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Scalable Synthesis of Enantiomerically Pure Bicyclo[2.2.2]octadiene Ligands

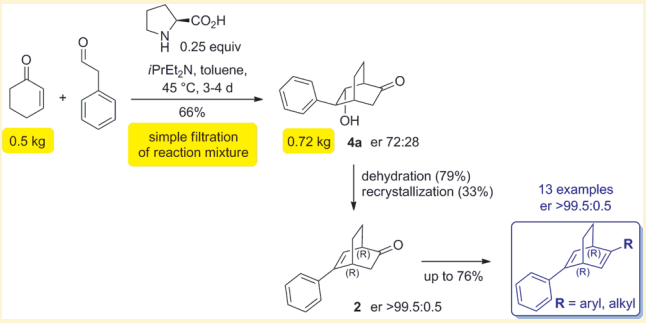
Stefan Abele,*[,†] Roman Inauen,[†] Dirk Spielvogel,[‡] and Christian Moessner[‡]

[†]Process Research Chemistry, Actelion Pharmaceuticals Ltd., Gewerbestrasse 16, CH-4123 Allschwil, Switzerland

[‡]Chemical Development and Catalysis, Solvias AG, Römerpark 2, CH-4303 Kaiseraugst, Switzerland

Supporting Information

ABSTRACT: An operationally simple and scalable synthesis of enantiomerically pure bicyclo[2.2.2]octadiene (bod*) ligands relying on an organocatalytic one-pot Michael addition−aldol reaction with cheap 2-cyclohexenone and phenylacetaldehyde is presented. The crystalline bicyclic product **4a** (6-hydroxy-5-phenylbicyclo[2.2.2]octan-2-one) is transformed into phenylbicyclo[2.2.2]oct-5-en-2-one **2**, a versatile starting material for the 2-step synthesis of both symmetrical, such as Hayashi's Ph-bod* ligand, as well as novel unsymmetrical chiral dienes.



INTRODUCTION

Since 2003, chiral dienes have gained considerable interest in metal-catalyzed asymmetric processes.[1,2] They have not only been successfully used for known catalytic enantioselective transformations (mainly 1,4-addition of organoboronic acids to α,β-unsaturated carbonyl compounds and 1,2-additions to imines) but proved superior in reactions where other types of ligands led to inferior results in terms of selectivity and notably catalytic activity.[3] Besides other factors like stability and scope, the widespread use of any new class of ligands is influenced by the ease and cost of their synthesis. Specifically, Hayashi's bicyclo[2.2.2]octadiene (bod*) ligands,[4] which display a broad scope and excellent selectivities, are still lacking a straightforward access in terms of scalability and costs (Figure 1).[5] Another type of chiral diene pioneered by Carreira is accessible from the chiral pool.[6,7] The Ph- and Bn-bod* ligands have been synthesized following two resolution routes, either by fractional crystallization of diastereomeric dihydrazones of (*R*)-5-(1-phenylethyl)semioxamazides or by separation with chiral HPLC, resulting in an overall yield of approximately 1% and 10%, respectively.[8] The key intermediate was racemic bicyclo[2.2.2]octane-2,5-dione **1** that is difficult to prepare on larger scales, as most intermediates are oils, thwarting a simple and scalable purification.[9]

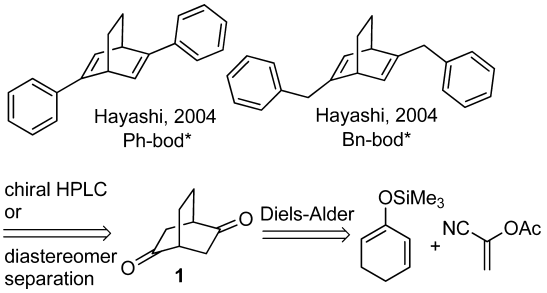


Figure 1. Hayashi's bod* ligands and reported syntheses.[4]

The need for a more expeditious and simplistic synthesis of bod* ligands has been explicitely expressed by several groups in order to stimulate wider acceptance and application of these versatile and powerful ligands.[10] Herein, we report a concise and scalable synthesis of enantiomerically pure bod* ligands relying on an organocatalytic tandem Michael addition−aldol reaction as the pivotal step and employing phenylbicyclo-[2.2.2]oct-5-en-2-one **2** as the common chiral intermediate. Besides the symmetrical bod* ligands known so far, unsymmetrical bod*-type ligands are also accessible with this new approach.

Recently, (*R*,*R*)-**2**[11] became readily accessible on a kilogram scale in our laboratories (Scheme 1).[12] Aldehyde **3** is easily obtained on multi-kg scale in 63% yield, starting with the Shibasaki reaction[13] of 2-cyclohexenone and dimethyl malonate. The key to success was the discovery of an intramolecular crystallization-induced diastereomer transformation (CIDT)[14] in the aldol reaction of the masked ketone aldehyde **3**, allowing the simple isolation of the highest melting stereoisomer **4a** from the crude reaction mixture among several isomers.

Our new approach as discussed below is based on results reported by Bella[15] involving the reaction of 2-cyclohexenone and phenylacetaldehydes in the presence of a cinchona alkaloid and a chiral secondary amine as organocatalysts (Scheme 2). The use of expensive cinchona alkaloids, a moderate dr

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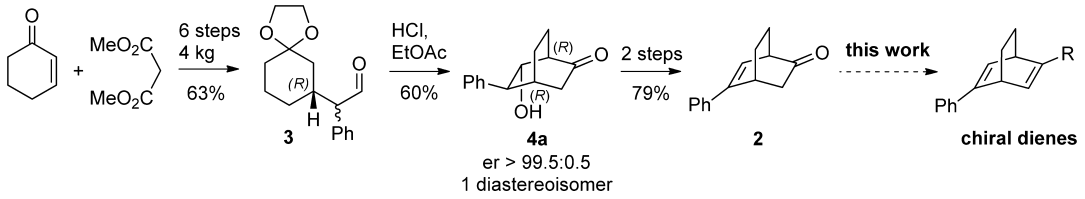
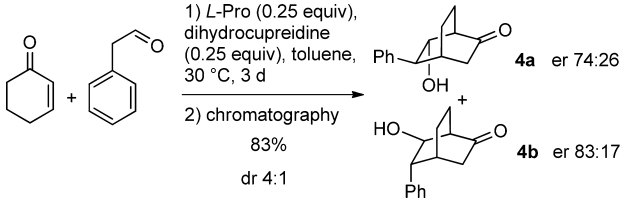
Scheme 1. Synthesis of Pivotal Intermediate 2[12] as Starting Material for the Synthesis of Chiral Dienes



Scheme 2. Organocatalytic Synthesis of Bicyclic Intermediate 4a (Example with Highest er with L-Proline)[15]

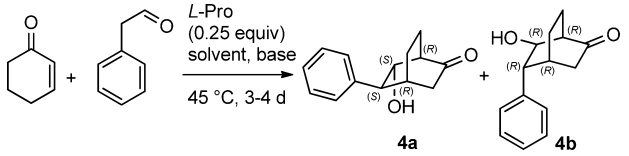


obtained with L-proline alone, and the required chromatography were perceived as obstacles for immediate scale up. Since the major isomer **4a** was also the key intermediate in our approach (Scheme 1), we were confident in capitalizing on our findings related to the CIDT in order to find a more efficient synthesis of the chiral bicycle **4a**. In view of our projected demands for this building block in one of our development programs, the overall cost of this process had to be taken into account in addition to the selectivity.[16]

RESULTS AND DISCUSSION

Inspired by the encouraging enantiomeric ratios (er) reported by Bella, the possibility to enrich and easily isolate **4a** from an isomeric mixture,[12] and the low costs of the starting materials,[17] we embarked on a screen of solvents, additives, organocatalysts, and temperatures for this reaction. In total, 96 experiments were run on a 96-well plate, followed by verification of selected screening hits on the gram scale (Supporting Information). The dr, i.e., the ratio of (**4a**+*ent*-**4a**)/(**4b**+*ent*-**4b**) in the reaction mixture, started at approximately 50:50 and grew to 92:8 at the end of the reaction. This could be explained by an equilibrium between **4a** and **4b** as observed in the aldol reaction of **3** to **4a** (Scheme 1). Under all conditions screened, the major products after some hours were the bicyclic alcohols **4** (40−60% a/a **4** by GC). Many lower level impurities are detectable by GC−MS, and their structure has been tentatively assigned on the basis of their mass. One set was identified as Baylis−Hillman products, and the other set could be conceivably derived from the addition of a second equivalent of phenylacetaldehyde to the Michael product followed by cyclization. It is noteworthy that using an oily mixture of isomers of **4** of lower purity afforded bicyclic ketone **2** that could *not* be purified by crystallization, giving an oily product of low purity.[12] The target was therefore to have **4a** accumulated in the reaction mixture. The best er (86:14) was achieved at 0 °C; however, the dr was only 50:50, more byproducts were formed, and the reaction took 21 days for completion. The best results in terms of yield, dr, and er of **4a** were obtained with 0.25 equiv of L-proline and 0.25 equiv of Hünig's base (*i*-Pr_2EtN) in toluene at 45 °C for 4 days (Table 1, entry 1). As a testimony to the scalability of this process, 717 g of **4a** (diastereomeric purity >99.5%, er 72:28) was obtained from 500 g of 2-cyclohexenone in 66% yield by this exceedingly simple and efficient process (entry 2): the product was isolated

Table 1. One-Pot Organocatalytic Michael−Aldol Reaction[a]



entry	scale	base	dr[b] IPC	yield of **4a** (%)	er **4a**[c]
1	25 g	Et_2-*i*-PrN	n.a.	53	74:26
2[d]	0.5 kg	Et_2-*i*-PrN	n.a.	66	72:28
3	5 g	Et_3N	n.a.	54	74:26
4	5 g	*n*-Bu_3N	92:8	53	70:30
5	5 g	*n*-Oct_3N	92:8	58	67:33
6	5 g	DABCO	84:16	41	75:25
7	5 g	DBU	n.a.	33	62:38
8	5 g	pyridine	94:6	54	62:38
9[d]	5 g	no base	n.a.[e]	41	63:37
10[f]	5 g	no base	66:34	29	62:38
11[g]	5 g	no base	79:21	32	63:37

[a]Conditions: 2-cyclohexenone, phenylacetaldehyde (1.1 equiv), L-proline (0.25 equiv), toluene (6−7 vol), base (0.25 equiv or without base), 45 °C, 3 d (entries 9−11) and 4 d (entries 1−8), water addition (2 vol), filtration, washing (water, toluene). Product **4a** was isolated with diastereomeric purity >99.5%. [b]dr in reaction mixture after 4 d. IPC (in-process control). [c]Ratio of **4a**:*ent*-**4a** of isolated product, chiral HPLC. [d]No water was added prior to filtration. [e]dr of mother liquor: approximately 50:50. [f]TBME instead of toluene. [g]EtOAc instead of toluene.

in pure form by simple filtration of the reaction mixture. This moderate enantioselectivity is counterbalanced not only by the low cost of L-proline and the two starting materials but also by the ease of upgrade of the enantiopurity by crystallization (vide infra).[18]

Similar results were obtained with Et_3N, *n*-Bu_3N, *n*-Oct_3N, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), and pyridine (entries 3−8). The dr of the reaction mixture was as high as 94:6, and the isolated product was consistently diastereomerically pure, with isolated yields and er's ranging from 33% to 66% and from 62:38 to 75:25, respectively. The absolute configuration of both **4a** and **4b** was ascertained by comparison with pure samples derived from our first enantioselective route (Scheme 1). It is interesting to note that *racemic* **4a** was produced in 32−36% yield when these reactions were run in the presence of water.

Surprisingly, similar diastereoselectivities and enantioselectivities were obtained when *no base* was used in toluene, TBME, and EtOAc (entries 9−11) since virtually no conversion was observed when the reaction of phenylacetaldehyde and 2-cyclohexenone was run without base in the presence of L-proline in toluene.[15a] In our hands, **4a** of excellent diastereomeric purity (>99.5%) was obtained by simple filtration, starting with a reaction mixture with a dr of as low as 66:34. The isomer distribution **4a**:**4b** does not seem to be

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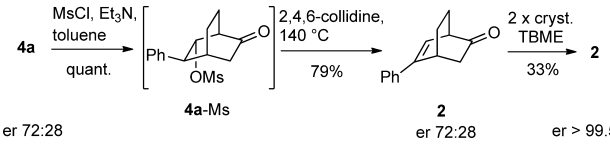
determined only by the steric and electronic factors governing the organocatalysis of proline and its derivatives[19,20] but also by the thermodynamic stability of the products following the intramolecular aldol reaction since we have shown that there is an equilibrium between **4b** and **4a** by retro-aldol reaction, accompanied by epimerization of the benzylic position through an enolate.[12] The predominance of isomer **4a** over **4b** could hence result from the differences in solubility as discussed above (CIDT). We speculate that a major driving force for this reaction is the crystallization of **4a**. We have no data indicating reversibility of the Michael addition step, though we cannot exclude it under modified reaction conditions.[21] A higher overall yielding process is conceivable if conditions are found to decouple the two reactions, i.e., first optimizing the enantioselectivity of the Michael addition prior subjecting the isomers to the CIDT; keeping both major diastereoisomers in solution until the end of the tandem sequence is a prerequisite for this alternative target.[22]

The dehydration to **2** was performed as already described (Scheme 3).[12] Having reached a limit for the er in the

Scheme 3. Dehydration of the Bicyclic Alcohol 4a and Upgrade of er[12]



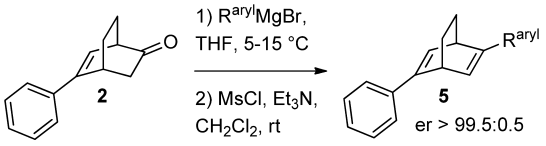
organocatalytic step, recrystallization of bicyclic alcohol **4a** or ketone **2** led to an enrichment of the desired enantiomer. It is favorable to proceed directly to ketone **2** giving slightly higher yields. Hence, the crude mesylate **4a**-Ms[23] was reacted to **2** (with an er of approximately 70:30), which was crystallized from heptane or TBME (on 36-g scale) to reach an er of >98:2 in 38% yield in a first crop. A second recrystallization delivers an er of >99.5:0.5 in 87% recovery. In summary, starting from 2-cyclohexenone to enantiopure bicyclic ketone **2**, six out of the nine steps have been skipped, allowing for an efficient production. The overall yield is 17%; only one intermediate (**4a**) is isolated.

Having secured a practical access to enantiomerically pure ketone **2**, two methods were applied to synthesize chiral dienes of the bod*-type. To access aryl-substituted dienes **5**, aryl Grignard reagents were added to ketone **2**, forming a mixture of tertiary alcohols that were dehydrated under mild conditions by treatment with MsCl and Et_3N at rt (Table 2). The yield of the crude dienes was good and the main byproduct detected was the arene derivative coming from Grignard hydrolysis. Because of the unpolar nature of these compounds, different methods were applied for their purification. Chromatography[24] was usually used on a gram scale, whereas a slurrying in methanol became the favored operation on a larger scale.[25]

Enantiomeric and chemical purities were consistently excellent (er >99.5:0.5, >99% a/a LC−MS). The absolute configuration was determined by spiking (*R*,*R*)-**5a** with a commercial sample of (*R*,*R*)-**5a** (Ph-bod*). The quality of **5a** synthesized by this organocatalytic route is equal or superior to that of a commercial sample of (1*R*,4*R*)-Ph-bod*.[26]

The addition of alkyl Grignard or lithium alkyl reagents to **2** proved to be difficult. *n*-BuLi afforded the carbinol as an endo/exo mixture (dr 40:60, 58%, 90% a/a) leading to a mixture of

Table 2. Synthesis of Chiral Dienes 5 (Diaryl)[a]

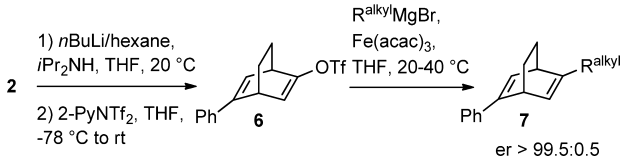


5	R^{aryl}	yield[b] (%)	mp (°C)
a	Ph (Ph-bod)*	65	74−77
b	2-MeC_6H_4	33	47−48
c	4-FC_6H_4	76	103−104
d	4-$MeOC_6H_4$	44	95−98
e	4-$C_6H_4OC_6H_4$	30	80−81
f	2-thienyl	72	69−72
g	4-$C_6H_4C_6H_4$	12	142[c]
h	1-naphthyl	30	resin
i	2-naphthyl	52	119−121
j[d]	3,5-difluoro-C_6H_3	4	oil

[a]Using phenylketone **2** with er >99.5:0.5. Purity of all dienes >99% a/a (LC−MS). [b]Yields after purification, unoptimized, er for all dienes >99.5:0.5, (*S*,*S*)-diene was not detected, determined by chiral HPLC methods, see the Supporting Information. [c]Melts with decomposition; DSC: peak temp 152 °C. [d]Unstable.

regioisomeric elimination products (*endo*- and *exo*-methylene products) upon treatment with MsCl and Et_3N. Therefore, the alkyl-substituted dienes **7** were accessed via the triflate **6**, which was cross-coupled with Grignard reagents, catalyzed by iron(III) acetylacetonate (Table 3).[10a] The triflate **6** was

Table 3. Synthesis of Chiral Dienes 7 (Phenylalkyl)[a]



7	R^{alkyl}	yield[b] (%)	mp (°C)
a	Me	45	oil
b	Bn	51	51−52
c[c]	isobutyl	35	oil

[a]Using phenyl ketone **2** with er >99.5:0.5. Purity of **7a** and **7b** > 98.8% a/a (LC−MS). [b]Yields after purification, unoptimized, er for both dienes >99.5:0.5, other enantiomer not detected, determined by chiral HPLC methods, see the Supporting Information. [c]Purity 97% a/a (LC−MS), unstable.

readily accessed by quenching the lithium enolate derived from **2** with Comins reagent.[27] The yields from the ketone **2** to the dienes **7a** and **7b** are comparable to the yields obtained by Hayashi for the transformation of the bis-triflate of diketone **1** to Ph-bod* or Bn-bod*.[4b]

Cross-coupling triflate **6** with allyl-, vinyl-, and propargylmagnesium bromide led to low conversion and decomposition. The chiral diene with R = H could not be isolated from the reaction of triflate **6** with formic acid, *n*-Bu_3N, and $PdCl_2(PPh_3)_2$, as the product degraded during aqueous workup. The 3,5-difluorophenyl diene **5j** (R^{aryl} = 3,5-difluorophenyl) and isobutyl diene **7c** (R^{alkyl} = isobutyl) were successfully synthesized and fully characterized. They proved to be stable at rt for some days; however, after storage at −20 °C for 9 months both had degraded as judged by ^1H NMR and

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LC−MS. All dienes in Tables 2 and 3 were stable as neat solids or oils at rt for at least 12 months.[28]

In a holistic view of the process efficiency toward chiral dienes **5**, the moderate overall yield caused by the low ee (44%) of the organocatalytic step is counterbalanced by the low cost of the organocatalyst (L-Pro), the low number of isolated intermediates (2 or 3), and the operational simplicity of the enantioselective step.[16] Acknowledging that good processes are inherently green processes,[29] the process mass intensity (PMI, kg reagents/1 kg of product)[30] was calculated for this new approach to Ph-bod* ligand **5a**. It was compared with the published route relying on separation of diastereomeric dihydrazones[4b] (Table 4).[31] Even though the overall yield has increased only by a factor of approximately 10, the PMI regarding the reagents decreased by a factor of 38 (or 28), paving the way to a much reduced cost for this class of ligands.

Table 4. Comparison of This Organocatalytic Route to 5a with Published Route[4b] (PMI: Mass of All Material Used To Make 1 kg of Product)

	present organocatalytic route (%)	published route[a] (%)	typical range for pharmaceuticals[32]
overall yield	11	1[b] (1.3)	n.a.
chemical steps	5	6 + 2 + 2 (5)	n.a.
isolated intermediates	2	7 (4)	n.a.
PMI without solvents and water	36	1365[b] (1019)	n.a.
solvent usage	207[c]	10174[b] (7646)	10−170

[a]Numbers in parentheses refer to the published route excluding the syntheses of the (cyclohexa-1,5-dien-1-yloxy)trimethylsilane, of 2-acetoxyacrylonitrile, and of (*R*)-5-(1-phenylethyl)semioxamazide; these starting materials are not readily available on a larger scale. [b]Starting from 2-cyclohexenone. [c]Major contribution is heptane used to crystallize the unpolar **2**.

CONCLUSION AND OUTLOOK

In conclusion, we have developed a concise and flexible access to various chiral dienes starting from cheap starting materials. This approach also delivers unsymmetrical (C_1-symmetrical) dienes, not accessible with the standard route (Figure 1) that affords the C_2-symmetrical ligands.[33] Since it was shown that one substituent on related chiral dienes was sufficient to control the enantioselectivity,[10b] application of our unsymmetrical dienes is currently being investigated in asymmetric transformations where known diene ligands gave only moderate results.[34] Fine-tuning properties such as stability, selectivity, and activity of the asymmetric catalysts is straightforward since our new synthetic route could deliver a large variety of ligands in a short time.

EXPERIMENTAL SECTION

General remarks: 1 vol or 1 wt means 1 L of solvent or 1 kg of reagent, respectively, with respect to the reference starting material. er and dr reported in this paper have not been validated by calibration. Therefore, we are reporting an er of >99.5:0.5 when the other enantiomer was not detectable by the chiral HPLC methods.[35] Compounds were characterized by mp (uncorrected), GC−MS, LC−MS, ^{1}H NMR (400 MHz), or ^{13}C NMR (100 MHz). High-resolution mass spectra (HRMS) were recorded for new compounds (ESI, quadrupole time-of-flight, Q-TOF). Temperatures are internal temperatures, and yields are given as is, unless otherwise stated. All reactions were run under an atmosphere of N_2

(1*R*,4*R*,5*S*,6*S*)-6-Hydroxy-5-phenylbicyclo[2.2.2]octan-2-one (4a). *General Method: Organocatalytic Tandem Michael−aldol Reaction (Table 1).* L-Proline (0.25 equiv) and the base (0.25 equiv) were added to a mixture of 2-cyclohexenone (1 wt, 1.00 equiv) and phenylacetaldehyde (1.10 equiv) in toluene (7 vol) at 20−25 °C. The mixture was stirred at 45 °C for 4 d. Preparation of a sample for in-process-control (IPC by LC−MS): sampled well-stirred mixture, evaporated sample to dryness at 20 °C under reduced pressure; 2 mg of the residue was dissolved in water/acetonitrile 1:1 (1 mL) for LC−MS. The suspension was cooled to 20−25 °C, water (2 vol) was added, and the mixture was stirred at 20−25 °C for 15 min. The suspension was filtered and washed with water (3 × 1 vol) and toluene (3 × 1 vol). The filter cake was dried under reduced pressure at 45 °C to yield **4a** as colorless solid. Diastereomeric purity and er (ratio of **4a**:*ent*-**4a**) were determined by chiral HPLC method (ChiralPak AS-H, 4.6 × 250 mm, 5 μm, heptane/2-propanol 60:40, 0.8 mL/min). LC−MS, ^{1}H NMR, and ^{13}C NMR data correspond to literature.[12]

Large-Scale Run. In a 4-L double-jacketed reactor L-proline (146.0 g, 0.25 equiv) and *N*-ethyldiisopropylamine (217 mL, 0.25 equiv) were added to a mixture of 2-cyclohexenone (496.5 g, purity 98%, 5.06 mol) and phenylacetaldehyde (743.3 g, purity 90%, 1.10 equiv) in toluene (3 L) at 23 °C. Note: addition of *N*-ethyldiisopropylamine led to an exotherm. The mixture was stirred at 45 °C for 4 d. Note: the initial cloudy yellow suspension turned into a thick, well-stirred suspension. The suspension was cooled to 20 °C, stirred at 20 °C for 1 h, and filtered. The filter cake was washed with water (3 × 500 mL, pH 9−10) and toluene (3 × 400 mL). The filter cake was dried under air for 2 h to yield **4a** as colorless solid (717 g, 66%): purity (LC−MS): 100% a/a, t_R = 1.19 min, $[M - 18 + 1]^+$ = 199; chiral HPLC: er 72:28, t_R = 14.8 min (*R*,*R*), (t_R = 12.4 min (*S*,*S*)), ^{1}H NMR ($CDCl_3$) corresponds to **4a**.[12]

*Recrystallization of **4a** (er 72:28) in Acetonitrile (32 vol).* Compound **4a** (5 g) was dissolved in acetonitrile (160 mL) at 82 °C. After being cooled to 23 °C, the suspension was filtered, washed with acetonitrile (2 × 1 mL), and dried under reduced pressure to afford **4a** as white solid (0.47 g, 9%). Chiral HPLC: er >99.5:0.5.

*Recrystallization of **4a** (er 72:28) in Acetonitrile (16 vol).* Compound **4a** (5 g) was dissolved in acetonitrile (80 mL) at 82 °C. After being cooled to 50 °C, the suspension was filtered, washed with acetonitrile (2 × 1 mL), and dried under reduced pressure to afford **4a** as a white solid (1.5 g, 30%). Chiral HPLC: er 91.6:8.4.

*Recrystallization of **4a** (er 72:28) in THF (10 vol).* Compound **4a** (5 g) was dissolved in THF (50 mL) at 66 °C. After cooling to 23 °C, the suspension was filtered, washed with THF (2 × 1 mL), and dried under reduced pressure to afford **4a** as white solid (1.17 g, 23%). Chiral HPLC: er 96.0:4.0.

(1*S*,4*S*,5*R*,6*R*)-6-Hydroxy-5-phenylbicyclo[2.2.2]octan-2-one (*ent*-4a). 2-Cyclohexenone (10 mL, 0.10 mol) and phenylacetaldehyde (14.6 mL, 1.10 equiv) were added to a mixture of D-proline (2.93 g, 0.25 equiv) and DIPEA (4.36 mL, 0.25 equiv) in toluene (70 mL) at 20−25 °C. The mixture was stirred at 45 °C for 3 d. IPC according to LC−MS indicated >99% conversion. The suspension was cooled to 20−25 °C and filtered. The filter cake was washed with water (3 × 10 mL) and toluene (3 × 10 mL). The filter cake was dried on the filter by sucking air through the filter to afford *ent*-**4a** as colorless solid (13.2 g, 60%). Chiral HPLC: er 27:73 (**4a**:*ent*-**4a**, t_R 14.8 min:12.4 min). Purity (LC−MS): 100% a/a, t_R 1.2 min. ^{1}H NMR ($CDCl_3$) corresponds to **4a**.

(1*R,4*R**,5*S**,6*S**)-6-Hydroxy-5-phenylbicyclo[2.2.2]octan-2-one (*rac*-4a).** *N*-Diisopropylethylamine (6.6 mL, 0.25 equiv) and 20 mM sodium phosphate buffer solution (pH 8, 14 mL) were added to a mixture of L-proline (5.87 g, 0.25 equiv), 2-cyclohexenone (20 g, 0.20 mol), and phenylacetaldehyde (29.9 g, 1.10 equiv) in toluene (140 mL) at 20−25 °C. The mixture was stirred at 45 °C for 10 d. The suspension (pH 8−9) was filtered. The filter cake was washed with water (3 × 10 mL), followed by toluene (3 × 20 mL). The filter cake was dried at 45 °C under reduced pressure to afford *rac*-**4a** as a white solid (15.7 g, 36%). Chiral HPLC: er 50:50, diastereoisomeric purity

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100% (chiral HPLC). Purity (LC−MS): 100% a/a, t_R = 1.2 min. ^{1}H NMR ($CDCl_3$) corresponds to **4a**.

(1*R*,4*R*)-5-Phenylbicyclo[2.2.2]oct-5-en-2-one (2). MsCl (46.5 mL, 1.3 equiv) was added to a suspension of bicyclic alcohol **4a** (100 g, er 72:28, 0.46 mol) and Et_3N (97 mL, 1.5 equiv) in toluene (500 mL) at 10−20 °C. After being stirred at 10−20 °C for 10 min, the mixture was washed with water (2 × 250 mL) and concentrated to dryness under reduced pressure to afford the mesylate **4a**-Ms as a light-yellow oil that solidified at rt (136 g, 100%). Purity (LC−MS): 100% a/a, t_R = 1.4 min, $[M - 96 + 1]^+$ = 199. ^{1}H NMR data ($CDCl_3$) in agreement with structure.[12] Half of the crude mesylate **4a**-Ms (67.8 g, 0.23 mol) was dissolved in 2,4,6-collidine (65 mL) and stirred at 140−145 °C for 80 min. HCl (2 N, 320 mL) and heptane (800 mL) were added, and the layers were separated. The organic phase was washed with 2 N HCl (2 × 170 mL) and water (170 mL) and filtered over $MgSO_4$. The filtrate was evaporated to dryness at 50 °C under reduced pressure to afford crude **2** as red oil (36 g, 79%). Purity (LC−MS): 95.2% a/a, t_R = 1.54 min. This crude product (36 g) was dissolved in TBME (30 mL) at 50 °C. After cooling to 0 °C and stirring at 0 °C for 0.5−1 h, the suspension was filtered, and the filter cake was washed with TBME (3 × 3 mL). The product was dried at 50 °C under reduced pressure to afford the first crop of **2** as a colorless solid (first crop: 11.95 g, 26%). Chiral HPLC (ChiralPak AS-H, 4.6 × 250 mm, 5 μm, heptane/2-propanol 60:40, 0.8 mL/min): er 98.3:1.7, t_R = 10.3 min (*R*,*R*) (t_R = 28.3 min (*S*,*S*)). The mother liquor was diluted with heptane (30 mL) and stirred at 0 °C for 0.5 h. The suspension was filtered, and the filter cake was washed with TBME (3 × 1 mL). The product was dried under reduced pressure at 50 °C to afford the second crop of **2** as a colorless solid (second crop: 1.63 g, 4%). Chiral HPLC: er 97.9:1.2, t_R = 10.3 min (*R*,*R*) (t_R = 28.3 min (*S*,*S*)). ^{1}H NMR ($CDCl_3$) corresponds to the structure.[12]

*Recrystallization of **2** (er 67:33) in Heptane.* Compound **2** (8 g) was dissolved in heptane (40 mL) at 40 °C, at which temperature seed crystals (er >99.5:0.5) were added. After being cooled to 23 °C, the suspension was filtered, washed with heptane (2 mL), and dried under reduced pressure to afford **2** as white solid (2.41 g, 30%). Chiral HPLC: er 97.6:2.4.

*Recrystallization of **2** (er 98.3:1.7) in TBME.* Compound **2** (3 g) was dissolved in TBME (3 mL) at 55 °C. The yellow solution was cooled to 20−25 °C, at which temperature crystallization occurred. The suspension was aged at 0 °C for 30 min, diluted with TBME (1 mL), stirred at 0 °C for 10 min, and filtered. The filter cake was washed with TBME (2 × 1 mL) and dried under reduced pressure at 45 °C to afford **2** as a white solid (2.6 g, 87%). Chiral HPLC: er 99.6:0.4.

*Recrystallization of **2** (er 69:31) in TBME.* Compound **2** (36.2 g) was dissolved in TBME (30 mL) at 50 °C. The solution was cooled to 0 °C. The suspension was aged at 0 °C for 30 min and filtered. The filter cake was washed with TBME (3 × 3 mL) and dried under reduced pressure at 45 °C to afford **2** as a white solid (11.95 g, 33%). Chiral HPLC: er 98.3:1.7.

Synthesis of Chiral Dienes 5 and 7. *General Method A1.* Arylmagnesium bromide (as a commercially available solution in THF, 2 equiv) was added to a solution of **2** (1 equiv) in THF (6 vol) at 5−15 °C. The reaction was allowed to warm to 20 °C and stirred for the indicated time. In-process-control (IPC) by LC−MS or TLC. After full conversion,[36] cold water (2−3 vol) was added at 0−20 °C. More water (10−30 vol) and TBME (10−40 vol) were added. The organic layer was concentrated to dryness under reduced pressure at 50 °C to afford the intermediate *tert*-alcohol as a mixture of endo/exo isomers.

General Method A2. The crude product obtained from general method A1 was used as such or purified by chromatography prior to the following dehydration step. Et_3N (6.0 equiv) and MsCl (2.6 equiv) were added to a solution of the *tert*-alcohol in CH_2Cl_2 (6−10 vol) at 0−10 °C. After the solution was stirred at 20−25 °C for the indicated time, >90% conversion was observed (LC−MS). Water (6−20 vol) was added at 10 °C, followed by CH_2Cl_2 (10−20 vol). The organic layer was washed with water (10−20 vol) and concentrated to dryness under reduced pressure at 40 °C to afford the crude chiral diene.

General Method B. Alkylmagnesium bromide (commercially available solution in Et_2O or THF, 2−4 equiv) was added with cooling to a mixture of triflate **6** (1.0 equiv) and iron(III) acetylacetonate (0.05−0.2 equiv) in THF (10−20 vol) at 20−40 °C. LC−MS was used for IPC. If full conversion was not obtained with stirring at 30−50 °C after the indicated time, additional alkylmagnesium bromide and iron(III) acetylacetonate were added, followed by stirring at 30−50 °C for the indicated time. Water (4 vol) was added with cooling, followed by TBME (6 vol). The organic phase was concentrated to dryness under reduced pressure at 50 °C to afford the crude diene.

*Racemic Dienes **5** and **7**.* For determination of er by chiral HPLC, the racemic dienes *rac*-**5a**−**i** and *rac*-**7a**,**b** were prepared in the same manner as described below for the (*R*,*R*)-isomers **5** and **7**.

(1*R*,4*R*)-2,5-Diphenylbicyclo[2.2.2]octa-2,5-diene (5a). Phenylmagnesium bromide (1 M in THF, 100 mL, 2 equiv) was added to a solution of **2** (10 g, 50.4 mmol) in THF (60 mL) at 5−15 °C. The reaction was allowed to warm to 20 °C and stirred for 1 h. IPC by LC−MS indicated full conversion. Cold water (30 mL) was added dropwise at 0−20 °C with cooling. More water (100 mL) and TBME (140 mL) were added. After phase separation, the aqueous phase was washed with TBME (50 mL). The combined organic phases were washed with 1/2-saturated NaCl solution (2 × 60 mL), filtered over $MgSO_4$, and concentrated to dryness under reduced pressure at 50 °C to afford the intermediate *tert*-alcohol as a yellow oil (15.8 g, 113%); this mixture of *exo*- and *endo*-alcohols was dissolved in CH_2Cl_2 (155 mL). Et_3N (48 mL, 6.0 equiv) and MsCl (11.6 mL, 2.6 equiv) were added at 0−10 °C. After the mixture was stirred at 20 °C for 2 h, IPC by LC−MS indicated full conversion. Water (40 mL) was added dropwise, followed by 1/2-saturated $NaHCO_3$ solution (120 mL) at 10−20 °C. CH_2Cl_2 (120 mL) was added, the phases were separated, and the organic phase was washed with 1/2-saturated $NaHCO_3$ solution (120 mL), dried over $MgSO_4$, and concentrated to dryness under reduced pressure at 50 °C to afford crude **5a** as red oil that turned into a mixture of solid and oil overnight (crude: 17.6 g, 135%). The crude product (15.5 g) was suspended in MeOH (20 mL) at 50 °C for 5 min. The suspension was cooled to 20 °C and filtered, and the filter cake was washed with MeOH (3 × 8 mL) and dried at 45 °C under reduced pressure to afford **5a** as a colorless solid (7.44 g, 65%): mp 74−77 °C (Aldrich sample (1*R*,4*R*)-Ph-bod*, no. 707171: mp 74−76 °C); $[\alpha]^{25}_D$ = −29.6 (*c* = 1.04, $CHCl_3$) (lit.[4a] $[\alpha]^{20}_D$ = −30 (*c* = 0.72, $CHCl_3$); Aldrich sample no. 707171 $[\alpha]^{22}_D$ = −37.0 (*c* = 1.03, $CHCl_3$)); GC−MS 99.5% a/a, t_R = 3.82 min, $[M + 1]^+$ = 259;[37] purity (LC−MS) >99.5% a/a, t_R = 2.1 min, $[M + 1]^+$ = 259; chiral HPLC (Chiralpak AD-H, 250 × 4.6 ID, 5 μm, heptane/EtOH 1:1, 0.8 mL/min): er >99.5:0.5, t_R = 5.7 min (*R*,*R*); spiked with *rac*-**5a** (t_R = 9.0 min (*S*,*S*)); ^{1}H NMR and ^{13}C NMR ($CDCl_3$) data and chiral HPLC data correspond to literature[4b] and to a commercial sample of (1*R*,4*R*)-Ph-bod* (Aldrich, 95%, No. 707171, [796966-15-9]). Differential scanning calorimetry (DSC): endotherm 67−81 °C, peak 78 °C, exotherm 192−159 °C (−114 J/g). HRMS (ESI) *m*/*z* calcd for $C_{20}H_{19}$ 259.1487 $[M + H]^+$, found 259.1481.

(1*R*,4*R*)-2-Phenyl-5-(*o*-tolyl)bicyclo[2.2.2]octa-2,5-diene (5b). Phenyl ketone **2** (5 g, 25.2 mmol) was reacted with *o*-tolylmagnesium bromide (2 M in THF) according to general method A1 for 50 min. After aqueous workup, the crude *tert*-alcohol was obtained (7 g, 96%) that was purified by chromatography on silica gel (30 g, eluent heptane/EtOAc 9:1) to afford the *tert*-alcohol (5.3 g, 72%). This intermediate was reacted with MsCl and Et_3N according to general method A2 for 80 min to afford crude **5b** as yellow oil (crude: 5.1 g, 74%). The crude product was triturated with heptane at 50 °C. The soluble part was separated from the insoluble red oil by decantation and purified by chromatography on silica gel (20 g, eluent heptane) to afford **5b** as colorless oil that solidified at rt (2.25 g, 33%): mp 47−48 °C; $[\alpha]^{25}_D$ = +80.7 (*c* = 1.13, $CHCl_3$); GC−MS 97.2% a/a, t_R = 3.80 min, $[M + 1]^+$ = 273; purity (LC−MS) 100% a/a, t_R = 2.14 min, $[M + 1]^+$ = 273; chiral HPLC (Chiralpak AZ-H, 250 × 4.6 i.d., 5 μm, heptane (0.05% Et_2NH)/EtOH (0.05% Et_2NH) 1.1, 0.8 mL/min) er >99.5:0.5, t_R = 5.0 min (*R*,*R*) (t_R = 5.2 min (*S*,*S*)); ^{1}H NMR ($CDCl_3$) δ 7.48−7.53 (m, 2 H), 7.34−7.43 (m, 2 H), 7.13−7.32 (m, 5 H), 6.72

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(dd, J_1 = 6.3 Hz, J_2 = 1.8 Hz, 1 H), 6.33 (dd, J_1 = 6.3 Hz, J_2 = 1.7 Hz, 1 H), 4.24 (d, J = 6.0 Hz, 1 H), 3.89 (d, J = 6.0 Hz, 1 H), 2.32 (s, 3 H), 1.49−1.68 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 148.2, 147.0, 140.2, 138.4, 135.7, 131.1, 130.3, 129.3, 128.5, 128.2, 126.8, 125.6, 124.9, 43.3, 39.9, 25.7, 25.5, 20.8; HRMS (ESI) m/z calcd for $C_{21}H_{21}$ 273.1643 $[M + H]^+$, found 273.1636.

(1*R*,4*R*)-2-(4-Fluorophenyl)-5-phenylbicyclo[2.2.2]octa-2,5-diene (5c). Phenyl ketone **2** (5 g, 25.2 mmol) was reacted with 4-fluorophenylmagnesium bromide (1 M in THF) according to general method A1 for 30 min. After aqueous workup, the crude *tert*-alcohol was obtained (7.74 g, 104%); 7.7 g thereof was reacted with MsCl and Et_3N according to general method A2 for 60 min to afford crude **5c** as a red oil (crude: 9.2 g, 132%). The crude product was triturated with heptane at 50 °C. The soluble part was separated from the insoluble red oil by decantation and purified by chromatography on silica gel (33 g, eluent heptane) to afford **5c** as a colorless solid (5.25 g, 76%): mp 103−104 °C; $[\alpha]^{25}_D$ = −19.6 (c = 1.12, $CHCl_3$); GC−MS 94.1% a/a, t_R = 3.77 min, $[M + 1]^+$ = 277; purity (LC−MS) 100% a/a, t_R = 2.13 min, $[M + 1]^+$ = 277; chiral HPLC (Chiralpak ID, 250 × 4.6 i.d., 5 μm, heptane/EtOH 9:1, 0.8 mL/min) er >99.5:0.5, t_R = 5.0 min (*R*,*R*) (t_R = 6.7 min (*S*,*S*)); ^{1}H NMR ($CDCl_3$) δ 7.33−7.49 (m, 6 H), 7.23−7.30 (m, 1 H), 7.00−7.08 (m, 2 H), 6.66 (dd, J_1 = 6.4 Hz, J_2 = 1.8 Hz, 1 H), 6.60 (dd, J_1 = 6.4 Hz, J_2 = 1.7 Hz, 1 H), 4.25 (d, J = 6.4 Hz, 1 H), 4.20 (d, J = 6.5 Hz, 1 H), 1.55−1.62 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 162.0 (d, J = 245 Hz), 146.9, 146.0, 138.1, 134.4 (d, J = 3.6 Hz), 129.0, 128.9 (d, J = 2.2 Hz), 128.5, 126.9, 126.4, 124.8, 115.3 (d, J = 22 Hz), 40.3, 40.1, 25.7; HRMS (ESI) m/z calcd for $C_{20}H_{18}F$ 277.1393 $[M + H]^+$, found 277.1396.

(1*R*,4*R*)-2-(4-Methoxyphenyl)-5-phenylbicyclo[2.2.2]octa-2,5-diene (5d). Phenyl ketone **2** (5 g, 25.2 mmol) was reacted with 4-methoxyphenylmagnesium bromide (0.5 M in THF) according to general method A1 for 60 min. After aqueous workup, the crude *tert*-alcohol was obtained (8.2 g, 106%); 7.64 g thereof was reacted with MsCl and Et_3N according to general method A2 for 15 min to afford crude **5d** as a beige solid (crude: 6.6 g, 98%). The crude product was dissolved in EtOAc (35 mL) at 50 °C, and the insoluble, slimy part was separated by decantation. The clear solution was stirred at rt, and the white precipitate was filtered off and washed with heptane to afford the first crop. The mother liquor was stirred at rt, filtered, and washed with heptane to afford the second crop. This procedure was repeated a second time to afford a third crop. All three crops were combined to afford **5d** as a colorless solid (3.0 g, 44%): mp 95−98 °C; $[\alpha]^{25}_D$ = −68.4 (c = 1.03, $CHCl_3$); TLC (heptane/EtOAc 9:1) one spot for all crops; GC−MS 97.1% a/a, t_R = 4.29 min, $[M + 1]^+$ = 289; purity (LC−MS) 100% a/a, t_R = 2.07 min, $[M + 1]^+$ = 289; chiral HPLC (Chiralpak ID, 250 × 4.6 i.d., 5 μm, heptane/EtOH 9:1, 0.8 mL/min) er >99.5:0.5, t_R = 6.0 min (*R*,*R*) (t_R = 10.3 min (*S*,*S*)); ^{1}H NMR ($CDCl_3$) δ 7.33−7.51 (m, 6 H), 7.23−7.30 (m, 1 H), 6.92 (d, J = 8.8 Hz, 2 H), 6.67 (dd, J_1 = 6.4 Hz, J_2 = 1.9 Hz, 1 H), 6.57 (dd, J_1 = 6.4 Hz, J_2 = 1.9 Hz, 1 H), 4.20−4.27 (m, 2 H), 3.85 (s, 3 H), 1.59 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 158.7, 147.0, 146.3, 138.3, 131.0, 129.2, 128.5, 127.2, 126.8, 125.9, 124.8, 113.9, 55.4, 40.1, 34.0, 25.9, 25.8; HRMS (ESI) m/z calcd for $C_{21}H_{21}O$ 289.1592 $[M + H]^+$, found 289.1588.

(1*R*,4*R*)-2-(4-Phenoxyphenyl)-5-phenylbicyclo[2.2.2]octa-2,5-diene (5e). Phenyl ketone **2** (5 g, 25.2 mmol) was reacted with 4-phenoxyphenylmagnesium bromide (0.5 M in THF) according to general method A1 for 40 min. After aqueous workup, the crude *tert*-alcohol was obtained (14 g, 151%) that was reacted with MsCl and Et_3N according to general method A2 for 60 min to afford crude **5c** as a red oil (crude: 15.1 g, 171%). The crude product was purified by chromatography on silica gel (45 g, eluent heptane) to afford **5e** as colorless solid (2.6 g, 30%): mp 80−81 °C; $[\alpha]^{25}_D$ = −15.9 (c = 1.06, $CHCl_3$); GC−MS 100% a/a, t_R = 3.46 min; purity (LC−MS) 98.7% a/a, t_R = 2.29 min, $[M + 1]^+$ = 351; chiral HPLC (Chiralpak AD-H, 250 × 4.6 i.d., 5 μm, heptane (0.05% Et_2NH)/EtOH (0.05% Et_2NH) 1:1, 0.8 mL/min) er >99.5:0.5, t_R = 9.2 min (*R*,*R*) (t_R = 15.0 min (*S*,*S*)); ^{1}H NMR ($CDCl_3$) δ 7.42−7.50 (m, 4 H), 7.33−7.41 (m, 4 H), 7.22−7.28 (m, 1 H), 7.08−7.15 (m, 1 H), 6.98−7.07 (m, 4 H), 6.66 (dd, J_1 = 6.3 Hz, J_2 = 1.5 Hz, 1 H), 6.62 (dd, J_1 = 6.4 Hz, J_2 = 1.6 Hz, 1 H), 4.20−4.28 (m, 2 H), 1.59 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 157.5, 156.2, 147.0, 146.2, 138.2, 133.5, 129.7, 129.1, 128.5, 128.4, 126.8, 126.1, 124.8, 123.1, 119.1, 118.7, 40.2, 40.1, 25.8, 25.8; HRMS (ESI) m/z calcd for $C_{26}H_{23}O$ 351.1749 $[M + H]^+$, found 351.1744.

2-((1*R*,4*R*)-5-Phenylbicyclo[2.2.2]octa-2,5-dien-2-yl)-thiophene (5f). 2-Thienylmagnesium bromide (1 M in THF, 200 mL, 2 equiv) was added to a solution of phenyl ketone **2** (20 g, 0.101 mol) in THF (120 mL) at 5−15 °C. The reaction was allowed to warm to 20 °C and stirred for 1 h. IPC by LC−MS indicated full conversion. Cold water (80 mL) was added at 0−20 °C with cooling. More water (170 mL) and TBME (200 mL) were added, and the mixture was filtered over Celite. After phase separation, TBME (100 mL) was added to the aqueous phase, and the mixture was filtered over Celite. The TBME phase was washed with 1/2-saturated NaCl solution (2 × 100 mL), filtered over $MgSO_4$, and concentrated to dryness under reduced pressure at 50 °C to afford the intermediate *tert*-alcohol as a brown oil (29.7 g, 113%); this intermediate mixture of *exo*- and *endo*-alcohols was dissolved in CH_2Cl_2 (280 mL). Et_3N (85 mL, 6.0 equiv) and MsCl (20.6 mL, 2.6 equiv) were added at 0−10 °C. After the mixture was stirred at 20 °C for 20 min, IPC by LC−MS indicated full conversion. Water (50 mL) was added dropwise, followed by 1/2-saturated $NaHCO_3$ solution (120 mL) at 10−20 °C. CH_2Cl_2 (100 mL) was added, the phases were separated, and the organic phase was washed with 1/2-saturated $NaHCO_3$ solution (120 mL), dried over $MgSO_4$, and concentrated to dryness under reduced pressure at 50 °C to afford crude **5f** as a black oil (crude: 30.1 g, 113%). MeOH (40 mL) was added to the crude product (30.1 g), and the supension was stirred at 50 °C for 10 min. The suspension was cooled to 20 °C, stirred at 20 °C for 1 h, and filtered, and the filter cake was washed with MeOH (4 × 5 mL) and dried at 45 °C under reduced pressure to afford **5f** as off-white solid (19.35 g, 72%): mp 69−72 °C; $[\alpha]^{25}_D$ = −116.7 (c = 1.04, $CHCl_3$); purity (LC−MS) 100% a/a, t_R = 2.1 min, $[M + 1]^+$ = 265; chiral HPLC (Chiralpak AD-H, 250 × 4.6 ID, 5 μm, heptane (0.05% Et_2NH)/EtOH (0.05% Et_2NH) 1:1, 0.8 mL/min) er >99.5:0.5, t_R = 5.6 min (*R*,*R*), (t_R = 9.5 min (*S*,*S*)); ^{1}H NMR ($CDCl_3$) δ 7.32−7.48 (m, 4 H), 7.22−7.28 (m, 1 H), 7.09−7.18 (m, 2 H), 6.98−7.03 (m, 1 H), 6.64 (d, J = 2.0 Hz, 1 H), 6.63 (d, J = 2.0 Hz, 1 H), 4.16−4.22 (m, 2 H), 1.56−1.65 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 147.1, 142.6, 141.1, 138.1, 128.6, 128.4, 127.9, 127.5, 126.9, 124.9, 123.6, 121.7, 41.0, 39.9, 26.0, 25.7. HRMS (ESI) m/z calcd for $C_{18}H_{17}S$ 265.1051 $[M + H]^+$, found 265.1046.

(1*R*,4*R*)-2-([1,1′-Biphenyl]-4-yl)-5-phenylbicyclo[2.2.2]octa-2,5-diene (5g). Phenyl ketone **2** (5 g, 25.2 mmol) was reacted with 4-biphenylmagnesium bromide (0.5 M in THF) according to general method A1 for 60 min. After aqueous workup, the crude product (15.3 g, 172%) was purified by chromatography on silica gel (40 g, eluent CH_2Cl_2/heptane 1:1) to obtain crude *tert* alcohol (6.7 g, 76%) which was reacted with MsCl and Et_3N according to general method A2 for 30 min to afford crude **5g** as beige solid (crude: 6.88 g, 81%): purity (LC−MS); 91% a/a. The crude product was suspended in TBME (70 mL) and filtered, and the filter cake washed with TBME (2 × 20 mL). The filtrate was concentrated under reduced pressure to approximately 30 mL. The suspension was filtered and washed with TBME to afford a first crop of **5g**. A second crop of **5g** was obtained by a similar treatment of the mother liquor. Both crops were combined to afford **5g** as colorless solid (1.33 g, 16%): purity (LC−MS) 95.8% a/a, t_R = 2.31 min, $[M + 1]^+$ = 335. A sample (83 mg) was triturated in acetonitrile/MeOH (5 mL) at reflux. The suspension was cooled to rt and filtered. The filter cake was washed with acetonitrile (0.5 mL) and dried at 50 °C under reduced pressure to afford a purified sample of **5g** as a white solid (sample: 64 mg, 12% overall from **2**): mp 152 °C (peak temp in DSC), 141 °C dec; $[\alpha]^{25}_D$ = −12.7 (c = 1.18, $CHCl_3$); purity (LC−MS) 100% a/a, t_R = 2.31 min, $[M + 1]^+$ = 335; chiral HPLC (Chiralpak OJ-3, 100 × 4.6 i.d., 3 μm, heptane (0.05% Et_2NH)/EtOH (0.05% Et_2NH) 1:1, 0.8 mL/min): er >99.5:0.5, t_R = 7.4 min (*R*,*R*), (t_R = 9.1 min (*S*,*S*)); ^{1}H NMR ($CDCl_3$) δ 7.52−7.66 (m, 6 H), 7.42−7.51 (m, 4 H), 7.34−7.41 (m, 3 H), 7.21−7.28 (m, 1 H), 6.73 (dd, J_1 = 6.4 Hz, J_2 = 1.9 Hz, 1 H), 6.68 (dd, J_1 = 6.4 Hz, J_2 = 1.9 Hz, 1 H), 4.26−4.32 (m, 2 H), 1.60−1.64 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 146.9, 146.4, 140.9, 139.6, 138.2, 137.1, 129.4, 129.2, 128.8,

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128.5, 127.2, 127.2, 126.9, 126.9, 125.2, 124.8, 40.2, 40.0, 25.8; HRMS (ESI) m/z calcd for $C_{26}H_{23}$ 335.1800 $[M + H]^+$, found 335.1804.

(1*R*,4*R*)-2-(Naphthalen-1-yl)-5-phenylbicyclo[2.2.2]octa-2,5-diene (5h). Phenyl ketone **2** (1.25 g, 6.3 mmol) was reacted with 1-naphthylmagnesium bromide (0.25 M in THF) according to general method A1 for 16 h. After aqueous workup, the crude product (2.8 g, 136%) was purified by chromatography on silica gel (7 g, eluent heptane/EtOAc 9:1) to obtain crude *tert*-alcohol (1.45 g, 75%). Another run starting with phenyl ketone **5h** (1.25 g) gave crude *tert*-alcohol (0.75 g, 39%). Both batches were combined (2.2 g) and reacted with MsCl and Et_3N according to general method A2 for 5 h to afford crude **5h** as beige oil (crude: 2.5 g, 64%). The crude product was purified by chromatography on silica gel (25 g, eluent heptane), to afford **5h** as colorless resin (1.16 g, 30%): $[\alpha]^{25}_D$ = +83.4 (c = 1.00, $CHCl_3$); GC−MS 98.5% a/a, t_R = 4.73 min, $[M + 1]^+$ = 309; purity (LC−MS) 100% a/a, t_R = 2.24 min, $[M + 1]^+$ = 309; chiral HPLC (Chiralpak AD-H, 250 × 4.6 ID, 5 μm, heptane/EtOH 1:1, 0.8 mL/min) er >99.5:0.5, t_R = 4.9 min (*R*,*R*), (t_R = 4.6 min (*S*,*S*)); ^{1}H NMR ($CDCl_3$) δ 7.94−8.00 (m, 1 H), 7.84−7.90 (m, 1 H), 7.76−7.81 (m, 1 H), 7.54−7.60 (m, 2 H), 7.37−7.53 (m, 5 H), 7.25−7.36 (m, 2 H), 6.85 (dd, J_1 = 6.3 Hz, J_2 = 2.0 Hz, 1 H), 6.54 (dd, J_1 = 6.3 Hz, J_2 = 1.9 Hz, 1 H), 4.31−4.36 (m, 1 H), 4.01−4.06 (m, 1 H), 1.52−1.78 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 147.4, 147.3, 138.7, 138.4, 133.9, 132.3, 131.7, 129.2, 128.6, 128.3, 127.3, 126.9, 126.2, 125.8, 125.7, 125.4, 125.0, 124.9, 44.2, 40.1, 25.9; HRMS (ESI) m/z calcd for $C_{24}H_{21}$ 309.1643 $[M + H]^+$, found 309.1640.

(1*R*,4*R*)-2-(Naphthalen-2-yl)-5-phenylbicyclo[2.2.2]octa-2,5-diene (5i). For the preparation of the 2-naphthyl Grignard reagent, magnesium (1.22 g, 50.4 mmol) in THF (10 mL) was treated with a solution of 2-bromonaphthalene (2.07 g, 10.1 mmol, 2 equiv) in THF (10 mL). A slight exotherm was observed, and the mixture became turbid. Additional THF (20 mL) was added, and the mixture was stirred at rt for 15 min. The 2-naphthyl Grignard solution was cooled to 0 °C, and a solution of phenyl ketone **2** (er >99.5:0.5, 1.0 g, 5.04 mmol, 1 equiv) in THF (10 mL) was added such that the temp did not exceed 15 °C. The reaction mixture was stirred at rt for 2 h. The reaction was quenched by addition of water (10 mL), the mixture was extracted twice with TBME (2 × 10 mL), and the combined organic phases were washed with water, dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure to afford the *tert*-alcohol as red viscous oil (2.53 g, 120%). The crude intermediate was dissolved in CH_2Cl_2 (60 mL), and Et_3N (5.4 mL, 38.8 mmol) was added. MsCl (1.6 mL, 20.2 mmol) was added at 5 °C over 20 min. A slight exotherm was observed, and the reaction mixture turned brown-red. The reaction mixture was stirred at rt for 16 h. Water (50 mL) was added, and the organic phase was washed with water (3×), dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure to yield crude **5i** (crude: 1.8 g, 116%). Purification by chromatography (50 g silica gel, ⌀ 3 cm, eluent heptane → heptane/EtOAc 10:2) afforded **5i** as off-white solid (810 mg, 52%). For analytical purposes, a sample (750 mg) was further purified by crystallization from heptane to give **5i** as white solid (210 mg, 28% recovery): mp 119−121 °C; $[\alpha]^{25}_D$ = +65.4 (c = 1.00, $CHCl_3$); TLC R_f (heptane) = 0.19; R_f (heptane/EtOAc 10:2) = 0.63; purity (LC−MS) 100% a/a, t_R = 2.08 min, $[M + 1]^+$ = 309; chiral HPLC (Chiralpak IA, 250 × 4.6 i.d., 5 μm, heptane/EtOH 9:1, 0.8 mL/min) er >99.5:0.5, t_R = 5.8 min (*R*,*R*) (t_R = 6.9 min (*S*,*S*)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.90 (m, 4 H), 7.55−7.60 (m, 2 H), 7.2−7.50 (m, 6 H), 6.80 (dd, J_1= 3 Hz, J_2 = 6 Hz, 1 H), 6.70 (dd, J_1 = 3 Hz, J_2 = 6 Hz, 1 H), 4.41 (d, J = 6 Hz, 1 H), 4.29 (d, J = 6 Hz, 1 H), 1.61 (s br, 4 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 129.9, 129.2, 128.5, 128.1, 127.6, 126.8, 126.1, 125.5, 124.8, 123.7, 122.8, 41.2, 39.9, 25.9, 25.8; HRMS (ESI) m/z calcd for $C_{24}H_{21}$ 309.1643 $[M + H]^+$, found 309.1637.

(1*R*,4*R*)-2-(3,5-Difluorophenyl)-5-phenylbicyclo[2.2.2]octa-2,5-diene (5j). Phenyl ketone **2** (5 g, 25.2 mmol) was reacted with 3,5-difluorophenylmagnesium bromide (0.5 M in THF) according to general method A1 for 105 min. After aqueous workup, the crude *tert*-alcohol was obtained (8.7 g, 110%); 8.15 g thereof was reacted with MsCl and Et_3N according to general method A2 for 70 min to afford crude **5j** as red-brown oil (crude: 8.5 g, 122%). The crude product was purified by chromatography on silica gel (40 g, eluent heptane) to yield a fraction (2.29 g) that was purified again by chromatography on silica gel (30 g, eluent heptane) to afford **5j** as colorless oil (0.28 g, 4%): GC−MS 94.3% a/a, t_R = 3.66 min, $[M + 1]^+$ = 295; purity (LC−MS) 100% a/a, t_R = 2.11 min; chiral HPLC (Chiralpak IA, 250 × 4.6 ID, 5 μm, heptane/EtOH 9:1, 0.8 mL/min) er >99.5:0.5, t_R = 7.2 min (*R*,*R*), (t_R = 11.4 min (*S*,*S*)); ^{1}H NMR ($CDCl_3$) δ 7.44−7.48 (m, 2 H), 7.33−7.40 (m, 2 H), 7.22−7.30 (m, 1 H), 6.93−7.00 (m, 2 H), 6.62−6.75 (m, 3 H), 4.28 (dd, J_1 = 6.5 Hz, J_2 = 1.8 Hz, 1 H), 4.16 (dd, J_1 = 6.0 Hz, J_2 = 1.4 Hz, 1 H), 1.53−1.62 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 163.3 (dd, J_1 = 247 Hz, J_2 = 14 Hz), 146.7, 145.2 (t, J = 3 Hz), 141.5 (t, J = 10 Hz), 137.9, 131.8, 128.7, 128.6, 127.0, 124.8, 107.5 (dd, J_1 = 18 Hz, J_2 = 7 Hz), 101.9 (t, J = 26 Hz), 40.2, 39.9, 25.7, 25.5; HRMS (ESI) m/z calcd for $C_{20}H_{16}F_2$: 295.1298 $[M + H]^+$, found 295.1303. After storage at −20 °C for 8 months, the sample had degraded, purity (LC−MS): 80.4% a/a.

(1*R*,4*R*)-5-Phenylbicyclo[2.2.2]octa-2,5-dien-2-yl Trifluoromethanesulfonate (6). *n*-Butyllithium in hexane (1.6 M, 70.3 mL, 1.5 equiv) was added to diisopropylamine (11.6 mL, 1.5 equiv) at −78 °C in THF (25 mL). The mixture was warmed to −20 °C and stirred at −20 °C for 10 min. After the mixture was cooled to −78 °C, a solution of phenyl ketone **2** (15 g, 75.7 mmol) in THF (44 mL) was added at −78 °C. After the mixture was stirred at −78 °C for 1 h, a solution of 1,1,1-trifluoro-*N*-(pyridin-2-yl)-*N*-((trifluoromethyl)-sulfonyl)methanesulfonamide[27] (40.6 g, 1.5 equiv) in THF (44 mL) was added. The brown solution was allowed to warm to rt. LC−MS indicated >99% conversion. Cold water (200 mL) was added, and THF was removed under reduced pressure at 50 °C. The mixture was extracted with TBME (500 mL). The organic phase was washed with 10% aqueous NaOH solution (600 mL) and water (190 mL) and evaporated to dryness under reduced pressure at 50 °C to afford the crude product **6** as dark-red resin (crude: 33 g, 132%). The crude product was purified by plug filtration over silica gel (190 g) using heptane/EtOAc 9:1, fraction size approximately 100 mL, to afford crude **6** as yellow oil (22 g, 88%): $[\alpha]^{25}_D$ = −5.90 (c = 1.10, $CHCl_3$); purity (LC−MS) 98.6% a/a, t_R = 2.02 min; ^{1}H NMR δ 7.20−7.52 (m, 5 H), 6.57 (dd, J_1 = 6.4 Hz, J_2 = 2.1 Hz, 1 H), 6.19 (dd, J_1 = 7.2 Hz, J_2 = 2.7 Hz, 1 H), 4.20 (m, 1 H), 3.76 (m, 1 H), 1.42−1.96 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 155.1, 147.0, 137.1, 128.6, 127.5, 127.3, 124.9, 120.3, 117.0, 40.7, 39.6, 25.8, 24.7; HRMS (ESI, negative mode) m/z calcd for $C_{15}H_{13}O_3F_3S$ 329.0459 $[M - H]^-$, found 329.0463.

(1*R*,4*R*)-2-Methyl-5-phenylbicyclo[2.2.2]octa-2,5-diene (7a). Methylmagnesium bromide (3 M in Et_2O, 4 mL, 2.00 equiv) was added with cooling to a mixture of triflate **6** (2 g, 6.05 mmol) and iron(III) acetylacetonate (0.106 g, 0.05 equiv) in THF (30 mL) at 22−30 °C. The mixture was stirred at 35−40 °C for 3 d. Additional iron(III) acetylacetonate (0.32 g, 0.15 equiv) and methylmagnesium bromide (3 M in Et_2O, 12 mL, 6.00 equiv) were added, and the mixture was stirred at 30−40 °C for 24 h. GC−MS showed 81% conversion. Water (20 mL) was added with cooling, followed by TBME (50 mL). The organic phase was concentrated to dryness under reduced pressure at 50 °C to afford crude **7a** (crude: 1.3 g, 109%): purity (LC−MS) 96.8% a/a, t_R = 2.0 min. The crude product was purified by chromatography on silica gel (4 g, eluent heptane), to afford **7a** as colorless oil (0.54 g, 45%): $[\alpha]^{25}_D$ = −20.7 (c = 1.11, $CHCl_3$); purity (LC−MS) 98.8% a/a, $[M + 1]^+$ = 197; chiral HPLC (Chiralpak AD-H, 250 × 4.6 i.d., 5 μm, heptane/EtOH 1:1, 0.8 mL/min) er >99.5:0.5, t_R = 4.4 min, (t_R = 4.7 min (*S*,*S*)); ^{1}H NMR ($CDCl_3$) δ 7.42−7.46 (m, 2 H), 7.30−7.37 (m, 2 H), 7.19−7.25 (m, 1 H), 6.56 (dd, J_1 = 6.3 Hz, J_2 = 1.9 Hz, 1 H), 4.00−4.04 (m, 1 H), 3.45−3.49 (m, 1 H), 1.87 (s, 3 H), 1.40−1.49 (m, 4 H); ^{13}C ($CDCl_3$) δ 147.0, 144.4, 138.5, 129.0, 128.4, 126.7, 126.6, 124.7, 43.1, 39.5, 26.2, 25.1, 19.3; HRMS (ESI) m/z calcd for $C_{15}H_{17}$ 197.1330 $[M + H]^+$, found 197.1326.

(1*R*,4*R*)-2-Benzyl-5-phenylbicyclo[2.2.2]octa-2,5-diene (7b). Benzylmagnesium bromide (19% in THF, 12 mL, 2.00 equiv) was added to a mixture of triflate **6** (1.9 g, 5.75 mmol) and iron(III)acetylacetonate (200 mg, 0.05 equiv) in THF (35 mL) at 35−40 °C. After 20 min of stirring at 33−40 °C, LC−MS indicated >99% conversion. Water (40 mL) was added with cooling, followed by

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TBME (60 mL). The organic phase was evaporated to dryness under reduced pressure at 50 °C to afford crude **7b** as yellow oil (crude: 1.94 g, 124%). The crude product was purified by chromatography on silica gel (10 g, eluent heptane) to afford two fractions with **7b** (1.55 g) which were submitted to a second chromatography on silica gel (50 g, eluent heptane), to afford **7b** as a colorless oil which solidified at rt (0.8 g, 51%): mp 51−52 °C; $[\alpha]^{25}_{D}$ = +33.9 (*c* = 1.01, $CHCl_3$); GC−MS 100% a/a, t_R = 3.84 min, $[M + 1]^+$ = 273; purity (LC−MS) 98.8% a/a, t_R = 2.19 min, $[M + 1]^+$ = 273; chiral HPLC (Chiralcel OJ-H, 250 × 4.6 i.d., 5 μm, heptane/EtOH 9:1, 0.8 mL/min) er 99.8:0.2, t_R = 12.0 min (t_R = 10.6 min (*S*,*S*)); ^{1}H NMR ($CDCl_3$) δ 7.41−7.46 (m, 2 H), 7.27−7.37 (m, 4 H), 7.15−7.26 (m, 4 H), 6.51 (dd, J_1 = 6.2 Hz, J_2 = 1.7 Hz, 1 H), 6.00 (d, *J* = 6.2 Hz, 1 H), 4.04−4.09 (m, 1 H), 3.52 (s, 2 H), 3.45−3.50 (m, 1 H), 1.23−1.55 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 147.2, 146.9, 139.5, 138.4, 129.3, 129.1, 128.4, 128.3, 128.2, 126.6, 126.0, 124.7, 41.6, 40.1, 39.6, 26.2, 25.6; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{21}$ 273.1643 $[M + H]^+$, found 273.1643.

(1*R*,4*R*)-2-Isobutyl-5-phenylbicyclo[2.2.2]octa-2,5-diene (7c). Isobutylmagnesium bromide (2 M in Et_2O, 3 mL, 2.0 equiv) was added with cooling to a mixture of triflate **6** (1 g, 3.03 mmol) and iron(III) acetylacetonate (214 mg, 0.2 equiv) in THF (15 mL) at 22−40 °C. After the mixture was stirred at 40−45 °C for 2.5 h, additional isobutylmagnesium bromide (2 M in Et_2O, 3 mL, 2.0 equiv) was added, followed by stirring at 40−45 °C for 2.5 h. LC−MS indicated >99% conversion. Water (20 mL) was added with cooling, followed by TBME (30 mL). The organic phase was evaporated to dryness at 50 °C under reduced pressure to afford crude **7c** as a yellow oil (crude: 0.65 g, 90%). The crude product was purified by chromatography on silica gel (14 g, eluent heptane) to afford **7c** as a colorless oil (0.25 g, 35%): purity (GC−MS) 95.7% a/a, t_R = 3.00 min, $[M + 1]^+$ = 239; purity (LC−MS) 97.0% a/a, t_R = 2.26 min; chiral HPLC (Chiralpak AD-H, 250 × 4.6 i.d., 5 μm, heptane/EtOH 1:1, 0.8 mL/min) t_R = 4.2 min, er >99.5:0.5;[38] ^{1}H NMR ($CDCl_3$) δ 7.40−7.47 (m, 2 H), 7.30−7.38 (m, 2 H), 7.17−7.26 (m, 1 H), 6.55 (dd, J_1 = 6.3 Hz, J_2 = 2.0 Hz, 1 H), 5.96 (dd, J_1 = 6.2 Hz, J_2 = 1.4 Hz, 1 H), 4.00−4.07 (m, 1 H), 3.47−3.55 (m, 1 H), 2.04 (d, *J* = 7.0 Hz, 2 H), 1.76−1.89 (m, 1 H), 1.37−1.51 (m, 4 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.4, 147.0, 138.6, 129.4, 128.4, 127.5, 126.5, 124.7, 43.6, 42.0, 39.5, 26.6, 26.0, 25.4, 22.8, 22.6. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{23}$ 239.1800 $[M + H]^+$, found 239.1801. After storage at −20 °C for 8 months the sample had degraded, purity (LC−MS): 38.3% a/a.

■ ASSOCIATED CONTENT

Supporting Information

Details for the GC−MS, LC−MS, chiral HPLC methods, ^{1}H and ^{13}C NMR spectra, chiral HPLC data of **4a**, **2**, **5** and **7**, and screening report for the organocatalytic reaction. This material is available free of charge via the Internet at http://pubs.acs.org/.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +41 61 565 67 59. E-Mail: stefan.abele@actelion.com.

Notes

The authors declare no competing financial interest.

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(21) (a) A reaction at 45 °C, stopped after 24 h (instead of 4–5 d), gave an isolated yield of 25% with a diastereomeric purity of 100% and a similar er of 70:30. (b) Submitting pure **4a** to the reaction conditions of the organocatalytic step (Table 1) did not lead to any isomerization—the chiral HPLC only showed the presence of **4a**.
(22) We acknowledge the reviewer for this proposal.
(23) Recrystallization of the mesylate **4a**-Ms with an er 72:28 in EtOAc/heptane led to an enrichment of the undesired minor enantiomer.
(24) Either silica gel using heptane or reversed-phase HPLC using water/acetonitrile (0.5% formic acid) as eluent was used. The silica gel chromatographies were run as "plug filtrations" with low relative amounts of SiO_2 (approximately 5 wt).
(25) A slurry in MeOH was applied for the efficient purification of **5a** (79 g) and **5f** (30 g).
(26) Analytical data of a commercial sample (1*R*,4*R*)-Ph-bod* (Aldrich No. 707171) in parentheses: purity (GC–MS): 99.5% a/a (98.1% a/a), purity (LC–MS): >99.5% a/a (97.4% a/a), enantiomeric ratio (chiral HPLC): er >99.5:0.5 (>99.5:0.5), mp 74–77 °C (74–76 °C), see also the Experimental Section.
(27) (a) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302. (b) *Org. Synth.* **1998**, *Coll. Vol. 9*, 165.
(28) Samples reanalyzed by LC–MS after storage at rt under air for 12 months showed no decomposition. Stress tests data of diene **5a** (100% a/a LC–MS): stirring at rt for 3 weeks with aqueous HCl/THF, silica gel in heptane, or aqueous NaOH/THF. Purity was monitored by LC–MS and TLC. Result: only acidic conditions (HCl/THF) led to decomposition.
(29) Laird, T. *Org. Process Res. Dev.* **2012**, *16*, 1–2.
(30) (a) The American Chemical Society Green Chemistry Institute's Pharmaceutical Roundtable has chosen PMI as the key metric for evaluating processes with regard to their efficiency and sutainability; see: Jimenez-Gonzalez, C.; Ponder, C.; Broxterman, Q. B.; Manley, J. B. *Org. Process Res. Dev.* **2011**, *15*, 912–917. (b) Dunn, P. J. In *Pharmaceutical Process Development*; Blacker, J. A., Williams, M. T., Eds.; Royal Society of Chemistry: London, 2011; Chapter 6.
(31) To account for the fact that small-scale protocols are normally not optimized with respect to solvent and waste, the most meaningful PMI is given for the reagents, i.e., without considering solvents and aqueous solutions. As the goal was to devise a route not relying on preparative chiral HPLC separation, the published route using resolution by chiral HPLC[4b] was not considered for this comparison. The trend is similar when routes involving resolution by chiral HPLC are compared, see refs 4b and 12.
(32) Derived from data submitted by several companies for for 21 products in phase 3 or commercial products. Published by the Pharmaceutical Roundtable (13 pharmaceutical companies and the American Chemical Society Green Chemistry Institute);[30b] see: Henderson, R. K.; Kindervater, J.; Manley, J. M., III. *International Conference on Green and Sustainable Chemistry*; Delft, Holland, July 2007.
(33) Bella has also used the 4-Cl-, 4-Br-, 4-OMe-phenylacetaldehyde and the 2-naphthylaldehyde in the organocatalytic step,[15a] affording bicyclic alcohols that would be ideal substrates for further C_2-symmetric dienes.
(34) For a study of eletronic effects of related dienes on catalytic efficiency, see (*R*,*R*)-1,4-dimethyl-2,5-diarylbicyclo[2.2.2]octa-2,5-dienes: Luo, Y.; Carnell, A. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2750–2754.
(35) Wernerova, M.; Hudlicky, T. *Synlett* **2010**, 2701–2707.
(36) The mass of the dehydrated eliminated product (chiral diene) was already detected in the LC–MS at the stage of the tertiary alcohols, prior to the addition of MsCl and Et_3N.
(37) In the GC–MS trace of the dienes, the largest mass signal—besides the $[M + 1]^+$ peak—was $[M - 28]^+$, indicative of an Alder–Rickert reaction with release of ethylene to give the *p*-terphenyl derivative.
(38) *rac*-**7c** was measured with a different chiral HPLC method. Still, the er is reported to be >99.5:0.5, as the starting material, ketone **2**, was enantiomerically pure. A racemization is not deemed conceivable.