Copper-Catalyzed Asymmetric Ring-Opening Reaction of Oxabenzonorbornadienes with Grignard and Aluminum Reagents

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Abstract: A highly enantioselective method for the copper-catalyzed desymmetrization of oxabenzonorbornadienes with aluminum reagents and SimplePhos as chiral ligand has been developed. The same reaction with Grignard reagents is also reported. A wide range of alkyl chains have been used with moderate to high enantioselectivity and high *trans* selectivity. The transfer of a methyl group is also reported with high enantiomeric and diastereomeric excess and yields for different substrates. We finally have been able to perform the first *trans* enantioselective desymmetrization of oxabenzonorbornadienes with an aromatic group.

Key words: copper catalysis, asymmetric transformation, Grignard reagents, aluminum reagents, SimplePhos

Formation of multiple stereocenters is one of the most important issues in modern organic chemistry. The desymmetrization of *meso* compounds has attracted much attention since many stereocenters can be easily established from simple transformations.[1] During the last decade, desymmetrization of oxabicyclic alkenes with transition metal catalysis has exploded.[2] Most of the described methodologies provide the formation of the *syn*-adduct.

A large variety of carbon nucleophiles have been used to perform this transformation. Initially organolithium reagents[2a,3] and organocuprates[4] showed limited success in affording *syn*-addition products in moderate to good yields. Only the introduction of softer organometallic nucleophiles in combination with transition metal catalysis allowed the asymmetric desymmetrization of oxabicyclic alkenes in good yields. Among all the nucleophiles used for this transformation, organozinc reagents in combination with palladium catalysis have been the most studied.[5] Other nucleophiles such as aluminum reagents in combination with titanium or zirconium,[6] organoboron with rhodium[7] or palladium[8] and Grignard reagents with zirconium[6] have also been employed. All these methodologies provide the *syn*-adduct resulting from an attack on the *exo* face of the oxabicyclic unit.

The *anti*-ring-opening reaction is less documented. The first report was from Lautens and co-workers with the rhodium-catalyzed desymmetrization of oxabenzonorbornadienes with heteroatomic nucleophiles.[9] Copper-catalyzed allylic alkylation appeared to be an efficient tool to form the *anti*-adduct with organometallic reagents. Feringa and co-workers applied a chiral copper–phosphoramidite catalyst to the addition of dialkylzinc to oxabenzonorbornadienes.[10] Following this report, Grignard reagents were applied with copper catalysis in non-enantioselective methods by Carretero and co-workers.[11] the enantioselective version was described by Zhou and co-workers.[12] The *anti* stereoselectivity of the reaction comes from a pure S_N2' mechanism.[10,11a] However limitations exist in all cases. Despite high yields and enantioselectivities obtained with dialkylzinc reagents, transfer of the methyl group occurred with low yield and conversion. Furthermore, one equivalent of zinc triflate is needed for the reaction to proceed.[10] Grignard reagents are far more reactive, but the enantioselective version suffers high limitations as only primary and linear alkyl Grignard reagents can be transferred.[12] Another lack in both methodologies is the absence of transfer of aromatic groups. Transfer of aryl groups in an *anti* fashion is only observed in racemic versions of the reaction.[11]

Recently, our group reported the synthesis of a new family of ligands: SimplePhos (e.g., **L1**, Figure 1).[13]

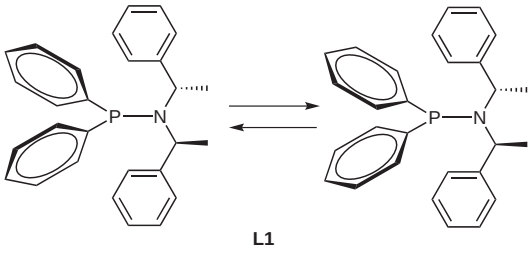

Figure 1 SimplePhos ligand (**L1**)

This family of ligands showed high efficiency in copper-catalyzed allylic alkylation and in desymmetrization of bicyclic hydrazines with trialkylaluminum reagents[13] as well as in S_N2' ring-opening reactions of vinyloxiranes.[14] In the course of our studies, we decided to investigate the application of SimplePhos ligands in copper-catalyzed desymmetrization of oxabenzonorbornadienes with Grignard and aluminum reagents.

Grignard Reagents

To complete our study on the copper-catalyzed allylic alkylation with Grignard reagents,[15] we turned our atten-

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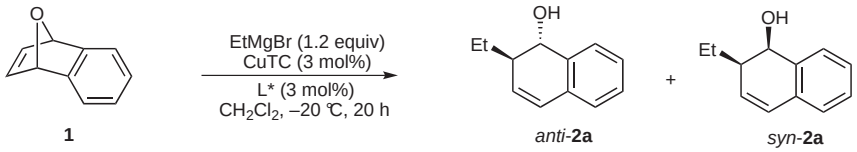


1 *anti*-**2a** *syn*-**2a**

Scheme 1 General procedure for the determination of the family of ligands

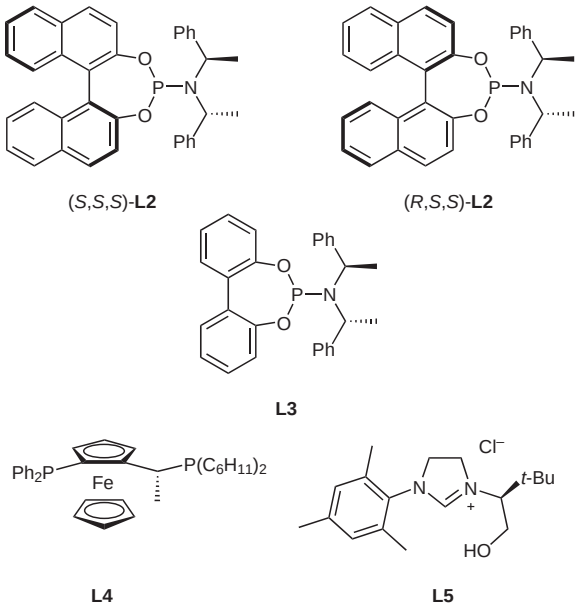


Figure 2 Preliminary tested ligands

Table 1 Preliminary Test of Ligands for the Desymmetrization of Oxabenzonorbornadiene **1** (Scheme 1)

Entry	Ligand	Product **2a**		
		Conv.[a] (%)	Ratio[b] *anti*/*syn*	ee[b] (%) *anti*
1	(*S*,*S*,*S*)-**L2**	87	98:2	56 (–)
2	(*R*,*S*,*S*)-**L2**	43	90:10	23 (–)
3	**L3**	85	92:8	36 (–)
4	**L4**	100	98:2	10 (+)
5	**L5**	10	62:38	13 (–)
6	**L1**	97	98:2	82 (–)

[a] Determined by GC-MS and ^{1}H NMR.
[b] Determined by chiral GC, the sign of the optical rotation is in parentheses.

tion to the desymmetrization of oxabenzonorbornadienes (Scheme 1).

We began our studies with the addition of ethylmagnesium bromide to oxabenzonorbornadiene **1**. First of all, the classical families of ligands (Figure 2) were tested to determine which family would be the more efficient (Table 1).

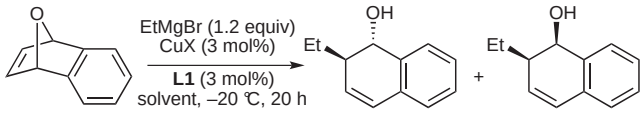
The tests were carried out in dichloromethane with copper thiophene-2-carboxylate (CuTC) as copper salt. The choice of the solvent was easy as both Carretero[11] and Zhou[12] explained that only nonpolar solvents gave good conversions and CuTC is known to be efficient in dichloromethane.

The phosphoramidite family confirms the observation made by Zhou and co-workers that only spiro-phosphoramidites gave interesting enantiomeric excesses.[12a] The atropos ligand **L2** showed an important match/mismatch effect as the match (*S*,*S*,*S*)-**L2** gave **2a** in good conversion, high diastereoselectivity but moderate enantiomeric excess (Table 1, entry 1); whereas the mismatch diastereomer (*R*,*S*,*S*)-**L2** gave only 43% conversion with moderate diastereoselectivity and an even lower enantiomeric excess (Table 1, entry 2). These two results show that the amine part-controls the enantioselectivity of the reaction. The tropos **L3** was slightly below (*S*,*S*,*S*)-**L2** in terms of enantioselectivity (Table 1, entry 3). The Josi-Phos ligand **L4** appears efficient in term of conversion and diastereoselectivity but only 10% ee was obtained (Table 1, entry 4). Carbene ligand **L5**[16] was also tested, but the reaction was very slow and low selectivities were obtained (Table 1, entry 5). We then turned our attention to the SimplePhos ligand **L1**.[13] We were delighted to see that in terms of conversion (97% conversion), diastereoselectivity (ratio *anti*/*syn* 98:2) and enantioselectivity (82% ee) good results were obtained (Table 1, entry 6). The absolute configuration of *anti*-**2a** was determined to be (1*S*,2*R*) by comparison with literature data {$[\alpha]_D^{20}$ –264.2 (*c* 1.01) 82% ee; 1*S*,2*R*)}.[10]

Once a good family of ligands was determined, we investigated the best conditions for this reaction. First of all the influence of the copper salt and the solvent were studied as their influence is known to be important in copper-catalyzed allylic alkylations (Table 2).[15,17,18]

First of all the effect of the solvent was investigated. It proved to have a dramatic effect on the enantioselectivity of the reaction. When the reaction was carried out in dichloromethane, 2-ethyl-1,2-dihydronaphthalen-1-ol (**2a**) was isolated in 90% yield with an *anti*/*syn* ratio of 98:2 and 82% ee (Table 2, entry 1). The solvent was then changed from dichloromethane to toluene; a dramatic effect was observed on the enantioselectivity as it dropped to 47% (Table 2, entry 2). As expected,[12a] diethyl ether was an even worse solvent as the alcohol **2a** was formed in nearly racemic form and a large amount of naphthalene was observed (Table 2, entry 3). To confirm the tendency with toluene, copper(II) triflate was used as the copper salt to eliminate the possibility of a unfavorable combination between toluene and CuTC. As no improvement was observed by changing the copper salt, we chose dichloromethane as the solvent (Table 2, entry 4).

Table 2 Copper Salt and Solvent Screening[a]



1 *anti*-**2a** *syn*-**2a**

Entry	Solvent	Cu salt	Conv.[b] (%)	Ratio[c] *anti*/*syn*	ee[c] (%) *anti*
1	CH_2Cl_2	CuTC	97 (90)	98:2	82
2	toluene	CuTC	98	97:3	47
3	Et_2O	CuTC	88	95:5	8
4	toluene	$Cu(OTf)_2$	98	95:5	50
5	CH_2Cl_2	$Cu(OTf)_2$	93	98:2	78
6	CH_2Cl_2	CuBr	98	98:2	80
7	CH_2Cl_2	CuCl	61	95:5	76
8	CH_2Cl_2	$Cu(OAc)_2 \cdot H_2O$	98	98:2	75
9[e]	CH_2Cl_2	CuTC	100	98:2	84
10[f]	CH_2Cl_2	CuTC	91	99:1	80

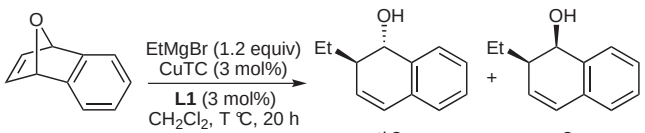
[a] Reaction conditions: **1** (1 mmol), Cu (3 mol%), **L1** (3 mol%), EtMgBr in Et_2O(1.2 equiv), solvent (6 mL); order of addition: substrate then Grignard reagent.
[b] Determined by GC-MS and ^{1}H NMR, the isolated yield is in parentheses.
[c] Determined by chiral GC, absolute configuration (–)-(1*S*,2*R*).
[d] Naphthalene (25%).
[e] **L1 (**6 mol%).
[f] Reverse addition order: Grignard reagent was added, then the substrate.

The effect of the copper salt is less important. Different copper(I) or copper(II) salts were tested (Table 2, entries 5–8). Only with copper(I) chloride was a decrease of the conversion observed (Table 1, entry 7). However CuTC remains slightly above the others copper salts. To complete the study the ratio ligand/copper was increased to 2:1. The enantioselectivity slightly increased from 82% to 84% ee, but 2-ethylnaphthalene was observed as a byproduct (Table 2, entry 9). Finally the reverse addition order was tested without any improvement (Table 2, entry 10).

The temperature was then changed. When the reaction was performed at room temperature, the enantioselectivity decreased to 56% ee and the *anti*/*syn* ratio decreased to 80:20 (Table 3, entry 2). It should be noted that a large of amount of reductive ring opening leading to racemic 1,2-dihydronaphthalen-1-ol occurred. This may be due to a β-hydride elimination on the cuprate, forming a copper hydride species. In order to increase the enantioselectivity of the reaction, the temperature was decreased to –40 °C, but no improvement was observed (Table 3, entry 3).

The ligand was then modified to study its influence on the outcome of the reaction (Figure 3). To have an idea of the

Table 3 Study of the Temperature



1 *anti*-**2a** *syn*-**2a**

Entry	Temp (°C)	Conv.[a] (%)	Ratio[b] *anti*/*syn*	ee[b] (%) *anti*
1	–20	97 (90)	98:2	82
2	22	70[c]	80:20	56
3	–40	90	98:2	78

[a] Determined by GC-MS and ^{1}H NMR, isolated yield is in parentheses.
[b] Determined by chiral GC.
[c] 13% of 1,2-dihydronaphthalen-1-ol detected.

influence of each part of the ligand, we envisaged modifying the bulk around the phosphorus part.

The steric bulk was increased in ligand **L6** and decreased in ligand **L7**.[19] When using **L6** as ligand, a decrease in the reactivity as well as in the enantioselectivity was observed (Table 4, entry 2).

Going from the two phenyl groups to two methyl groups had a dramatic effect on the enantioselectivity of the reaction as **2a** was obtained with only 28% ee (Table 4, entry 3). The attempt to decrease the rotation rate between the two aryl groups was also not beneficial to the enantioselectivity (Table 4, entry 4). The bulk of the amino part was increased with **L9**, but the result obtained was almost the same than with **L1** (Table 4, compare entries 1 and 5). Finally, adding chelating groups on the aromatic groups of the amino part was detrimental to the reaction as the conversion dropped to less than 10% after 20 hours and the enantiomeric excess was only 60% (Table 4, entry 6).

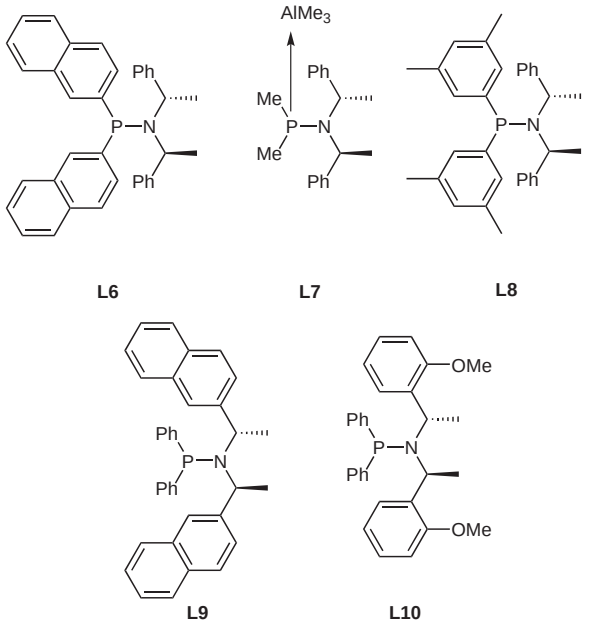


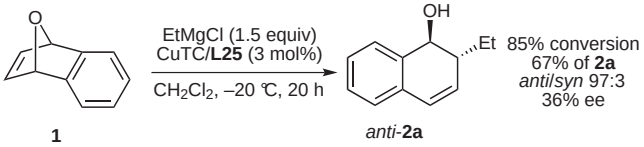
Figure 3 Ligands used for this study

Table 4 Modification of SimplePhos Ligand for the Desymmetrization of Oxabenzonorbornadiene **1** (Scheme 1)[a]

Entry	Ligand	Product **2a**		
		Conv.[b] (%)	Ratio[c] *anti*/*syn*	ee[c] (%) *anti*
1	**L1**	93 (90)	98:2	82
2	**L6**	65	92:8	62
3	**L7**	100	99:1	28
4	**L8**	93	96:4	74
5	**L9**	98	99:1	80
6	**L10**	9	92:8	60

[a] Reaction conditions: **1** (1 mmol), CuTC (3 mol%), **L** (3 mol%), EtMgBr in Et_2O (1.2 equiv), CH_2Cl_2 (6 mL), –20 °C; order of addition: substrate then Grignard reagent.
[b] Determined by GC-MS and ^1H NMR in parentheses isolated yield.
[c] Determined by chiral GC.

Before broadening the scope of the reaction, the reaction was performed with ethylmagnesium chloride to check if the same halogen effect exists with SimplePhos ligand as with phosphoramidite ligands (Scheme 2).[12a]



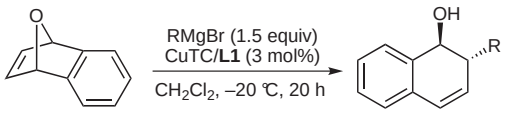
Scheme 2 Effect of the Grignard reagent counterion

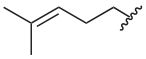
The conversion after 20 hours was 85% [**2a** (67%), naphthalene (17%), and 2-ethylnaphthalene (1%)]. The enantiomeric excess dropped to only 36%. The role of the counterion of the Grignard reagent appears to be crucial to the enantioselectivity of the reaction. However, it does not seem to play a role in the catalytic cycle as copper(I) chloride gave the same level of enantioselectivity as CuTC with ethylmagnesium bromide (Table 2, entries 1 and 7).

With the set of conditions in hand, the scope of the Grignard reagent was then studied (Table 5). Addition of ethylmagnesium bromide gave *trans*-2-ethyl-1,2-dihydronaphthalen-1-ol (*anti*-**2a**) in 90% yield and 82% ee (Table 5, entry 1).

Methylmagnesium bromide appeared to be less reactive than ethylmagnesium bromide. The temperature had to be increased to room temperature in order to have full conversion (Table 5, entries 2 and 3). 2-Methyl-1,2-dihydronaphthalen-1-ol (**2b**) was obtained in 84% yield with ratio *anti*/*syn* 90:10 and 72% ee (Table 5, entry 3); at this temperature naphthalene was detected as a side product. When a longer alkyl chain was used the enantioselectivity remains in the same range (Table 5, entry 4). The bulk of the alkyl chain was increased in the β-position going to an isobutyl chain. Despite good conversion and diastereoselectivity, the enantioselectivity for **2d** decreased to 62%

Table 5 Scope of the Grignard Reagent[a]



Entry	R	Product	Yield[b] (%)	Ratio[c] *anti*/*syn*	ee[c] (%) *anti*
1	Et	**2a**	90	98:2	82
2	Me	**2b**	(<10)	–	71
3[d]	Me	**2b**	84	90:10	72
4	*n*-Bu	**2c**	86	98:2	76
5	*i*-Bu	**2d**	(73)	95:5	62
6	$(CH_2)_2Ph$	**2e**	64	98.2	57
7		**2f**	95	97:3	64
8	*i*-Pr	**2g**	75[e]	90:10	30
9[f]	*i*-Pr	**2g**	(65)	95:5	54
10	Ph	**2h**	89	98:2	0

[a] Reaction conditions: **1** (1 mmol), CuTC (3 mol%), **L1** (3 mol%), RMgBr in Et_2O(1.2 equiv), CH_2Cl_2 (6 mL), –20 °C; order of addition: substrate then Grignard reagent.
[b] Isolated yield, conversion determined by GC-MS and ^1H NMR in parentheses.
[c] Determined by chiral GC.
[d] Reaction run at r.t.
[e] Naphthalene (20%) was detected by ^1H NMR.
[f] Reaction run at –40 °C.

ee (Table 5, entry 5). Phenethylmagnesium bromide induced lower enantioselectivity in **2e** (Table 5, entry 6). The functionalized 4-methylpent-3-enylmagnesium bromide gave result in the same range, *trans*-2-(4-methylpent-3-enyl)-1,2-dihydronaphthalen-1-ol (**2f**) was obtained in 95% yield, with high *anti/syn* ratio but moderate 64% ee (Table 5, entry 7). Moving to secondary Grignard reagents was more problematic, at –20 °C isopropylmagnesium bromide gave full conversion, however naphthalene was also formed. The alcohol **2g** was obtained in moderate *anti*/*syn* ratio (90:10) and only 30% ee (Table 5, entry 8). Decreasing the temperature to –40 °C, decreased the conversion but also the amount of side product (10% of naphthalene). An increase in the *anti*/*syn* ratio as well as the enantiomeric excess was also observed (Table 5, entry 9). Finally phenylmagnesium bromide was tested and the corresponding alcohol **2h** was obtained in 89% yield with high diastereoselectivity but as a racemic mixture (Table 5, entry 10).[12] Finally, we investigated the substrate scope for the reaction (Figure 4).

We wanted to modify the aromatic ring of the oxabenzonorbornadiene (Table 6) and also to apply the methodology to nonbenzylic oxabicyclic alkenes.

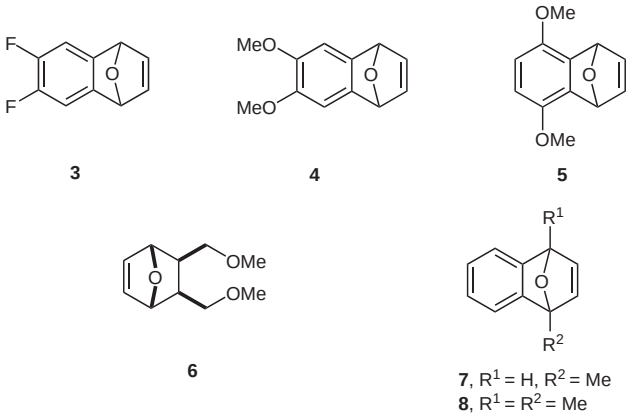
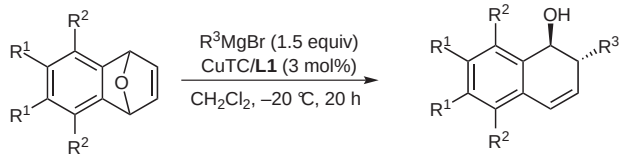


Figure 4 Substrates studied

Table 6 Substrate Scope; Oxabenzonorbornadienes Derivatives

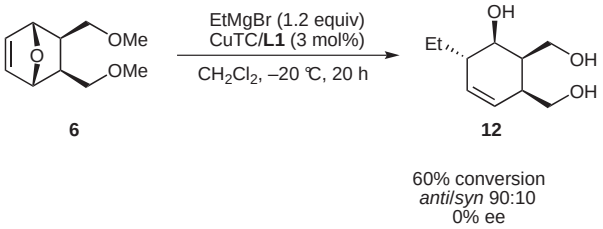


3, R^1 = F, R^2 = H
4, R^1 = OMe, R^2 = H
5, R^1 = H, R^2 = OMe

Entry	Substrate	R^3	Product	Conv.[a] (%)	Ratio[b] *anti*/*syn*	ee[c] (%)
1	**3**	Et	**9a**	100 (85)	96:4	64
2[d]	**4**	Me	**10b**	40[e]	>95:5	20
3	**4**	Et	**10a**	100 (53)[f]	>95:5	20
4[g]	**4**	Et	**10a**	50[h]	>95:5	31
5	**5**	Me	**11b**	–[i]	–	–

[a] Determined by GC-MS and ^{1}H NMR, isolated yield is in parentheses.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral SFC.
[d] Reaction run at r.t.
[e] 2,3-Dimethoxynaphthalene (11%) was detected.
[f] 2,3-Dimethoxynaphthalene (37%) was detected.
[g] Reaction run at – 40 °C.
[h] 2,3-Dimethoxynaphthalene (25%) was detected.
[i] No traces of the desired product.

The electron density of the aromatic group plays a very important role in the control of the reaction. Decreasing the electron density of the aromatic ring induced a decrease in the enantiomeric excess to 64% (Table 6, entry 1). Electron-rich substrates were then studied. Substrate **4** reacted with both methyl- and ethylmagnesium bromide to give the corresponding alcohols **10b** and **10a** in low yield and with very low enantiomeric excess (Table 6, entries 2 and 3). A large amount of 2,3-dimethoxynaphthalene was also formed. Decreasing the temperature to –40 °C with ethylmagnesium bromide allowed a slight increase in the enantioselectivity to 31% ee, but still a large amount of byproduct was observed (Table 6, entry 4). The substrate bearing the two methoxy groups in the *ortho* positions could not be desymmetrized under these conditions; only byproducts such 1,4-dimethoxynaphthalene and 6-ethyl-1,4-dimethoxynaphthalene were formed (Table 6, entry 5).



Scheme 3 Desymmetrization of a nonbenzylic substrate

When nonbenzylic substrate **6** was used the result was not enthusiastic (Scheme 3). The reaction was clean even if the conversion was not complete after 20 hours; the resulting alcohol **12** was obtained in racemic mixture in a ratio *anti*/*syn* 90:10. However this substrate is known to be very challenging as its asymmetric desymmetrization in *anti* fashion has not previously been reported.

The described methodology with Grignard reagents showed interesting results with the simple oxabenzonorbornadiene **1** compared to the previous published results with Grignard reagents,[12] but is very limited in substrate scope. To overcome this problem, we turned our attention to the aluminum reagents.

Aluminum Reagents

The major problem with dialkylzinc reagents and oxabenzonorbornadiene is their low reactivity. To obtain good conversion Feringa and co-workers had to add one equivalent of zinc triflate to act as a Lewis acid.[10] Organoaluminum reagents are known to be more Lewis acidic than their zinc analogues. This property combined with the high oxophilicity of aluminum (Al–O bond strength 138 kcal/mol) made aluminum reagents interesting candidates to act as nucleophiles in the desymmetrization reaction of oxabenzonorbornadiene derivatives. Moreover as they are produced on industrial scale, they are inexpensive and a large variety of primary trialkylaluminum are commercially available (Me_3Al, Et_3Al, *n*-Pr_3Al, *n*-Bu_3Al, *i*-Bu_3Al). Vinylaluminums and arylaluminums are also easily available via hydroalumination of alkynes[20] or Li/Al exchange.[21]

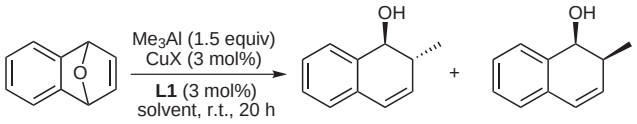
Based on our study with Grignard reagents, SimplePhos ligands were chosen as ligands to determine the best conditions. The copper salt and solvent screening was then performed (Table 7).

The counterion of the copper salt has a dramatic effect on the outcome of the reaction. CuTC leads to a very clean reaction with excellent diastereoselectivity and 89% ee (Table 7, entry 1). When OTf was used as the counterion, despite complete conversion no trace of **2b** was detected,

only 1-naphthol and 1-methylnaphthalene were detected, whatever the oxidation state of the copper (Table 7, entries 2 and 3). When bromine was used as the counterion, the product was obtained in moderate conversion, diastereoselectivity and enantioselectivity (35%, 80:20, 50% ee, respectively) in both cases (Table 7, entries 5 and 6). In the same family of counterion, copper(I) chloride gave interesting results with 81% ee for 40% conversion and ratio *anti*/*syn* 90:10 (Table 7, entry 4), whereas copper(I) iodide gave no reaction (Table 7, entry 7). Copper(I) acetate monohydrate showed low reactivity but high selectivities (Table 7, entry 8). As the counterion seems to be influential on the outcome of the reaction, we decided to try the noncoordinated tetrakis(acetonitrile)copper(I) tetrafluoroborate as the copper salt (Table 7, entry 9). Despite good diastereo- and enantioselectivities (95:5, 88% ee), a large amount of byproduct was formed (Table 7, entry 9). It appeared that CuTC is the copper salt of choice for such a reaction. Then different solvents were tested; the conversion decreased to only 15% when toluene was used as solvent (Table 7, entry 10) and no reaction was observed in tetrahydrofuran (Table 7, entry 11). The conversion issue was solved by using diethyl ether as solvent with 90% conversion without lost of enantioselectivity. However a small decrease in diastereoselectivity was observed (Table 7, entry 12). Finally, methyl *tert*-butyl ether (MTBE) appeared to be the solvent of choice with full conversion within 20 hours in 93% isolated yield in perfect diastereoselectivity and high enantiomeric excess (Table 7, entry 13). The temperature was decreased to 0 °C but no real improvement was observed (Table 7, entry 14). In order to improve the enantiomeric excess, modification of the ligand was envisaged.

Modifications of the SimplePhos ligand were studied first. An increase of the bulk on the phosphorus part of **L6** did not lead to any improvement. The resulting *anti*-product *anti*-**2b** was obtained as a single diastereoisomer in 90% ee (Table 8, entry 2). The amino part of the ligand was modified from a diphenyl to a bis(2-naphthyl) in **L9**, but the enantiomeric excess did not increase significantly (Table 8, entry 3). It appears that neither modification of the phosphorus part nor of the amino part influenced the outcome of the reaction. At this stage we turned our attention to phosphoramidite ligand as the reaction was performed in coordinating solvent.[17] (*S*,*S*,*S*)-**L2** led to the formation

Table 7 Copper Salt and Solvent Screening

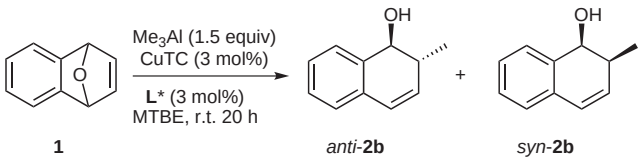


1 *anti*-**2b** *syn*-**2b**

Entry	Copper	Solvent	Conv.[a] (%)	Ratio[b] *anti*/*syn*	ee[b] (%)
1	CuTC	CH_2Cl_2	54	99:1	89
2[c]	$Cu(OTf)_2$	CH_2Cl_2	–	–	–
3[c]	$CuOTf·C_6H_6$	CH_2Cl_2	–	–	–
4	CuCl	CH_2Cl_2	40[d]	90:10	81
5	CuBr	CH_2Cl_2	35	80:20	50
6	$CuBr·Me_2S$	CH_2Cl_2	36	80:20	50
7	CuI	CH_2Cl_2	0	–	–
8	$Cu(OAc)·H_2O$	CH_2Cl_2	30	95:5	89
9	$Cu(MeCN)_4·BF_4$	CH_2Cl_2	66[e]	95:5	88
10	CuTC	toluene	15	–	–
11	CuTC	THF	0	–	–
12	CuTC	Et_2O	90	91:9	90
13	CuTC	MTBE	100 (93)	99:1	91
14[f]	CuTC	MTBE	100	99:1	92

[a] Determined by ^{1}H NMR, isolated yield is in parentheses.
[b] Determined by chiral GC.
[c] Only 1-naphthol (40%) and 1-methylnaphthalene (60%) were detected.
[d] 1-Naphthol and 1-methylnaphthalene were detected.
[e] 1-Naphthol (20%) was detected.
[f] Reaction performed at 0 °C

Table 8 Influence of the Ligand



1 *anti*-**2b** *syn*-**2b**

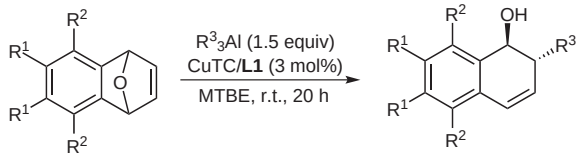
Entry	Ligand	Conv.[a] (%)	Ratio[a] *anti*/*syn*	ee[b] (%)
1	**L1**	100	99:1	91 (–)
2	**L6**	100	99:1	90 (–)
3	**L9**	100	99:1	92 (–)
4	(*S*,*S*,*S*)-**L2**	100	99:1	66 (+)
5	(*R*,*S*,*S*)-**L2**	100	99:1	45 (–)
6	**L3**	100	99:1	57 (–)

[a] Determined by ^{1}H NMR.
[b] Determined by chiral GC, sign of optical rotation is in parentheses.

of **2b** with 66% ee with a change in the selectivity (Table 8, entry 4), whereas (*R*,*S*,*S*)-**L2** allowed the formation of **2b** with only 45% ee (Table 8, entry 5). The biphenyl-based phosphoramidite **L3** gave a less selective reaction (Table 8, entry 6). As the SimplePhos ligand **L1** gave the most elective reaction, it was used for further investigations. To extend the scope of the reaction, other aluminum reagents and oxabenzonorbornadiene derivatives **3**, **4**, and **5** were investigated.

First of all, the enantioselective reduction of **1** with diisobutylaluminum hydride was envisaged. Unfortunately under the reaction conditions only naphthalene was formed (Table 9, entry 1). All the commercially available trialkylaluminum reagents were tested on oxabenzonorbornadiene **1**. To our great delight only a slight decrease in the yield was observed going from trimethyl- to triethylaluminum and the same range of enantiomeric excesses were observed (Table 9, entries 2 and 3). Even longer alkyl can be introduced without loss of enantioselectivity (Table 9, entries 4 and 5). The low isolated yield with tripropylaluminum is probably due to a concentration problem of the aluminum in the bottle as tributylaluminum gave high isolated yield. We were very surprised to

Table 9 Substrate and Aluminum



1, $R^1 = R^2 = H$
3, $R^1 = F$, $R^2 = H$
4, $R^1 = OMe$, $R^2 = H$
5, $R^1 = H$, $R^2 = OMe$

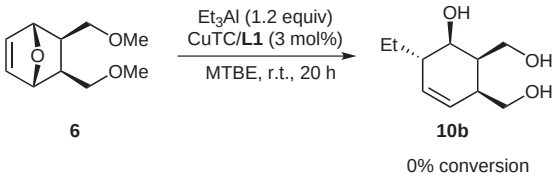
2a,**c**,**d**,**i**,**j**, **9b**, **10a**,**b**, **11a**–**c**

2j, $R^1 = R^2 = H$, R = H
2a, $R^1 = R^2 = H$, R = Et
2i, $R^1 = R^2 = H$, R = *n*-Pr
2c, $R^1 = R^2 = H$, R = *n*-Bu
2d, $R^1 = R^2 = H$, R = *i*-Bu
7b, $R^1 = F$, $R^2 = H$, R = Me
8a, $R^1 = OMe$, $R^2 = H$, R = Et
8b, $R^1 = OMe$, $R^2 = H$, R = Me
9a, $R^1 = H$, $R^2 = OMe$, R = Et
9b, $R^1 = H$, $R^2 = OMe$, R = Me
9d, $R^1 = H$, $R^2 = OMe$, R = *i*-Bu

Entry	Substrate	R^3	Product	Yield[a] (%)	Ratio[b] *anti*/*syn*	ee[c] (%)
1[d]	**1**	H	**2j**	(100)[e]	–	–
2	**1**	Me	**2b**	93	99:1	94
3	**1**	Et	**2a**	79	99:1	92
4	**1**	*n*-Pr	**2i**	50	99:1	87
5	**1**	*n*-Bu	**2c**	95	99:1	87
6	**1**	*i*-Bu	**2d**	71	99:1	94
7	**3**	Me	**9b**	85	94:6	91
8	**4**	Me	**10b**	69	99:1	88
9	**4**	Et	**10a**	95	99:1	89
10	**5**	Me	**11b**	88	93:7	87
11	**5**	Et	**11a**	(100)	99:1	88
12	**5**	*i*-Bu	**11d**	–	–	–

[a] Isolated yield, the conversion is in parentheses.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral GC or SFC.
[d] DIBAL-H was used as nucleophile.
[e] No traces of the desired alcohol were detected.

see that even triisobutylaluminum was transferred in good yield and with a high enantioselectivity (94% ee) (Table 9, entry 6). The electron-deficient oxabenzonorbornadiene derivative **3**, reacted with trimethylaluminum to give **9b** in good yield and 91% ee (Table 9, entry 7). High enantioselectivities were also achieved with electron-enriched substrates (Table 9, entries 8–11). A large amount of 2,3-dimethoxynaphthalene was obtained when **4** was reacted with trimethylaluminum (Table 9, entry 8), whereas using triethylaluminum gave **10a** in high yield and enantioselectivity (Table 9, entry 9). When trimethylaluminum was used on **5** the corresponding alcohol **11b** was obtained in good yield (Table 9, entry 10). However, the ethyl adduct **11a** could not be purified due to aromatization. Finally triisobutylaluminum was tested on **5**, but no traces of the desired alcohol were detected (Table 9, entry 12). We next turn our attention to the nonbenzylic substrate **6** (Scheme 4). We were disappointed to see that no reaction occurred.



Scheme 4 Attempt of desymmetrization of **6** with triethylaluminum

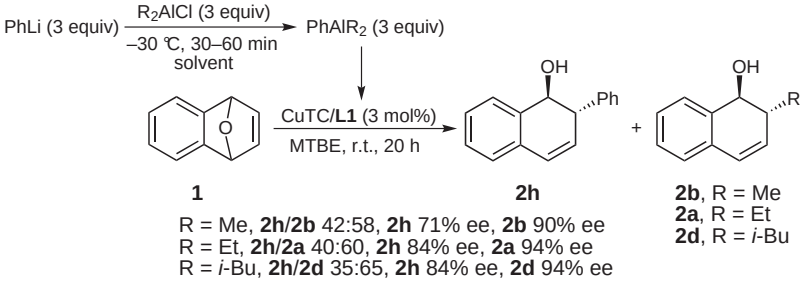
We decided to take advantage of the easy formation of vinyl-[20] and arylaluminum reagents[21] to have access to new compounds. The tandem hydroalumination/asymmetric allylic alkylation was performed using the standard conditions (3 mol% of catalyst) but no reaction was observed. We then increased the catalyst loading to 10 mol%, but only the reduced ring-opening product was observed in a racemic mixture. The tandem lithium–aluminum exchange/asymmetric allylic alkylation was then performed (Scheme 5).

Three reactants were used to transmetalate from lithium to aluminum. When dimethylaluminum chloride was used, the phenyl group was transferred in 42% with 71% ee, whereas the methyl group was transferred in 58% with 90% ee. To increase the amount of phenyl group transfer we envisaged using diethylaluminum chloride or diisobutylaluminum chloride as transmetalating agents. However no improvement was found on the relative transfer of phenyl vs alkyl group, but the enantiomeric excess increased to 84% (Scheme 5).

Finally, we have applied the previously described methodology to substituted oxabenzonorbornadienes, but in the non-aromatic ring (Table 10). In this series, an unexpected byproduct **14** was observed, probably due to a cationic rearrangement.

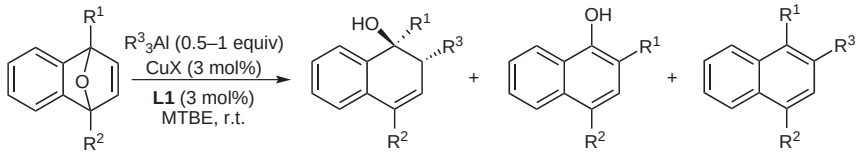
The monosubstituted oxabenzonorbornadiene **7** gave moderate to good result with different organoaluminum reagents as nucleophiles (Me_3Al, Et_3Al, *n*-Pr_3Al, Ph_3Al). The reaction with **7** (which is chiral, but racemic) corresponds to a kinetic resolution. Therefore, only 0.5 equivalent of R_3Al was added, and the maximum expected yield should be 50%. The Lewis character of the aluminum atom plays a very important role and induces the ring opening of the oxygen bridge to form two secondary products **14** and **15**. If this Lewis character increases, more byproducts are produced, and in this case the diastereomeric excesses and enantiomeric excesses increase (Table 10, entries 1–4). The *anti/syn* ratios obtained for substrates **7** and **8** are very good (99:1) (Table 10, entries 1–6) and in all cases in favor of the *anti*-product. The disubstituted oxabenzonorbornadiene **8** gave moderate conversion 75–77% and very good enantiomeric excess 94–97% (Table 10, entries 5 and 6). However the formation of product **13e** was dramatically dependent on the copper salt. If copper(I) chloride is replaced by copper(I) acetate monohydrate, the expected product **13e** is the major one.

In summary, we have shown that SimplePhos ligands are efficient ligands to perform the desymmetrization of oxabenzonorbornadiene **1** with Grignard reagents. However this reaction is substrate limited as modification of the aromatic cycle or the use of nonbenzylic substrate is very detrimental to the reaction. However we were able to transfer bulky groups such as isobutyl or phenethyl that were not transferable under the previously described conditions with Grignard reagents.[12a] The aluminum reagents are far more interesting as the only limitation is with substrate **6**, which is still challenging in copper-catalyzed desymmetrization. The aluminum reagents are Lewis acidic enough to react without additives in high yield and enantioselectivity. Finally, we have described the first copper-catalyzed asymmetric desymmetrization of oxabenzonorbornadienes with aryl groups with high enantioselectivity.



Scheme 5 Tandem Li–Al exchange/asymmetric allylic alkylation

Table 10 Substituted Oxabenzonorbornadienes



7, R^1 = H, R^2 = Me
8, R^1 = R^2 = Me

13 **14** **15**

Entry	Substrate	R^3	Product	Conv. (%)	Ratio[a] **13**/**14**/**15**	Ratio *anti*/*syn*	ee[b] (%)
1	**7**[c]	Me	**13a**	100	86:8:6	>99:1	61
2	**7**[c]	Et	**13b**	100	26:52:22	>99:1	85
3	**7**[c]	*n*-Pr	**13c**	100	19:14:63	>99:1	57
4	**7**[c]	Ph	**13d**	100	60:12:28	>99:1	11
5	**8**[d]	Et	**13e**	75	6:3:84	>99:1	97
6	**8**[e]	Et	**13e**	77	44:17:39	>99:1	94

[a] Determined by ^{1}H NMR.
[b] Determined by chiral SFC.
[c] Reaction realized with CuTC.
[d] Reaction realized with CuCl.
[e] Reaction realized with Cu(OAc)·H_2O.

All reactions were carried out under an argon atmosphere with oven-dried glassware. Solvents were dried by filtration over alumina previously activated (350 °C, 12 h, N_2) before use. All solvents were degassed by N_2 bubbling before use to all experiments. Grignard reagents (in Et_2O) and trialkylaluminum reagents (in hexane) were used without any further purification. CuTC (Frontier Scientific) was used without further purification. The reactions were followed by GC-MS Hewlett Packard (EI mode) HP6890-5973 or by TLC (visualization by UV and anisaldehyde, $KMnO_4$ or PMA staining). Flash chromatography was performed using silica gel 32–63 μm, 60 Å. ^{1}H (300, 400 or 500 MHz) and ^{13}C (75, 100 or 125 MHz) NMR spectra were recorded in $CDCl_3$ or C_6D_6 on Bruker AMX-300, -400 or -500 spectrometers. Chemical shifts are relative to residual deuterated solvent. Enantiomeric excess values were determined by chiral GC measurement on either an HP6890 (H_2 as vector gas) or an HP6850 (H_2 or He as vector gas) with the stated column. Temperature programs are described as follows: initial temperature (°C) – initial time (min) – temperature gradient (°C/min) – final temperature (°C), gas flow (cm/s). In some cases, enantiomeric excess values were determined by chiral SFC measurement on a Berger SFC with the stated column. Gradient programs are described as follows: initial methanol concentration (%) – initial time (min) – percent gradient of methanol (%/min) – final methanol concentration (%).

Copper-Catalyzed Allylic Alkylation with Grignard Reagents; General Procedure A

In a dried Schlenck tube under an N_2 atmosphere were placed CuTC (2.9 mg, 0.015 mmol, 3 mol%) and **L1** (6.8 mg, 0.015 mmol, 3 mol%). CH_2Cl_2 was added (3 mL) and the mixture was stirred at r.t. for 20 min. The oxabicyclic alkene (0.5 mmol) was added and the system cooled down to the desired temperature if required. RMgBr in Et_2O (0.6 mmol) was added dropwise over a period of 3 min. The mixture was stirred for 20 h and then quenched with MeOH and 1 M HCl before being allowed to reach r.t. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography.

Copper-Catalyzed Allylic Alkylation with Aluminum Reagents; General Procedure B

In a dried Schlenck tube under an N_2 atmosphere were placed CuTC (2.9 mg, 0.015 mmol, 3 mol%) and **L1** (6.8 mg, 0.015 mmol, 3 mol%). MTBE was added (3 mL) and mixture was stirred at r.t. for 20 min. The oxabicyclic alkene (0.5 mmol) was added. R_3Al in hexanes (0.6 mmol) was added dropwise over a period of 3 min. The mixture was stirred for 20 h and then quenched with H_2O and 1 M HCl. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography.

(1*S*,2*R*)-*trans*-2-Ethyl-1,2-dihydronaphthalen-1-ol (2a)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure A: 90% yield; 96% de; 82% ee (–20 °C); procedure B: 79% yield; 98% de; 92% ee.

Chiral separation: GC (Hydrodex B-6-TBDM, 100-0-1-170 47 cm/s): t_{R1} = 44.0 min, t_{R2} = 45.3 min.

$[\alpha]_D^{20}$ –264.2 (*c* 1.01, $CHCl_3$, 82% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 6.6, 1.1 Hz, 1 H), 7.25–7.15 (m, 2 H), 7.06 (dd, *J* = 6.6, 1.3 Hz, 1 H), 6.45 (d, *J* = 9.5 Hz, 1 H), 5.96 (dd, *J* = 9.5, 4.8 Hz, 1 H), 4.49 (d, *J* = 4.8 Hz, 1 H), 2.48–2.39 (m, 1 H), 1.75 (1 H, OH), 1.49–1.22 (m, 2 H), 0.91 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8, 132.3, 130.7, 128.4, 127.7, 127.6, 126.4, 126.1, 72.1, 43.9, 24.5, 11.5.

(1*S*,2*R*)-*trans*-2-Methyl-1,2-dihydronaphthalen-1-ol (2b)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure A: 84% yield; 80% de; 72% ee (r.t.); procedure B: 93% yield; 98% de; 91% ee.

Chiral separation: GC (Chirasil DEX-CB, 100-30-1-170 30 cm/s): t_{R1} = 64.4 min, t_{R2} = 68.2 min.

$[\alpha]_D^{20}$ –242.6 (*c* 0.69, $CHCl_3$, 91% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 6.2 Hz, 1 H), 7.29–7.19 (m, 2 H), 7.09 (d, *J* = 6.2 Hz, 1 H), 6.43 (d, *J* = 9.5 Hz, 1 H), 5.91 (dd, *J* = 9.5, 4.4 Hz, 1 H), 4.44 (d, *J* = 5.8 Hz, 1 H), 2.68–2.56 (m, 1 H), 1.74 (d, *J* = 5.8 Hz, 1 H), 1.05 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 132.3, 128.3, 127.6, 127.2, 126.4, 125.8, 125.7, 74.1, 37.4, 16.9.

(1*S*,2*R*)-*trans*-2-Butyl-1,2-dihydronaphthalen-1-ol (2c)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure A: 86% yield; 96% de; 76% ee (–20 °C); procedure B: 95% yield; 98% de; 87% ee.

Chiral separation: SFC (OD-H, 10%-2-1-15%): t_{R1} = 3.9 min, t_{R2} = 4.2 min.

$[\alpha]_D^{20}$ –286.3 (*c* 0.73, $CHCl_3$, 87% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 6.6 Hz, 1 H), 7.26–7.14 (m, 2 H), 7.05 (d, *J* = 6.6 Hz, 1 H), 6.44 (d, *J* = 9.5 Hz, 1 H), 5.98 (dd, *J* = 9.5, 4.8 Hz, 1 H), 4.46 (d, *J* = 4.8 Hz, 1 H), 2.55–2.46 (m, 1 H), 1.76 (1 H, OH), 1.42–1.18 (m, 6 H), 0.83 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 132.3, 131.01, 128.4, 127.8, 127.5, 126.4, 125.8, 72.3, 42.4, 31.3, 29.2, 22.8, 13.9.

(1*S*,2*R*)-*trans*-2-Isobutyl-1,2-dihydronaphthalen-1-ol (2d)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure A: 73% conversion, 90% de; 62% ee (–20 °C); procedure B: 71% yield; 98% de; 94% ee.

Chiral separation: GC (Chirasil DEX-CB, 120-0-1-170 30 cm/s): t_{R1} = 37.1 min, t_{R2} = 47.9 min.

$[\alpha]_D^{20}$ –345.9 (*c* 0.66, $CHCl_3$, 94% ee).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 3 H), 7.12 (dd, *J* = 7.0, 2.1 Hz, 1 H), 6.51 (d, *J* = 9.7 Hz, 1 H), 6.03 (dd, *J* = 9.7, 4.8 Hz, 1 H), 4.47 (t, *J* = 4.5 Hz, 1 H), 2.74–2.62 (m, 1 H), 1.82–1.63 (m, 2 H), 1.21–1.13 (m, 2 H), 0.93 (d, *J* = 4.8 Hz, 3 H), 0.90 (d, *J* = 4.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 132.3, 131.0, 128.6, 128.2, 127.6, 126.5, 125.7, 72.7, 40.7, 40.2, 25.5, 23.3, 22.1.

(1*S*,2*R*)-*trans*-2-Phenethyl-1,2-dihydronaphthalen-1-ol (2e)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure A: 64% yield; 96% de; 57% ee (–20 °C).

Chiral separation: SFC (OJ-H, 10%-2-1-15%): t_{R1} = 8.9 min, t_{R2} = 10.0 min.

$[\alpha]_D^{20}$ –198.5 (*c* 0.77, $CHCl_3$, 64% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 1 H), 7.26 (m, 4 H), 7.16 (m, 4 H), 6.55 (d, *J* = 9.6 Hz, 1 H), 6.08 (dd, *J* = 9.6, 4.8 Hz, 1 H), 4.56 (d, *J* = 4.3 Hz, 1 H), 2.78–2.59 (m, 3 H), 1.81–1.57 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 135.6, 132.4, 130.5, 128.7, 128.5, 128.4, 128.0, 127.9, 126.7, 126.5, 126.0, 72.5, 42.0, 33.6, 33.4.

MS (EI): *m*/*z* = 250 (21), 232 (39), 159 (16), 141 (100), 131 (30), 115 (28), 105 (14), 91 (61), 65 (13).

(1*S*,2*R*)-*trans*-2-(4-Methylpent-3-enyl)-1,2-dihydronaphthalen-1-ol (2f)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure A: 95% yield; 94% de; 64% ee (–20 °C).

Chiral separation: SFC (OD-H, 5%-2-1-15%): t_{R1} = 6.6 min, t_{R2} = 7.1 min.

$[\alpha]_D^{20}$ –205.9 (*c* 0.67, $CHCl_3$, 64% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 1 H), 7.26 (m, 2 H), 7.11 (m, 1 H), 6.50 (d, *J* = 9.9 Hz, 1 H), 6.03 (dd, *J* = 9.7, 4.8 Hz, 1 H), 5.09 (m, 1 H), 4.53 (d, *J* = 4.3 Hz, 1 H), 2.59 (m, 1 H), 2.07 (m, 2 H), 1.67 (s, 4 H, CH_3, OH), 1.60 (s, 3 H), 1.43 (m, 1 H), 1.32 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 132.5, 132.2, 131.0, 128.7, 128.1, 127.8, 127.8, 126.7, 126.1, 124.2, 72.6, 42.1, 31.8, 25.8, 25.6, 17.8.

MS (EI): *m*/*z* = 228 (56), 157 (100), 144 (30), 128 (14), 115 (22), 91 (14), 55 (13).

(1*S*,2*R*)-*trans*-2-Isopropyl-1,2-dihydronaphthalen-1-ol (2g)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure A: 65% conversion; 90% de; 54% ee (–40 °C).

Chiral separation: SFC (IC-H, 2%-2-1-15%): t_{R1} = 7.3 min, t_{R2} = 8.0 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 6.9 Hz, 1 H), 7.31–7.18 (m, 2 H), 7.11 (d, *J* = 7.7 Hz, 1 H), 6.55 (d, *J* = 9.5 Hz, 1 H), 5.97 (dd, *J* = 9.5, 4.8 Hz, 1 H), 4.65 (dd, *J* = 6.6, 4.4 Hz, 1 H), 2.46–2.38 (m, 1 H), 1.74 (dq, *J* = 13.5, 6.6 Hz, 1 H), 1.63 (d, *J* = 6.6 Hz, 1 H, OH), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.80 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.4, 128.8, 128.4, 127.7, 127.5, 126.8, 126.7, 126.5, 70.8, 41.9, 29.8, 20.7, 19.3.

(1*S*,2*R*)-*trans*-2-Phenyl-1,2-dihydronaphthalen-1-ol (2h)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure A: 89% yield; 96% de; 0% ee (–20 °C); procedure B: 95% yield of a mixture of phenyl and alkyl transfer; 98% de; 84% ee.

Chiral separation: SFC (OJ-H, 2%-2-1-15%): t_{R1} = 10.9 min, t_{R2} = 13.6 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (dd, *J* = 7.3, 2.4 Hz, 1 H), 7.34–7.24 (m, 7 H), 7.18 (dd, *J* = 7.3, 2.4 Hz, 1 H), 6.67 (dd, *J* = 9.7, 2.0 Hz, 1 H), 6.04 (dd, *J* = 9.7, 3.6 Hz, 1 H), 4.84 (dd, *J* = 7.7, 5.3 Hz, 1 H), 3.83–3.79 (m, 1 H), 1.96 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 135.6, 132.6, 129.8, 128.8 (2 C), 128.4, 128.2, 128.1, 127.6, 127.2, 126.4, 74.3, 50.1.

(1*S*,2*R*)-*trans*-2-Propyl-1,2-dihydronaphthalen-1-ol (2i)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure B: 50% yield; 98% de; 87% ee.

Chiral separation: SFC (OD-H, 10%-2-1-15%): t_{R1} = 3.8 min, t_{R2} = 4.1 min.

$[\alpha]_D^{20}$ –323.7 (*c* 0.49, $CHCl_3$, 87% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (dd, *J* = 6.1, 0.7 Hz, 1 H), 7.26 (m, 3 H), 7.11 (dd, *J* = 7, 1.3 Hz, 1 H), 6.50 (d, *J* = 10.6 Hz, 1 H), 6.02 (dd, *J* = 10.6, 4.8 Hz, 1 H), 4.52 (d, *J* = 4.3 Hz, 1 H), 2.50 (m, 1 H), 1.57 (br, 1 H), 1.43–1.34 (m, 3 H), 1.27 (m, 1 H), 0.90 (t, *J* = 7.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 132.5, 131.1, 128.7, 128.1, 127.8, 126.6, 126.0, 72.6, 42.4, 34.0, 20.4, 14.4.

MS (EI): *m*/*z* = 188 (28), 159 (35), 145 (100), 117 (27), 91 (17), 51 (6).

(1*S*,2*R*)-*trans*-2-Ethyl-6,7-difluoro-1,2-dihydronaphthalen-1-ol (9a)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure A: 85% yield; 92% de; 64% ee.

Chiral separation: GC (Hydrodex B-6-TBDM, 90-0-1-170 47 cm/s): t_{R1} = 63.4 min, t_{R2} = 64.1 min.

$[\alpha]_D^{20}$ –132.2 (*c* 0.50, $CHCl_3$, 64% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (dd, *J* = 10.4, 8.1 Hz, 1 H), 6.90 (dd, *J* = 10.4, 7.8 Hz, 1 H), 6.39 (d, *J* = 9.6 Hz, 1 H), 5.99 (dd, *J* = 9.6, 4.5 Hz, 1 H), 4.49 (d, *J* = 5.8 Hz, 1 H), 2.45 (m, 1 H), 1.82 (br, 1 H), 1.54–1.47 (m, 1 H), 1.40–1.33 (m, 1 H), 0.97 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150 (m), 148 (m), 133 (m), 131.4, 129.5 (m), 124.7, 116.6 (d, *J* = 19 Hz), 115.1 (d, *J* = 19 Hz), 43.8, 24.4, 11.4.

^{19}F NMR (270 MHz, $CDCl_3$): δ = – 138.85 (dd, *J* = 21.7, 3.1 Hz), –139.65 (dd, *J* = 21.7, 3.1 Hz).

(1*S*,2*R*)-*trans*-6,7-Difluoro-2-methyl-1,2-dihydronaphthalen-1-ol (9b)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure B: 85% yield; 88% de; 91% ee.

$[\alpha]_D^{20}$ –169.5 (*c* 0.56, $CHCl_3$, 91% ee).

Chiral separation: GC (Hydrodex B-6-TBDM, 90-0-1-170 47 cm/s): t_{R1} = 63.4 min, t_{R2} = 64.1 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (m, 2 H), 6.90 (dd, *J* = 10.6, 7.6 Hz, 1 H), 6.34 (dd, *J* = 9.6, 1.5 Hz, 1 H), 5.92 (dd, *J* = 9.6, 4 Hz, 1 H), 4.41 (d, *J* = 7.3 Hz, 1 H), 2.59 (m, 1 H), 1.64 (br, 1 H), 1.09 (d, *J* = 7.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5 (dd, *J* = 41.2, 12.2 Hz), 148.1 (dd, *J* = 41.8, 12.2 Hz), 133.2, 133.1 (m), 129.5 (m), 124, 116.2 (d, *J* = 18 Hz), 115.0 (d, *J* = 18 Hz), 73.6, 37.4, 17.1.

^{19}F NMR (270 MHz, $CDCl_3$) : δ = –138.85 (dd, *J* = 21.7, 3.1 Hz), –139.65 (dd, *J* = 21.7, 3.1 Hz).

(1*S*,2*R*)-*trans*-2-Ethyl-6,7-dimethoxy-1,2-dihydronaphthalen-1-ol (10a)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15) as a yellow oil; procedure A: 50% yield; >90% de; 31% ee (–40 °C); procedure B: 95% yield; 98% de; 89% ee.

Chiral separation: SFC (AD-H, 5%-2-1-15%): t_{R1} = 8.4 min, t_{R2} = 10.2 min.

$[\alpha]_D^{20}$ –175.7 (*c* 0.69, $CHCl_3$, 89% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (s, 1 H), 6.48 (s, 1 H), 6.34 (d, *J* = 9.6 Hz, 1 H), 5.79 (dd, *J* = 9.6, 4.29 Hz, 1 H), 4.46 (d, *J* = 6.1 Hz, 1 H), 3.44 (s, 3 H), 3.41 (s, 3 H), 2.39 (m, 1 H), 1.47–1.25 (m, 3 H), 0.88 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.8, 149.7, 129.9, 128.8, 128.6, 126.3, 126, 112.3, 111.2, 72.3, 55.8, 44.7, 25, 11.6.

(1*S*,2*R*)-*trans*-6,7-Dimethoxy-2-methyl-1,2-dihydronaphthalen-1-ol (10b)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15) as a white solid; procedure A: 40% yield; 90% de; 20% ee (–20 °C); procedure B: 69% yield; 98% de; 88% ee.

Chiral separation: SFC (AD-H, 5%-2-1-15%): t_{R1} = 9.3 min, t_{R2} = 10.3 min.

$[\alpha]_D^{20}$ –185.5 (*c* 0.74, $CHCl_3$, 88% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 1 H), 6.48 (s, 1 H), 6.30 (dd, *J* = 9.5, 1.5 Hz, 1 H), 5.68 (dd, *J* = 9.5, 4.1 Hz, 1 H), 4.34 (m, 1 H), 3.45 (s, 3 H), 3.41 (s, 3 H), 2.51 (m, 1 H), 0.97 (d, *J* = 5.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.73, 149.71, 130.7, 129.9, 127.9, 126, 111.8, 111.1, 74.5, 55.8, 55.7, 38.2, 17.5.

MS (EI): *m*/*z* = 220 (95), 202 (100), 178 (13), 159 (22), 115 (22), 91 (11), 77 (11), 51 (11).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}O_3$: 220.1099; found: 220.1096.

(1*S*,2*R*)-*trans*-2-Ethyl-5,8-dimethoxy-1,2-dihydronaphthalen-1-ol (11a)

The crude could not be purified by flash chromatography (silica gel) due to decomposition; procedure B: 100% conversion; 98% de; 88% ee.

Chiral separation: SFC (AD-H, 5%-2-1-15%): t_{R1} = 8.1 min, t_{R2} = 8.7 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (dd, *J* = 9.9, 0.5 Hz, 1.H), 6.78 (d, *J* = 9.1 Hz, 1 H), 6.78 (d, *J* = 8.8 Hz, 1 H), 6.08 (ddd, *J* = 9.9, 5.6, 1.3 Hz, 1 H), 4.99 (br, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 2.53 (m, 1 H), 1.58 (br, 1 H), 1.34–1.25 (m, 2 H), 0.94 (t, *J* = 7.6 Hz, 3 H).

(1*S*,2*R*)-*trans*-5,8-Dimethoxy-2-methyl-1,2-dihydronaphthalen-1-ol (11b)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15) as a white solid; procedure B: 88% yield; 86% de; 87% ee.

Chiral separation: SFC (AS-H, 5%-2-1-15%): t_{R1} = 4.1 min, t_{R2} = 5.6 min.

$[\alpha]_D^{20}$ –223.3 (*c* 0.76, $CHCl_3$, 87% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (dd, *J* = 0.8 Hz, 1 H), 6.48 (d, *J* = 9.1 Hz, 1 H), 6.44 (d, *J* = 8.8 Hz, 1 H), 5.89 (ddd, *J* = 9.8, 5.3, 1 Hz, 1 H), 5.14 (d, *J* = 1.8 Hz, 1 H), 3.36 (s, 3 H), 3.34 (s, 3 H), 2.70 (m, 1 H), 2.14 (br, 1 H), 0.86 (s, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 150.0, 132.2, 124.9, 122.8, 119.1, 110.9, 110.5, 67.3, 55.63, 55.59, 36.9, 17.3.

(1*S*,2*R*)-*trans*-2,4-Dimethyl-1,2-dihydronaphthalen-1-ol (13a)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure B: 20% yield; 99% de; 61% ee.

Chiral separation: GC (CP-Chirasil-DEX CB, 100-30-1-155-0-20-170-2 30 cm/s): t_{R1} = 74.03 min, t_{R2} = 75.10 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.43 (d, *J* = 7.1 Hz, 1 H), 7.31–7.27 (m, 3 H), 5.7 (d, *J* = 2.8 Hz, 1 H), 4.44–4.41 (t, *J* = 13.9, 6.8 Hz, 1 H), 2.61–2.53 (m, 1 H), 2.08 (s, 3 H), 1.75–1.73 (d, *J* = 7.4 Hz, 1 H, OH), 1.07–1.05 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.90, 134.35, 130.80, 129.42, 128.49, 127.7, 127.1, 123.59, 74.87, 37.65, 19.42, 17.6.

(1*S*,2*R*)-*trans*-2-Ethyl-4-methyl-1,2-dihydronaphthalen-1-ol (13b)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure B: 22% yield; 99% de; 85% ee.

Chiral separation: SFC (Chiralpak AD: 5%-2-1-15%): t_{R1} = 5.43 min, t_{R2} = 6.25 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.44 (m, 4 H), 5.72 (m, 1 H), 4.52 (d, *J* = 4.8 Hz, 1 H), 2.48 (m, 1 H), 2.1 (s, 3 H), 1.5–1.4 (m, 2 H), 0.95 (s, 3 H).

(1*S*,2*R*)-*trans*-4-Methyl-2-propyl-1,2-dihydronaphthalen-1-ol (13c)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 85:15); procedure B: <10% yield; 99% de; 57% ee.

Chiral separation: SFC (Chiralcel OD-H: 5%-2-1-15%): t_{R1} = 5.93 min, t_{R2} = 6.33 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 4 H), 5.82–5.81 (d, *J* = 4.8 Hz, 1 H), 4.50–4.47 (t, *J* = 12.1, 6.3 Hz, 1 H), 2.51–2.54 (m, 1 H), 2.09 (s, 3 H), 1.75–1.73 (d, *J* = 7.3 Hz, 1 H, OH), 1.44–1.25 (dm, 4 H), 0.91–0.88 (t, *J* = 14.4, 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.66, 134.25, 130.82, 128.74, 127.95, 127.90, 127.79, 123.69, 73.17, 42.39, 34.25, 20.60, 19.56, 14.60.

(1*S*,2*R*)-*trans*-4-Methyl-2-phenyl-1,2-dihydronaphthalen-1-ol (13d)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 90:10); procedure B: 16% yield; 99% de; 11% ee.

Chiral separation: SFC (Chiralcel OD-H: 5%-2-1-15%): t_{R1} = 9.69 min, t_{R2} = 10.45 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 9 H), 5.95 (s, 1 H), 4.92–4.88 (t, *J* = 13.9, 6.3 Hz, 1 H), 3.84 (s, 1 H), 2.19 (s, 3 H), 1.49–1.47 (d, *J* = 8.4 Hz, 1 H, OH).

(1*S*,2*R*)-*trans*-2-Ethyl-1,4-dimethyl-1,2-dihydronaphthalen-1-ol (13e)

The crude product was purified by flash chromatography (silica gel, pentane then cyclohexane–EtOAc, 90:10); procedure B: 35% yield; 99% de; 97% ee.

Chiral separation: SFC (Chiralpak AD: 5%-2-1-15%): t_{R1} = 4.57 min, t_{R2} = 5.65 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (m, 1 H), 7.35–7.26 (m, 3 H), 5.75 (s, 1 H), 2.30 (m, 1 H), 2.10 (s, 3 H), 1.9–1.8 (m, 2 H), 1.32 (s, 3 H), 1.0 (t, *J* = 7.2 Hz, 3 H).

References

(1) (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (b) Rovis, T. In *New Frontiers in Asymmetric Catalysis*; Mikami, K.; Lautens, M., Eds.; Wiley: New Jersey, **2007**, 275–311.

(2) (a) Lautens, M. *Synlett* **1993**, 177. (b) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1. (c) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.

(3) (a) Caple, R.; Chen, G. M. S.; Nelson, J. D. *J. Org. Chem.* **1971**, *36*, 2874. (b) Arjona, O.; Fernandez de la Pradilla, R.; Garcia, E.; Martin-Domenech, A.; Plumet, J. *Tetrahedron Lett.* **1989**, *30*, 6437. (c) Lautens, M.; Gajda, C.; Chiu, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1193.

(4) Lautens, M.; Di Felice, C.; Huboux, A. *Tetrahedron Lett.* **1989**, *30*, 6817.

(5) (a) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804. (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *Org. Lett.* **2000**, *2*, 1971. (c) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834. (d) Priego, J.; García Mancheño, O.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *Chem. Commun.* **2002**, 2512. (e) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437. (f) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 3944. (g) Dotta, P.; Kuwar, P. G. A.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2004**, *23*, 2295. (h) Li, M.; Yan, X.-X.; Hong, W.; Zhu, X.-Z.; Cao, B.-X.; Sun, J.; Hou, X.-L. *Org. Lett.* **2004**, *6*, 2833. (i) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934. (j) Cabrera, S.; Gómez Arrayás, R.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 17938.

(6) Millward, D. B.; Sammis, G.; Waymouth, R. M. *J. Org. Chem.* **2000**, *65*, 3902.

(7) (a) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390. (b) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311. (c) Webster, R.; Bing, Ch.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444.

(8) Zhang, T.-K.; Mo, D.-L.; Dai, L.-X.; Hou, X.-L. *Org. Lett.* **2008**, *10*, 3689.

(9) (a) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170. (b) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043. (c) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884.

(10) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2002**, *4*, 2703.

(11) (a) Gomez Arrayas, R.; Cabrera, S.; Carretero, J. C. *Org. Lett.* **2003**, *5*, 1333. (b) Gomez Arrayas, R.; Cabrera, S.; Carretero, J. C. *Synthesis* **2006**, 1205.

(12) (a) Zhang, W.; Wang, L.-X.; Shi, W.-J.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 3734. (b) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581. (c) Zhang, W.; Zhu, S.-F.; Qiao, X.-Ch.; Zhou, Q.-L. *Chem. Asian J.* **2008**, *3*, 2105.

(13) Palais, L.; Mikhel, I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vuagnoux-d'Augustin, M.; Rosset, S.; Bernardinelli, G.; Alexakis, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7462.

(14) Millet, R.; Alexakis, A. *Synlett* **2008**, 1797.

(15) (a) Alexakis, A.; Malan, Ch.; Lea, L.; Tissot-Croset, K.; Polet, D.; Falciola, C. *Chimia* **2006**, *60*, 124. (b) Falciola, C.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765.

(16) Clavier, H.; Coutable, L.; Toupet, L.; Guillemin, J.-C.; Mauduit, M. *J. Organomet. Chem.* **2005**, *690*, 5237.

(17) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262.

(18) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, *20*, 675.

(19) Bournaud, C.; Falciola, C.; Lecourt, T.; Rosset, S.; Alexakis, A.; Micouin, L. *Org. Lett.* **2006**, *8*, 3581.

(20) Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375.

(21) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8211.