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Solvent effects on the asymmetric Pauson–Khand-type reaction by rhodium

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ABSTRACT

The reaction efficiency and enantioselectivity of an asymmetric Pauson–Khand-type reaction catalyzed by cationic rhodium are heavily dependent on the solvent. Coordinating solvents, such as THF, provide a faster reaction and better stereoselectivity than non-coordinating solvents, such as toluene. These beneficial effects can be attributed to a significant increase in the more reactive catalytic species of [Rh(bisphosphane ligand)*(solvent)$_n$]$^+$ (**3**) than of [Rh(bisphosphine ligand)*CO(solvent)]$^+$(**4**) and [Rh(bisphosphine ligand)*(CO)$_2$]$^+$ (**5**) in a coordinating solvent.

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Since the first report of the rhodium-catalyzed enantioselective Pauson–Khand type reaction (hereafter called PKR) under a CO atmosphere in the presence of an atropisomeric ligand BINAP (Scheme 1),[1] systematic efforts have been made by us and others to perfect this protocol in terms of the chemical yield and enantioselectivity.[2]

Among the various factors, the effect of the CO concentration, tethers, reaction temperature and electronic and steric characteristics of the ligands on the reaction efficiency and enantioselectivity have been examined extensively.[3] From these studies, the protocol of the reaction conditions for selected substrates has been improved substantially.[4]

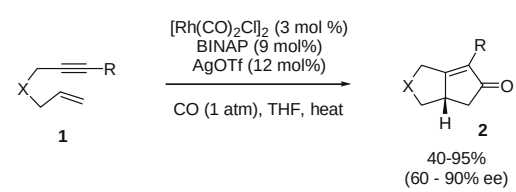
At the very inception of this study, various solvents were screened to optimize the reaction rate and enantioselectivity. THF was found to exhibit significantly better results than the other solvents. Therefore, the reaction protocol was optimized mainly in THF. However, this study was interested in the role of the solvent because it is important to understand the effects of many factors involved in the reaction.

The solvent was suggested to have two roles.

Firstly, it was assumed that the solvent may change the proportions of various potential catalytic species, which are in equilibrium. Carbon monoxide is a critical component of the Pauson–Khand reaction. However, it is well known that a higher concentration of CO (even under atmospheric pressure) decelerates the reaction considerably. This was explained by assuming that CO-saturated catalytic species [Rh(bisphosphane ligand)*(CO)$_2$]$^+$ (**5**), which is inefficient for a presumed rate-determining step of enyne (**1**) complexation under a given set of conditions, was dominant in an equilibrium with other species, such as [Rh(bisphosphane ligand)*(solvent)$_n$]$^+$ (**3**) and [Rh(bisphosphine ligand)*CO(solvent)]$^+$ (**4**) (possibility 1 in Scheme 2).[5] This undesirable shift in equilibrium was reinforced in a non-coordinating solvent such as toluene. On the other hand, in a coordinating solvent, such as THF, the solvent would compete with CO to bind to the metal center and cause a substantial increase in the concentration of the more reactive species **3** and/or **4**. Therefore, under the right conditions, the reaction in a coordinating solvent proceeded even at ambient temperature while the reaction in toluene required a higher reaction temperature and longer reaction time.[4]

Secondly, intervention by a coordinating solvent in the metallacyclo-pentene (**9**) formation step, which appears to be responsible for the stereoselectivity, might equally account for the faster reaction rate and better stereoselectivity in THF (possibility 2 in Scheme 2). A few consequences would be expected if this intervention of THF in the transition state is the case.

An improvement in stereoselectivity can be achieved by an exaggeration of the difference in free activation energy between the two competing diastereomers **10**. Such exaggeration would be achieved by introducing sterically hindered THFs (case 2 in



Scheme 1. An asymmetric Pauson–Khand type reaction by rhodium.

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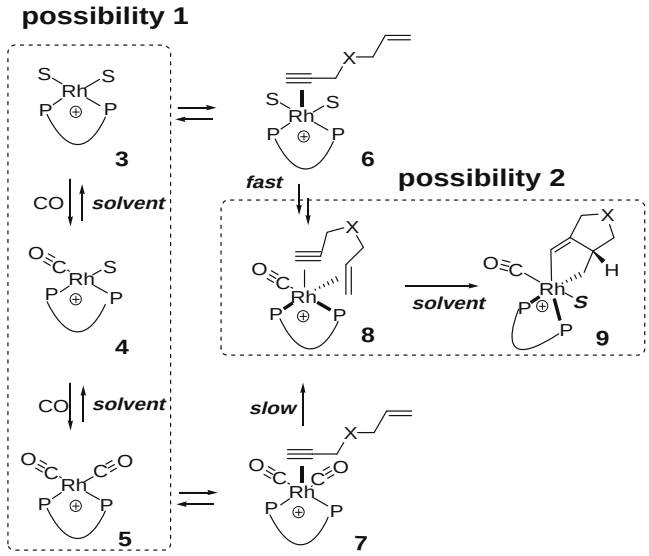


Scheme 2. Two possible working hypotheses for the role of the solvent.

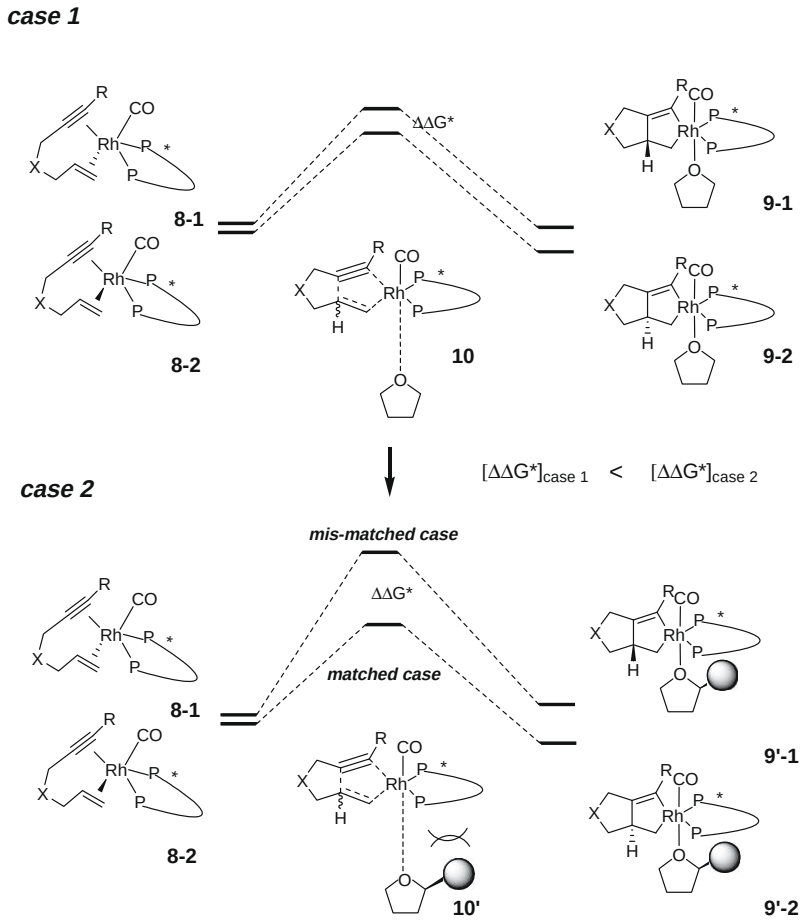
Scheme 3). In addition, when chiral THFs are used, it might be possible to discriminate matched cases or mismatched cases between chiral solvents and chiral ligands. For example, if a combination of one enantiomer of a ligand with a given chiral THF afforded greater steric congestion in **10′** than the other enantiomer, the energy difference between the two competing diastereomers in **10′** would be amplified, which should improve the enantioselectivity.

To test these hypotheses in one experiment, PKR was performed in the chiral THF derivatives, **11** and **12**.

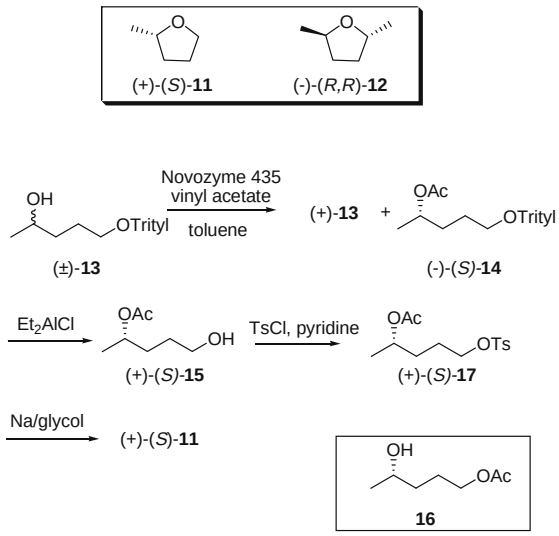
The requisite chiral THFs were prepared using the literature procedure. (−)-(*R*,*R*)-2,5-Dimethyltetrahydofuran (**12**) was prepared as previously reported.[6] (+)-(*S*)-2-Methyltetrahydrofuran (**11**) was prepared using a slight modification of a known method, as shown in Scheme 4. Deprotection of the trityl protecting group of (−)-(*R*)-**14** (99% ee)[7] with the suppression of trans-acetylation to compound **16** was realized using diethylaluminum chloride (93%, **15**/**16** = >15:1). The resulting alcohol (+)-(*R*)-**15** was tosylated to give (+)-(*R*)-**17**. Treatment of compound **17** with sodium in ethylene glycol and subsequent continuous distillation provided (+)-(*S*)-**11** in 84% yield ($[\alpha]_D^{25}$ +19.5, *c* = 0.005 g/mL, CH_2Cl_2).[8]

With chiral THFs **11** and **12** in hand, the PK reaction was first carried out with a benchmarking substrate **1-a** under a thermal reaction protocol. Under an atmospheric pressure of CO at 80 °C, the reaction in THF with (*R*)-BINAP was complete within one hour and afforded the corresponding product **2-a** in 77% yield and 85% ee. On the other hand, the reaction in toluene proceeded only half-way at 80 °C, even after 12 h. Higher reaction temperature (120 °C) and prolonged reaction time (6 h) were required for the reaction in toluene to produce **2-a** in 90% yield, but the enantioselectivity was significantly lower (66% ee, entry 3 in Table 1), as previously reported.

The reaction in the substituted THFs was then attempted. The reactions in either (+)-**11** or (−)-**12** were slower than those in

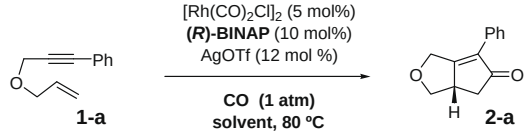


Scheme 3. Intervention of the solvent in the transition intermediate and an exaggeration of the activation energy difference by the introduction of substituent on THF.



Scheme 4. Chiral THF derivatives and the preparation of (+)-(*S*)-2-methyltetrahydrofuran.

Table 1
PKR in various solvents under 1 atm of CO



Entry	Solvent	*t* (h)	Yield (conversion) (%)/ee (%) (abs. configuration)
1	THF	1	72/85 (*R*)
2	Toluene at 80 °C	12	30 (35)/74 (*R*)
3	Toluene at 120 °C	6	90 (100)/66 (*R*)
4	(+)-**11** w/(*R*)-BINAP	3	**80**/**87** (*R*)
5	(+)-**11** w/(*S*)-BINAP	3	**75**/**87** (*S*)
6	(−)-**12** w/(*R*)-BINAP	6	10 (15)/79 (*R*)
7	(−)-**12** w/(*S*)-BINAP	6	5 (10)/64 (*S*)

THF. In particular, the reaction in (−)-**12** was as slow as that in toluene (entries 2 and 6).

In (+)-**11**, although the reaction was substantially slower than that in THF (entries 1 and 4), it proceeded to a reasonable pace (1 h in THF vs 3 h in (+)-**11**). With (*R*)-BINAP, (*R*)-**2-a** was obtained in comparable chemical yield (77% in THF vs 80% in (+)-**11**) and enantioselectivity (85% ee in THF vs 87% ee in (+)-**11**) with the same absolute configuration, *R*, irrespective of the chirality of the solvent. Obviously, the extra substituent on THF slowed down the reaction rate substantially, but did not affect the stereoselectivity.

This suggests that the solvent might not participate in the transient intermediates, **10** or **10′**, as proposed in case 1 in Scheme 3. This was confirmed by the following experiment. When (*S*)-BINAP was used in (+)-**11** under otherwise identical conditions, (*S*)-**2-a** was obtained as expected. However, the enantioselectivity for **2-a** remained unchanged (87% ee for (*R*)-**2-a** with (*R*)-BINAP vs 87% ee for (*S*)-**2-a** with (*S*)-BINAP). It was expected that if possibility 2 was working, there might be significant differences in stereoselectivity between the cases using (*R*)-BINAP and (*S*)-BINAP. This is because the severe steric hindrance on **10′** caused by the substituents on THF would make the energy difference between the two competing diastereomers more significant in one chiral solvent and chiral ligand combination than in another. The same degree of stereoselectivity with only an inversion of the absolute configuration suggests that the solvent played no role in the reaction pathway from **8** to **9**, which was in contrast to expectations (entries 4 and 5).

Similar observations were made from the reaction at ambient temperature. It is well documented that the reaction under a reduced pressure of CO would proceed even at ambient temperature. However, there were trade-offs to be balanced carefully when the reaction was carried out under this condition. While the equilibrium between catalytic species favored the most reactive species **3** under a reduced CO pressure to make the reaction proceed even at ambient temperature, the competitive formation of CO-missing cyclization products was inevitable due to the insufficient CO concentration.[4,5] As described previously, the reaction was well optimized to yield a >90% chemical yield of **2-a** together with >90% ee by maximizing the beneficial effects of *xylyl*BINAP.[4] Nonetheless, this study adopted the reaction protocol with the less efficient BINAP for a direct comparison with the results under thermal conditions and to make subsequent improvements.

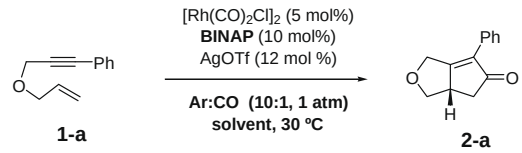
Like the thermal reaction, the reaction in THF under a reduced CO pressure (0.1 atm) was complete at 23 °C in 1 h to give the corresponding product **2-a** in 80% yield with 90% ee. However, the reaction in toluene was much less effective, and required a substantially higher reaction temperature (40 °C) for proper initiation as well as a prolonged reaction time (12 h) for the complete consumption of **1-a** (entry 2 in Table 2). With this mildly forcing condition, the reaction yielded the corresponding PKR product **2-a** in only 60% even after the complete consumption of **1-a** due to the formation of a substantial amount of CO-missing cyclization products.

The PK reaction of **1-a** in (+)-**11** with (*R*)-BINAP at ambient temperatures provided a somewhat lower chemical yield of (*R*)-**2-a** (62%) than that in the parent THF (80%) and required a slightly longer reaction time for completion, but the stereoselectivity under this condition was comparable to that in THF (entries 1 and 3 in Table 2). On the other hand, the reaction in (−)-**12** did not occur at ambient temperature.

These observations can be explained by assuming possibility 1 in Scheme 3. In an eligible competitor with CO to bind the metallic center, such as THF, there was a sufficient concentration of catalyst **3**; hence the reaction initiated smoothly at 23 °C. However, in toluene, which could not rival CO in binding to metals, a rather reluctant catalyst **5** became the dominant species. Therefore, the reaction was not initiated unless sufficient energy was supplied.

(+)-2-Methyltetrahydrofuran, (+)-**11**, positioned itself between THF and toluene in terms of their coordinating power to the metal. This explains why the reaction proceeded in (+)-**11** at ambient temperature, albeit noticeably slower than in THF. In addition,

Table 2
PKR at ambient temperature in various solvents under 0.1 atm of CO



Entry	Solvent	*t* (h)	Yield (conversion) (%)/ee (%) (abs. configuration)
1	THF	1	80 (100)/90 (*R*)
2	Toluene at 40 °C	12	60 (90)/91 (*R*)
4	(+)-**11** w/(*R*)-BINAP	3	**62** (**80**)/**93** (*R*)
5	(+)-**11** w/(*S*)-BINAP	3	**60** (**70**)/**91** (*S*)
6	(−)-**12** w/(*R*)-BINAP	6	No initiation at 30 °C
7	(−)-**12** w/(*S*)-BINAP	6	No initiation at 30 °C

the sluggish reaction in (−)-**12** like that in toluene was understandable.

Significantly higher stereoselectivity, particularly in the reaction at ambient temperature, and often at the cost of the yield of the PKR product, was attributed mainly to the lower reaction temperature. However, the possible parallel kinetic resolution of two diastereomers **8** in competition could not be eliminated because of the relatively lower chemical yield of **2-a**: one diastereomer led to a PKR product, and another led to CO-missing cyclization side products.

The replacement of a ligand from (*R*)-BINAP to (*S*)-BINAP in (+)-**11** at ambient temperature did not cause a noticeable change in stereoselectivity except for an inversion of the absolute configuration, as previously noted under thermal conditions. This observation excludes possibility 2.

Based on these observations, it can be concluded that the reaction rate is governed solely by the proportion of the catalytic species **3**, **4,** and **5** during the catalytic cycle of the reaction, which is dependent on the coordinating power of the solvents. As the steric hindrance on THF increases, the ability to coordinate to the metal center decreases significantly. Therefore, while (+)-**11** behaved more like THF, (−)-**12** behaved more like toluene. With a significant amount of catalyst **3**, the reaction can proceed at lower temperatures, and the enantioselectivity can also be improved. Interestingly, even subtle changes in the structure of the solvent, such as the introduction of methyl groups on THF, had a significant effect on the reactivity and stereoselectivity.

Direct physical evidence, for example, measurement of the chemical shift of ^{103}Rh to determine the ratio of the proposed catalytic species under CO, was desirable. However, the intrinsic limitation in the measurement, such as the low sensitivity of ^{103}Rh in the NMR study, made obtaining significant data difficult.

In conclusion, the PK reaction was accelerated substantially using a coordinating solvent, and better enantioselectivity was obtained. This was attributed to the coordinating solvents forcing the equilibrium between catalytic species to favor most reactive species **3**. As a result, the reaction was effected even at lower reaction temperatures, and the enantioselectivity was improved significantly. Moreover, under a reduced CO pressure, the portion of catalyst **3** becomes more substantial, and the reaction proceeded even at ambient temperatures with higher enantioselectivity.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.060.

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