chem. Int. Ed.* **2005**, *44*, 4611; b) R. Shintani, W.-L. Duan, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 5628; c) J.-L. Ye, P.-Q. Huang, X. Lu, *J. Org. Chem.* **2007**, *72*, 35; d) E. Dardennes, S. Labano, N. S. Simpkins, C. Wilson, *Tetrahedron Lett.* **2007**, *48*, 6380.

[12] O. Riant, H. B. Kagan, *Tetrahedron Lett.* **1989**, *30*, 7403.

[13] a) K. Tokioka, S. Masuda, T. Fujii, Y. Hata, Y. Yamamoto, *Tetrahedron: Asymmetry* **1997**, *8*, 101; b) K. Uemae, S. Masuda, Y. Yamamoto, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1002; c) F. Fache, O. Piva, *Tetrahedron Lett.* **2001**, *42*, 5655; d) J. Shen, T. T. Nguyen, Y.-P. Goh, W. Ye, X. Fu, J. Xu, C.-H. Tan, *J. Am. Chem. Soc.* **2006**, *128*, 13692; e) D. Akalay, G. Dürner, M. W. Göbel, *Eur. J. Org. Chem.* **2008**, 2365; for an asymmetric organocatalytic Diels–Alder cycloaddition between 3-hydroxy-2-pyridones and maleimides, see: f) J. Y.-T. Soh, C.-H. Tan, *J. Am. Chem. Soc.* **2009**, *131*, 6904.

[14] a) G. Bartoli, M. Bosco, A. Carlone, A. Cavalli, M. Locatelli, A. Mazzanti, P. Ricci, L. Sambri, P. Melchiorre, *Angew. Chem. Int. Ed.* **2006**, *118*, 5088; *Angew. Chem. Int. Ed.* **2006**, *45*, 4966; b) W. Ye, Z. Jiang, Y. Zhao, S. L. M. Goh, D. Leow, Y.-T. Soh, C.-H. Tan, *Adv. Synth. Catal.* **2007**, *349*, 2454; c) Z. Jiang, W. Ye, Y. Yang, C.-H. Tan, *Adv. Synth. Catal.* **2008**, *350*, 2345.

[15] G.-L. Zhao, Y. Xu, H. Sundén, L. Eriksson, M. Sayah, A. Córdova, *Chem. Commun.* **2007**, 734.

[16] L. Zu, H. Xie, H. Li, J. Wang, W. Jiang, W. Wang, *Adv. Synth. Catal.* **2007**, *349*, 1882.

[17] J. Lu, W.-J. Zhou, F. Liu, T.-P. Loh, *Adv. Synth. Catal.* **2008**, *350*, 1796.

[18] a) O. O. Grygorenko, N. A. Kopylova, P. K. Mikhailiuk, A. Meissner, I. V. Komarov, *Tetrahedron: Asymmetry* **2007**, *18*, 290; b) M. Damodiran, P. M. Sivakumar, R. SenthilKumar, D. Muralidharan, B. V. N. P. Kumar, M. Doble, P. T. Perumal, *Chem. Biol. Drug Des.* **2009**, *74*, 494; c) E. Guth, M. Farris, M. Bovee, C. S. Francklyn, *J. Biol. Chem.* **2009**, *284*, 20753; d) E. E. Shul'ts, T. G. Tolstikova, S. E. Tolstikov, V. T. Daibova, M. M. Shakirov, A. V. Bolkunov, M. P. Dolgikh, *Pharm. Chem. J.* **2007**, *41*, 74; e) R. M. de Figueiredo, M. Voith, R. Fröhlich, M. Christmann, *Synlett* **2007**, 391; f) R. M. de Figueiredo, R. Fröhlich, M. Christmann, *Angew. Chem.* **2007**, *119*, 2941; *Angew. Chem. Int. Ed.* **2007**, *46*, 2883.

[19] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; b) T. Inokuma, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2006**, *128*, 9413.

[20] When 2-*tert*-butyl-4-phenyloxazol-5(4*H*)-one was treated with *N*-phenylmaleimide (**2a**) in toluene at room temperature in the presence of (*S*,*S*)-**I** (10 mol%), the reaction afforded a complex mixture regioisomers: C-4/C-2 3.5:1. The C-4 regioisomer was produced with a 2.5:1 d.r. The major diastereomer of this compound was isolated in 35% yield after column chromatography and with a 85:15 e.r.

[21] CCDC-767697 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[22] After submission of this work, addition of oxazolones to α,β-unsaturated acylphosphonates was reported: H. Jiang, M. W. Paixao, D. Monge, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 2775.

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