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Enantioselective Synthesis of *cis*-1,2-Disubstituted Cyclopentanes and Cyclohexanes by Suzuki–Miyaura Cross-Coupling and Iridium-Catalyzed Asymmetric Hydrogenation

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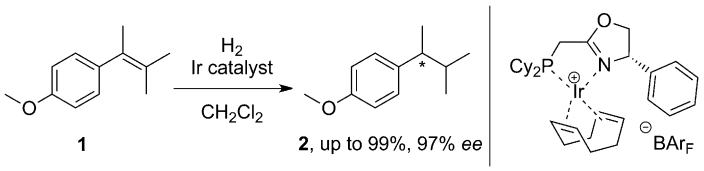
Abstract: A series of 1,2-disubstituted cyclohexene derivatives was prepared through Suzuki–Miyaura cross-coupling of 2-bromo-1-cyclohexenecarbaldehyde or 2-carbomethoxy-1-cyclohexen-1-yl triflate with arylboronates. These tetrasubstituted cyclic alkenes were subjected to Ir-catalyzed asymmetric hydrogenation. In this way *cis*-1-methoxymethyl-2-arylcyclohexanes were obtained in high yield with excellent enantio- and diastereoselectivities (up to >99% *ee*, >99% *cis*) by using phosphinomethyloxazolines as ligands. Asymmetric hydrogenation of analogous cyclopentene derivatives, prepared by Suzuki–Miyaura cross-coupling, proved to be more difficult and proceeded with lower enantioselectivities of up to 88% *ee*. The synthetic potential of this cross-coupling/asymmetric-hydrogenation strategy was demonstrated by an enantioselective route to chiral hexahydrofluorenones.

Keywords: alkenes · asymmetric synthesis · enantioselectivity · hydrogenation · iridium · palladium

Introduction

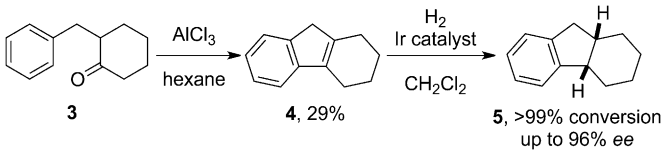
Asymmetric hydrogenation of prochiral olefins is one of the most efficient and reliable methods for the enantioselective introduction of stereogenic centers. Although Rh– and Ru–diphosphane complexes have been widely used for the enantioselective hydrogenation of suitably functionalized olefins that bind to the catalyst through heteroatom substituents,[1] iridium complexes, particularly those with chiral P,N ligands, have proved to be the catalysts of choice for the asymmetric hydrogenation of olefins lacking coordinating groups.[2] Recently, we have shown that even tetra-substituted, unfunctionalized olefins can be hydrogenated with high efficiency and enantioselectivity by using chiral iridium catalysts.[3] In this way two adjacent stereogenic centers can be introduced enantio- and diastereoselectively in a single step. However, tetra-substituted olefins are often difficult to synthesize.[4] Herein, we report an efficient two-step sequence for the introduction of two stereogenic centers in cyclopentanes and cyclohexanes, involving a Suzuki–Miyaura cross-coupling reaction, leading to a tetra-substituted C=C bond, followed by an Ir-catalyzed asymmetric hydrogenation.

In our initial work on the iridium-catalyzed asymmetric hydrogenation of tetra-substituted olefins by using alkene **1** as a test substrate, 2-(phosphanylmethyl)oxazolines were found to be the most efficient ligands (Scheme 1).[3] Subsequent studies showed that a range of tetra-substituted alkenes could be hydrogenated with Ir complexes based on these ligands. In many cases high enantioselectivities were achieved, often under surprisingly mild conditions at only 1–5 bar hydrogen pressure.



Scheme 1. Enantioselective hydrogenation of compound **1**.

In connection with this work, tricyclic olefins, like compound **4**, attracted our interest (Scheme 2) because the corresponding hexahydrofluorene motif **5** forms the core carbon skeleton of various natural products, for example, taiwaniaquinol B[5a]. Furthermore, Banwell et al. have shown that methoxy-substituted derivative **10** (Scheme 3) can be used as a precursor for the construction of the carbocyclic framework of the gibberilins.[5b]



Scheme 2. Synthesis and subsequent asymmetric hydrogenation of tetrahydrofluorene **4**.

Initially, we used a procedure described by Colonge and Sibeud to synthesize olefin **4**.[6] The key step in this method is an intramolecular Friedel–Crafts-type reaction of 2-ben-

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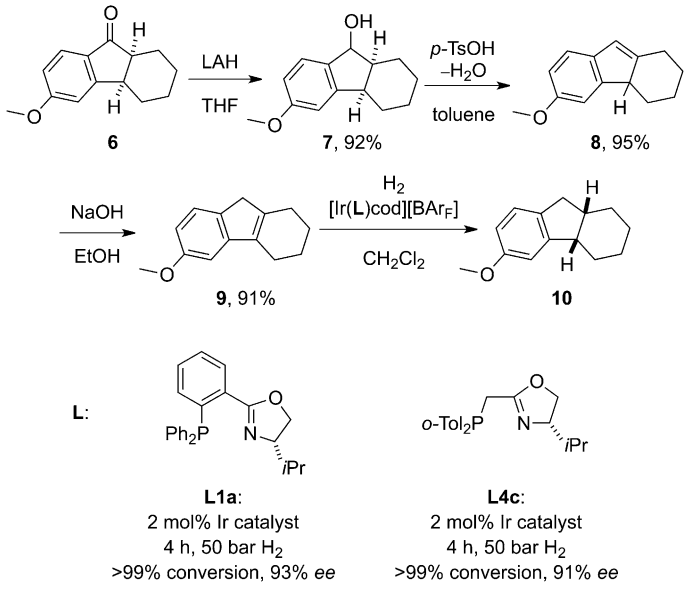
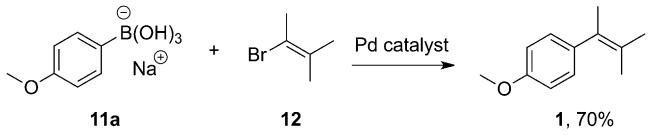


Scheme 3. General route to tetrahydrofluorene **9**. See the Supporting Information for details (Ts = tosyl; cod = 1,5-cyclooctadiene; BAr_F = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.

zylcyclohexanone, which gives the tetra-substituted olefin directly (Scheme 2). However, because this method shows low functional-group tolerance, it is not suitable for the synthesis of olefins like **9**. An alternative route to this class of tricyclic olefins has been described by House et al.,[7] starting from tetrahydrofluorenones, which can be converted into the corresponding tetra-substituted olefins by a reduction/elimination/isomerization sequence (Scheme 3). We used this method for the synthesis of **9** and obtained the tetra-substituted olefin in high overall yield (80%) starting from the known hexahydrofluorenone **6**.[5b] When we applied compound **9** in the iridium-catalyzed asymmetric hydrogenation, the results were similar to those obtained for olefin **4**. Thus, compound **10** was obtained in up to 93% *ee* with full conversion by using ligand **L1a**.

Although we were pleased to have a reliable method for the synthesis of this class of tricyclic olefin in hand, the detour of dehydration and subsequent isomerization is only applicable for a limited range of substrates, such as indenes or dihydronaphthalenes. In many other cases elimination of water from a tertiary alcohol gives an isomeric mixture of olefins. As even small amounts of undesired double-bond isomers can lead to a significant decrease in enantioselectivity, a more general approach was required. For this purpose, we evaluated an alternative route through Suzuki–Miyaura cross-coupling by using a Pd/N-heterocyclic carbene (NHC) system described by Trudell, Nolan et al.[8] This method worked well for olefin **1**, which was obtained in 70% yield (Scheme 4).

Encouraged by this result, we decided to extend the method to cyclic bromoolefins, such as readily available 2-bromo-1-cyclohexenecarbaldehyde **13**.[9] The resulting aryl-substituted cyclohexenecarbaldehydes[10] can be transformed



Scheme 4. Synthesis of **1** by using Pd-catalyzed cross-coupling.

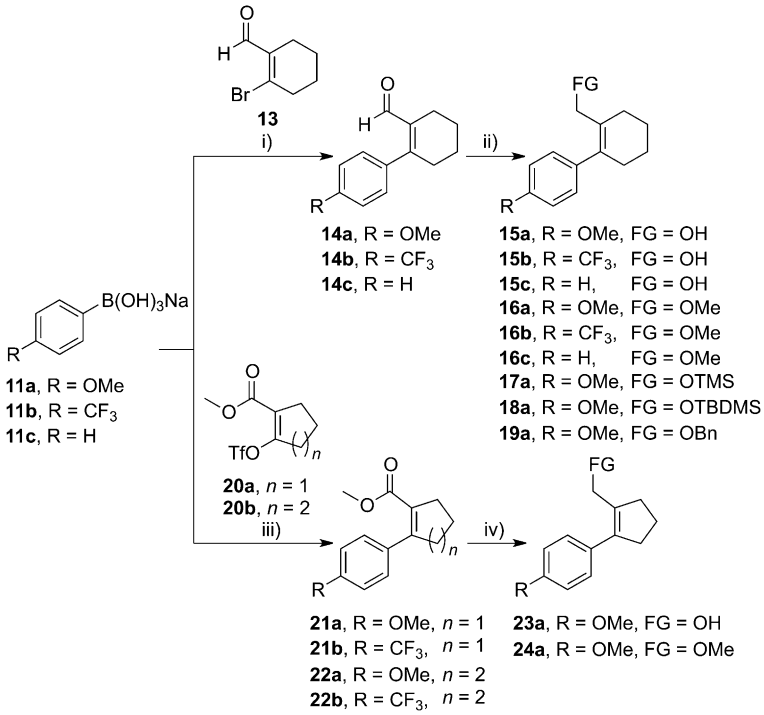
into a wide range of functionalized tetra-substituted olefins, which give access to synthetically useful classes of chiral compounds by enantioselective iridium-catalyzed hydrogenation.

Results and Discussion

Synthesis of cyclic, tetra-substituted olefins through phosphine-free Suzuki–Miyaura cross-coupling: Since traces of phosphine contaminants may act as inhibitors in the iridium-catalyzed asymmetric hydrogenation and could lead to a reduction in the turnover number of the catalyst and the enantioselectivity, we searched for a phosphine-free Suzuki–Miyaura cross-coupling procedure.[11] Two general routes to 1,2-disubstituted cyclohexenes and cyclopentenes are shown in Scheme 5. An initial set of 1,2-disubstituted cyclohexenes was obtained from bromoaldehyde **13**.[12,13] However, this approach was not suited for the synthesis of 1,2-disubstituted cyclopentenes because 2-bromocyclopent-1-enecarbaldehyde proved to be too unstable under the reaction conditions. However, trifluoromethanesulfonate **20** was successfully used under similar reaction conditions for the synthesis of esters **21** and **22**.

Initially, we used a relatively high catalyst loading (2 mol% Pd) with **IMes** (1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) as the ligand precursor for the Suzuki–Miyaura cross-coupling of boronate **11a** with bromoaldehyde **13**.[8] An initial test reaction with dioxane as the solvent gave desired 1,2-disubstituted cyclohexene **14a** in essentially quantitative yield (98%). The catalyst loading could be reduced to 0.2 mol% when **IMes** was used as the ligand, whereas without the ligand the product was obtained in only 55% yield. Further test reactions showed that no ligand is needed if the reaction is carried out in a THF/H_2O solvent mixture. Under these conditions the product was formed in up to 89% yield by using only 0.1 mol% [$Pd_2(dba)_3$] (Table 1; dba = dibenzylideneacetone).

Next, we explored the electronic substituent effects on the scope of the reaction. We found that replacing the electron-donating methoxy group with a hydrogen atom or with an electron-withdrawing trifluoromethyl group resulted in diminished reactivity under the conditions used previously. In the reaction with (trifluoromethylphenyl)borate **11b** only 24% of product **14b** was isolated and the corresponding unsubstituted phenylborate **11c** gave only traces of the desired product. However, the yields could be significantly improved by changing the solvent. In dibutyl ether trifluoromethyl-substituted borate **11b** was converted into product



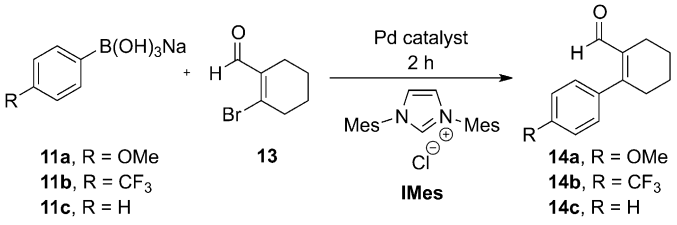
Scheme 5. Suzuki–Miyaura cross-coupling reactions starting from bromoaldehyde **13** or triflates **20a** and **20b**.Reagents and conditions: i) $Pd_2(dba)_3$, THF/H_2O, 66 °C, 2 h; ii) **15a–c**: $NaBH_4$, MeOH, 0 °C - RT, 1 h; **16a-c**: NaH, MeI, THF, RT, 2 h; **17a**: Et_3N, TMSCl, CH_2Cl_2, RT, 1 h; **18a**: Imidazol, TBDMSCl, DMF, RT, 14 h; **19a**: NaH, $(n\text{Bu})_4$NI, BnBr, THF, RT, 14 h; iii) **21a–b**: $Pd_2(dba)_3$, THF, 66 °C, 4 h; **22a-b**: $Pd_2(dba)_3$, THF/H_2O, 66 °C, 14 h; iv) **23a**: LiAlH4, THF, 0 °C - RT, 10 min.; **24a**: NaH, MeI, THF, RT, 2 h.

yields were still much lower than in the cross-coupling with methoxy-substituted borate **11a**.

Similar conditions were applied for the cross-coupling of trifluoromethanesulfonate **20a** with boronates **11a** and **11b**. The yields of cross-coupling products were optimal when no ligand was used (Table 2). With only 0.1 mol% $[Pd_2(dba)_3]$, olefin **21a** was obtained in quantitative yield and even *p*-CF_3-substituted olefin **21b** could be obtained in 72% yield.

However, this method proved to be inefficient for triflate **20b** (Scheme 6). By using the conditions established for the reaction of **20a**, no product was obtained with borate **11a**. Further investigation of the reaction conditions showed that catalytic amounts of both the **IMes** ligand and water had to be

Table 1. Suzuki–Miyaura cross-coupling by using bromoaldehyde **13**.[a]

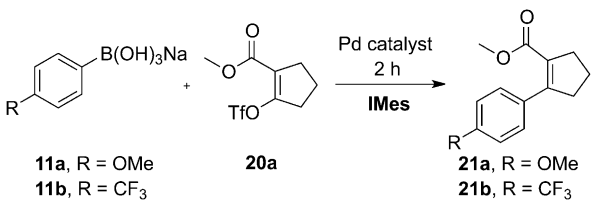


R	Solvent	*T* [°C]	Catalyst loading [mol% $Pd_2(dba)_3$]	Ligand loading [mol%][b]	Yield [%][d]
OMe	dioxane	90	1.0	2.0	98
OMe	dioxane	90	0.1	0.2	99
OMe	dioxane	90	0.1	–	55
OMe	THF/H_2O[d]	66	1.0	2.0	86
OMe	THF/H_2O[d]	66	0.1	0.2	90
OMe	THF/H_2O[d]	66	0.1	–	89
OMe	EtOH/H_2O[e]	66	1.0	2.0	54
OMe	EtOH/H_2O[e]	66	0.1	0.2	60
OMe	EtOH/H_2O[e]	66	0.1	–	57
CF_3	THF/H_2O[d]	66	0.1	–	24
CF_3	butylether	120	0.1	–	40
H	THF/H_2O[d]	66	0.1	–	<5
H	dioxane	90	0.1	–	47

[a] Full experimental conditions are given in the Supporting Information. [b] **IMes** (1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) was used as the ligand. [c] Determined by GC. [d] Ratio of 2:1. [e] Ratio of 1:1.

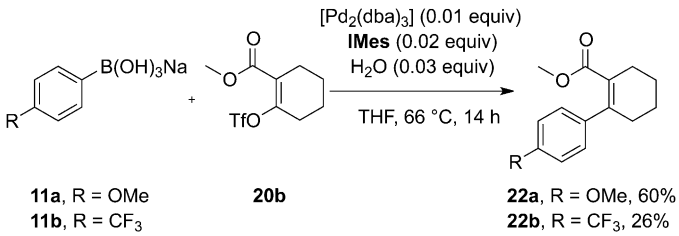
14b in up to 40% yield. For the synthesis of **14c** the best results were obtained in dioxane (47% yield). Nevertheless,

Table 2. Suzuki–Miyaura cross-coupling by using trifluoromethanesulfonate **20a**.[a]



R	Solvent	*T* [°C]	Catalyst loading [mol% $Pd_2(dba)_3$]	Ligand loading [mol%][b]	Yield [%][c]
OMe	THF	66	1.0	2.0	92
OMe	THF	66	0.1	–	99
CF_3	THF	66	1.0	2.0	39
CF_3	THF	66	0.1	–	72

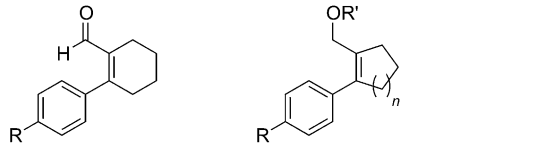
[a] Full experimental conditions are given in the Supporting Information. [b] **IMes** was used as the ligand. [c] Determined by GC.



Scheme 6. Optimized reaction conditions for the Suzuki–Miyaura cross-coupling by using trifluoromethanesulfonate **20b**.

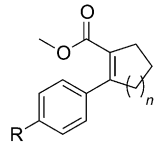
added to obtain ester **22a** (up to 60% yield). It appears that these coupling reactions are quite sensitive to the conditions applied and careful optimization is often necessary to obtain satisfying results.

Other 1,2-disubstituted cyclohexenes were obtained by functional-group interconversion of aldehydes **14a**–**14c** (Scheme 7). Thus, allylic alcohols **15a**–**15c**, for example,



14a, R = OMe
14b, R = CF_3
14c, R = H

15a, R = OMe, R' = H, *n* = 2
15b, R = CF_3, R' = H, *n* = 2
15c, R = H, R' = H, *n* = 2



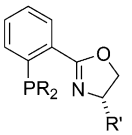
21a, R = OMe, *n* = 1
21b, R = CF_3, *n* = 1
22a, R = OMe, *n* = 2
22b, R = CF_3, *n* = 2

16a, R = OMe, R' = Me, *n* = 2
16b, R = CF_3, R' = Me, *n* = 2
16c, R = H, R' = Me, *n* = 2
17a, R = OMe, R' = TMS, *n* = 2
18a, R = OMe, R' = TBDMS, *n* = 2
19a, R = OMe, R' = Bn, *n* = 2
23a, R = OMe, R' = H, *n* = 1
24a, R = OMe, R' = Me, *n* = 1

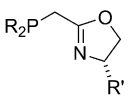
Scheme 7. Substrates applied in the Ir-catalyzed asymmetric hydrogenation reaction (TMS = trimethyl silyl; TBDMS = *tert*-butyl dimethyl silyl; Bn = benzyl).

were generated by reduction of the corresponding aldehydes with $NaBH_4$ (>99%). Protection of these alcohols gave methyl ethers **16a**–**16c** (>95%), TMS ether **17a** (88%), TBDMS ether **18a** (92%), and benzyl ether **19a** (97%). The 1,2-disubstituted allylic alcohol **23a** was generated from methyl ester **21a** by reduction with $LiAlH_4$ (>99%) and converted into methyl ether **24a** (95%).

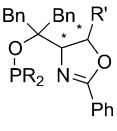
Ir-catalyzed hydrogenation of cyclic tetra-substituted olefins: The set of tetra-substituted cyclic olefins described in the previous section (Scheme 7) was subjected to hydrogenation with a range of different Ir catalysts (Scheme 8), including the Ir–phosphanylmethyl complexes (Ir–**L4**) that were found to be particularly efficient for the hydrogenation of tetra-substituted C=C bonds.[3] The enantioselectivity and reactivity of these substrates strongly depended on the functional group next to the C=C bond. Aldehyde **14a**, for example, which was directly accessible from the Suzuki–Miyaura cross-coupling, showed no reactivity; even at a H_2 pressure of 100 bar with an extended reaction time of 14 h at 40°C no reduction occurred. For methyl esters **22a** and **22b**, on the other hand, full conversion was achieved after 14 h. However, the products were obtained as *cis*/*trans* mixtures in low enantiomeric excess. When allylic alcohol **15a** was used as the substrate, the desired product was not obtained. Instead, a *cis*/*trans* mixture of the methyl-substituted cyclohexane **25** was obtained, presumably by elimination of water followed by reduction of the resulting dienes



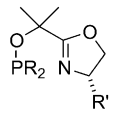
L1a: R = Ph, R' = *i*Pr, (*S*)
L1b: R = *o*-Tol, R' = *t*Bu, (*S*)
L1c: R = Cy, R' = *t*Bu, (*S*)
L1d: R = *t*Bu, R' = *t*Bu, (*S*)
L1e: R = *i*Pr, R' = *t*Bu, (*S*)



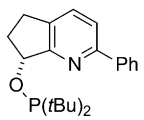
L4a: R = Cy, R' = *i*Pr, (*S*)
L4b: R = Ph, R' = *i*Pr, (*S*)
L4c: R = *o*-Tol, R' = *i*Pr, (*S*)
L4d: R = *t*Bu, R' = *i*Pr, (*S*)
L4e: R = Xyl, R' = *i*Pr, (*S*)
L4f: R = Cy, R' = *t*Bu, (*S*)
L4g: R = *t*Bu, R' = *t*Bu, (*S*)
L4h: R = *o*-Tol, R' = *t*Bu, (*S*)
L4i: R =Xyl, R' = *t*Bu, (*S*)
L4j: R = Cp, R' = Ph, (*S*)
L4k: R = Cy, R' = Ph, (*R*)
L4l: R = Ph, R' = Ph, (*R*)
L4m: R = *t*Bu, R' = Ph, (*R*) and (*S*)
L4n: R = Cy, R' = Bn, (*S*)
L4o: R = *o*-Tol, R' = Bn, (*S*)
L4p: R = *t*Bu, R' = Bn, (*S*)



L2a: R = Ph, R' = Me, (*R*,*R*)
L2b: R = Cy, R' = Me, (*S*,*S*)



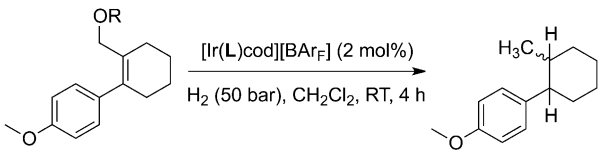
L3a: R = Ph, R' = *i*Pr, (*S*)
L3b: R = *o*-Tol, R' = *t*Bu, (*S*)
L3c: R = *t*Bu, R' = *i*Pr, (*S*)
L3d: R = *t*Bu, R' = *t*Bu, (*S*)



L5

Scheme 8. P,N ligands used in the Ir-catalyzed hydrogenation reaction (Cy = cyclohexyl; *o*-Tol = *ortho*-tolyl; Xyl = xylyl).[2a,14]

(Scheme 9). We assume that this undesired reaction was caused by acidic Ir hydrides, which are formed during the hydrogenation reaction.[15] To verify this assumption, we in-



15a, R = H
17a, R = TMS
19a, R = Bn

25

Scheme 9. Hydrogenation of **15a**, **17a**, and **19a**.

vestigated the reaction of allylic alcohol **15a** with several Lewis and Brønsted acids. As expected, elimination of water was observed, giving several isomeric dienes that could be converted into methylcyclohexane **25** under hydrogenation conditions.

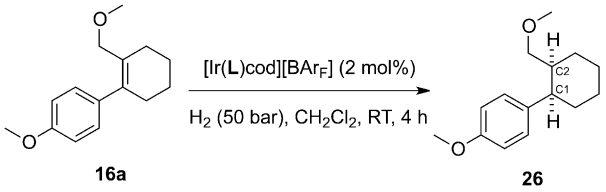
We hoped to circumvent this problem by using a suitable protecting group. First, silyl protecting groups were tested. Trimethylsilyl ether **17a** was cleaved under the reaction conditions, so the more acid-stable *tert*-butyldimethylsilyl ether was used instead. The resulting olefin (**18a**) could be hydrogenated without any side reactions, however, the product was obtained as a *cis*/*trans* mixture, as previously observed in the hydrogenation of methyl esters **22a** and **22b**. As an alternative, the benzyl protecting group was tested (**19a**), but proved to be unsuitable, since it was also cleaved under

the reaction conditions and water was subsequently eliminated from the resulting allylic alcohol.

A solution to this problem was found by protecting allylic alcohol **15a** as the methyl ether (**16a**). Its stability against Brønsted acids and low steric demand resulted in excellent results by using Ir complexes with ligands **L4** (Table 3). Surprisingly, all other ligand classes led to an elimination reaction, as previously observed for allylic alcohol **15a**, TMS ether **17a**, and benzyl ether **19a**. Hydrogenation of methyl ether **16a** with various Ir–**L4** complexes gave good to excellent enantioselectivities (up to >99% *ee*) and full conversion into desired cyclohexane **26**. In general, ligands with phenyl substituents at the oxazoline ring proved to be best suited for this substrate. Both conversion and enantioselectivity were significantly higher when complexes with ligands **L4k**–**L4m** were used. Neither the enantioselectivity nor the conversion changed if the amount of catalyst **L4m** was reduced from 2.0 to 1.0 mol%, although at 0.5 mol% catalyst loading the conversion decreased significantly to 4% after a reaction time of 4 h. With a catalyst loading of 0.1 mol% no product was formed.

The analogous phenyl-substituted alkene **16c** proved to be a more difficult substrate. Although full conversion was obtained with most phosphanylmethyloxazoline ligands (**L4**), only ligands **L4j**, **L4k**, and **L4m** gave desired product **27** in more than 90% *ee*. The most efficient catalyst in this case was the Ir complex with ligand **L4j**, leading to compound **27** in >98% *ee* and 92% yield (Table 4).

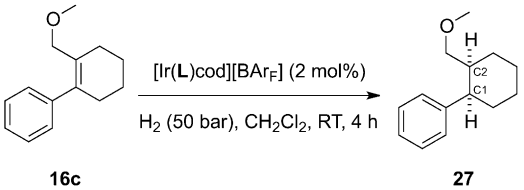
Table 3. Ir-catalyzed hydrogenation of substrate **16a**.[a]



Ligand **L**	Conversion [%][b]	Yield **26** [%][b]	*ee* [%][c]
(*S*)-**L1b**	>99	–[d]	–
(*S*)-**L1c**	>99	–[d]	–
(*S*)-**L1d**	28	–[d]	–
(*S*)-**L1e**	18	–[d]	–
(*R*,*R*)-**L2a**	>99	–[d]	–
(*S*,*S*)-**L2b**	>99	–[d]	–
(*S*)-**L3a**	>99	–[d]	–
(*S*)-**L3b**	>99	–[d]	–
(*S*)-**L4a**	>99	92	75 (1*R*,2*S*)
(*S*)-**L4b**	>99	74	75 (1*R*,2*S*)
(*S*)-**L4c**	>99	56	69 (1*R*,2*S*)
(*S*)-**L4d**	>99	81	80 (1*R*,2*S*)
(*S*)-**L4f**	>99	58	78 (1*R*,2*S*)
(*S*)-**L4g**	>99	28	86 (1*R*,2*S*)
(*R*)-**L4k**	>99	97	95 (1*S*,2*R*)
(*R*)-**L4l**	>99	>99	96 (1*S*,2*R*)
(*S*)-**L4m**	>99	99	>99 (1*R*,2*S*)
(*R*)-**L4m**	>99	99	>99 (1*S*,2*R*)
(*S*)-**L4n**	>99	98	80 (1*R*,2*S*)
(*S*)-**L4o**	>99	64	78 (1*R*,2*S*)
(*S*)-**L4p**	>99	94	87 (1*R*,2*S*)
(*R*)-**L5**	>99	–[d]	–

[a] Full experimental conditions are given in the Supporting Information. [b] Conversions and yields were determined by GC. [c] The *ee* value was determined by GC on a chiral stationary phase (DiMeTBuSil-β-cyclodextrin (OV1701)); the absolute configuration is based on X-ray analysis. [d] Formation of **25** occurred.

Table 4. Ir-catalyzed hydrogenation of substrate **16c**.[a]

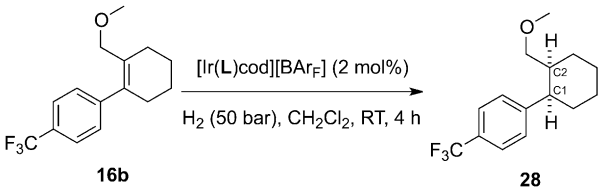


Ligand **L**	Conversion [%][b]	Yield **27** [%][b]	*ee* [%][c]
(*S*)-**L4a**	98	46	71 (1*R*,2*S*)
(*S*)-**L4b**	>99	6	36 (1*R*,2*S*)
(*S*)-**L4d**	>99	18	72 (1*R*,2*S*)
(*S*)-**L4e**	76	25	71 (1*R*,2*S*)
(*S*)-**L4f**	>99	6	55 (1*R*,2*S*)
(*S*)-**L4g**	>99	2	50 (1*R*,2*S*)
(*S*)-**L4h**	>99	6	32 (1*R*,2*S*)
(*S*)-**L4i**	97	2	29 (1*R*,2*S*)
(*S*)-**L4j**	>99	92	>98 (1*R*,2*S*)
(*R*)-**L4k**	>99	96	94 (1*S*,2*R*)
(*S*)-**L4m**	>99	69	>98 (1*R*,2*S*)
(*S*)-**L4n**	90	80	79 (1*R*,2*S*)
(*S*)-**L4p**	>99	56	79 (1*R*,2*S*)

[a] Full experimental conditions are given in the Supporting Information. [b] Conversions and yields were determined by GC. [c] Determined by GC on a chiral stationary phase (OV1701); assignment of absolute configuration in analogy to **26**.

Changing the substituent at the *para* position of the phenyl ring to CF_3 (**16b**) led to decreased conversion and enantioselectivity for most of the **L4** ligands. Interestingly, with ligand **L4j**, full conversion and a yield of 92% of the desired product with an *ee* of 96% was obtained (Table 5).

Table 5. Ir-catalyzed hydrogenation of substrate **16b**.[a]

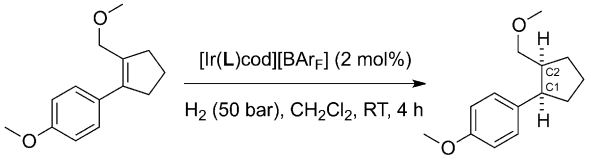


Ligand **L**	Conversion [%][b]	Yield **28** [%][b]	*ee* [%][c]
(*S*)-**L4a**	22	2	58 (1*R*,2*S*)
(*S*)-**L4d**	45	7	56 (1*R*,2*S*)
(*S*)-**L4g**	77	1	20 (1*R*,2*S*)
(*S*)-**L4h**	40	1	12 (1*R*,2*S*)
(*S*)-**L4i**	35	1	14 (1*R*,2*S*)
(*S*)-**L4j**	>99	92	96 (1*R*,2*S*)
(*R*)-**L4k**	34	26	89 (1*S*,2*R*)
(*S*)-**L4m**	75	40	95 (1*R*,2*S*)
(*R*)-**L4n**	>99	71	48 (1*S*,2*R*)
(*S*)-**L4p**	59	33	70 (1*R*,2*S*)

[a] Full experimental conditions are given in the Supporting Information. [b] Conversions and yields were determined by GC. [c] Determined by GC on a chiral stationary phase (OV1701); assignment of absolute configuration in analogy to **26**.

Next, we explored the hydrogenation of 1,2-disubstituted cyclopentenes. As observed for methyl esters **22a** and **22b**, a *cis*/*trans* mixture was obtained after hydrogenation of methyl esters **21a** and **21b**. Allylic alcohol **23a** showed similar reactivity to the cyclohexene analogue **15a**, resulting in a *cis*/*trans* mixture of 4-methoxyphenyl-2-methylcyclopentane. For the hydrogenation of methyl ether **24a**, full conversion into desired product **29** was obtained with all ligands applied. Compared with previous results from the hydrogenation of 1,2-disubstituted cyclohexenes, the enantioselectivities were rather low (Table 6). The highest enantiomeric

Table 6. Ir-catalyzed hydrogenation of substrate **24a**.[a]



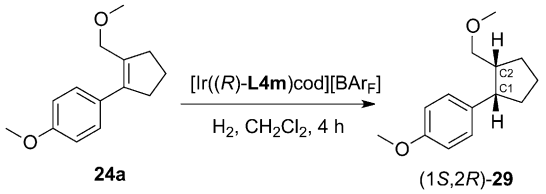
Ligand **L**	Conversion [%][b]	Yield **29** [%][b]	*ee* [%][c]
(*S*)-**L1a**	>99	>99	33 (+)
(*R*,*R*)-**L2a**	>99	>99	25 (−)
(*S*)-**L3a**	>99	>99	40 (+)
(*S*)-**L4a**	>99	>99	16 (+)
(*S*)-**L4b**	>99	>99	34 (+)
(*S*)-**L4d**	>99	>99	28 (+)
(*S*)-**L4f**	>99	>99	57 (+)
(*S*)-**L4j**	>99	>99	0 (+)
(*R*)-**L4k**	>99	>99	57 (−)
(*S*)-**L4m**	>99	>99	77 (+)
(*S*)-**L4n**	>99	>99	1 (+)
(*S*)-**L4p**	>99	>99	1 (+)
(*R*)-**L5**	>99	89	1 (−)

[a] Full experimental conditions are given in the Supporting Information. [b] Conversions and yields were determined by GC. [c] Determined by GC on a chiral stationary phase (DEtTBuSil-β-cyclodextrin (SE54)).

excess was obtained with ligand **L4m** (77% *ee*), which was subsequently used for further optimization of the reaction conditions. Lowering the hydrogen pressure from 50 to 5 to 1 bar caused a significant decrease in enantioselectivity, but still gave full conversion to desired product **29** (Table 7). Slightly higher enantiomeric excesses were obtained by reducing the catalyst loading at low hydrogen pressure (5 and 1 bar). On the other hand, this behavior was not observed at higher hydrogen pressure. At 50 bar, enantioselectivities decreased when the catalyst loading was reduced. At 5 bar, lower temperatures had a positive effect on the enantioselectivity, although the conversion was unaffected. Under the optimized conditions for conversion of **24a** (−20 °C, hydrogen (50 bar), catalyst (2.0 mol%)), the desired product was obtained quantitatively with an enantiomeric excess of 88%.

Synthesis of hexahydrofluorenone 32: As mentioned in the introduction, enantioselective routes to chiral hexahydrofluorenes are of interest because these compounds occur as

Table 7. Pressure, temperature, and catalyst-loading dependence in the Ir-catalyzed hydrogenation of substrate **24a**.[a]

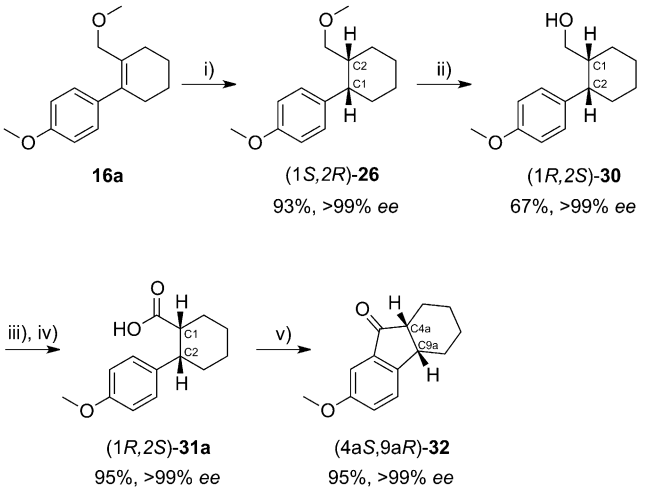


Pressure H_2 [bar]	*T* [°C]	Catalyst loading [mol%]	Conversion [%][b]	Yield **29** [%][b]	*ee* (−) [%][c]
1	25	2.0	>99	98	53
1	25	1.0	>99	>99	55
1	25	0.5	>99	>99	59
5	25	2.0	>99	>99	63
5	25	1.0	>99	>99	65
5	25	0.5	>99	>99	69
5	0	2.0	>99	>99	75
5	0	1.0	>99	>99	78
5	0	0.5	>99	>99	79
5	−20	2.0	>99	>99	81
5	−20	1.0	>99	>99	82
5	−20	0.5	>99	>99	83
50	−20	2.0	>99	>99	88
50	−20	1.0	>99	>99	86
50	−20	0.5	>99	>99	78
50	−20	0.1	>99	>99	74

[a] Full experimental conditions are given in the Supporting Information. [b] Conversions and yields were determined by GC. [c] Determined by GC on a chiral stationary phase (SE54).

structural elements in various natural products. To demonstrate the potential of the Suzuki–Miyaura cross-coupling/Ir-catalyzed asymmetric hydrogenation sequence for accessing tricyclic ring systems of this type, we chose hexahydrofluorenone **32** as our target structure.

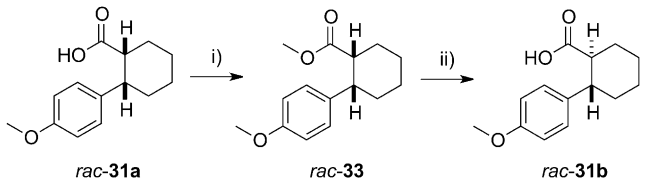
The synthetic sequence leading to compound **32** is shown in Scheme 10. Asymmetric hydrogenation of allyl methyl



Scheme 10. Reaction conditions: i) [Ir((*R*)-**L4m**)cod][BAr_F] (1 mol%), H_2 (50 bar), RT, 4 h; ii) BBr_3 (1.0 equiv), CH_2Cl_2, −78→25 °C, 30 min then H_2O; iii) Dess–Martin periodinane (DMP; 1.2 equiv), CH_2Cl_2, RT, 2 h; iv) H_3NSO_3 (1.8 equiv), sodium chlorite (1.8 equiv), THF/H_2O, RT, 1.5 h; v) oxalyl chloride (1.0 equiv) then $AlCl_3$ (2.5 equiv), CH_2Cl_2, 0 °C (30 min)→25 °C, 2 h.

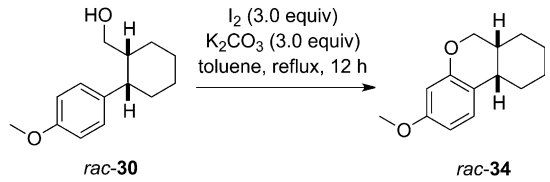
ether **16a** with [Ir((*R*)-**L4m**)cod][BAr_F] (1 mol%) provided cyclohexane **26** in 93% yield and >99% *ee*. Chemoselective O-demethylation with boron tribromide (70% yield, >99% *ee*) gave alcohol **30**, which was oxidized with DMP[16] to afford the corresponding aldehyde (95% yield, >99% *ee*). Oxidation to carboxylic acid **31a** was accomplished by using sodium chlorite and sulfamic acid (95%, >99% *ee*).[17] Finally, an intramolecular Friedel–Crafts-type reaction gave desired hexahydrofluorenone **32** in 95% yield and a very high enantiomeric purity of >99% *ee*. The absolute configuration of alcohol **30** was determined to be (1*R*,2*S*) by X-ray analysis of the corresponding *para*-bromobenzoic ester (see the Supporting Information). The absolute configuration of all cyclohexane products was assigned based on this analysis.

As shown in Scheme 11, *cis* compound **31a** also gives access to the *trans* isomer by epimerization of the corresponding ester (**33**). This was demonstrated in the racemic series starting from *rac*-**31a**, which was converted into methyl ester *rac*-**33**. Subsequent treatment with NaOMe in refluxing MeOH afforded, after acidic workup, the *trans*-configured carboxylic acid *rac*-**31b** in 95% overall yield (d.r. >20:1 by NMR spectroscopy).



Scheme 11. Reaction conditions: i) MeOH, H_2SO_4 (catalytic), reflux, 5 h; ii) NaOMe, MeOH, 80°C, 4 h then HCl (1 M).

In connection with the synthesis of hexahydrofluorenone **32**, an alternative oxidation method for alcohol **30** was tested by using iodine and K_2CO_3 in refluxing toluene (Scheme 12).[18] Surprisingly, under these conditions *rac*-**30** was converted into *O*-heterocycle *rac*-**34** in 53% yield. The structure of this compound was established by 2D NMR spectroscopy. It appears that an *ortho* or *para* iodination occurred with subsequent intramolecular addition of the hydroxy group to the oxonium intermediate, followed by elimination of HI. Further investigations into the scope of the reaction showed this cyclization to be limited to compound *rac*-**30** (see the Supporting Information).



Scheme 12. Synthesis of the *O*-heterocycle *rac*-**34**.

Conclusion

We have shown that *cis*-1,2-disubstituted cyclohexane derivatives are readily accessible in a high enantiomeric purity of up to 99% *ee* through a sequence involving Suzuki–Miyaura cross-coupling and Ir-catalyzed asymmetric hydrogenation. Asymmetric hydrogenation of the cyclopentene series proved to be more difficult, giving lower enantioselectivities of up to 88% *ee*. The utility of this synthetic strategy was further demonstrated by an enantioselective route to chiral hexahydrofluorenones.

Experimental Section

General: All chemicals were purchased from commercial sources and used as received. Anhydrous solvents were obtained in sure-seal bottles from Fluka or purified by using standard methods.[19] Air-sensitive reactions were carried out in an atmosphere of purified nitrogen by using a glove box or standard Schlenk techniques under an argon atmosphere.

General procedure for Suzuki–Miyaura cross-coupling reactions by using bromoaldehyde 13: Under an argon atmosphere the appropriate boronate (**11a–11c**; 25.0 mmol, 1.20 equiv), bromoaldehyde **13** (20.9 mmol, 1.00 equiv), [$Pd_2(dba)_3$] (0.1 mol%), and a mixture of THF/H_2O (2:1) were added to a vial containing a stirring bar and the system was sealed with a screw cap. After stirring for 2 h at 66°C, the reaction mixture was cooled to room temperature and saturated $NaHCO_3$ was added. The aqueous layer was extracted with *tert*-butyl methyl ether (3×10 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo and purification of the brown residue by column chromatography (silica gel, h×d: 11×2 cm, hexane/ethyl acetate 20:1) gave an orange solid. Residual traces of palladium were removed by sublimation to afford the desired product.

General procedure for Suzuki–Miyaura cross-coupling reactions by using trifluoromethylsulfonate 20a: Under an argon atmosphere the appropriate boronate (**11a** or **11b**; 1.30 equiv) and [$Pd_2(dba)_3$] (0.1 mol%) were added to a vial containing a stirring bar and dissolved in THF (1 mL). Triflate **20a** (100 mg, 0.37 mmol, 1.00 equiv) was dissolved in THF (1 mL) and added to the vial. The degassed system was sealed with a screw cap and stirred for 4 h at 66°C. The reaction mixture was then cooled to room temperature and saturated $NaHCO_3$ was added. The aqueous layer was extracted with *tert*-butyl methyl ether (3×5 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo and purification of the residue by column chromatography (silica gel, h×d: 10×2 cm, hexane/ethyl acetate 20:1) afforded the desired product.

General procedure for Suzuki–Miyaura cross-coupling reaction by using trifluoromethylsulfonate 20b: Under an argon atmosphere the appropriate boronate (**11a** or **11b**; 1.30 equiv), [$Pd_2(dba)_3$] (1.00 mol%), 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (**IMes**, 2.40 mg, 2.00 mol%), and water (3.00 mol%) were added to a vial containing a stirring bar and dissolved in THF (1 mL). Triflate **20b** (1.00 equiv) was dissolved in THF (1 mL) and added to the vial. The degassed system was sealed with a screw cap and stirred for 14 h at 66°C. The reaction mixture was then cooled to room temperature and saturated $NaHCO_3$ was added. The aqueous layer was extracted with *tert*-butyl methyl ether (3×5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo and purification of the residue by column chromatography (silica gel, h×d: 10×2 cm, hexane/ethyl acetate 20:1) afforded the desired product.

General asymmetric hydrogenation procedure: A high pressure steel autoclave (Premex Reactor AG; Lengnau, Switzerland; Model HPM-005) with a dry glass insert and a magnetic stirring bar was taken into a glove box. The glass insert was charged with the appropriate catalyst (1–2 mol%; see Table 7) and the degassed substrate solution (10 mL, 0.22 M)

freshly prepared from the corresponding substrate and dichloromethane (stirred over basic alumina and filtered). The autoclave was sealed, taken out of the glove box, attached to a high-pressure hydrogen line and purged with H_2. The autoclave was sealed under the appropriate H_2 pressure (see Table 7) and the mixture was stirred for 4–12 h at the appropriate temperature. After release of H_2, the solution was concentrated in a stream of nitrogen, dissolved in a mixture of *n*-hexanes/methyl *tert*-butyl ether (4:1; 30 mL) as an eluent and passed through a silica gel plug. The filtrate was concentrated in vacuo and analyzed without further purification for conversion (GC) and *ee* (GC or HPLC).

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