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Rhodium-Catalyzed Enantioselective Intramolecular [4+2] Cycloaddition using a Chiral Phosphine-Phosphite Ligand: Importance of Microwave-Assisted Catalyst Conditioning

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Abstract: The use of modular α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL)- and 1,1′-bi-2-naphthol (BINOL)-derived phosphine-phosphite ligands (L_2*) in the asymmetric rhodium-catalyzed intramolecular [4+2]cycloaddition ("neutral" Diels–Alder reaction) of (*E*,*E*)-1,6,8-decatriene derivatives (including a 4-oxa and a 4-aza analogue) was investigated. Initial screening of a small ligand library led to the identification of a most promising, TADDOL-derived ligand bearing a phenyl group adjacent to the phosphite moiety at the arene backbone. In the course of further optimization studies, the formation of a new, more selective catalyst species during the reaction time was observed. By irradiating the pre-catalyst with microwaves prior to substrate addition high enantioselectivities (up to 93% *ee*) were achieved. The new cyclization protocol was successfully applied to all three substrates investigated to give the bicyclic products in good yield and selectivity. ^{31}P NMR and ESI-MS measurements indicated the formation of a $[Rh(L_2*)_2]^+$ species as the more selective (pre-) catalyst.

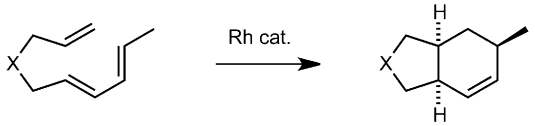
Keywords: asymmetric catalysis; chiral P,P ligands; [4+2]cycloaddition; Diels–Alder reaction; enantioselectivity; rhodium(I) complexes

Cycloadditions, such as the most prominent Diels–Alder reaction,[1] open particularly powerful options for the construction of polycyclic systems in an atom-economical fashion.[2] With the emergence of transition metal catalysis, the toolset of classical (pericyclic) cycloaddition chemistry has been greatly expanded and even "uncommon" types of (formal) cycloadditions, such as [2+2+2],[3] [2+2+1],[4] or [5+2][5] processes have been developed and applied as strategic key steps in natural product synthesis.[6]

Transition metal catalysis also allows one to overcome certain limitations of the classical Diels–Alder reaction. For instance, so-called "neutral" Diels–Alder reactions, involving non-activated dienes and dienophiles, often cannot be achieved under thermal (or Lewis acid-catalyzed) conditions. However, it has been shown that certain transition metal complexes are able to efficiently catalyze such transformations, in particular in cases where an alkyne (or allene) acts as the dienophile.[7]

Intramolecular [4+2]cycloadditions of trienes of type **1** represent an interesting challenge, as the resulting hexahydroindenes (or their hetero analogues) of type **2** resemble relevant substructures of natural products (Scheme 1). As an important breakthrough, Livinghouse and co-workers reported in 1990 that the conversion of **1a** to *rac*-**2a** could be achieved in high yield using $[(i\text{-}C_3HF_6O)_3P]_2RhCl$ as a catalyst.[8]

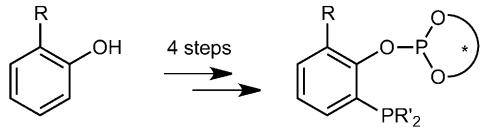
The chirogenic nature of this Rh-catalyzed transformation opens the possibility to perform it in an asymmetric fashion by using chiral ligands. A first enantioselective version was disclosed by Livinghouse who used DIOP in the synthesis of **2a** (73% *ee*)[9] and **2b**



1a (X = O)
1b (X = NTs)
1c (X = $C(CO_2Me)_2$)

2a (X = O)
2b (X = NTs)
2c (X = $C(CO_2Me)_2$)

Scheme 1. Rh-catalyzed intramolecular [4+2]cycloadditions of trienes of type **1**.



3 4

Scheme 2. Phenol-derived phosphine-phosphite ligands of type **4**.

(79% *ee*).[10] An important advance was reported by Gilbertson and co-workers who succeeded in converting **1a** to **2a** with >98% *ee* (64% yield) using preformed [(Rh(NBD)BINAP)SbF_6] as a pre-catalyst, which was activated by hydrogenation prior to substrate addition.[11] In the course of another study, the synthesis of **2b** was achieved in 91% *ee* using a rather specialized sila-bridged P-chirogenic diphosphine.[12]

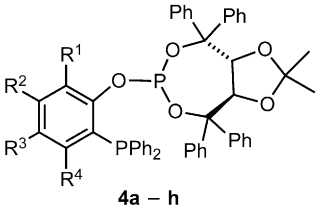
Still, in contrast to the structurally related diene-yne substrates, diene-enes of type **1** represent rather difficult substrates for enantioselective Diels–Alder-type transformations challenging the development of a generally applicable catalyst system.

A few years ago, we elaborated an efficient modular synthesis of phenol-derived phosphine-phosphites of type **4** using chiral diols such as TADDOL or BINOL as a source of chirality (Scheme 2).[13]

This new class of readily available chiral ligands was then shown to possess a promising potential for asymmetric metal catalysis (especially Cu- and Rh-catalyzed transformations).[14] We therefore envisioned that such ligands could also serve in the Rh-catalyzed [4+2] cycloaddition of tethered diene-enes of type **1**. We here report on the successful realization of this idea and the elaboration of an optimized protocol for such transformations.

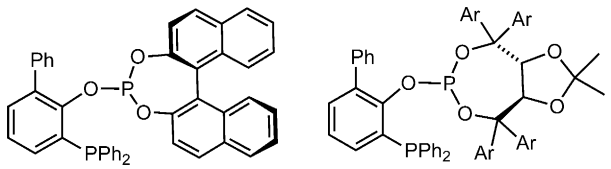
We started our investigation with a primary ligand screening. For this purpose, we used the reaction of substrate **1a** in CH_2Cl_2 as a solvent under the conditions developed by Gilbertson[11] with the difference that the Rh complexes were formed *in situ* (without isolation). The tested ligands of type **4** (Figure 1) were prepared as previously reported.[13] As the only new ligand the 4-fluorophenyl-TADDOL derivative **4j** was synthesized along the established route.[13a]

The results of the initial ligand testing are summarized in Table 1. Firstly, it was found that the ligands (despite their seemingly structural similarity) behaved quite differently. Most importantly, a tremendous effect of the phenolic backbone substitution pattern on the activity and selectivity of the catalyst was observed. While a methyl substituent in the R^4 position of the ligand **4** strongly reduced the activity (reaction rate), the variation of the substituent R^1 (*ortho* to the phosphite moiety) had a great impact on the enantioselectivity. Ligands **4a**, **4h** and **4j** led to full conversion within 3 days,[15] while a promising enantioselectivity



4a – h

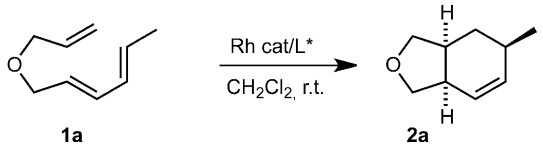
	R^1	R^2	R^3	R^4
4a	Me	Me	H	H
4b	*i*-Bu	H	H	H
4c	*i*-Pr	H	H	H
4d	*i*-Pr	H	H	Me
4e	Me	H	H	Me
4f	*i*-Bu	H	*i*-Bu	H
4g	Me	H	H	H
4h	Ph	H	H	H



4i 4j Ar = 4-F-C_6H_4

Figure 1. Phophine-phosphite ligands of type **4** used in the present study.

Table 1. Screening of different ligands of type **4** in the Rh-catalyzed [4+2] cycloaddition of substrate **1a**.[a]



1a 2a

Entry	Ligand (L_2*)	Conversion[b]	*ee* [%][c]	Major enantiomer[d]
1	**4a**	+	6	*ent*-**2a**
2	**4b**	–	6	*ent*-**2a**
3	**4c**	–	5	*ent*-**2a**
4	**4d**	– –	–	–
5	**4e**	–	48	**2a**
6	**4f**	–	7	*ent*-**2a**
7	**4g**	–	8	*ent*-**2a**
8	**4h**	+	62	**2a**
9	**4i**	–	25	*ent*-**2a**
10	**4j**	+	62	**2a**

[a] *Conditions:* 6 mol% of catalyst prepared from $[Rh(NBD)Cl]_2$, $AgSbF_6$, L_2* (0.5:1:1.2) and activation with H_2; reaction carried out in CH_2Cl_2 at room temperature.

[b] Complete (+), incomplete (–), or no (– –) conversion after 3 days.

[c] The enantiomeric excess (*ee*) of **2a**/*ent*-**2a** was determined by GC analysis after 3 days.

[d] The absolute configuration was assigned by GC comparison with a reference sample of *ent*-**2a** prepared according to ref.[11] using (*S*,*S*)-DIOP as a ligand.

(62% *ee*) was found only for the phenyl-substituted ligands **4h** and **4j** (Table 1, entries 8 and 10). Exchanging the TADDOL unit for BINOL (**4h**→**4i**) led to a dramatic decrease in enantioselectivity (entry 9). The fluorophenyl-TADDOL-based ligand **4j** performed similar to its non-fluorinated congener **4h** (entry 10).

Table 2. Influence of different solvents on the rate and selectivity of the Rh-catalyzed reaction of **1a** to **2a** in the presence of ligand **4h**.[a]

Entry	Solvent	Conversion[b]	*ee* [%][c]
1	CH_2Cl_2	+	62
2	EtOAc	+	72
3	THF	–	44
4	2-Me-THF	–	40
5	Et_2O	–	36
6	MTBE	–	52
7	toluene	–	72
8	DCE	+	54
9	DMSO	– –	–
10	HFIP	–	32
11	ethyl formate	+	60

[a] *Conditions:* 6 mol% of catalyst prepared from $[Rh(NBD)Cl]_2$, $AgSbF_6$, **4h** (0.5:1:1.2) and activation with H_2; room temperature.
[b] Complete (+), incomplete (–), or no (– –) conversion after 3 days.
[c] The enantiomeric excess (*ee*) of **2a** was determined by GC analysis after full conversion of substrate **1a** or after 7 days.

Table 3. Rh-catalyzed [4+2] cycloadditions according to Scheme 1 using ligand **4h** with and without catalyst pre-conditioning.[a]

Entry	Substrate	Conditions	Reaction time [days]	Yield [%][b]	*ee* [%]
1	**1a**	A	3	54[c)]	72
2	**1a**	B	1	44[c)]	90
3[d]	**1b**	A	8	69	51
4[d]	**1b**	B	1	83	90
5	**1c**	A	7	11	31
6	**1c**	B	1	79	68

[a] *Conditions A:* 6 mol% of catalyst prepared from $[Rh(NBD)Cl]_2$, $AgSbF_6$, **4h** (0.5:1:1.2) and activation with H_2; EtOAc; room temperature. *Conditions B:* 6 mol% of microwave-conditioned catalyst prepared from $[Rh(NBD)Cl]_2$, $AgSbF_6$, **4h** (0.5:1:1.6) and subsequent activation with H_2; the reaction was then carried out in EtOAc at 50 °C in the microwave reactor.
[b] Isolated yield after purification.
[c] Reduced yield because of a high volatility of the product.
[d] 10 mol% of catalyst used.

In all cases, the *cis*-bicyclic products (**2a**/*ent*-**2a**) were obtained as pure diastereomers (GC-MS).

Having identified **4h** as a promising ligand, the next goal was to further optimize the reaction conditions. For this purpose, we tested a series of different solvents, again using the transformation of **1a** to **2a** as a standard (Table 2). While both EtOAc and toluene gave rise to an improved enantioselectivity of 72% *ee*, the reaction was much faster in EtOAc.[11,16] Noteworthy, no conversion was observed in DMSO, and other polar solvents such as ethyl formate or hexafluoro-2-propanol (HFIP) were less effective. We therefore used EtOAc as a solvent of choice for all further experiments (see below).

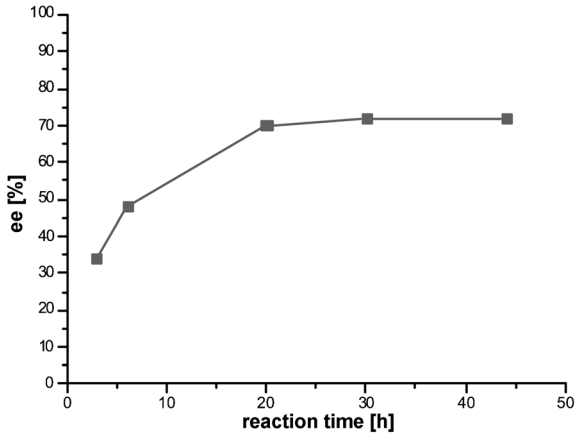


Figure 2. Increase of the enantioselectivitiy during the reaction of **1a** to **2a** in EtOAc at room temperature according to Table 3, entry 1 (>95% conversion after 44 h).

At this point, we probed the conditions developed so far (using ligand **4h** in EtOAc at room temperature) also on a preparative scale. We found that all three substrates (**1a–c**) afforded the expected products (**2a–c**) with at least significant selectivity (Table 3, entries 1, 3, and 5). In the case of **2a** the rather low isolated yield reflects the high volatility of the product. In the case of **2b** a higher catalyst load (10 mol%) was used to accelerate the very slow reaction.[15] Noteworthy is the fact that **2c** formed at all, because substrate **1c** is known to yield a different (monocyclic) product under related conditions in the presence of other ligands.[17] Nevertheless, the moderate yields and enantioselectivities as well as the rather long reaction times required further optimization efforts.

A surprising observation was made when we monitored the enantioselectivity during the conversion of **1a** (Table 3, entry 1). As depicted in Figure 2, the enantioselectivity strongly improved within the first 20 h (from 30% to 70% *ee*).

We assumed that this phenomenon resulted from the slow formation of a secondary catalyst species that is far more selective than the initial one. To probe this assumption we performed an experiment using a catalyst solution in EtOAc which was "preconditioned" at 80 °C for 2 h. And indeed, an improved enantioselectivity was observed in this case (60% *ee* after 3 h; 78% *ee* after 90% conversion). An even more efficient conditioning was achieved under rather harsh microwave conditions (120 °C in EtOAc, 5.0 bar, 45 min). While the resulting brownish-orange catalyst solution was poorly active at room temperature, it performed very well at elevated temperatures.

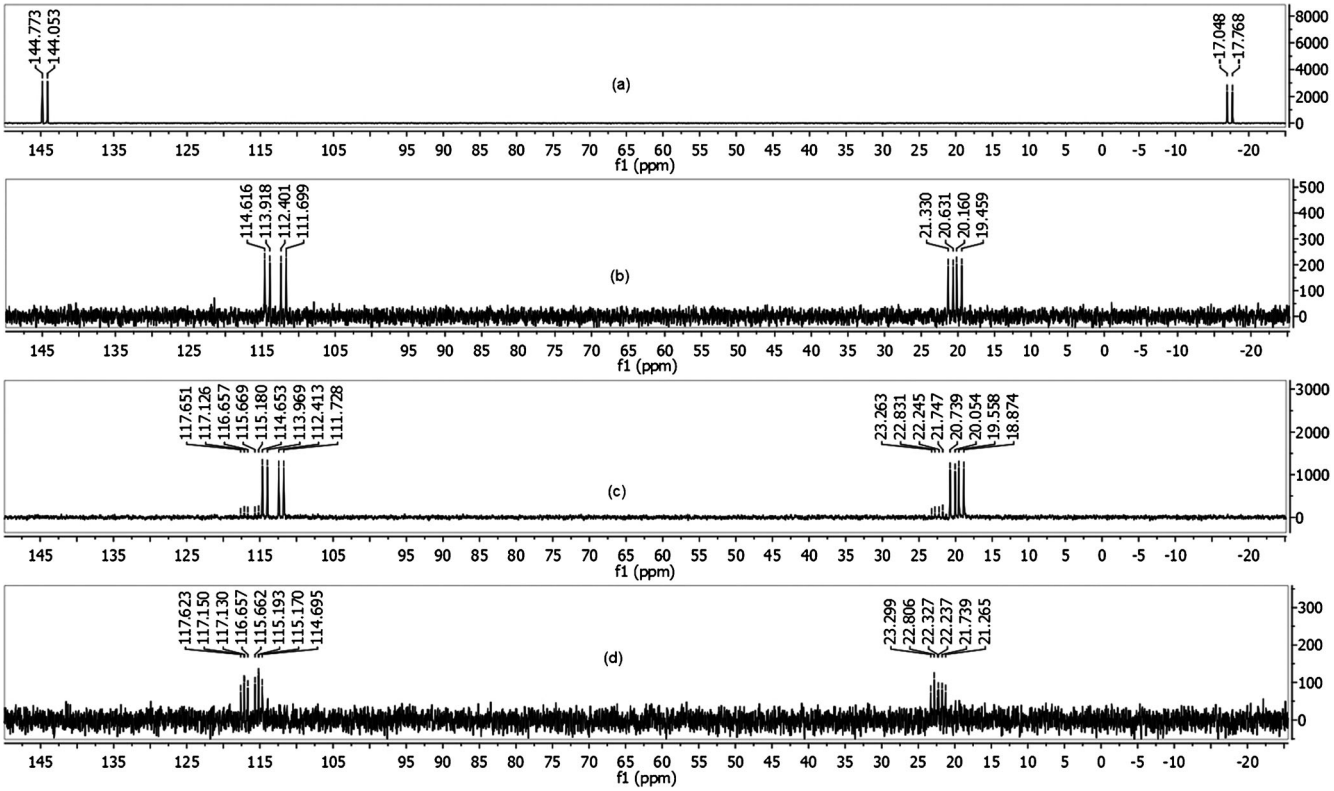


Figure 3. ^{31}P NMR spectra (in EtOAc/C_6D_6): (**a**) free ligand **4h** (L_2*); (**b**) freshly prepared pre-catalyst, i.e., [Rh(NBD)L_2*]$^+$$SbF_6^-$; (**c**) aged pre-catalyst after 24 h at room temperature, and (**d**) conditioned pre-catalyst (microwave, 120 °C, 45 min).

Best results were obtained at 50 °C in a microwave reactor. Under these conditions, the intramolecular [4+2] cycloaddition of all three substrates (**1a–c**) was achieved in good yield within 20 h and with a remarkable level of selectivity (Table 3, entries 2, 4 and 6). Noteworthy, the microwave-assisted reactions proceeded also much more cleanly than those performed at the same temperature in an oil bath.

Of course, we were curious about the chemical nature of the "more selective" catalyst species. In a first attempt to shed some light on the molecular changes occurring during the conditioning we investigated different solutions by means of ^{31}P NMR spectroscopy. Figure 3 shows the ^{31}P NMR spectra (in EtOAc) of (**a**) the free ligand (L_2*, that is, **4h**), (**b**) the standard catalyst solution, that is, [Rh(NBD)L_2*]$^+$$SbF_6^-$, (**c**) the "aged" catalyst solution after 24 h at room temperature containing small amounts of a different complex, and (**d**) the catalyst solution after microwave treatment (45 min, 120 °C). Obviously, the original complex was completely converted into a new species in the course of the conditioning process.

The NMR data (see Table 4) nicely show the changes of the chemical shifts of both the phosphine and the phosphite teeth of **4h** on Rh-complexation,

Table 4. ^{31}P NMR data of different species in EtOAc (compare Figure 3).

Species	δ [ppm] (coupling)
4h (free ligand)	144.4 (d, J = 88 Hz), 17.4 (d, J = 88 Hz)
[Rh(NBD)L_2*]$^+$$SbF_6^-$	113.2 (dd, J = 269/85 Hz), 20.4 (dd, J = 142/85 Hz)
[Rh(L_2*)$_2$]$^+$$SbF_6^-$	116.2 (ddd, J = 238/60/58 Hz), 22.3 (ddd, J = 130/60/58 Hz)

which is also connected to a signal splitting resulting from P–Rh (J_1) coupling. The additional couplings within the species formed during the conditioning process indicate the presence of an additional L_2* ligand at the Rh center, that is, the formation of a [Rh(L_2*)$_2$]$^+$ species.

The NMR-based proposal of a RhL_4^+ species (i.e. [Rh(L_2*)$_2$]$^+$$SbF_6^-$) was further corroborated by mass spectrometric measurements. The ESI (+) mass spectrum showed a signal at m/z = 1800.473 corresponding to the [Rh(**4h**)$_2$]$^+$ ion (see the Supporting Information). The identity of this signal was confirmed by a collision-induced dissociation (CID) experiment (LTQ-MS^2) where a main product ion showed up at

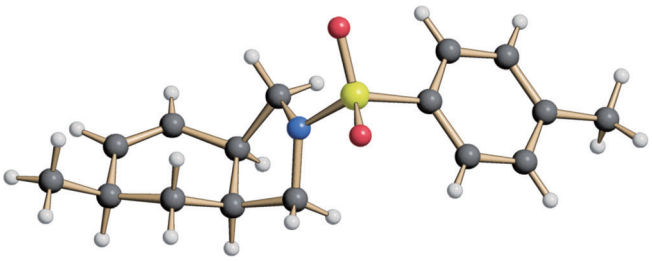


Figure 4. Structure of **2b** in the crystalline state confirming the relative and absolute configuration.

m/z = 951.187 resulting from dissociation of one molecule of ligand **4h**.

The formation of a $Rh(L_2)_2^+$ complex as the only major phosphorus-containing species in our catalyst solutions (after conditioning) was initially rather surprising to us. However, a literature search revealed that related complexes had been identified in certain hydrogenation reactions and found to be less active but more enantioselective in comparison to the RhL_2^+ systems.[18] Under our optimized conditions (compare Table 3, conditions B) an excess of the chiral ligand was employed ($Rh/L_2^* = 1:1.6$) to suppress any achiral background catalysis. After we had realized that two ligand (L_2^*) molecules are actually required per rhodium atom to generate the selective catalyst, we performed a control experiment employing an increased amount of the ligand **4h** {$[Rh(NBD)Cl]_2$:$AgSbF_6$:**4h** = 0.5:1:2}. In this case the product (**2b**) was indeed obtained with a slightly improved enantioselectivity (93% *ee*).

Throughout the study, the enantiomeric analyses of the products of type **2** were performed by means of chiral GC (**2a**), chiral HPLC (**2b**) or chiral NMR shift reagents (**2c**) using racemic reference samples. For this purpose, the heteroatom-tethered substrates **1a** and **1b** were cyclized using dppe as an achiral ligand to give *rac*-**2a**[19] and *rac*-**2b**, respectively. To obtain a sample of *rac*-**2c**, however, the ligand *rac*-**4h** (derived from *rac*-TADDOL) was employed. The absolute configuration of **2a** was assigned according to Gilbertson.[11] In the case of **2b** the relative and absolute configuration was unambiguously confirmed by means of X-ray crystal structure analysis (Figure 4).[20] We therefore assume that all products (**2a–c**) prepared using ligand **4h** belong to the same stereochemical series.

In conclusion, we have developed a reliable microwave protocol for the enantioselective Rh-catalyzed intramolecular [4+2] cycloaddition of tethered dieneenes. Employing the chiral ligand **4h** (identified by screening a small set of modular phophine-phosphite ligands) the bicyclic products (**2a–c**) were obtained as single diastereomers with good to excellent enantiomeric purities (up to 93% *ee*). As an important detail, a $[Rh(L_2^*)_2]^+$ species (generated by microwave-assisted catalyst conditioning) was identified and suggested to act as a more selective (pre-)catalyst.

Experimental Section

Pre-catalyst Preparation and Conditioning

In a Schlenk flask under an atmosphere of argon $[Rh(NBD)Cl]_2$ (5.5 mg, 0.012 mmol) was dissolved in anhydrous CH_2Cl_2 (0.5 mL) and $AgSbF_6$ (8.3 mg, 0.024 mmol) was added in one portion. After stirring for 10 min, the red solution was carefully needled off the precipitated AgCl (which was washed twice with 1 mL of anhydrous CH_2Cl_2) and the Rh-containing CH_2Cl_2 solutions were combined with a solution of the ligand (0.038 mmol) in anhydrous CH_2Cl_2 (0.5 mL). The resulting orange solution was allowed to stir for 45 min at room temperature before the solvent was removed under vacuum. The obtained pre-catalyst (0.024 mmol) was dissolved in anhydrous EtOAc (4.0 mL) and the solution was transferred into a septum-sealed microwave vial under argon. The solution was then heated in a CEM microwave reactor at 300 W until a pressure of 5.0 bar was reached. The stirred solution was then kept for 45 min at 120 °C with a maximum power of 300 W and 5.0 bar pressure.

General Cyclization Procedure (Table 3, Conditions B)

Under an atmosphere of argon, a Schlenk flask was filled with the conditioned pre-catalyst (0.024 mmol) in EtOAc (4.0 mL) prepared as described above. To activate the catalyst, H_2 was bubbled through the solution for 2 min, followed by argon for 2 min. Then, a solution of the substrate (**1a–c**) (0.40 mmol) in EtOAc (2.0 mL) was added and the mixture was degassed (3 freeze-pump-thaw cycles) before it was stirred at 50 °C in the microwave for 20 h. The reaction progress could be monitored by TLC or GC.

Acknowledgements

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