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Rh-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to α, β-Unsaturated Ketones with DIFLUORPHOS and SYNPHOS Analogues

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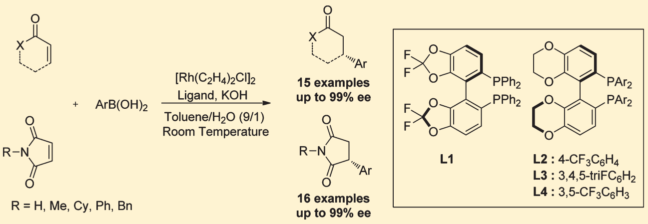
S Supporting Information

ABSTRACT: Applications of electron-deficient DIFLUORPHOS and SYNPHOS analogues in the rhodium-catalyzed asymmetric conjugate addition of boronic acids to α,β-unsaturated ketones afford the 1,4-addition adducts in yields up to 92% and with 99% ee. Particularly, a Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to nonsubstituted maleimide substrates using the (*R*)-3,5-diCF$_3$-SYNPHOS ligand is also reported. This protocol provides access to various enantioenriched 3-substituted succinimide units of biological interest, in high yields and good to excellent ee up to 93%, which could be upgraded up to 99% ee, after a single crystallization.



INTRODUCTION

The transition-metal-catalyzed 1,4-addition of organometallic reagents to activated alkenes is one of the most powerful processes for C−C bond formation.[1] In particular, the Rh-catalyzed asymmetric conjugate addition of organoboron reagents has received a lot of attention since the seminal breakthrough reported by Hayashi, Miyaura et al.[2] in 1998. Consequently, during the past two decades, a plethora of highly efficient catalytic systems has been reported to give chiral Michael 1,4-products with outstanding high level of selectivity (>95% ee) for a wide- range of activated alkenes including α,β-unsaturated ketones, esters, amides, phosphonates, and nitroalkenes.[3] However, despite significant recent advances in this area, there are still some challenging substrates for this reaction including nonsubstituted maleimide derivatives. In this context, only few efficient catalytic systems have been reported for asymmetric 1,4-addition of boronic acid reagents to maleimides,[4] despite the fact that the corresponding 3-substituted succinimide units can be found in several natural products and marketed drug molecules.[5] Among them, the rhodium complexes coordinated with chiral dienes and phosphine-olefin ligands described by Hayashi et al.,[4a−c,f] Carnell et al,.[4h] and Grützmacher et al.[4d] represent, to date, the most active catalyst systems for this particular reaction, resulting in high to excellent selectivity ranging from 80% to 99% ee. In contrast to the efficient enantioselective Rh-catalyzed synthesis of 1,4-adducts bearing a quaternary stereocenter,[4c] Hayashi et al. have clearly demonstrated that atropisomeric ligands[4a] such as BINAP,[6] SEGPHOS,[7] P-PHOS,[8] and phosphoramidite[9] turned out to be not suitable for the rhodium-promoted conjugate addition of nonsubstituted challenging maleimide derivatives, since the corresponding 3-substituted succinimides were obtained in low to moderate ee in the range of 21−58%. Surprisingly, to the best of our knowledge, no improvement in terms of enantioselectivity based on the use of atropisomeric ligands has been reported to date for this transformation. Two exceptions should be noted. In 2007, Miyaura et al.[4e] described the Pd-catalyzed asymmetric 1,4-addition of 3-methoxyphenylboronic acid with *N*-phenyl and *N*-methyl substituted maleimide derivatives using CHIRAPHOS as ligand, providing the desired 1,4-addition products in 40% and 90% ee, respectively. Interestingly, these authors have also demonstrated that the *N*-H maleimide compound, which is known to be an inactive substrate for this reaction, also reacted under the above conditions to give the corresponding 1,4-adduct in high enantiomeric excess up to 90%. Shintani and Hayashi et al.[4g] have reported 83% and 85% ee for the reaction of 1-(2-*tert*-butylphenyl)maleimide substrate with phenylboronic acid in the presence of 5 mol % of Rh catalysts bearing (*S*)-BINAP[6] and (*S*)-phosphoramidite,[9] respectively. Recently, it has been shown by several groups including ourselves[10,11] that the catalytic activity for Rh-promoted 1,4-addition of arylboronic acids at room temperature could be significantly enhanced by using electron-deficient ligands. In 2009, Sakai et al.[10] reported a highly active Rh/MeO-F$_{12}$BIPHEP catalyst for the asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated ketone with excellent enantioselectivities up to 99%. In this context, the introduction of electron-withdrawing substituents on SYNPHOS[12] ligand enabled us to observe a significant electronic effect of (*R*)-3,5-diCF$_3$-SYNPHOS,[11] which plays a crucial role in the rhodium-mediated conjugate addition of arylboronic acids to a range of cyclic and acyclic enones.[11] In our ongoing program toward the design and applications of atropisomeric ligands,[11−15] we report herein catalytic enantioselective conjugate addition of arylboronic acids using electron-deficient diphosphines such as DIFLUORPHOS **L1**,[12a,15] (*R*)-4-CF$_3$-SYNPHOS **L2**, (*R*)-3,4,5-triF-SYNPHOS **L3**, and (*R*)-3,5-diCF$_3$-SYNPHOS **L4** at room temperature and a rhodium-catalyzed enantioselective conjugate addition of a range of arylboronic acids to

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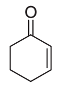
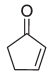
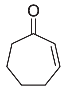
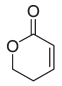
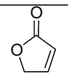
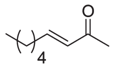
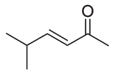
Table 1. Rh-Catalyzed Conjugate Addition of Phenylboronic Acid to α,*β*-Unsaturated Ketones with Ligands L1−L4

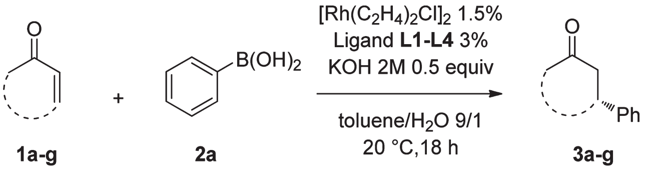
entry	substrate	ligand	product	yield (%)[a]	ee (%)[b]
1		**L1**	**3a**	56	94
2		**L2**		92	99
3		**L3**		82	99
4	**1a**	**L4**		95	99
5		**L1**	**3b**	41	99
6		**L2**		69	88
7		**L3**		77	97
8	**1b**	**L4**		84	96
9		**L1**	**3c**	70	92
10		**L2**		80	96
11		**L3**		63	91
12	**1c**	**L4**		84	99
13		**L1**	**3d**	44	93
14		**L2**		80	97
15		**L3**		41	94
16	**1d**	**L4**		70	90
17		**L1**	**3e**	23	99
18		**L2**		77	97
19		**L3**		69	86
20	**1e**	**L4**		48	77
21[c]		**L1**	**3f**	63	94
22		**L2**		57	93
23		**L3**		56	88
24	**1f**	**L4**		92	93
25[c]		**L1**	**3g**	62	96
26		**L2**		65	99
27		**L3**		5	nd
28	**1g**	**L4**		76	97

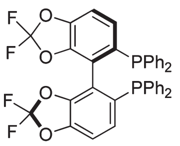
[a] After flash column chromatography on silica gel. [b] Determined by chiral stationary phase HPLC analysis. [c] Reaction carried out at 30 °C.

nonsubstituted *N*-methyl maleimide substrate using (*R*)-3,5-diCF$_3$-SYNPHOS **L4**.

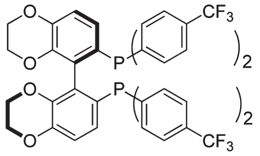
RESULTS AND DISCUSSION

We first examined the catalytic properties of (*R*)-DIFLUORPHOS **L1**, (*R*)-*p*-CF$_3$-SYNPHOS **L2**, (*R*)-3,4,5-triF-SYNPHOS **L3**, and (*R*)-3,5-diCF$_3$-SYNPHOS **L4** in the Rh-catalyzed asymmetric 1,4-addition of phenylboronic acid to α,*β*-unsaturated ketones at room temperature (Table 1). The reaction was performed using 1.5 mol % of the corresponding rhodium complexes in the presence of KOH in toluene/H$_2$O (9:1) at 20 °C for 18 h. As shown in Table 1, high enantioselectivities ranging from 77% to 99% were obtained for the reaction between phenylboronic acid **2a** and α,*β*-unsaturated cyclic ketones **1a**−**1e** using ligands **L1**−**L4**. Although (*R*)-DIFLUORPHOS **L1** led to excellent enantiofacial discrimination up to 99%, moderate to good yields in a range of 23−70% were reached at room temperature (entries 5, 9, 13, 17, 21). Significant better yields were obtained using, respectively, (*R*)-*p*-CF$_3$-SYNPHOS **L2**, (*R*)-3,4,5-triF-SYNPHOS **L3**, and (*R*)-3,5-diCF$_3$-SYNPHOS **L4** for all the considered cyclic substrates (entries 2−4, 6−8, 10−12, 14−16, 41−95% yield) with excellent enantioselectivities up to 99% for cyclohexenone **1a** (entries 2−4), cyclopentenone **1b** (entries 6−8, 88−97% ee), and cycloheptenone **1c** (entries 10−12, 91−99% ee). A similar trend was observed for 5,6-dihydro-2*H*-pyran-2-one **1d** and 2(5*H*)-furanone **1e** (entries 14−16, 18−20, 77−97% ee). Acyclic alkenones **1f** and **1g** afforded the corresponding 1,4-adducts **3f** and **3g** with good yields (entries 21−28, 57−92% except for entry 27) and high enantioselectivities in the range of 88−99% with all of the examined ligands **L1**−**L4**.

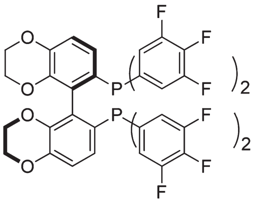




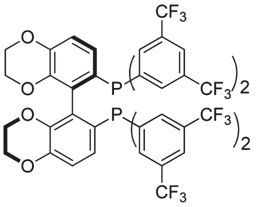
(*R*)-DIFLUORPHOS
L1



(*R*)-*p*-CF$_3$-SYNPHOS
L2



(*R*)-3,4,5-triF-SYNPHOS
L3

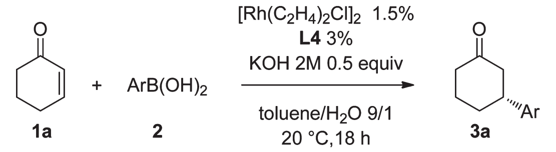


(*R*)-3,5-diCF$_3$-SYNPHOS
L4

In this context, (*R*)-3,5-diCF$_3$-SYNPHOS **L4** was selected for the next experiments. Extending the rhodium(I)/(*R*)-3,5-diCF$_3$-SYNPHOS-catalyzed addition to a variety of boronic acids and cyclohexenone **1a** demonstrated excellent selectivities with either with the electron-rich 4-MeC$_6$H$_4$, 3,5-diMeC$_6$H$_3$, 4-MeOC$_6$H$_4$, and 3-MeOC$_6$H$_4$ boronic acids (Table 2, entries 1−4, up to 99% ee) or the electron-poor 4-BrC$_6$H$_4$ and 3-ClC$_6$H$_4$ boronic acids (Table 2, entries 5, 6, up to 99% ee). A high selectivity up to 93% was also obtained with the hindered *o*-tolyl and naphthyl boronic acids (entries 7, 8).

We next turned our attention to the Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to challenging α,*β*-unsaturated monosubtituted maleimides using (*R*)-3,5-diCF$_3$-SYNPHOS **L4**. To establish the optimum reaction conditions, we preliminarily studied the 1,4-addition of phenylboronic acid **2a** to various *N*-substituted maleimide substrates **4a**−**e**, in the presence of 3 mol % of [Rh(C$_2$H$_4$)$_2$Cl$_2$]$_2$/(*R*)-3,5-diCF$_3$-SYNPHOS catalyst. Several parameters such as metal precursor, solvent, base, temperature, reaction time, and catalyst loading were examined, and some representative results of these experiences are summarized in Table 3. We found that the nature of the substituent on the *N*-atom of the maleimide had a dramatic impact on the stereochemical outcome of the reaction (Table 3, entries 1−5). Whereas almost no reaction occurred with the unprotected maleimide **4a**, all other substrates **4b**−**e** tested gave full conversions but different selectivities ranging from 48% to 88% ee for the *N*-methyl derivative **4e**. Other rhodium precursors

Table 2. Rhodium(I)/(*R*)-3,5-diCF$_3$-SYNPHOS-Catalyzed Addition of Arylboronic Acids 2 to Cyclohexenone 1a



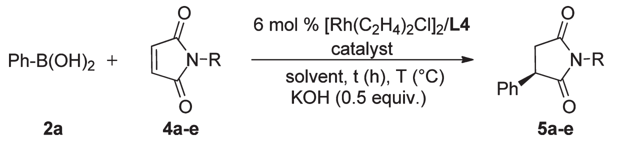
entry	Ar of boronic acid	yield (%)[a]	ee (%)[b]
1	4-MeC$_6$H$_4$	90	99
2	3,5-diMeC$_6$H$_3$	90	99
3	4-MeOC$_6$H$_4$	84	99
4	3-MeOC$_6$H$_4$	50	96
5	4-BrC$_6$H$_4$	81	99
6	3-ClC$_6$H$_4$	82	99
7	2-MeC$_6$H$_4$	86	93
8	1-naphthyl	81	90

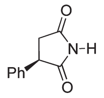
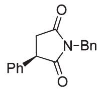
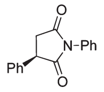
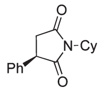
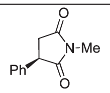
[a] After flash column chromatography on silica gel. [b] Determined by chiral stationary phase HPLC analysis.

with the potential for use as the catalyst in the reaction were also screened. However, a significant decrease in the catalytic performance was observed when the reaction was carried out with [RhcodCl]$_2$, [RhcodBr]$_2$, and [Rh(C$_2$H$_4$)$_2$acac] (see Table S1 in Supporting Information). Further studies showed that this reaction was strongly solvent-dependent. Nonpolar solvents gave higher catalytic activity (Table 3, entries 6−9) than polar solvents (Table 3, entries 10−11), the most efficient one being toluene/H$_2$O, which allowed the isolation of the 3-substituted succinimide **4e** with an enantiomeric excess of 89% (Table 3, entry 6). Additionally, we found that KOH was the most suitable base for this reaction, giving rise to the desired product in 89% ee with complete conversion. Inferior results in terms of both conversion and selectivity were obtained when other organic or inorganic bases were used (see Table S2 in Supporting Information). Decreasing the temperature of the reaction from 50 to 30 °C led to a substantial improvement in the selectivity with 93% ee, whereas running the reaction at 15 °C did not further improve the enantioselectivity (Table 3, compare entry 6 vs 12 and 13). Interestingly, the reaction proceeded well even at a lower catalyst loading, although a slight decrease of the selectivity was observed (Table 3, entries 15, 16). Through these screenings, the best reaction conditions were therefore set as the following: 3 mol % of [Rh(C$_2$H$_4$)$_2$Cl]$_2$/**L4** as catalyst, toluene/H$_2$O (9:1) as solvent, in the presence of 0.5 equiv of KOH as base, at 30 °C for 3 h.

Under the optimized reaction conditions, we then investigated the scope of the Rh/(*R*)-3,5-diCF$_3$-SYNPHOS catalyzed asymmetric 1,4-addition of various arylboronic acids **2a**−**n** to *N*-methylmaleimide substrate **4e**. As highlighted in Table 4, the reaction proceeded well in all cases, giving the desired products in high yields and good enantioselectivities (Table 4, entries 1−14, 75−90% yields, 80−93% ee). It appears from data of Table 4 that the position and electronic nature of the substituents on the aromatic ring of the arylboronic acid **2** significantly affect the selectivity of the reaction. Reaction conducted with arylboronic acids **2b**−**g** bearing electron-withdrawing substituents resulted in the formation of the desired products **5f**−**k** in lower catalytic efficiency to those obtained with phenylboronic acid **2a** (Table 4, compare entries 1 vs 2−7, 75−82% yields, 80−89% ee).

Table 3. Optimization of the Rh-Catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid 2a to Various Maleimides 4[a]

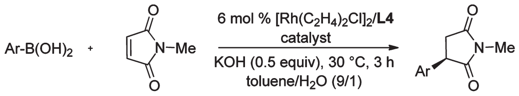


entry	solvent (9/1)	t(h)	T(°C)	product	conv. (%)[b]	ee (%)[c]
1	dioxane/H$_2$O	18	50	 **5a**	10	nd
2	dioxane/H$_2$O	18	50	 **5b**	>99	48
3	dioxane/H$_2$O	18	50	 **5c**	>99	67
4	dioxane/H$_2$O	18	50	 **5d**	>99	80
5	dioxane/H$_2$O	18	50	 **5e**	>99	88
6	toluene/H$_2$O	18	50	**5e**	>99	89
7	THF/H$_2$O	18	50		50	80
8	DCE/H$_2$O	18	50		>99	87
9	DME/H$_2$O	18	50		>99	40
10	*i*PrOH/H$_2$O	18	50		30	12
11	MeOH/H$_2$O	18	50		30	2
12	toluene/H$_2$O	18	30		>99	93
13	toluene/H$_2$O	18	15		>99	90
14	toluene/H$_2$O	3	30		>99	93
15[d]	toluene/H$_2$O	3	30		>99	92
16[e]	toluene/H$_2$O	3	30		>99	90

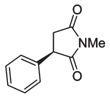
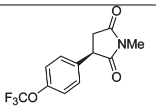
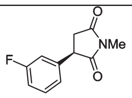
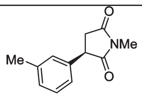
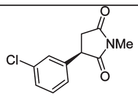
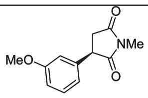
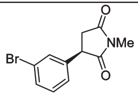
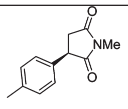
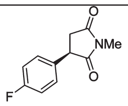
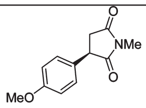
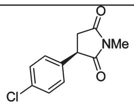
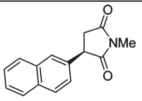
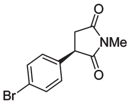
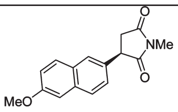
[a] Reaction conditions (unless otherwise specified): 0.3 mmol of **4** with 2 equiv of **2a**, 6 mol % of catalyst. [b] Determined by ^{1}H NMR of crude product. [c] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC). Absolute configuration was determined to be *R* by comparison of the specific rotation with reported data. [d] 4 mol % of catalyst. [e] 2 mol % of catalyst.

The only exception was the enantioselectivity of 92% obtained with boronic acid **2h**, bearing the trifluoromethyl group, which is known to be a long-range electron-withdrawing substituent[16] (Table 4, entry 8). In contrast, reaction performed with arylboronic acids **2i**−**n** having electron-donating groups provide the corresponding α-substituted succinimides **5m**−**r** with comparable or slightly lower results in terms of both yield and selectivity compared with those obtained with phenylboronic acid **2a** (Table 4, compare entries 1 vs 9−14, 80−90% yields, 90−93% ee). Finally, we were pleased to find that the enantiomeric excesses of all the 1,4-addition products **5e**−**r** could be easily upgraded up to 93−99%, after a single crystallization, as outlined in Table 4.

Table 4. Scope of the Asymmetric 1,4-Addition Reaction of Arylboronic Acids to Maleimide 4e[a]



2a-n **4e** **5e-r**

Entry	Boronic acids Ar	Product	Yield[b] (%)	ee[c] (%)	Entry	Boronic acids Ar	Product	Yield[b] (%)	ee[c] (%)
1	C_6H_5 **2a**	 **5e**	88	93 (99)[d]	8	4-CF_3O-C_6H_4 **2h**	 **5l**	80	92 (99)
2	3-F-C_6H_4 **2b**	 **5f**	81	89 (99)	9	3-Me-C_6H_4 **2i**	 **5m**	83	91 (94)
3	3-Cl-C_6H_4 **2c**	 **5g**	75	87 (99)	10	3-MeO-C_6H_4 **2j**	 **5n**	85	90 (99)
4	3-Br-C_6H_4 **2d**	 **5h**	81	80 (97)	11	4-Me-C_6H_4 **2k**	 **5o**	80	91 (97)
5	4-F-C_6H_4 **2e**	 **5i**	81	87 (97)	12	4-MeO-C_6H_4 **2l**	 **5p**	80	93 (94)
6	4-Cl-C_6H_4 **2f**	 **5j**	80	87 (96)	13[e]	$C_{10}H_7$ **2m**	 **5q**	80	92 (98)
7	4-Br-C_6H_4 **2g**	 **5k**	82	85 (96)	14[e]	6-MeO-$C_{10}H_6$ **2n**	 **5r**	90	90 (93)

[a] Reaction conditions (unless otherwise specified): 0.3 mmol of **4e** with 2 equiv of **2**, 3 mol % of catalyst. [b] After flash column chromatography on silica gel. [c] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC). Absolute configuration was determined to be *R* by comparison of the specific rotation with reported data. [d] Numbers in parentheses indicate the ee values after a single crystallization. [e] Reaction run in dioxane/H_2O (9:1).

■ CONCLUSION

In summary, this study demonstrates that electron-deficient ligands DIFLUORPHOS and SYNPHOS derivatives can be used in the rhodium-catalyzed conjugate addition of α,β-unsaturated ketones at room temperature with high yields and ee's up to 99%. We have successfully developed a Rh/(*R*)-3,5-diCF$_3$-SYNPHOS catalyzed asymmetric 1,4-addition of arylboronic acids to challenging maleimide substrates. A salient feature of our catalytic system relies on the fact that the reaction could be performed at 30 °C for 3 h, affording various synthetically and biologically important chiral 3-substituted succinimide derivatives in high yields and excellent enantiomeric excesses up to >99%, after a single crystallization. Furthermore, it is worth noting that these results are the best ones reported so far in the literature for this particular class of substrates with atropisomeric diphosphine ligands.

■ EXPERIMENTAL SECTION

General Information. All reactions were run under an atmosphere of argon. Reaction vessels were flame-dried under vacuum and cooled under a stream of argon. Toluene and dichloroethane (DCE) were distilled on calcium hydride prior to use. THF, dioxane, and dimethoxyether (DME) were distilled on sodium/benzophenone prior to use. Isopropanol and methanol were distilled on sodium prior to use. All the solvents including distilled water were degassed prior to use. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a 300 MHz apparatus. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane (TMS) relative to the singlet at 7.26 ppm for deuterochloroform. Coupling constants are reported in hertz (Hz). The following abbreviations are used: s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, br, broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a 75 MHz apparatus. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the center line of the triplet at 77.0 ppm for deuterochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling. Analytical thin layer chromatography (TLC) was carried out using commercial silica gel plates, and spots were detected with UV light and revealed with $KMnO_4$ or Kagi–Mosher solutions. Enantiomeric excesses were determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) using Chiralcel columns (AD-H or AS-H) and eluting with a $scCO_2$/isopropanol mixture as indicated. Optical rotations were measured on a polarimeter at 589 nm (sodium lamp). Melting points (mp) were determined on a slow fusion melting point apparatus.

General Procedure for Asymmetric 1,4-Conjugate Addition of Arylboronic Acids to Nonsubstituted Maleimide Substrates. In a 10 mL sealed tube under argon were introduced successively 3 mol % of the rhodium complex and 21 mg of ligand (*R*)-3,5-diCF$_3$-SYNPHOS **L4** (0.018 mmol, 6 mol %) in 0.75 mL of degassed solvent (*c* = 0.4 M). The solution was stirred 5 min, and then 0.075 mL of a 2 M aqueous solution of KOH (0.15 mmol, 0.5 equiv) was added. The mixture was stirred at room temperature for 10 min, and then arylboronic acid (0.6 mmol, 2 equiv) and desired maleimide compound (0.3 mmol, 1 equiv) were successively added. The reaction mixture was stirred at the desired temperature under argon for the indicated time, and then a saturated aqueous solution of ammonium chloride was added. The aqueous phase was extracted three times with dichloromethane. The organic layers were combined and dried over magnesium sulfate, and the solvents were evaporated under reduced pressure. The crude residue was then purified by flash chromatography on silica gel (cyclohexane/AcOEt).

(*R*)-1-Methyl-3-phenyl-pyrrolidine-2,5-dione[4a] (5e). Pale yellow solid: 0.050 g, 88% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.35–7.20 (m, 3H), 7.19–7.10 (m, 2H), 3.96 (dd, *J* = 9.60 Hz, 4.80 Hz, 1H), 3.15 (dd, *J* = 18.30 Hz, 9.60 Hz, 1H), 3.01 (s, 3H), 2.77 (dd, *J* = 18.60 Hz, 4.80 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.8, 176.2, 137.04, 129.2, 128.0, 127.4, 45.9, 37.1, 25.2. $[\alpha]^{25}_{D} = -61.4$ (*c* 0.945; CHCl$_3$) ee = 93% (ee > 99%, 82% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, *P* = 150 bar, scCO$_2$/*i*PrOH 90:10, flow 4 mL/min, λ = 215 nm, t_R [(*R*)-enantiomer] = 1.87 mn (major), t_R [(*S*)-enantiomer] = 2.05 mn (minor).

(*R*)-3-(3-Fluoro-phenyl)-1-methyl-pyrrolidine-2,5-dione (5f). Pale yellow solid: 0.050 g, 81% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.40–7.30 (m, 1H), 7.05–6.90 (m, 3H), 4.04 (dd, *J* = 9.57 Hz, 4.95 Hz, 1H), 3.23 (dd, *J* = 18.48 Hz, 9.67 Hz, 1H), 3.08 (s, 3H), 2.81 (dd, *J* = 18.42 Hz, 4.94 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.1, 175.8, 163.0 (d), 139.2 (d), 130.8 (d), 123.0 (d), 115.0 (d), 114.7 (d), 45.5, 36.8, 25.3. $[\alpha]^{25}_{D} = -57.1$ (*c* 0.98; CHCl$_3$) ee = 89% (ee = 99%, 70% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, *P* = 150 bar, scCO$_2$/*i*PrOH 94:6, flow 4 mL/min, λ = 215 nm, t_R [(*R*)-enantiomer] = 3.52 mn (major), t_R [(*S*)-enantiomer] = 4.10 mn (minor). Mp = 76 °C. HRMS (EI): *m*/*z* calcd for $C_{11}H_{10}FNO_2$-Na (M$^+$) 230.0588, found 230.0591.

(*R*)-3-(3-Chloro-phenyl)-1-methyl-pyrrolidine-2,5-dione (5g). Pale yellow solid: 0.050 g, 75% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.35–7.28 (m, 2H), 7.22 (s, 1H), 7.15–7.08 (m, 1H), 4.0 (dd, *J* = 9.30 Hz, 4.80 Hz, 1H), 3.22 (dd, *J* = 18.30 Hz, 9.60 Hz, 1H), 3.07 (s, 3H), 2.81 (dd, *J* = 18.60 Hz, 5.10 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.1, 175.7, 138.8, 135.0, 130.4, 128.2, 127.7, 125.6, 45.5, 36.8, 25.3. $[\alpha]^{25}_{D} = -54.1$ (*c* 1.09; CHCl$_3$) ee = 87% (ee = 99%, 62% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, *P* = 150 bar, scCO$_2$/*i*PrOH 90:10, flow 4 mL/min, λ = 215 nm, t_R [(*S*)-enantiomer] = 2.46 mn (minor), t_R [(*R*)-enantiomer] = 2.64 mn (major). Mp = 77 °C. HRMS (EI): *m*/*z* calcd for $C_{11}H_{10}ClNO_2Na$ (M$^+$) 246.0292, found 246.0293.

(*R*)-3-(3-Bromo-phenyl)-1-methyl-pyrrolidine-2,5-dione (5h). Pale yellow solid: 0.065 g, 81% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.50–7.40 (m, 1H), 7.39 (s, 1H), 7.30–7.12 (m, 2H), 4.0 (dd, *J* = 9.30 Hz, 4.80 Hz, 1H), 3.21 (dd, *J* = 18.60 Hz, 9.60 Hz, 1H), 3.08 (s, 3H), 2.80 (dd, *J* = 18.60 Hz, 5.10 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.1, 175.7, 139.1, 131.2, 130.7, 130.6, 126.1, 123.2, 45.4, 36.8, 25.3. $[\alpha]^{25}_{D} = -50.0$ (*c* 1.1; CHCl$_3$) ee = 80% (97%, 68% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, *P* = 150 bar, scCO$_2$/*i*PrOH 90:10, flow 4 mL/min, λ = 215 nm, t_R [(*S*)-enantiomer] = 2.94 mn (minor), t_R [(*R*)-enantiomer] = 3.32 mn (major). Mp = 80 °C. HRMS (EI): *m*/*z* calcd for $C_{11}H_{10}BrNO_2Na$ (M$^+$) 291.9767, found 291.9767.

(*R*)-3-(4-Fluoro-phenyl)-1-methyl-pyrrolidine-2,5-dione (5i). Pale yellow solid: 0.050 g, 81% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.23–7.17 (m, 2H), 7.10–7.0 (m, 2H), 4.0 (dd, *J* = 9.60 Hz, 4.80 Hz, 1H), 3.21 (dd, *J* = 18.30 Hz, 9.60 Hz, 1H), 3.07 (s, 3H), 2.79 (dd, *J* = 18.30 Hz, 4.80 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.6, 175.9, 162.3 (d), 132.7 (d), 129.1 (d), 116.1 (d), 45.1, 37.03, 25.2. $[\alpha]^{25}_{D} = -57.8$ (*c* 0.94; CHCl$_3$) ee = 87% (ee = 97%, 71% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, *P* = 150 bar, scCO$_2$/*i*PrOH 90:10, flow 4 mL/min, λ = 215 nm, t_R [(*R*)-enantiomer] = 1.66 mn (major), t_R [(*S*)-enantiomer] = 1.94 mn (minor). Mp = 101 °C. HRMS (EI): *m*/*z* calcd for $C_{11}H_{10}FNO_2Na$ (M$^+$) 230.0588, found 230.0591.

(*R*)-3-(4-Chloro-phenyl)-1-methyl-pyrrolidine-2,5-dione (5j). Pale yellow solid: 0.054 g, 80% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.35 (d, *J* = 8.60 Hz, 2H), 7.15 (d, J = 8.40 Hz, 2H), 4.0 (dd, *J* = 9.60 Hz, 4.94 Hz, 1H), 3.20 (dd, *J* = 18.50 Hz, 9.60 Hz, 1H), 3.06 (s, 3H), 2.80 (dd, *J* = 18.40 Hz, 4.90 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.3, 175.8, 135.3, 133.9, 129.3, 128.8, 45.2, 36.8, 25.2. $[\alpha]^{25}_{D} = -63.9$ (*c* 1.04; CHCl$_3$) ee = 87% (ee = 96%, 72% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, *P* = 150 bar, scCO$_2$/*i*PrOH 90:10, flow 4 mL/min, λ = 215 nm, t_R [(*R*)-enantiomer] = 2.55 mn (major), t_R [(*S*)-enantiomer] = 3.29 mn (minor). Mp = 95 °C. HRMS (EI): *m*/*z* calcd for $C_{11}H_{10}ClNO_2Na$ (M$^+$) 246.0292, found 246.0294.

(*R*)-3-(4-Bromo-phenyl)-1-methyl-pyrrolidine-2,5-dione (5k). Pale yellow solid: 0.066 g, 82% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.49 (d, *J* = 8.40 Hz, 2H), 7.11 (d, *J* = 8.40 Hz, 2H), 3.99 (dd, *J* = 9.60 Hz, 5.10 Hz, 1H), 3.21 (dd, *J* = 18.60 Hz, 9.60 Hz, 1H), 3.06 (s, 3H), 2.78 (dd, *J* = 18.30 Hz, 4.80 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.2, 175.8, 135.9, 132.3, 129.1, 122.0, 45.3, 36.8, 25.3. $[\alpha]^{25}_{D} = -44.0$ (*c* 0.92; CHCl$_3$) ee = 85% (ee = 96%, 73% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column,

P = 150 bar, scCO$_2$/iPrOH 90:10, flow 4 mL/min, λ = 215 nm, t_R [(R)-enantiomer] = 3.24 mn (major), t_R [(S)-enantiomer] = 4.30 mn (minor). Mp = 96 °C. HRMS (EI): m/z calcd for $C_{11}H_{10}BrNO_2Na$ (M$^+$) 291.9767, found 291.9767.

(*R*)-1-Methyl-3-(4-trifluoromethoxy-phenyl)-pyrrolidine-2,5-dione (5l). Pale yellow solid: 0.065 g, 80% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.30−7.20 (m, 4H), 4.06 (dd, J = 9.60 Hz, 5.10 Hz, 1H), 3.23 (dd, J = 18.30 Hz, 9.60 Hz, 1H), 3.07 (s, 3H), 2.81 (dd, J = 18.60 Hz, 5.10 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.3, 175.7, 148.8, 135.5, 128.9, 121.7, 45.2, 36.8, 25.3. $[\alpha]^{25}{}_D$ = −52.0 (c 1.02; CHCl$_3$) ee = 92% (ee = 99%, 72% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, P = 150 bar, scCO$_2$/iPrOH 94/6, flow 4 mL/min, λ = 215 nm, t_R [(R)-enantiomer] = 2.10 mn (major), t_R [(S)-enantiomer] = 2.51 mn (minor). Mp = 54 °C. HRMS (EI): m/z calcd for $C_{12}H_{10}F_3NO_3Na$ (M$^+$) 296.0505, found 296.0507.

(*R*)-1-Methyl-3-*m*-tolyl-pyrrolidine-2,5-dione (5m). Pale yellow solid: 0.050 g, 83% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.30−7.22 (m, 1H), 7.14−7.10 (m, 1H), 7.0−6.98 (m, 2H), 3.99 (dd, J = 9.52 Hz, 4.73 Hz, 1H), 3.20 (dd, J = 18.47 Hz, 9.47 Hz, 1H), 3.08 (s, 3H), 2.82 (dd, J = 18.47 Hz, 4.71 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.9, 176.3, 138.9, 137.0, 129.0, 128.7, 128.0, 124.4, 45.9, 37.2, 25.2, 21.4. $[\alpha]^{25}{}_D$ = −62.3 (c 1.06; CHCl$_3$) ee = 91% (ee = 94%, 78% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, P = 150 bar, scCO$_2$/iPrOH 94/6, flow 4 mL/min, λ = 215 nm, t_R [(R)-enantiomer] = 3.44 mn (major), t_R [(S)-enantiomer] = 4.31 mn (minor). Mp = 82 °C. HRMS (EI): m/z calcd for $C_{12}H_{13}NO_2Na$ (M$^+$) 226.0838, found 226.0841.

(*R*)-3-(3-Methoxy-phenyl)-1-methyl-pyrrolidine-2,5-dione (5n). Pale yellow solid: 0.056 g, 85% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.35−7.25 (m, 1H), 6.90−6.75 (m, 3H), 4.0 (dd, J = 9.30 Hz, 4.80 Hz, 1H), 3.82 (s, 3H), 3.21 (dd, J = 18.30 Hz, 9.30 Hz, 1H), 3.08 (s, 3H), 2.84 (dd, J = 18.30 Hz, 4.80 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.6, 176.2, 160.0, 138.5, 130.2, 119.4, 113.5, 113.0, 55.2, 45.9, 37.0, 25.2. $[\alpha]^{25}{}_D$ = −47.7 (c 0.65; CHCl$_3$) ee = 90% (ee = 99%, 75% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, P = 150 bar, scCO$_2$/iPrOH 90:10, flow 4 mL/min, λ = 215 nm, t_R [(S)-enantiomer] = 2.42 mn (minor) t_R [(R)-enantiomer] = 2.68 mn (major). Mp = 74 °C. HRMS (EI): m/z calcd for $C_{12}H_{13}NO_3Na$ (M$^+$) 242.0788, found 242.0785.

(*R*)-1-Methyl-3-*p*-tolyl-pyrrolidine-2,5-dione (5o). Pale yellow solid: 0.049 g, 80% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.18 (d, J = 8.10 Hz, 2H), 7.10 (d, J = 8.10 Hz, 2H), 3.99 (dd, J = 9.60 Hz, 4.80 Hz, 1H), 3.19 (dd, J = 18.60 Hz, 9.60 Hz, 1H), 3.06 (s, 3H), 2.81 (dd, J = 18.60 Hz, 4.80 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 178.0, 176.4, 137.7, 134.0, 129.8, 127.2, 45.6, 37.1, 25.2, 21.0. $[\alpha]^{25}{}_D$ = −69.6 (c 0.86; CHCl$_3$) ee = 91% (ee = 97%, 73% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, P = 150 bar, scCO$_2$/iPrOH 90:10, flow 4 mL/min, λ = 215 nm, t_R [(R)-enantiomer] = 2.08 mn (major), t_R [(S)-enantiomer] = 2.28 mn (minor). Mp = 84 °C. HRMS (EI): m/z calcd for $C_{12}H_{13}NO_2Na$ (M$^+$) 226.0838, found 226.0841.

(*R*)-3-(4-Methoxy-phenyl)-1-methyl-pyrrolidine-2,5-dione (5p). Pale yellow solid: 0.053 g, 80% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.13 (d, J = 8.70 Hz, 2H), 6.89 (d, J = 8.70 Hz, 2H), 3.97 (dd, J = 9.60 Hz, 4.80 Hz, 1H), 3.79 (s, 3H), 3.19 (dd, J = 18.30 Hz, 9.30 Hz, 1H), 3.06 (s, 3H), 2.79 (dd, J = 18.30 Hz, 4.80 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 178.1, 176.3, 159.1, 128.9, 128.4, 114.5, 55.3, 45.1, 37.1, 25.1. $[\alpha]^{25}{}_D$ = −53.8 (c 0.39; CHCl$_3$) ee = 93% (ee = 94%, 77% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, P = 150 bar, scCO$_2$/iPrOH 90:10, flow 4 mL/min, λ = 215 nm, t_R [(R)-enantiomer] = 2.71 mn (major), t_R [(S)-enantiomer] = 3.07 mn (minor). Mp = 108 °C. HRMS (EI): m/z calcd for $C_{12}H_{13}NO_3Na$ (M$^+$) 242.0788, found 242.0786.

(*R*)-1-Methyl-3-naphthalen-2-yl-pyrrolidine-2,5-dione (5q). Pale yellow solid: 0.057 g, 80% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.89−7.75 (m, 3H), 7.70 (s, 1H), 7.52−7.45 (m, 2H), 7.30−7.25 (m, 1H), 4.19 (dd, J = 9.60 Hz, 4.80 Hz, 1H), 3.27 (dd, J = 18.60 Hz, 9.60 Hz, 1H), 3.11 (s, 3H), 2.92 (dd, J = 18.60 Hz, 4.80 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 177.8, 176.2, 134.2, 133.3, 132.7, 129.2, 127.7, 127.6, 126.6, 126.3, 124.7, 46.0, 37.1, 25.2. $[\alpha]^{25}{}_D$ = −98.9 (c 0.99; CHCl$_3$) ee = 92% (ee = 98%, 73% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AD-H column, P = 150 bar, scCO$_2$/iPrOH 90:10, flow 4 mL/min, λ = 215 nm, t_R [(R)-enantiomer] = 5.24 mn (major), t_R [(S)-enantiomer] = 5.78 mn (minor). Mp = 142 °C. HRMS (EI): m/z calcd for $C_{15}H_{13}NO_2Na$ (M$^+$) 262.0838, found 262.0842.

(*R*)-3-(6-Methoxy-naphtalen-2-yl)-1-methyl-pyrrolidine-2,5-dione (5r). Pale yellow solid: 0.072 g, 90% yield. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.72 (dd, J = 8.70 Hz, 14.40 Hz, 2H), 7.62 (s, 1H), 7.25−7.10 (m, 3H), 4.16 (dd, J = 9.60 Hz, 4.80 Hz, 1H), 3.92 (s, 3H), 3.27 (dd, J = 18.60 Hz, 9.60 Hz, 1H), 3.10 (s, 3H), 2.92 (dd, J = 18.30 Hz, 4.50 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 178.0, 176.3, 158.0, 134.0, 131.9, 129.2, 128.8, 128.0, 126.3, 125.3, 119.5, 105.6, 55.3, 45.9, 37.2, 25.2. $[\alpha]^{25}{}_D$ = −79.4 (c 1.02; CHCl$_3$) ee = 90% (ee = 93%, 86% yield after a single crystallization in absolute EtOH). CSP-SFC: Chiralcel AS-H column, P = 150 bar, scCO$_2$/iPrOH 90:10, flow 4 mL/min, λ = 215 nm, t_R [(R)-enantiomer] = 5.41 mn (major), t_R [(S)-enantiomer] = 6.39 mn (minor). Mp = 155 °C. HRMS (EI): m/z calcd for $C_{16}H_{15}NO_3Na$ (M$^+$) 292.0944, found 292.0947.

■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Experimental details and copies of ^{1}H and ^{13}C NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13. (b) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279. (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2797. (d) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039.

(2) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

(3) For reviews, see: (a) Hayashi, T. *Synlett* **2001**, 879. (b) Hayashi, T. *Chem. Rev.* **2003**, *103*, 2829. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (d) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313. (e) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288. (f) Hayashi, T. *Pure Appl. Chem.* **2004**, *76*, 465. (g) Miyaura, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (h) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093 and references therein.

(4) (a) Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425. (b) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611. (c) Shintani, R.; Duan, W. L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628. (d) Piras, E.; Läng, F.; Rüegger, H.; Stein, D.; Wörle, M.; Grützmacher, H. *Chem.—Eur. J.*

2006, *12*, 5849. (e) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Lett.* **2007**, *36*, 1442. (f) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130. (g) Duan, W.-L.; Shintani, R.; Hayashi, T. *Tetrahedron* **2007**, *63*, 8529. (h) Luo, Y.; Carnell, A. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2750. (i) Thaler, T.; Guo, L.-N.; Steib, A. K.; Raducan, M.; Karaghiosoff, K.; Mayer, P.; Knochel, P. *Org. Lett.* **2011**, *13*, 3182.

(5) (a) Ahmed, S. *Drug Des. Discovery* **1996**, *14*, 77. (b) Curtin, M. L.; Garland, R. B.; Heyman, H. R.; Frey, R. R.; Michaelodes, M. R.; Li, J.; Pease, L. J.; Glaser, K. B.; Marcotte, P. A.; Davidsen, S. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2919.(c) Tonnaer, J.; Alphons, D. M. PCT Int. Appl. WO2004110437, 2004. (d) Ballini, R.; Bosica, G.; Cioci, G.; Fiorini, D.; Petrini, M. *Tetrahedron* **2003**, *59*, 3603.

(6) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

(7) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(8) Shi, Q.; Xu, L.; Li, X.; Jia, X.; Wang, R.; Au-Yeung, T. T.-L.; Chan, A. S. C.; Hayashi, T.; Cao, R.; Hong, M. *Tetrahedron Lett.* **2003**, *44*, 6505.

(9) Boiteau, J.-G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2003**, *68*, 9481.

(10) (a) Korenaga, T.; Osaki, K.; Maenishi, R.; Sakai, T. *Org. Lett.* **2009**, *11*, 2325. (b) Korenaga, T.; Maenishi, R.; Hayashi, K.; Sakai, T. *Adv. Synth. Catal.* **2010**, *352*, 3247.

(11) Berhal, F.; Esseiva, O.; Martin, C.-H.; Tone, H.; Genet, J.-P.; Ayad, T.; Ratovelomana-Vidal, V. *Org. Lett.* **2011**, *13*, 2806.

(12) (a) Duprat de Paule, S.; Champion, N.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Dellis, P. French Patent 2830254, 2001; WO Patent 03029259, 2003. (b) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, 1931. (c) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Deschaux, G.; Dellis, P. *Org. Process Res. Dev.* **2003**, *7*, 399.

(13) Guerreiro, P.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Dellis, P. *Tetrahedron Lett.* **2001**, *42*, 3423.

(14) Lesseure, L.; Le Boucher d'Herouville, F.; Püntener, K.; Scalone, M.; Genet, J.-P.; Michelet, V. *Org. Lett.* **2011**, *13*, 3250.

(15) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 320.

(16) Castagnetti, C.; Schlosser, M. *Chem.—Eur. J.* **2002**, *8*, 799.