JOC The Journal of Organic Chemistry

Article

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Rhodium Phosphine–Phosphite Catalysts in the Hydrogenation of Challenging *N*-(3,4-dihydronaphthalen-2-yl) Amide Derivatives

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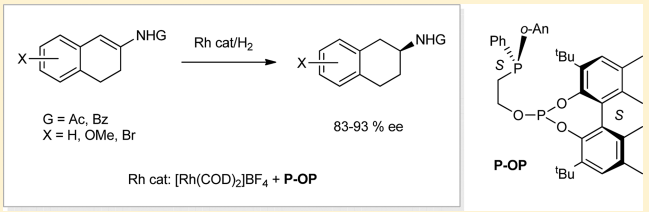
Supporting Information

ABSTRACT: The enantioselective catalytic hydrogenation of *N*-(3,4-dihydronaphthalen-2-yl) amides (**1**) with rhodium catalysts bearing phosphine–phosphite ligands **4** has been studied. A wide catalyst screening, facilitated by the modular structure of **4**, has found a highly enantioselective catalyst for this reaction. This catalyst gives a 93% ee in the hydrogenation of **1a** and also produces high enantioselectivities, ranging from 83 to 93% ee, in the hydrogenation of several OMe- and Br-substituted substrates. In contrast, the structurally related enol esters **2** are very reluctant to undergo hydrogenation. A coordination study of the representative enamide **1d** has shown an unusual η^6-arene coordination mode, over the typical O,C,C chelating mode for enamides, as the preferred one for this substrate in a Rh(I) complex. Deuteration reactions of **1c,d** indicate a clean *syn* addition of deuterium to the double bond without an isotopic effect on the enantioselectivity.



INTRODUCTION

Chiral 2-aminotetralines comprise an important class of compounds in medicinal chemistry.[1] Comprehensive information covering the biological properties of a large number of examples can be found in the literature, and remarkably, several examples have found application in the pharmaceutical industry (Figure 1).[2] Due to the importance of these chiral derivatives, the development of efficient procedures for the synthesis of a broad range of these amines is highly desirable. As *N*-(3,4-dihydronaphthalen-2-yl) amides can readily be prepared in one step from commercially available 2-tetralones,[3] the hydrogenation of these enamides provides a straightforward procedure for the preparation of chiral 2-aminotetraline derivatives.

Diverse catalysts,[4−6] mostly based on ruthenium and rhodium complexes, have been examined in the hydrogenation of the aforementioned enamides with very dissimilar performances. Thus, ruthenium catalysts with diphosphine ligands have provided good activity and enantioselectivity levels in the hydrogenation of several examples under relatively high hydrogen pressures (20−100 atm).[1a,4] In contrast with that, rhodium catalysts usually show higher activity but have consistently given low enantioselectivities in the hydrogenation of the representative substrate *N*-(3,4-dihydronaphthalen-2-yl) acetamide (**A**; Figure 2).[5] This is a rather surprising aspect, considering that compound **A** possesses the auxiliary amide carbonyl group needed for substrate chelation[7] and a vast range of Rh catalysts were tested in the hydrogenation of this substrate.

A notable exception among the rhodium catalysts described has been provided by a supramolecular complex containing phosphine and phosphite ligands, named Supraphos, described by the Reek group.[8] Following an approach based on the generation of chelating ligands from monodentate assembling ligands, these researchers have obtained a catalyst which provides an outstanding 94% ee in the hydrogenation of *N*-(3,4-dihydronaphthalen-2-yl)acetamide.

A comparison between compound **A** and types of enamides which typically provide highly enantioselective hydrogenations with Rh catalysts, such as dehydroamino acids (**B**), enamido phosphonates (**C**), and aryl enamides (**D**),[9] reveals some important differences. First of all, compounds **B** and **C**, and to a lesser extent **D**, possess an electron-withdrawing group bonded to the same carbon (α) as the amido group. This arrangement favors the regioselectivity of the olefin insertion step to give the α-alkyl intermediate **F**. In contrast, the substitution of the accepting group by an alkyl group and the presence of a β-aryl group may favor the formation of the β-alkyl intermediate **G** in the hydrogenation of substrates **A**.[10] Moreover, several studies have connected a change in the regioselectivity of the olefin insertion step with a product enantioreversal.[10a,11] Thus, if a competition between α- and β-alkyl pathways occurs, a severe drop in enantioselectivity may also take place. Moreover, the cyclic nature of enamides **A**, which imposes an *E* olefin configuration, probably impedes the achievement of high enantioselectivities. In this regard, it should be mentioned that Zhang and co-workers have recently demonstrated that the hydrogenation of *E* isomers of acyclic enamides **E** occurs with significantly lower enantioselectivity than that of *Z* isomers.[12] Likewise, (*E*)-α-acetamidocinnamic acid derivatives usually give less enantioselective hydrogenations than the *Z* isomers (**B**).[13]

Received: February 15, 2013
Published: March 13, 2013

   dx.doi.org/10.1021/jo400345v | J. Org. Chem. 2013, 78, 3997−4005

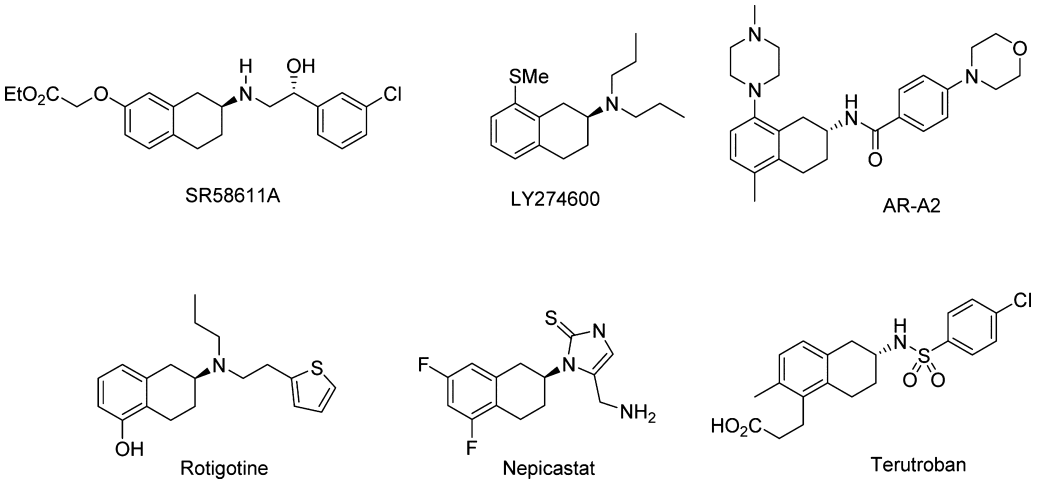


Figure 1. Chiral aminotetralines with pharmaceutical applications.

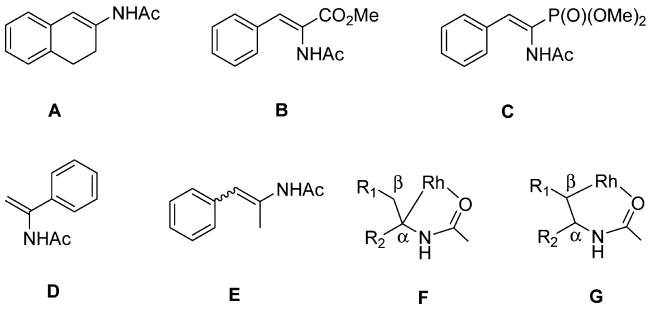


Figure 2. Structures **A**–**G**.

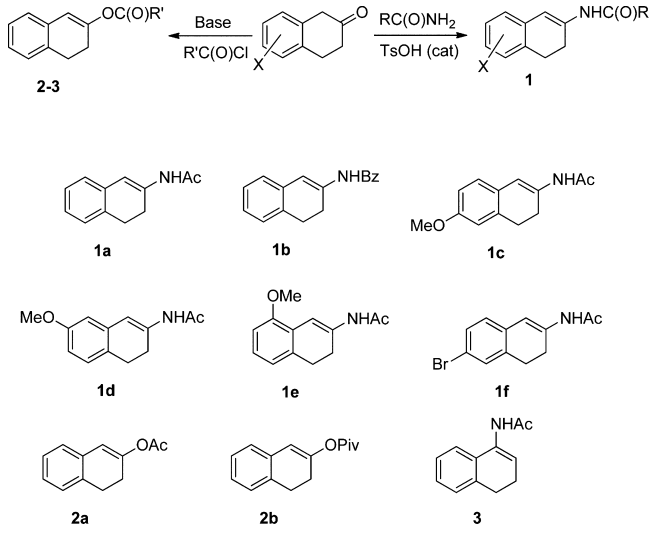
In recent years, we have studied the application of chiral phosphine–phosphites in the hydrogenation of several types of olefins by Rh catalysts.[11c,14] From this background and inspired by the results reported for the Supraphos catalysts, we were interested in investigating the performance of rhodium complexes based on the conventional phosphine–phosphites developed in our laboratory in the hydrogenation of the challenging enamide **A**. Herein, we describe an extensive catalyst screening using a family of phosphine–phosphite ligands in the hydrogenation of several *N*-(3,4-dihydronaphthalen-2-yl) amides. Following a systematic optimization procedure, a highly enantioselective catalyst for these kinds of substrates has been found.

RESULTS AND DISCUSSION

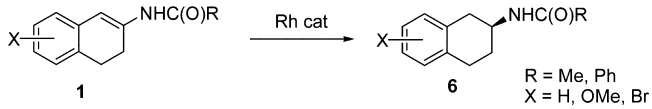
Synthesis of Substrates. A series of *N*-(3,4-dihydronaphthalen-2-yl) amides **1** has been prepared by condensation between commercially available 2-tetralones and acetamide or benzamide in the presence of a catalytic amount of acid in moderate yields (Scheme 1).[3] In the set, several methoxy-substituted examples have been considered, as they can provide a convenient access to important hydroxy-2-aminotetralines.[15] Likewise, the structurally similar enol esters **2** were prepared from 2-tetralone using literature procedures.[16] For comparative purposes, enamide **3** derived from α-tetralone was also included.

Influence of the Ligand in the Asymmetric Hydrogenation. The hydrogenation of the representative enamide **1a** with Rh catalyst precursors based on phosphine–phosphite ligands **4** (Scheme 2, Chart 1), either using isolated catalyst precursors with the formulation $[Rh(COD)(\mathbf{4})]BF_4$ (**5**)[14] or

Scheme 1. Synthesis and Structures of Investigated Olefin Substrates



Scheme 2. Hydrogenation Reaction of Enamides 1



Rh cat: $[Rh(COD)(\mathbf{4})]BF_4$ or $[Rh(COD)_2]BF_4$ + **4** (1.1 equiv.)

generated in situ from $[Rh(COD)_2]BF_4$ and an stoichiometric amount of **4**, has been investigated. The library of chiral ligands contains examples which mainly differ in the nature of the backbone: benzene (**4a**), ethane (**4b**–**d**), or substituted ethane (**4e**–**k**). Moreover, the ligands in the set differ in the position of the stereogenic elements. Thus, ligands **4l**,**m** possess a *P*-stereogenic phosphino fragment. On the other hand, ligands **4e**–**h** contain a stereogenic center at the β-position (to the phosphine) of the backbone, while for ligands **4j**,**k** the stereogenic center is at an α-position. In addition, all of the examples contain an atropisomeric phosphite fragment.

In an initial approach, we examined precatalysts **5a**,**b** in the reduction of **1a** at 20 bar of hydrogen and room temperature, as low conversions at 4 bar of hydrogen were observed. Among them, the catalyst based on the less rigid **4b** offered superior

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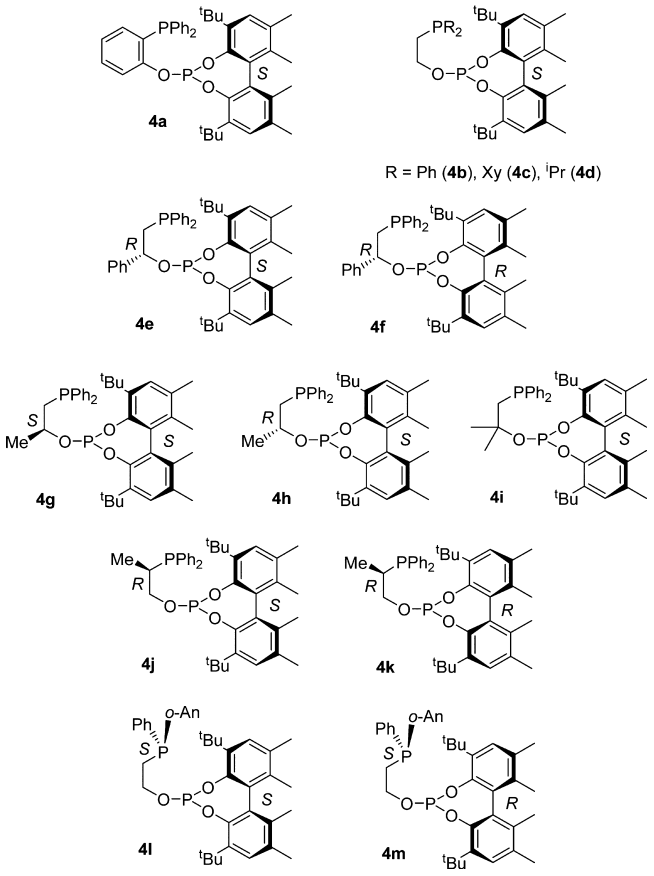
Chart 1. Phosphine-Phosphite Ligands 4 Used in This Study



activity and enantioselectivity (entries 1 and 2, Table 1). An attempt to increase conversion by using alternative phosphine fragments proved to be fruitless (entries 3 and 4). After these preliminary results, we performed a set of reactions under different initial hydrogen pressures (entries 5 and 6), without improvement over the value obtained at 20 atm. In addition, an increase in temperature up to 40 °C had a deleterious effect on enantioselectivity (entry 7).

Table 1. Hydrogenation of 1a using the Complexes $[Rh(COD)(4)]BF_4$[a]

entry	P-OP ligand	$P(H_2)$, atm	conversn, %	ee, % (confign)
1	**4a**	20	18	68 (*S*)
2	**4b**	20	63	81 (*S*)
3[b]	**4c**	20	15	46 (*S*)
4	**4d**	20	67	38 (*S*)
5	**4b**	10	50	63 (*S*)
6	**4b**	30	64	77 (*S*)
7[c]	**4b**	30	92	53 (*S*)
8[d]	**4a**	20	100	*rac*
9[d]	**4b**	20	100	*rac*
10[d]	**4d**	20	100	*rac*

[a]Reactions were carried out in CH_2Cl_2 at room temperature unless otherwise specified: S/C = 100, reaction time 21 h. Conversion was determined by ^{1}H NMR and enantiomeric excess by chiral GC. The configuration was determined by comparing the sign of optical rotation with literature data.[5d] [b]Precatalyst prepared in situ from $[Rh(COD)_2]BF_4$ and 1.1 equiv of **4c**. [c]Reaction performed at 40 °C. [d]Reactions performed in the presence of 20 equiv of DIPEA.

On the other hand, considering that the Rh−Supraphos catalytic system is capable of providing high enantioselectivities in the presence of a considerable amount of diisopropylethylamine (DIPEA) as an additive,[8,17] the hydrogenation of **1a** with catalyst precursors **5a,b,d** in the presence of 20 equiv of DIPEA was examined. Most notably, the base has a critical influence on the present catalytic system. It produces an important increase in conversion, particularly for the catalyst based on **4a**, although racemic products were unexpectedly obtained (entries 8−10).[18,19] It is noteworthy that catalysts with different phosphine groups and dynamic properties give no enantioselectivity, pointing to a general effect of the additive. It therefore seems apparent that the addition of base leads to an alternative catalyst. In connection with this, it should be mentioned that the deprotonation of cationic dihydrides to give neutral monohydrides, which are highly active olefin hydrogenation catalysts, has been well documented in the literature.[20] In comparison with diphosphine catalysts, the presence of the π-acceptor phosphite group in the P-OP ligand should increase the acidity of corresponding cationic dihydrides, favoring deprotonation by the amine. However, the complexity of the system does not allow us to confidently assign the lack of enantioselectivity to the purported monohydride $Rh(H)(P\text{-}OP)(S)_n$ (S = solvent, n = 1−3) over other alternatives such as the formation of metallic clusters upon addition of base[21] and the dissociation or the decomposition of the chiral ligand. Therefore, a specific study covering alternative ligands, additives, and substrates is needed to clarify this effect.

Finally, from a practical point of view, it is interesting to note that similar results were obtained with **5b** and the catalyst generated in situ from $[Rh(COD)_2]BF_4$ and 1.1 equiv of **4b** (entry 1, Table 2). Thus, the analysis of the influence of the ligand was performed with catalyst precursors generated in situ.

Table 2. Hydrogenation of 1a with Catalysts Prepared from $[Rh(COD)_2]BF_4$ and 4[a]

entry	P-OP ligand	conversn, %	ee, % (confign)
1	**4b**	69	80 (*S*)
2	**4e**	38	76 (*S*)
3	**4f**	80	60 (*R*)
4	**4g**	33	63 (*S*)
5	**4h**	20	75 (*S*)
6	**4i**	82	8 (*S*)
7	**4j**	70	75 (*S*)
8	**4k**	41	81 (*R*)
9	**4l**	90	93 (*S*)
10	**4m**	70	77 (*R*)

[a]Reactions were carried out at room temperature with an initial hydrogen pressure of 20 bar unless otherwise specified: S/C = 100, reaction time 21 h. Conversion was determined by ^{1}H NMR and enantiomeric excess by chiral GC.

After the result shown by the ethane-bridged complex **5b**, we tried to improve catalyst enantioselectivity by tuning the backbone structure with substituents in either α- or β-positions with a defined stereochemistry.[14d] Pairs of ligands with β-Ph (**4e,f**) and β-Me (**4g,h**) substituents, with different relative backbone configuration to the biphenyl phosphite fragment, and a β-Me_2 example (**4i**) were then tested (entries 2−6). No improvement over the result obtained with **4b** was obtained; we therefore conclude that the presence of the β-substituent is detrimental in these reactions. In contrast, catalysts with an α-

dx.doi.org/10.1021/jo400345v | J. Org. Chem. 2013, 78, 3997−4005

Me group to the phosphine group provided relatively good enantioselectivity values of 75% ee (**4j**, entry 7) and 81% ee (**4k**, entry 8). The latter catalyst is only slightly more enantioselective than the catalyst based on **4b**, and the small improvement does not justify the introduction of an additional stereogenic center. Overall, the simplest ethane backbone looks more suitable for this reaction. However, the latter results offered a hint for a further enhancement of the catalyst. The presence of the α-methyl group in ligands **4j,k** favors a chiral distribution of aryl phosphine substituents[22] and prompted us to investigate examples with a *P*-stereogenic biarylphosphino fragment. Thus, diastereomeric ligands **4l,m** bearing a P(*o*-An)Ph group were examined.[14d] Most noteworthy, the catalyst based on ligand **4l** produced a significant improvement in enantioselectivity, up to 93% ee (entry 9). On the other hand, the catalyst bearing ligand **4m** gave lower enantioselectivity (77% ee, entry 10). A comparison between these results indicates that the configuration of the product is determined by the configuration of the phosphite, as observed before in the hydrogenation of methyl (*Z*)-(α)-*N*-acetamidocinnamate (MAC) and other olefins.[14] It should also be mentioned that the enantioselectivity provided by the catalyst based on **4l** is very close to the best value obtained with a Rh catalyst in this reaction (94% ee).[8]

Scope of the Reaction. We further investigated the scope of the catalyst bearing **4l** in the reduction of enamides **1** (Table 3). It is worth noting that relatively high enantioselectivities, between 83 and 93% ee, were observed in these reactions. Thus, benzamide **1b** gave a 93% ee, although it was less reactive than **1a**, and produced a moderate conversion (entry 1). An increase in the temperature to 40 °C raised the conversion to 70%, but the enantioselectivity decreased to 82% ee (entry 2). Alternatively, the catalyst bearing ligand **4k** produced lower levels of conversion and enantioselectivity (entry 3). Methoxy-substituted substrates **1c,d** provided good conversions with enantioselectivities of 88 and 86% ee (entries 4 and 5), respectively. Most interestingly, substrate **1e**, which should apparently be more encumbered than the latter enamides, is significantly more reactive. Thus, catalysts bearing ligands **4a,m,l** gave full conversions for this substrate (entries 6–8). Among the catalysts investigated, that based on **4l** again produced the best enantioselectivity (93% ee). Moreover, bromide **1f** showed a lower reactivity under our standard conditions, giving conversions of 67% and 83% ee (entry 9). The reaction at 40 °C showed a slightly higher conversion (70%) and a lower enantioselectivity (80% ee, entry 10). Alternatively, the diastereomeric catalyst based on ligand **4m** showed a better conversion and a lower enantioselectivity than the catalyst with **4l** (entry 11). A perusal of the literature indicates that hydrogenations of substrates **1c,e,f** have not been reported before, while the catalyst with **4l** provides the highest enantioselectivity among Rh complexes in the hydrogenation of **1b,d**. For the latter substrates, the best enantioselectivities, 96 and 95% ee, respectively, have been provided by Ru complexes.[4c,e]

In addition, we were interested in examining the possibility of hydrogenating structurally related enol esters **2**, as an appealing approach to the synthesis of chiral 2-hydroxytetralines. Unexpectedly, substrates **2** were very unreactive and no conversion was observed in reactions performed with catalyst precursor **5b** under the reaction conditions used for enamides **1** (entries 12 and 13).

For comparison, the performance of catalysts based on some ligands **4** in the hydrogenation of the enamide **3** has also been examined. Then, the catalyst based on **4l** provided full conversion, giving the hydrogenated compound (*R*)-**7** with a respectable 77% ee (entry 14, Table 3). The diastereomeric catalyst precursor bearing ligand **4m** provided the opposite enantiomer (*S*)-**7** with a 57% ee (entry 15). The configuration of the product is therefore determined by the configuration of the phosphite fragment, as observed in the hydrogenation of substrates **1**. Moreover, the configurations of **7** and **6d** indicate the same sense for addition of hydrogen to **3** and **1d**, respectively (Figure 3).

Further Mechanistic Considerations. The challenging nature of substrates **1** for Rh hydrogenation, along with the lack of mechanistic information about this particular reaction in the literature, prompted us to investigate several fundamental features of these substrates connected with their hydro-

Table 3. Hydrogenation of Substrates 1–3 with Catalysts Prepared from $[Rh(COD)_2]BF_4$ and 4[a]

entry	P-OP ligand	substrate	conversn, %	ee, % (confign)[b]
1	**4l**	**1b**	40	93 (*S*)
2[c]	**4l**	**1b**	70	82 (*S*)
3	**4k**	**1b**	24	50 (*R*)
4	**4l**	**1c**	82	88 (*S*)
5	**4l**	**1d**	80	86 (*S*)
6	**4a**	**1e**	100	83 (*S*)
7	**4m**	**1e**	100	81 (*R*)
8	**4l**	**1e**	100	93 (*S*)
9	**4l**	**1f**	67	83 (*S*)
10[c]	**4l**	**1f**	70	81 (*S*)
11	**4m**	**1f**	75	68 (*R*)
12	**4b**	**2a**	<5	n.d.
13	**4b**	**2b**	<5	n.d.
14	**4l**	**3**	100	77 (*R*)
15	**4m**	**3**	100	57 (*S*)

[a]Reactions were carried out at room temperature unless otherwise specified: S/C = 100, reaction time 21 h. Conversion was determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. [b]The configuration for **6d** has been assigned by comparing the optical rotation with literature data,[4e] while for the rest of compounds the configuration has been assigned by analogy to that observed in hydrogenations of **1a,d**. [c]Reaction performed at 40 °C.

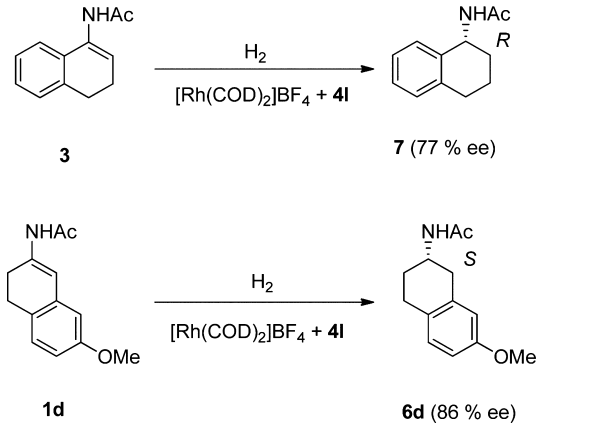


Figure 3. Comparison of product configurations in the hydrogenations of **3** and **1d**.

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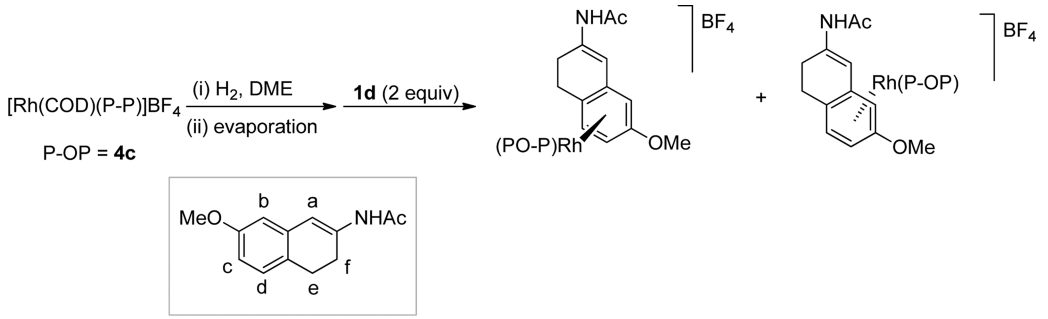

Figure 4. Synthesis of the arene complex [Rh(**4c**)(η^6-**1d**)]BF_4.

Table 4. ^{1}H and ^{13}C{^{1}H} NMR Data of 1d and Isomers of the Complex [Rh(4c)(η^6-1d)]BF_4[a]

entry	compd	H^a	H^b	H^c	H^d	C^a	C^b	C^c	C^d
1	**1d**	7.09	6.58	6.59	6.96	110.8	111.2	111.7	128.0
2	[Rh(**4c**)(**1d**)]$^+$ (maj)	6.76	4.97	5.84	4.12	102.9	85.5	91.8	94.9
3[b]	[Rh(**4c**)(**1d**)]$^+$ (min)	6.39	5.92	5.81	4.65	104.6	91.8	n. a.	n. a.

[a]All spectra measured in CD_2Cl_2 except ^{13}C{^{1}H} NMR of [Rh(**1d**)(**4l**)]BF_4, recorded in $CDCl_3$. See Figure 4 for the notation. [b]Signals for C^c and C^d nuclei of the minor isomer were not detected in the HMQC experiment due to low concentration.

genations. In this respect, the first aspect of interest regards the coordination mode of enamides **1** toward a [Rh(**4**)]$^+$ fragment. For this purpose, the representative enamide **1d** was chosen.

A compound with composition [Rh(**4c**)(**1d**)]BF_4 was prepared by hydrogenation of [Rh(COD)(**4c**)]BF_4 in DME, followed by evaporation of the solvent, dissolution in CD_2Cl_2, and addition of 2 equiv of **1d** (Figure 4). An analysis of the resulting mixture by ^{31}P{^{1}H} NMR showed the presence of two species in a ca. 3:1 ratio characterized by rather similar spectral data. The major species appears as two doublets of doublets centered at 125.8 ppm ($^1J_{RhP}$ = 322 Hz, $^2J_{PP}$ = 76 Hz) and 24.8 ppm ($^1J_{RhP}$ = 187 Hz), for the phosphine and phosphite fragments, respectively. The minor species likewise appears as two doublets of doublets centered at 127.5 ppm ($^1J_{RhP}$ = 330 Hz, $^2J_{PP}$ = 76 Hz) and 23.6 ppm ($^1J_{RhP}$ = 188 Hz). In addition, an analysis of the major compound by a 2D COSY experiment allowed us to identify the signals for H^c and H^d, while the 2D NOESY experiment showed contacts between H^b and H^c with the OMe group, as well as between H^a and H^b. From this information it can be concluded that H^a, H^b, H^c, and H^d appeared at 6.76, 4.97, 5.84 (d, $^3J_{HH}$ = 7.0 Hz), and 4.12 (d) ppm, respectively, in the major compound (Table 4, entry 2). For comparison, it should be mentioned that H^a appeared in the free substrate at 7.09 ppm, while the aromatic protons H^b, H^c, and H^d showed signals at 6.59, 6.58 (d, $^3J_{HH}$ = 7.5 Hz), and 6.96 (d) ppm, respectively (entry 1). Therefore, there is an important high-field displacement of the signals of aromatic protons upon coordination of **1d**. These shifts are in good accord with a η^6-arene coordination mode.[23] In addition, the relatively high values for $^1J_{RhP}$ are similar to values found before for other arene adducts of Rh compounds with phosphine−phosphite ligands.[11c] This coordination mode can be further confirmed by the chemical shifts of the corresponding C^b−C^d nuclei in the ^{13}C{^{1}H} NMR experiment, assigned with the help of a HMQC experiment. Therefore, CH^b, CH^c, and CH^d signals appeared for the major isomer at 85.0, 92.2, and 94.8 ppm, respectively (entry 2). For comparison, the corresponding signals appear in the free substrate at 111.2, 111.7, and 128.0 ppm, respectively (entry 1). Similar high-field shifts were observed in the ^{1}H NMR spectrum for the minor species, and H^b, H^c, and H^d signals are centered at 5.93, 4.64, and 5.81 ppm, respectively (entry 3), also supporting a η^6-arene coordination. From these data, it is reasonable to propose that the two compounds observed in solution are diastereomers resulting from coordination of **1d** by each of its diastereotopic faces. Interestingly, no exchange between adducts was observed in the 2D EXSY experiment, pointing to a slow decoordination of the arene adduct on the NMR time scale.

It is remarkable to note that the η^6-arene coordination mode exhibited by **1d** is unusual for an *N*-acyl enamide, which typically shows a O,C,C chelating mode in Rh(I) complexes.[7] In contrast, arene complexes formed by the corresponding hydrogenated products, therefore lacking the olefin bond, are well-known in the literature.[24]

The participation of complexes of the formula [Rh(**4**)(η^6-**1**)]$^+$ in the catalytic reaction would, however, depend on the mechanism of the hydrogenation of **1**. In a detailed study, Gridnev and Imamoto have compared the energy profile of several mechanistic pathways for the hydrogeanation of MAC with Rh catalysts bearing strong donor diphosphines,[25] pointing to routes involving hydrogen addition prior to olefin coordination as the most favorable ones. In addition, the hydrogenations described herein were performed at moderate hydrogen pressures, while the compound [Rh(**4c**)(η^6-**1d**)]BF_4 was formed in the absence of hydrogen. However, considering that the stability of Rh(III) dihydrides is favored by electron-rich ligands,[26] the low donor ability of P-OP ligands may shift the preference to an unsaturated pathway (i.e., olefin coordination prior to hydrogen addition). At this respect, Maseras and Vidal have proposed an unsaturated mechanism for the hydrogenation of MAC with Rh catalysts bearing phosphine−phosphite ligands.[27] If an analogous pathway is followed in the present system, dissociation of the arene ring from the 18-electron [Rh(**4**)(η^6-**1**)]$^+$ and recoordination of **1** in the less stable [Rh(**4**)(*O,C,C*-**1**)]$^+$ (Figure 5) should occur to start the hydrogenation cycle. Moreover, it should be recalled that Heller has nicely demonstrated the detrimental effect that the formation of stable η^6-arene complexes produces on hydrogenation rates, due to the reduced available amount of rhodium complex for catalysis.[23c] Following this reasoning, the coordination mode exhibited by **1d** would agree with the relatively low rates exhibited by substrates **1**. As an illustrative

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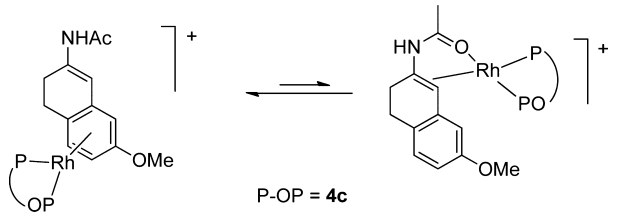


Figure 5. Expected formation of the $[Rh(\mathbf{4c})(O,C,C\text{-}\mathbf{1d})]^+$ complex from $[Rh(\mathbf{4c})(\eta^6\text{-}\mathbf{1d})]^+$.

comparison, it can be mentioned that hydrogenations of MAC or dimethyl itaconate with complexes **5** at S/C = 100 under 1 bar of hydrogen are typically finished after 1−2 h, while under these reaction conditions conversion after 72 h for substrates **1a,c,d** were 70, 56, and 53%, using the catalyst bearing ligand **4l**. Likewise, the lack of reactivity of enol esters **2** can also be attributed to the formation of η^6-arene species, as the inability of α-acyloxyacrylates to displace η^6-benzene has been reported before.[28]

In addition, we considered it of fundamental interest to investigate the deuteration of selected substrates **1c,d** under our standard conditions (20 bar of D_2, S/C = 100, room temperature). An analysis of product **6d** by ^1H, ^2H, and $^{13}C\{^1H\}$ NMR showed a single isotopomer in solution, in which labeling was observed in positions H^{a1} and H^g (Figure 6), in good accord with the characteristic *cis* addition to the double bond. No deuterium incorporation was observed either in position 3 or in the aromatic ring. Likewise, compound **6c** showed a similar pattern. An analysis of the enantioselectivity of these reactions indicated values of 89 and 87% ee for **6c,d**, respectively, identical within the experimental error with those of the hydrogenation reactions (88 and 86% ee, respectively). In this context it is pertinent to recall the enantioreversal observed in the hydrogenation of α- and β-acyloxyvinylphosphonates with complexes **5**, which has been rationalized by the formation of α- and β-alkyl intermediates, respectively.[11c] Thus, a possible factor for erosion of enantioselectivity in the hydrogenation of substrates **1** could be a competition between α- and β-alkyl pathways, considering that they can provide opposite enantiomers.[11] In this regard, a mechanistic study has connected the observation of an isotopic effect on enantioselectivity in Rh-catalyzed enamide hydrogenation with the competition between α- and β-alkyl pathways.[29] On the basis of that line of reasoning, the absence of isotopic effects observed in the hydrogenations of **1c,d** would agree with an absence of competition between the two pathways.

CONCLUSIONS

The enantioselective catalytic hydrogenation of enamides **1** with rhodium catalysts based on modular phosphine−phosphite ligands **4** has been studied. A broad screening with these catalysts indicates that the hydrogenation of **1** is very sensitive to subtle changes in the ligand backbone, pointing to the need for a precise optimization of the catalyst structure for substrates **1**. Following this approach, a highly enantioselective

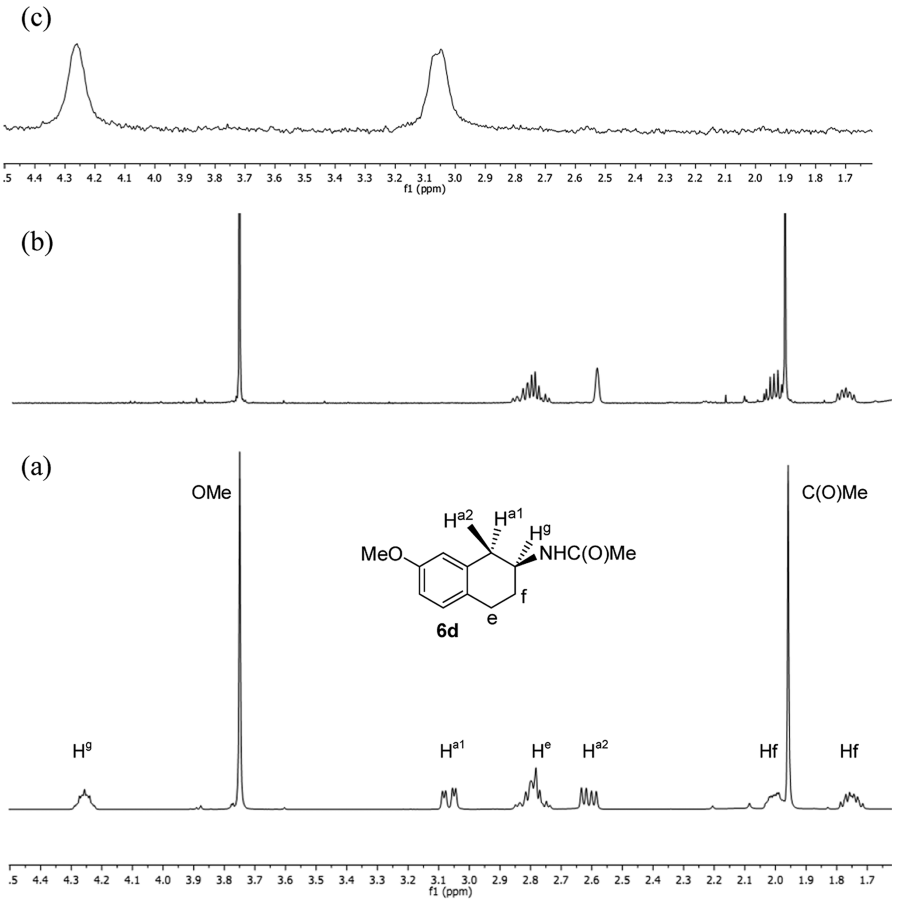


Figure 6. ^1H NMR spectrum of **6d** (a) and the ^1H (b) and ^2H NMR spectra (c) of the product obtained by deuteration of **1d** with $[Rh(COD)(\mathbf{4b})]BF_4$.

dx.doi.org/10.1021/jo400345v | J. Org. Chem. 2013, 78, 3997−4005

catalyst based on a ligand with an ethane backbone and a *P*-stereogenic phosphine fragment, with matched phosphine and biphenyl configurations, has been found. This catalyst provides high enantioselectivities, ranging from 83 to 93% ee, in the hydrogenation of several OMe- and Br-substituted substrates **1**. In contrast, structurally related enol esters **2** show very little reactivity. Unexpectedly, the addition of DIPEA to the reaction has a dramatic effect, increasing catalyst activity but leading to racemic products.

Coordination studies of the representative enamide **1d** have shown a marked preference for a η^6-arene coordination in a Rh(I) complex, which is in accord with the relatively low rates shown by these substrates. Moreover, deuterations of substrates **1c,d** under the standard reaction conditions show a clean *cis* addition to the double bond, without an isotopic effect on enantioselectivity. The results obtained, however, did not show a distinctive feature of the hydrogenation of substrates **1**, responsible for the rather difficult control of enantioselectivity in these reactions.

EXPERIMENTAL SECTION

General Procedures. All reactions and manipulations were performed under nitrogen or argon, either in a glovebox or using standard Schlenk-type techniques. All solvents were distilled under nitrogen with the following desiccants: sodium benzophenone ketyl for diethyl ether (Et_2O) and tetrahydrofuran (THF), sodium for hexanes and toluene, CaH_2 for dichloromethane (CH_2Cl_2), and NaOMe for methanol (MeOH). Phosphine−phosphite ligands **4** were prepared as described previously.[14] Enamides **1**,[3] enol esters **2**,[16] and enamide **3**[30] were synthesized according to literature procedures. All other reagents were purchased from commercial suppliers and used as received. $^{31}P\{^1H\}$ NMR shifts were referenced to external 85% H_3PO_4, while $^{13}C\{^1H\}$ and ^1H NMR shifts were referenced to the residual signals of deuterated solvents. All data are reported in ppm downfield from $SiMe_4$. All NMR measurements were carried out at 25 °C, unless otherwise stated. HRMS data were obtained on a quadrupole analyzer.

[Rh(COD)(4c)]BF_4 (5c). Ligand **4c** (0.100 g, 0.15 mmol) dissolved in CH_2Cl_2 (5 mL) was added dropwise to a solution of $[Rh(COD)_2]$-BF_4 (0.056 g, 0.15 mmol) in CH_2Cl_2 (5 mL). The resulting orange solution was stirred for 1 h, concentrated to one-fourth of its initial volume, and filtered. Et_2O (20 mL) was added to the above solution to precipitate the complex. The solid was filtered off, washed with Et_2O (3 × 10 mL), and dried: yellow solid (0.104 g, 69%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 11 Hz, 2H), 7.29 (s, 1H), 7.25 (s, 1H), 7.16 (s, 1H), 7.15 (s, 1H), 6.92 (d, J = 11 Hz, 2H), 5.86 (br s, 1H), 5.17 (br s, 1H), 4.60 (m, 1H), 4.37 (br s, 2H), 3.98 (m, 2H), 3.01 (m, 1H), 2.47 (m, 3H), 2.42 (s, 6H), 2.35 (s, 6H), 2.30 (s, 3H), 2.24 (s, 3H), 2.17 (m, 2H), 2.03 (m, 4H), 1.84 (s, 3H), 1.76 (s, 3H), 1.66 (s, 9H), 1.38 (s, 9H). $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 118.7 (dd, J_{PRh} = 246 Hz, J_{PP} = 60 Hz, P−O), 4.05 (dd, J_{PRh} = 140 Hz, P−C). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.7 (d, J = 6 Hz), 144.0 (d, J = 13 Hz), 139.7 (d, J = 11 Hz), 139.5 (d, J = 10 Hz), 137.0, 137.0, 136.3, 135.5, 134.9, 134.0, 133.5, 133.0, 132.9, 129.8, 129.8, 129.3, 129.2, 129.1, 128.7, 128.6, 128.4, 128.2, 128.2, 110.5 (dd, J = 13 Hz, J = 6 Hz), 107.3 (dd, J = 12 Hz, J = 6 Hz), 106.2 (m), 94.8 (m), 64.9, 35.0, 35.0, 32.4, 31.8, 31.3, 30.7, 30.3, 28.8, 26.0 (dd, J = 31 Hz, J = 13 Hz), 21.7, 21.6, 20.6, 20.5, 16.8, 16.6. Anal. Calcd for $C_{50}H_{66}BF_4O_3P_2Rh$: C, 62.12; H, 6.88. Found: C, 61.92; H, 7.15.

General Procedure for the Synthesis of Enamides 1. Enamides **1** were prepared by an adaptation of a literature procedure[3] as described below. In a 250 mL round-bottom flask equipped with a Dean−Stark apparatus were introduced the ketone (10 mmol), the primary amide (25 mmol), and TsOH (1 mmol) in toluene (60 mL). The mixture was refluxed for 20 h under an inert atmosphere. After the mixture was cooled to room temperature, 150 mL of a saturated solution of sodium hydrogen carbonate was added and the mixture was warmed to 60 °C for 30 min. After the mixture was cooled to room temperature, the organic layer was extracted and the extract was washed with water (3 × 100 mL), dried over magnesium sulfate, and concentrated. The enamide was purified by chromatography on silica gel or isolated by crystallization.

*N-(6-Methoxy-3,4-dihydronaphthalen-2-yl)acetamide (**1c**).* Obtained following the general procedure as a white powder (0.61 g, 50% yield) after flash column chromatography on silica gel (AcOEt/hexane, 6/1): mp 124−127 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.01 (s, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.65 (m, 3H), 3.78 (s, 3H), 2.86 (t, J = 7.5 Hz, 2H), 2.43 (t, J = 7.5 Hz, 2H), 2.10 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 168.4, 158.1, 134.5, 132.8, 127.7, 127.1, 113.7, 111.4, 111.3, 55.4, 28.5, 27.5, 24.8. HRMS (EI): m/z 217.1102, $[M]^+$ (exact mass calcd for $C_{13}H_{15}NO_2$: 217.1103).

*N-(8-Methoxy-3,4-dihydronaphthalen-2-yl)acetamide (**1e**).* Obtained as a white powder by crystallization in a CH_2Cl_2/*n*-hexane (1/1) mixture (0.6 g, 50% yield): mp 168−171 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.17 (s, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.70 (d, J = 7.8 Hz, 2H), 6.65 (br s, 1H), 3.81 (s, 3H), 2.86 (t, J = 8.0 Hz, 2H), 2.52 (t, J = 8.0 Hz, 2H), 2.10 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 168.2, 154.7, 135.0, 134.4, 126.4, 123.4, 119.8, 108.9, 105.7, 55.6, 28.4, 26.9, 24.8. HRMS (EI): m/z 217.1110, $[M]^+$ (exact mass calcd for $C_{13}H_{15}NO_2$: 217.1103).

*N-(6-Bromo-3,4-dihydronaphthalen-2-yl)acetamide (**1f**).* Prepared according to the general procedure and purified by crystallization in toluene. White crystalline solid (0.34 g, 30% yield): mp 196−199 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H), 7.07 (s, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.58 (br s, 1H), 2.85 (t, J = 8.1 Hz, 2H), 2.41 (t, J = 8.1 Hz, 2H), 2.12 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 168.5, 135.3, 134.7, 133.8, 130.0, 129.8, 127.6, 110.5, 27.8, 27.5, 24.9. HRMS (EI): m/z 265.0103, $[M]^+$ (exact mass calcd for $C_{12}H_{12}NOBr$: 265.0102).

General Procedure for Catalytic Hydrogenation Reactions. In a glovebox, the appropriate olefin (0.036 mmol), phosphine−phosphite ligand (0.46 μmol), and $[Rh(COD)_2]BF_4$ (0.42 μmol) from freshly prepared stock solutions in CH_2Cl_2 (total volume 0.5 mL) were added to a 2 mL glass vial. Vials were placed in a steel reaction vessel (Model HEL CAT18) that holds up to 18 reactions. The reactor was purged three times with H_2 and finally pressurized to the required pressure. In the case of deuteration reactions the reactor was purged with Ar, partially evacuated under vacuum, and filled with D_2 at 20 atm. After the desired reaction time, the reactor was slowly depressurized, solutions were evaporated, and conversions were determined by ^1H NMR. The resulting mixtures were dissolved in EtOAc and filtered through a short pad of silica to remove the catalyst. Enantiomeric excess was analyzed by chiral GC or HPLC, as follows. *N*-(1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (**6a**): GC, Supelco β-DEX 110; 100 °C (2 min), then 2 °C/min up to 190 °C; 28.0 psi of He; t_1 = 46.41 min, t_2 = 46.59 min. *N*-(1,2,3,4-tetrahydronaphthalen-2-yl)benzamide (**6b**): HPLC, Daicel Chiralcel OJ-H 90/10 *n*-hexane/i-PrOH, t_1 = 18.5 min, t_2 = 22.3 min. *N*-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (**6c**): HPLC, Daicel Chiralcel OJ-H 90/10 *n*-hexane/i-PrOH, t_1 = 20.82 min, t_2 = 30.70 min. *N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (**6d**): HPLC, Daicel Chiralcel OJ-H 90/10 *n*-hexane/i-PrOH, t_1 = 20.6 min, t_2 = 32.9 min. *N*-(8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (**6e**): HPLC, Daicel Chiralcel OJ-H 90/10 *n*-hexane/i-PrOH, t_1 = 12.12 min, t_2 = 13.54 min. *N*-(6-bromo-1,2,3,4-dihydronaphthalen-2-yl)acetamide (**6f**): HPLC, Daicel Chiralcel OJ-H 90/10 *n*-hexane/i-PrOH, t_1 = 11.09 min, t_2 = 13.18 min. *N*-(1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (**7**): HPLC, Daicel Chiralcel OJ-H 99.5/0.5 *n*-hexane/i-PrOH, t_1 = 14.6 min, t_2 = 15.6 min.

*N-(6-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (**6c**).* Obtained with a 82% conversion following the general procedure, further purified by preparative TLC (CH_2Cl_2/*n*-hexane 9/1) giving **6c** as a yellow solid (26% yield): mp 109−112 °C. $[\alpha]_D^{20}$ = −25.1° (*c* 0.1, $CHCl_3$, *S* enantiomer 88% ee). ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, J = 8.4 Hz, 1H), 6.70 (dd, J = 2.4 Hz, J = 8.4 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 5.51 (br s, 1H), 4.28 (m, 1H), 3.78 (s, 3H), 3.05 (dd, J = 4.9 Hz, J = 15.9 Hz, 1H), 2.85 (m, 2H; CH_2), 2.57 (dd, J = 7.7 Hz, J = 16.0 Hz, 1H), 2.03 (m, 1H), 1.98 (s, 3H), 1.79 (m, 1H). $^{13}C\{^1H\}$

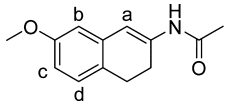
dx.doi.org/10.1021/jo400345v | J. Org. Chem. 2013, 78, 3997−4005

NMR (100.6 MHz, $CDCl_3$): δ 169.9, 158.1, 136.7), 130.5, 126.0, 113.5, 112.5, 55.4, 45.5, 35.0, 28.5, 27.3, 23.7. HRMS (EI): m/z 219.1256, $[M]^+$ (exact mass calcd for $C_{13}H_{17}NO_2$: 219.1259).

*N-(8-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (**6e**).* According to the general procedure, obtained with a 95% yield: yellow powder; mp 119−122 °C. $[\alpha]_D^{20}$ = −27.0° (*c* 0.1,$CHCl_3$, *S* enantiomer 93% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (t, J = 8.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.65 (br s, 1H), 4.27 (m, 1H), 3.80 (s, 3H), 3.06 (dd, J = 6.0 Hz, J = 17.3 Hz, 1H), 2.85 (m, 2H), 2.45 (dd, J = 8.0 Hz, J = 17.3 Hz 1H), 2.04 (m, 1H), 2.10 (s, 3H), 1.76 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.0, 157.6, 137.0, 126.6, 123.1, 121.1, 107.2, 55.4, 45.3, 29.8, 28.3, 27.3, 23.6. HRMS (EI): m/z 219.1258, $[M]^+$ (exact mass calcd for $C_{13}H_{17}NO_2$: 219.1259).

*N-(6-Bromo-1,2,3,4-dihydronaphthalen-2-yl)acetamide (**6f**).* According to the general procedure compound **6f** was obtained with a 70% conversion. Attempts to separate it from remaining **3f** were unsuccessful; therefore, **6f** was assessed by NMR and HRMS. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (m, 2H), 6.93 (d, J = 8.0 Hz, 1H), 5.48 (br s, 1H), 4.27 (m, 1H), 3.07 (dd, J = 4.8 Hz, J = 16.5 Hz, 1H), 2.85 (m, 2H; CH_2), 2.57 (dd, J = 8.1 Hz, J = 16.5 Hz, 1H), 2.04 (m, 1H), 1.99 (s, 3H), 1.73 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 169.7, 162.6, 137.9, 133.1, 131.7, 131.2, 129.2, 45.0, 35.4, 29.9, 28.4, 27.0, 23.7. HRMS (CI): m/z 268.0347, $[M + H]^+$ (exact mass calcd for $C_{12}H_{15}BrNO$: 268.0337).

[Rh(4c)(1d)]BF_4.



Compound **5c** (18 mg, 0.02 mmol) was dissolved in DME (0.5 mL) and the solution pressurized with 4 bar of hydrogen. The reaction was monitored until dissapearance of the starting material, and the resulting solution was evaporated to dryness. The resulting residue was dissolved in CD_2Cl_2, and **1d** (9 mg, 0.04 mmol) was added. The resulting solution showed the enamide adduct as a mixture of two isomers (major and minor) in a ca. 3/1 ratio. Assignments of aromatic protons of coordinated **1d** (see illustration above) have been made with the help of NOESY, COSY, and HMQC experiments. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.82 (s, 1H), 7.38 (s, 1H), 7.27 (d, J = 10.5 Hz, 2H), 7.26 (s, 1H), 7.17 (s, 2H), 7.02 (d, J = 12.0 Hz, 2H), 6.76 (s, 1H, H^a), 5.85 (dd, J = 7.0 Hz, J = 2.0 Hz, 1H, H^c), 4.97 (s, 1H, H^b), 4.34 (m, 2H), 4.10 (d, J = 7.0 Hz, 1H, H^d), 4.03 (m, 2H), 3.09 (s, 3H), 2.60 (m, 2H), 2.41 (s, 3H), 2.36 (s, 6H), 2.33 (s, 6H), 2.26 (m, 2H), 2.25 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 1.52 (s, 9H), 1.45 (s, 9H). ^{31}P{^{1}H} NMR (CD_2Cl_2, 162 MHz): δ 136.4 (dd, J_{RhP} = 345 Hz, J_{PP} = 69 Hz, PO), 26.4 (dd, J_{RhP} = 191 Hz, J_{PP} = 69 Hz, PC). ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 170.2, 145.9, 142.3, 139.3, 139.1, 139.0, 137.2, 136.3, 136.2, 135.6, 134.1, 134.0, 133.8, 133.1, 132.8, 132.2, 131.9, 131.8, 130.1, 130.0, 129.6, 129.5, 128.7, 127.9, 110.6, 102.5 (CH^a), 94.4 (CH^d), 91.0 (CH^c), 84.5 (CH^b), 63.9, 55.8, 33.0, 32.9, 32.1, 31.8, 26.8, 25.1, 24.6, 21.5, 21.4, 21.3, 20.5, 20.2, 16.7, 16.3. Characteristic signals for the minor isomer are as follows. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 6.25 (s, 1H, H arom, H^b), 5.84 (d, J = 7.0 Hz, 1H, H arom, H^c), 4.43 (s, 1H, H arom, H^d), 3.58 (s, 3H, C(O)Me). ^{31}P{^{1}H} NMR (CD_2Cl_2, 162 MHz): δ 139.3 (dd, J_{RhP} = 354 Hz, J_{PP} = 74 Hz, PO), 27.7 (dd, J_{RhP} = 191 Hz, J_{PP} = 74 Hz, PC). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 90.6 (CH^c), 91.0 (CH^b), 56.3 (OMe). Due to low intensity, CH^c and CH^d signals for the minor isomer could not be located. MS (ESI): m/z 988.4, $[M]^+$ (mass calcd for $C_{55}H_{69}NO_5P_2Rh$: 988.4).

■ ASSOCIATED CONTENT

Supporting Information

Figures giving NMR spectra for compounds **1**, **6**, [Rh(COD)(**4c**)]BF_4, and [Rh(**4c**)(**1d**)]BF_4 and MS-ESI spectra for [Rh(**4c**)(**1e**)]$^+$. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Prof. Ilya Gridnev (Tohoku University) for helpful comments. The MICINN (CTQ2009-11867 and CONSOLIDER-INGENIO, CSD2007-00006, FEDER support) and Junta de Andalucía (2008/FQM-3830 and 2009/FQM-4832) are also acknowledged for financial support. P.K. acknowledges the EU for an early stage researcher contract (PITN 2008-215193). We also thank CITIUS for technical support on NMR and HRMS experiments.

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