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# 4-Methyltetrahydropyran: a Versatile Alternative Solvent for the Preparation of Chiral BINOL Catalysts and the Asymmetric Alkylation of Aldehydes

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**Abstract:** We herein report that the highly hydrophobic ether 4-MeTHP constitutes a promising resource for the development of sustainable synthetic methodologies grounded on the use of organometallic reagents. The beneficial effects of 4-MeTHP as reaction media are illustrated in the organolithium-promoted anionic *ortho*-Fries rearrangement of 1,1'-bi-2-naphthol (BINOL)-based carbamates under bench-type conditions. The use of 4-MeTHP induces a remarkable and unexpected stability of the organolithiums species, enabling the efficient preparation of chiral (bis)carboxamide catalysts. Furthermore, superior performances of 4-MeTHP than other environmentally responsible solvents are observed using the synthesized BINOL catalysts in the asymmetric addition of organozinc reagents to aldehydes. Spectroscopic studies in solution suggest that 4-MeTHP plays a key role in these reactions by inducing the preferential formation of a reactive monomeric dinuclear complex. This methodology allows for the asymmetric assembly of enantioenriched secondary alcohols in good yields and high stereoselectivity, working at 0 °C and under air.

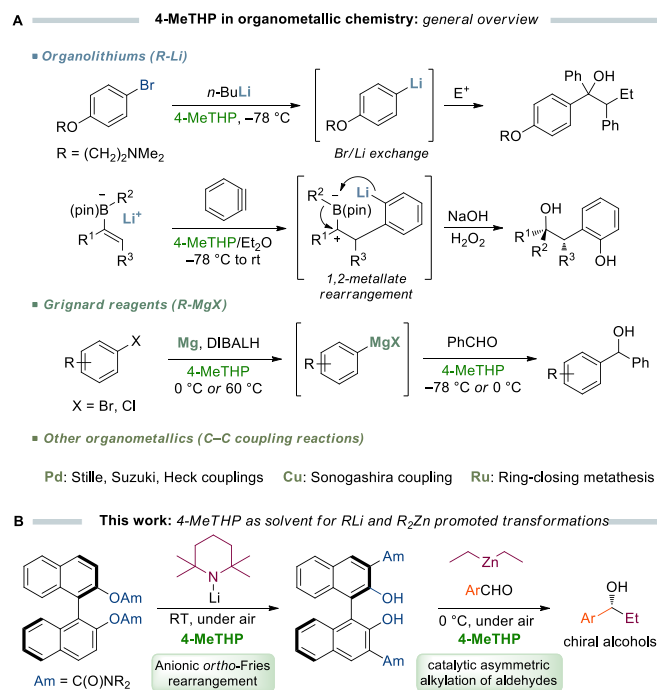
## Introduction

Since the formulation of the twelve principles of Green Chemistry,<sup>[1]</sup> many efforts have been devoted to the development of more sustainable and eco-friendly synthetic strategies to assemble structurally complex molecular scaffolds.<sup>[2]</sup> The use of reagents in catalytic quantities,<sup>[3]</sup> the preferable choice of highly atom-economy transformations, such as rearrangement reactions,<sup>[4]</sup> and the possibility to perform these processes under bench-type conditions (room temperature, under air) using alternative and more sustainable reaction media, such as water,<sup>[5]</sup> Deep Eutectic Solvents (DES),<sup>[6]</sup> 2-methyltetrahydrofuran (2-MeTHF)<sup>[7]</sup> or cyclopentyl methyl ether (CPME)<sup>[8]</sup> is of great value in terms of efficiency and environmental sustainability.<sup>[9]</sup> In this context, 4-methyltetrahydropyran (4-MeTHP) has recently

emerged as a new convenient alternative solvent owing to its peculiar physico-chemical properties, such as high hydrophobicity and high boiling point, remarkable stability under acidic or alkaline conditions, and similar solvency to THF and 2-MeTHF.<sup>[10]</sup> Despite its promising applications in a series of synthetic transformations, including radical reactions and transition-metal catalyzed processes,<sup>[10-11]</sup> the use of 4-MeTHP in polar organometallic chemistry is still rather unexplored (Figure 1, A).<sup>[10, 12]</sup>

Among the multitude of rearrangement reactions, the anionic *ortho*-Fries rearrangement (AoF) is a powerful synthetic method to produce relevant functionalized (poly)aromatic compounds. In particular, the AoF offers the possibility to introduce significant structural variations useful for a popular class of naphthalene-based chiral ligands, the 1,1'-bi(2-naphthol) derivatives (BINOLs), especially at their C-3 and C-3' positions.<sup>[13]</sup> This enables the straightforward preparation of chiral ligands or catalysts with finely tuned stereochemical and reactivity profiles.<sup>[14]</sup> Of these, 3,3'-(bis)carboxamide BINOL derivatives are of particular synthetic interest owing to their ability to form Lewis acid-Lewis base type-complexes with dialkylzinc, making them powerful chiral catalysts for the asymmetric addition of organozinc to aldehydes.<sup>[15]</sup> Previously reported synthetic methods for their preparation relies on a three-step reaction sequence starting from BINOL (*O*-protection, *ortho*-metalation and carboxylation followed by amidation)<sup>[15a]</sup> or to an AoF migration sequence under strictly controlled Schlenk conditions (e.g. use of dry THF at -80 °C, need of highly pyrophoric *s*-BuLi in combination with a stoichiometric amount of toxic TMEDA, long reaction time).<sup>[16]</sup>

Despite the recent significant advances in the aerobic preparation of chiral BINOL catalysts,<sup>[17]</sup> some challenges still need to be overcome, such as the use of toxic reagents/solvents. In the course of our studies on the reactivity of alkali-metal organometallic reagents under bench-type aerobic conditions,<sup>[18]</sup> we recently demonstrated the possibility to perform the anionic



**Figure 1.** a) State-of-the-art of the employment of 4-methyltetrahydropyran (4-MeTHP) as reaction media in synthetic transformations promoted by organometallic reagents,<sup>[10–12]</sup> and b) aim of this work.

*ortho*-Fries rearrangement of *O*-aryl carbamates with high chemo- and regioselectivity under more eco-friendly and thermodynamic conditions, using CPME as sustainable reaction media, working at room temperature, and under air/moisture.<sup>[19]</sup>

As an extension of our methodology, we now exploit the usefulness of the highly hydrophobic ethereal solvent 4-MeTHP for the preparation of a series of 3,3'-(bis)carboxamide BINOL derivatives by means of a double AoF rearrangement promoted by LiTMP under bench-type aerobic conditions (Figure 1, B). The herein described methodology is amenable to scale-up and recyclability protocols, allowing the easy reuse of both the solvent 4-MeTHP and the free amine 2,2,6,6-tetramethylpiperidine (TMP). To further highlight the potential of 4-MeTHP as reaction medium in organometallic promoted transformations, the synthesized BINOL derivatives have been employed as chiral catalysts in the enantioselective alkylation of aldehydes, using diethylzinc as model alkylating agent (Figure 1, B).<sup>[20]</sup> The beneficial effect of 4-MeTHP on the catalytic activity of these chiral ligands is herein compared with other environmentally responsible solvents (2-MeTHF, CPME) and the classical VOCs commonly employed in this transformation. Spectroscopic insights into the constitution of the active BINOL-Zn(II) complexes in these eco-friendly reaction media, using <sup>1</sup>H DOSY NMR solution-state techniques, are also provided.

## Results and Discussion

We initially focused our efforts on the preparation of the BINOL 3,3'-(bis)carboxamides by the anionic *ortho*-Fries rearrangement of carbamates under bench-type reaction

conditions. We started our preliminary investigations using the sterically hindered bis(*N,N*-diisopropyl) *O*-aryl carbamate **1a**, prepared by carbamoylation of racemic BINOL, as a model substrate. On the basis of our previous results,<sup>[19]</sup> the lithiation/*ortho*-Fries rearrangement sequence was initially investigated using the sterically hindered LiTMP as metalating agent and CPME as reaction media. Hence, a solution of compound **1a** (0.2 mmol, 0.2 M) in CPME was reacted with a freshly prepared 1 M solution of LiTMP in 2-MeTHF, at room temperature and under air (Table 1, entry 1), in the absence of an external electrophile. Aqueous quench of the reaction mixture after 5 min released the desired BINOL 3,3'-(bis)carboxamide **2a** arising from two anionic 1,3-*O*-C carbo-Fries rearrangements, albeit in low yield (22%). Under these conditions, a considerable amount of mono-migrated byproduct (42%) was detected in the crude reaction mixture (see Supporting Information). Running the metalation/migration sequence for 2 h had a little effect on the reaction yield (entry 2), whereas increasing the amount of the metalating agent (6 equiv, 3 equiv for each *ortho*-metalation site) significantly improved the yield of **2a** to 50% within only 5 min (entry 3). Full conversion of **1a** into the desired 3,3'-(bis)carboxamide **2a** was then achieved under these metalation conditions in good yield (72%) in 1 h (entry 4).

**Table 1.** Anionic *ortho*-Fries rearrangement of carbamates **1** under different reaction conditions.<sup>[a]</sup>

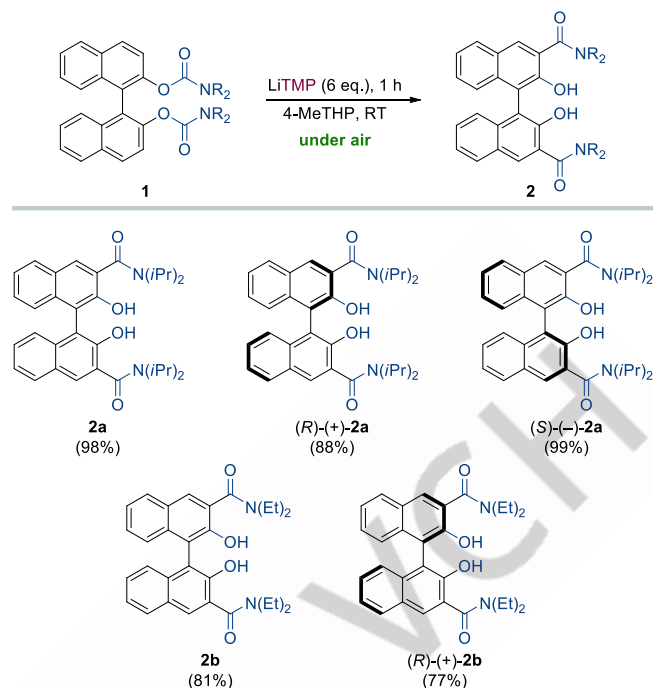
R = *i*Pr (**1a**), Et (**1b**)

Entry	Substrate	R'Li (eq.)	Solvent	Time (min)	<b>2</b> [%] <sup>[b]</sup>
1	<b>1a</b>	LiTMP (4)	CPME	5	<b>2a</b> (22)
2	<b>1a</b>	LiTMP (4)	CPME	120	<b>2a</b> (33)
3	<b>1a</b>	LiTMP (6)	CPME	5	<b>2a</b> (50)
4	<b>1a</b>	LiTMP (6)	CPME	60	<b>2a</b> (72)
5	<b>1b</b>	LiTMP (6)	CPME	60	<b>2b</b> (68)
6	<b>1a</b>	LDA (6)	CPME	60	<b>2a</b> (26)
7	<b>1a</b>	LiTMP (6)	2-MeTHF	60	<b>2a</b> (86)
8	<b>1a</b>	LiTMP (6)	4-MeTHP	60	<b>2a</b> (92) <sup>[c]</sup>

[a] Reaction conditions: **1** (0.2 mmol), RLi, solvent (1 mL; CPME = cyclopentyl methyl ether, 2-MeTHF = 2-methyltetrahydrofuran, 4-MeTHP = 4-methyltetrahydropyran), room temperature, under air. [b] Determined by quantitative <sup>1</sup>H NMR using CH<sub>3</sub>NO<sub>2</sub> as the internal standard. [c] Isolated yield: 80%.

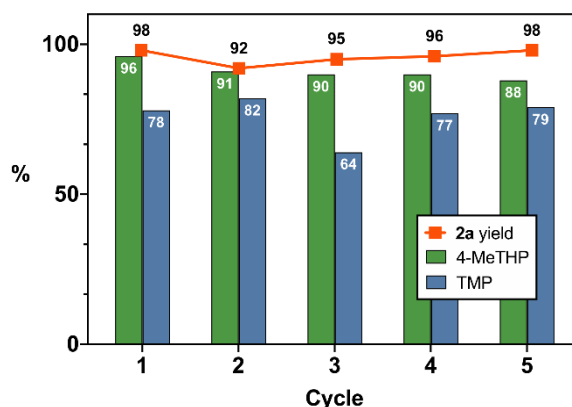
Under the same conditions, metalation of the less hindered bis(*N,N*-diethyl) carbamate **1b** was less effective, and the corresponding bis-functionalized BINOL derivative **2b** was produced in a moderate 68% yield (entry 5). Running the *ortho*-lithiation and AoF of **1a** with the less basic LDA promoted the formation of the Fries product **2a** in a low 26% yield (entry 6), whereas the use of alkylolithiums was ineffective due to the predominant formation of  $S_NAc$  (*n*-BuLi) or dearomatization (*t*-BuLi)<sup>[21]</sup> byproducts (see Table S1 in Supporting Information). In order to ameliorate the reaction yield, we next investigated the use of more polar and coordinating solvents, which might increase the stability and the reactivity of the lithiated species in solution and prevent the protonolysis process.<sup>[22]</sup> Hence, using the bio-based solvent 2-MeTHF the anionic Fries rearrangement proceeds smoothly in 1 h, releasing **2a** in 86% yield (entry 7). Pleasingly, the best results have been obtained when the emerging hydrophobic cyclic ether 4-MeTHP was employed as reaction media, and the desired double rearranged product **2a** was obtained in 92% yield working at room temperature, and under air (entry 8). Noteworthy, the stability of the metalating agent and/or of the generated *ortho*-aryl (di)anion(s) of **1** is remarkable under these conditions. The complete conversion of **1**, together with the high reaction yield observed in 4-MeTHP,<sup>[23]</sup> suggested that almost no protonolysis of neither LiTMP nor lithiated **1** occurred, even working under air for such unusual long reaction time (1 h). Whereas the superior performances of 4-MeTHP than CPME in the formation and reactivity of Grignard reagents have been recently illustrated,<sup>[10]</sup> its role in the chemistry of organolithium compounds remains hitherto almost unexplored. To the best of our knowledge, this is the first experimental evidence of the beneficial effect of this emerging eco-friendly solvent on the stability of lithium amides, which might be ascribed to putative coordinative and/or to hydrophobicity effects. However, further studies are needed to fully understand this experimental evidence.

With the aim to assess the robustness of this new synthetic protocol, we investigated the scalability of the process. Hence, a gram scale synthesis of **2a** was carried out starting from 1.1 g of **1a** and 10 mL of 4-MeTHP under the optimized reaction conditions (Scheme 1). The reaction proceeded smoothly in 1 h at RT under air, releasing the racemic BINOL derivative **2a** in 98% yield (1.06 g) after purification. Comparable results were obtained using the racemic (bis)carbamate **1b** as substrate (81%), and the procedure was efficiently exploited for the gram-scale preparation of chiral BINOL 3,3'-(bis)carboxamides (*R*)-(+)-**2a** (88%), (*S*)-(-)-**2a** (99%), and (*R*)-(+)-**2b** (77%) with excellent yields and chemoselectivity. Furthermore, we also investigated the recyclability/reusability of both the solvent (4-MeTHP) and the free amine 2,2,6,6-tetramethylpiperidine (TMP). To this end, a 0.5 M solution of LiTMP in 4-MeTHP was freshly prepared<sup>[24]</sup> and reacted with a solution of **1a** (1.0 mmol, 540 mg) in 5 mL of 4-MeTHP under the optimized reaction conditions. A facile acid-base workup procedure using 4-MeTHP as extraction solvent allowed the recovery of TMP (78%, Figure 2), and a fractional distillation of the combined organic layers at atmospheric pressure allowed the easy recovery of the 4-MeTHP fraction (96%, Figure 2) without contamination of *n*-hexanes. The racemic



**Scheme 1.** Gram-scale synthesis of BINOL 3,3'-(bis)carboxamides **2** by AoF rearrangement of **1** under aerobic conditions. Reaction conditions: **1** (2 mmol), LiTMP (12 mmol, 1 M in 2-MeTHF), 4-MeTHP (10 mL), 1 h, RT, under air. Reported yields refer to isolated products.

BINOL derivative **2a** was recovered in 98% yield (529 mg) after purification. Remarkably, both the recovered 4-MeTHP and TMP were reused in subsequent recycling steps to increase the sustainability of the whole process. As shown in Figure 2, nearly quantitative yields of **2a** were obtained for each recycling step, allowing the preparation of 2.6 g of desired product, with an overall yield of 96% over 5 cycles.

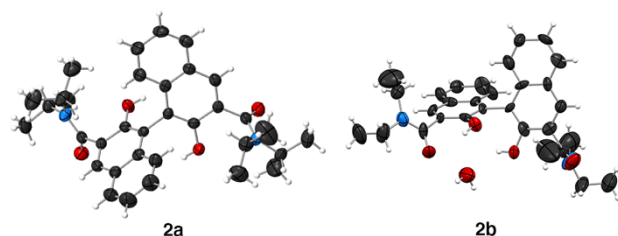


**Figure 2.** Recyclability of 4-MeTHP and 2,2,6,6-tetramethylpiperidine (TMP) over 5 recycling steps. Yields of **2a** refer to isolated products.

Prior to investigations into the activity of BINOL 3,3'-(bis)carboxamides as chiral ligands, efforts were made to obtain solid-state structures of the functionalized BINOL derivatives **2**. Racemic (bis)carboxamide **2a** was crystallized by the slow, room temperature evaporation of a diethyl ether solution, into the

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monoclinic  $P2_1/c$  space group. The X-ray crystal structure of **2a** is shown in Figure 3, and compared with the racemic bis-(*N,N*-diethyl)carboxamide **2b**, which crystallized as hydrate from a methanol solution into the monoclinic space group  $P2_1/c$ .<sup>[25]</sup> Analyses of the crystal structures of **2a** and **2b** revealed the true racemic nature of the compounds, with the two enantiomers positioned in specific sites of the crystal lattice. The crystal structure of racemic **2a** confirmed the expected characteristic quasi-perpendicular arrangement of the naphthyl rings, where the torsion angle at the positions bearing the oxygen atoms is  $\pm 106.6(3)^\circ$ . The crystal structure of **2b** shows a similar quasi-perpendicular disposition of the two aromatic rings, however with a smaller torsion angle of  $\pm 74.8(11)^\circ$ . Conformationally, the two compounds show also different torsion angles between the naphthalene scaffolds and the amide group. This is due to the extended pattern of hydrogen bonds between similar molecules for **2a** or with water in **2b** (see Table S16 and Figure S27 in Supporting Information).



**Figure 3.** Single molecule crystal structures of racemic BINOLs **2a** and **2b**. Thermal ellipsoids drawn at the 50% probability level. (*R*)-enantiomer is shown for **2a** and (*S*)-enantiomer is shown for **2b**.

We next investigated the behaviour of chiral carboxamides **2** in the catalytic enantioselective addition of dialkylzinc to aldehydes,<sup>[20, 26]</sup> with the aim to design an eco-efficient process focused on the use of unconventional, environmentally friendly ethereal solvents under aerobic bench-type conditions. Considering the aforementioned remarkable performances of 4-MeTHP with organolithium reagents, this solvent potentially represents a valuable alternative to the common VOCs employed in this organozinc-mediated transformation as reaction media, such as THF,<sup>[15a]</sup> toluene,<sup>[27]</sup> and dichloromethane.<sup>[28]</sup>

We started our studies using chiral BINOL 3,3'-(bis)carboxamide (*R*)-(+)-**2a** to promote the catalytic addition of diethylzinc to 3-phenyl-2-propynal **3a** at room temperature. Aldehyde **3a** was treated with  $\text{Et}_2\text{Zn}$  (2 equiv, 1 M solution in hexanes) in the presence of a catalytic amount of (*R*)-(+)-**2a** (10 mol%), using 4-MeTHP as solvent, at room temperature and under air. After 12 h, aqueous quench of the reaction mixture afforded the desired secondary alcohol (*R*)-**4a** in 64% yield and 62% ee (Table 2, entry 1). The use of CPME was less effective, releasing product (*R*)-**4a** in a moderate 32% yield and 70% enantiomeric excess (entry 2), and comparable results were obtained in 2-MeTHF (entry 3). When the temperature was lowered to 0 °C, the enantioselectivity of the alkylation improved using both 4-MeTHP (entry 4) and 2-MeTHF (entry 5) as reaction media, with a superior yield of (*R*)-**4a** in 4-MeTHP compared to 2-MeTHF (55% vs 37%, respectively).

**Table 2.** Enantioselective alkylation of **3a** with diethylzinc and (*R*)-(+)-**2a** under different reaction conditions.<sup>[a]</sup>

Entry	Solvent	Time (h)	T (°C)	<b>4a</b> yield [%] <sup>[b]</sup>	e.e [%] <sup>[c]</sup>
1	4-MeTHP	12	25	( <i>R</i> )- <b>4a</b> (64)	62
2	CPME	12	25	( <i>R</i> )- <b>4a</b> (32)	70
3	2-MeTHF	12	25	( <i>R</i> )- <b>4a</b> (32)	68
4	4-MeTHP	12	0	( <i>R</i> )- <b>4a</b> (55)	72
5	2-MeTHF	12	0	( <i>R</i> )- <b>4a</b> (37)	78
6	4-MeTHP	12	-20	( <i>R</i> )- <b>4a</b> (20)	79
7	4-MeTHP	24	0	( <i>R</i> )- <b>4a</b> (87)	78
8 <sup>[d]</sup>	4-MeTHP	24	0	( <i>S</i> )- <b>4a</b> (90)	78
9 <sup>[e]</sup>	4-MeTHP	24	0	( <i>R</i> )- <b>4a</b> (84)	50
10	DCM	24	0	( <i>R</i> )- <b>4a</b> (24)	46
11	Toluene	24	0	— <sup>[f]</sup>	—
12	Et <sub>2</sub> O	24	0	( <i>R</i> )- <b>4a</b> (92)	57
13	THF	24	0	( <i>R</i> )- <b>4a</b> (59)	80

[a] Reaction conditions: **3a** (0.2 mmol),  $\text{Et}_2\text{Zn}$  (0.4 mmol, 1.0 M in hexanes), solvent (3.3 mL), under air. [b] Determined by quantitative  $^1\text{H}$  NMR using  $\text{CH}_3\text{NO}_2$  or *n*-heptane as the internal standard. [c] Compared to racemic samples generated using  $\text{EtMgBr}$ . The absolute configuration was assessed by comparison of the optical rotation of **4a** with data reported in the literature and was determined as (*R*). The ee values (%) were determined by chiral HPLC analyses (see Supporting Information). [d] (*S*)-(–)-**2a** was used as ligand. [e] (*R*)-(+)-**2b** was used as ligand. [f] Aldehyde **3a** was recovered unreacted.

Performing the alkylation at -20 °C had a detrimental effect on the reaction yield (entry 6), whilst compound (*R*)-**4a** was obtained with a good enantioselectivity of 79%. Pleasingly, running the reaction in 4-MeTHP at 0 °C for a longer time of 24 h released the product (*R*)-**4a** in 87% yield and a satisfactory 78% ee (entry 7). As expected, the use of (*S*)-(–)-**2a** as catalyst (entry 8) delivered the enantiomer (*S*)-**4a** with the same enantioselectivity and in comparable yield (90%). When the less sterically hindered (*R*)-(+)-**2b** was used as chiral ligand under these conditions, the enantioenriched alcohol (*R*)-**4a** was obtained in comparable yield (84%), however with a consistent loss in enantioselectivity (entry 9). Classical VOCs (entries 10-13) were less effective than 4-MeTHP to promote the asymmetric ethylation of **3a** under these conditions. Unsatisfactory results in terms of conversion and enantioselectivity were obtained using non-ethereal solvents as DCM (entry 10) or toluene (entry 11). On the other hand, the reaction proceeds in very good yield (92%) using diethyl ether as

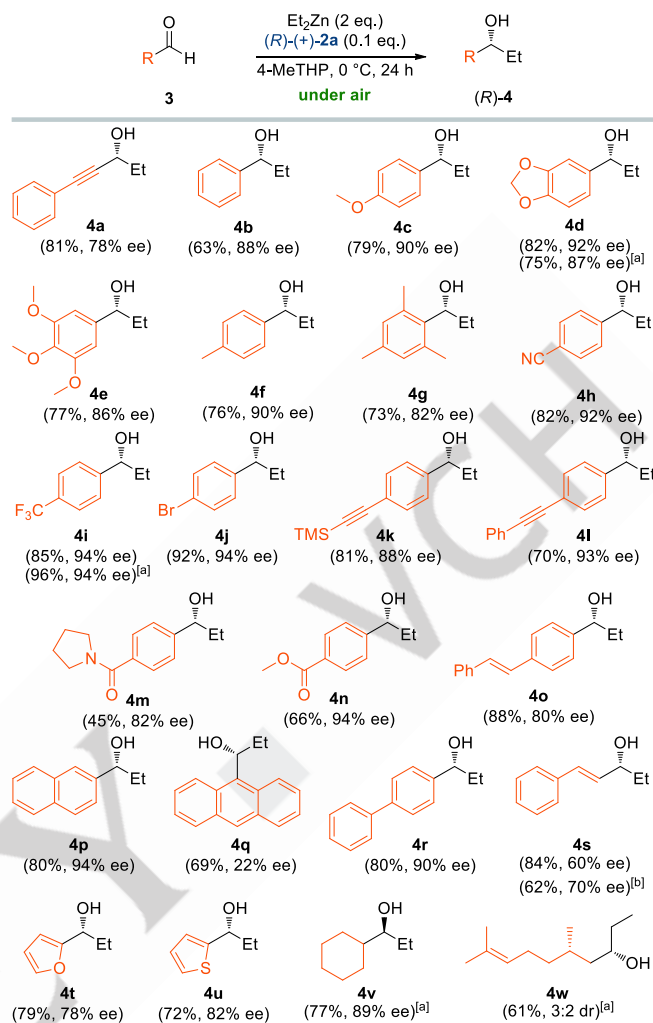


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solvent, however with low enantioselectivity (57% ee, entry 12). Running the alkylation in THF released the alcohol (*R*)-**4a** in a moderate 59% yield and restored the enantioselectivity of the reaction to 80% ee (entry 13). Overall, these results shown that 4-MeTHP represents a promising alternative to conventional solvents for the catalytic BINOL-Zn(II) complex-mediated enantioselective alkylation of aldehydes under bench-type reaction conditions, using BINOL-derived (bis)carboxamides **2** as chiral ligands, at 0 °C and under air.

With satisfactory conditions in place, the scope and limitations of this transformation were evaluated for a series of functionalized aromatic aldehydes **3** using the chiral BINOL derivative (*R*)-(+)-**2a** (Scheme 2). Pleasingly, the reaction proceeded smoothly en route to a variety of chiral secondary alcohols **4a-w** in good yields and excellent enantioselectivities. Using benzaldehyde **3b** as substrate, the resulting chiral benzyl alcohol (*R*)-**4b** was delivered in 63% yield and 88% ee. The alkylation of substituted aromatic aldehydes released a series of enantioenriched benzyl alcohols bearing electron-donating (**4c-e**), neutral (**4f-g**), electron-withdrawing (**4h-i**), and brominated (**4j**) groups on the aromatic ring with superior yields (73-92%) and enantioselectivities (82-94%) after workup. Comparable yields and enantioselectivity were obtained when aldehydes **3d** and **3i** were reacted with diethylzinc in the presence of (*S*)-(-)-**2a**, allowing the formation of the corresponding (*S*) enantiomers of alcohols **4d** and **4i** in 87% and 94% ee, respectively. Our methodology also allowed the chemo- and enantioselective preparation of chiral alcohols bearing unsaturated substituents (**4k-l**, **4o**), amide (**4m**) and ester (**4n**) functionalities on the aromatic ring, with less satisfactory yields for compounds **4m** (45%) and **4n** (66%), however in a satisfying stereoselective fashion. Polycyclic  $\beta$ -naphthyl (**3p**) or biphenyl (**3r**) carboxaldehydes also performed as well, whereas ethylation of the bulkier 9-anthraldehyde **3q** proceeded with an unexpected low enantioselectivity (22% ee).<sup>[29]</sup> Alkylation of the  $\alpha,\beta$ -unsaturated cinnamic aldehyde proceeded toward the chiral allyl alcohol **4s** with a non-negligible decrease of the enantioselectivity of the reaction (60% ee) despite the good yield (84%). The use of the less sterically hindered catalyst (*R*)-(+)-**2b** slightly ameliorated the asymmetric ethylation of *trans*-cinnamaldehyde (70% ee), albeit **4s** was produced in a lower yield (62%).<sup>[30]</sup> Assorted heteroaromatic and aliphatic aldehydes served as competent partner as well, releasing the desired chiral alcohols **4t-w** in good yields and enantioselectivities. Attempts with other linear aliphatic aldehydes, such as 3-phenylpropanal, hexanal and dodecanal, were however unsuccessful, affording complex reaction mixtures with trace amounts of addition products.<sup>[31]</sup>

To gain more structural and mechanistic insights into the BINOL 3,3'-(bis)carboxamide-assisted asymmetric alkylation of aldehydes, we carried out spectroscopic investigations to evaluate the constitution of the BINOL-Zn(II) complexes formed in solution using the selected environmentally responsible solvents. Previously reported studies disclosed a significant solvent dependence on the structure of these complexes. X-ray studies of a (*R*)-(+)-**2b**/Zn(II) complex, obtained by crystallization of a 1:1 solution of (*R*)-(+)-**2b** and Et<sub>2</sub>Zn in DCM/hexane, revealed the formation of a C<sub>2</sub>-symmetric trimeric structure, inactive as



**Scheme 2.** Enantioselective addition of diethylzinc to aldehydes with (*R*)-(+)-**2a** under aerobic conditions. Reaction conditions: **3** (0.5 mmol, 0.15 M in 4-MeTHP), Et<sub>2</sub>Zn (1.0 mmol, 1.0 M in hexanes), (*R*)-(+)-**2a** (0.05 mmol, 10 mol%), 24 h, 0 °C, under air. Reported yields refer to isolated products. The absolute configuration was assessed by comparison of the optical rotation with data reported in the literature and was determined as (*R*). The ee values (%) were determined by chiral HPLC analyses (see Supporting Information). [a] (*S*)-(-)-**2a** (0.05 mmol, 10 mol%) was used as ligand. Yields and ee values (%) refer to the (*S*)-**4** enantiomer. [b] (*R*)-(+)-**2b** (0.05 mmol, 10 mol%) was used as ligand.

catalyst, which is presumably retained in solution, as observed by <sup>1</sup>H NMR studies in CD<sub>2</sub>Cl<sub>2</sub>. However, the trimer promptly converts into a monomeric complex upon coordination of an extra Et<sub>2</sub>Zn molecule in the presence of an excess of diethylzinc.<sup>[15a]</sup> By contrast, a similar <sup>1</sup>H NMR analysis in THF-*d*<sub>8</sub> indicated the possible presence of different isomers (both monomeric and trimeric) in solution, in which the solvent coordinated to the Lewis acidic Zn(II) ion might play a significant role both in the formation and in the evolution of the reaction intermediate.<sup>[15a]</sup> However, the behaviour in solution of these BINOL 3,3'-(bis)carboxamides-Zn(II) complex still remains rather unexplored.

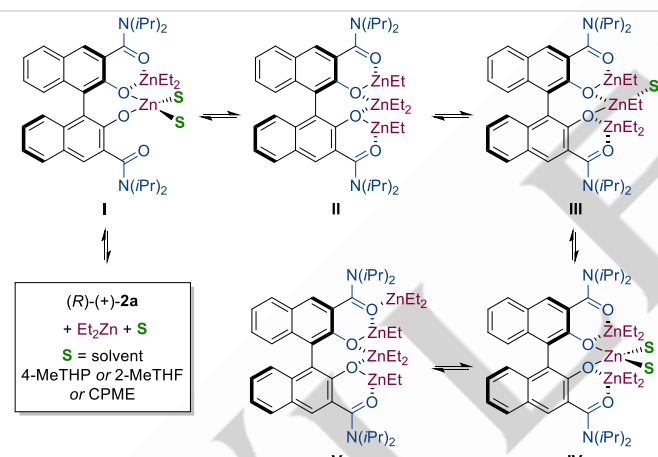
In order to better understand the constitution of these complexes in solution, a <sup>1</sup>H DOSY NMR solution-state study has been carried out using the Internal Calibration Curve method (ICC).<sup>[32]</sup> Hexaphenylbenzene (HPB), phenanthrene (Phe) and the solvent used in the experiments were employed as internal

standards. Solutions of (*R*)-(+)-**2a** and Et<sub>2</sub>Zn at the same molar ratio employed for the reactivity studies (1:20) in the selected solvents (4-MeTHP, 2-MeTHF or CPME, 0.4 mL) were analysed by <sup>1</sup>H DOSY NMR, and the molecular weight of the new species formed in solution were experimentally determined by ICC (Table 3, see Supporting Information for details). The results were compared with a series of monomeric BINOL-Zn(II) complexes I-V, the putative active species generated in the presence of an excess of Et<sub>2</sub>Zn under normal catalytic reaction, according to previously reported literature studies.<sup>[15, 33]</sup>

We first focused our analysis on 4-MeTHP, the most performant solvent in the above-described enantioselective alkylation reactions. Analysis of the <sup>1</sup>H DOSY NMR spectra revealed the formation in solution of a new species with MW<sub>exp</sub> = 928.24 g mol<sup>-1</sup>, as calculated from the diffusion coefficient ( $D = 6.296 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ , see Supporting Information).

This result revealed the preferential formation of the smaller monomeric dinuclear complex I ( $\Delta_{\text{MW}} = < 0.1\%$ , Table 3) in 4-MeTHP solution, with two molecules of solvent coordinated to the Lewis acidic Zn(II) ion and a diethylzinc unit anchored to the Lewis basic amide carbonyl.<sup>[15a]</sup> An analogous fit was found in CPME solution ( $D = 8.001 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ , MW<sub>exp</sub> = 911.84 g mol<sup>-1</sup>), where the constitution of the dinuclear disolvated aggregate I seems

**Table 3.** <sup>1</sup>H DOSY NMR solution-state studies of (*R*)-(+)-**2a** and Et<sub>2</sub>Zn by using an ICC in 4-MeTHP, 2-MeTHF and CPME.<sup>[a]</sup>



	MW <sub>exp</sub> (g/mol)	I $\Delta_{\text{MW}}$	II $\Delta_{\text{MW}}$	III $\Delta_{\text{MW}}$	IV $\Delta_{\text{MW}}$	V $\Delta_{\text{MW}}$
4-MeTHP	928.24	<0.1%	9%	-3%	-12%	-5%
2-MeTHF	932.42	4%	9%	-0.5%	-9%	-4%
CPME	911.84	-2%	7%	-4%	-14%	-7%

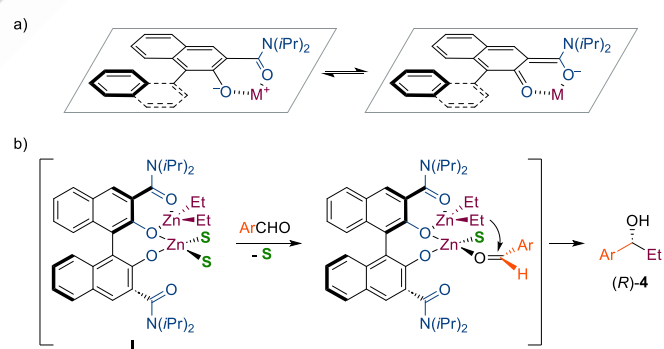
[a] Selected structures of mono- (III), di- (I, IV) or unsolvated (II, V) BINOL-Zn(II) complexes are shown. Molecular weights were determined by <sup>1</sup>H DOSY NMR experiments using the Internal Calibration Curve method (ICC) with hexaphenylbenzene (HPB), phenanthrene (Phe) and the solvent as internal standards. Experimental conditions: (*R*)-(+)-**2a** (0.013 mmol), Et<sub>2</sub>Zn (0.26 mmol, 1 M in hexanes), solvent (0.4 mL). Percent differences between the determined molecular weight (MW<sub>exp</sub>) and the calculated MW of complexes I-V are reported. See Supporting Information for details.

preferred over other higher aggregates ( $\Delta_{\text{MW}} = -2\%$ ). These results show that in polar reaction media, such as 4-MeTHP and

CPME,<sup>[34]</sup> and in the presence of a large excess of diethylzinc, only monomeric adducts are formed in solution, and no higher oligomeric species were detected by analysis of the diffusion coefficients. These findings are in good agreement with the previous work by Katsuki and co-workers, which speculated the formation of Zn(II) adduct I to explain the observed asymmetric induction in the alkylation reaction.<sup>[15a]</sup>

The presence of complex I suggested in fact a catalysis by a flat, conjugated BINOL-Zn(II) complex, conformationally stabilized by metal-chelation (Figure 4, a). The constitution of I might in fact results in the formation of a transition state in which the electrophile (the aldehyde) replaces one of the solvent molecules coordinated to the Lewis acidic central Zn(II) ion (Figure 4, b), while chelation of the diethylzinc by the Lewis basic amide carbonyl and the phenolic oxygen direct one of the ethyl group toward the *re*-face of the electrophile.

A good correlation was also observed for the monosolvated trinuclear complex III both in 4-MeTHP ( $\Delta_{\text{MW}} = -3\%$ ) and in CPME ( $\Delta_{\text{MW}} = -4\%$ ) and for the unsolvated tetranuclear Zn(II) complex V in 4-MeTHP ( $\Delta_{\text{MW}} = -5\%$ ), whereas the trinuclear (II) and tetranuclear (IV) complexes<sup>[33]</sup> are presumably not formed despite the large excess of diethylzinc present in solution (Table 3). By contrast, <sup>1</sup>H DOSY NMR experiments in 2-MeTHF suggested the preferential formation of the monosolvated trinuclear-type complex III ( $D = 8.712 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ , MW<sub>exp</sub> = 932.42 g mol<sup>-1</sup>,  $\Delta_{\text{MW}} = -0.5\%$ ). The constitution of a single-solvated adduct could rationalize the low yields observed for the alkylation of **3a** when 2-MeTHF was used as reaction media in place of 4-MeTHP (see Table 2, entries 4-5). Assuming that the solvation of the Lewis acidic Zn(II) ion prevents the aggregation of the complex in solution, the lower degree of solvation of III might result in a decrease of the catalytic activity, however with preserved enantioselectivity owing to the formation of a conformationally stable O-Zn-O chelated species.



**Figure 4.** a)  $\pi$ -conjugated, flat metal-chelated conformation of I and b) proposed transition state model for the asymmetric alkylation of aldehydes catalysed by BINOL-Zn(II) dinuclear complex I.<sup>[15]</sup>

## Conclusion

In summary, our report discloses that the highly hydrophobic ether 4-MeTHP constitutes a promising and convenient alternative to the classic organic solvents for the development of sustainable synthetic methodologies grounded on the use of organometallic reagents. The beneficial effects of 4-MeTHP as reaction media have been first highlighted in the anionic *ortho*-

Fries rearrangement of BINOL-derived carbamates promoted by a lithium amide at room temperature, in the presence of air and moisture.

The use of 4-MeTHP induced a remarkable and unexpected stability either of the metalating agent and/or of the generated aryllithiums even for 1 h, an unusual long reaction time for organolithium-promoted transformations under aerobic conditions. This protocol allowed the gram-scale preparation of a class of chiral BINOL-based ligands, the 3,3'-(bis)carboxamide derivatives, also allowing the easy recyclability of both the solvent 4-MeTHP and the free amine TMP, which are of great value in terms of efficiency and environmental sustainability.

Furthermore, superior performances of 4-MeTHP than CPME and 2-MeTHF have been observed when the synthesized chiral BINOL-3,3'-(bis)carboxamides have been employed as chiral catalysts in the asymmetric addition of organozinc reagents to aldehydes. Our results clearly indicate that 4-MeTHP represents a promising alternative to the conventional solvents (THF, toluene, dichloromethane) commonly employed for the catalytic BINOL-Zn(II) complex-promoted alkylation of aldehydes. The methodology allowed for the assembly of a series of enantioenriched secondary alcohols in good yields and high stereoselectivity, working at 0 °C and under air. Solution-state <sup>1</sup>H DOSY NMR studies suggest that 4-MeTHP plays a key role in these reactions by inducing the preferential formation of a monomeric BINOL-Zn(II) dinuclear complex, in which the dissolution of the Lewis acidic metal ion centre might prevent aggregation of the catalyst, and consequent loss of reactivity.

## Experimental section

**SAFETY NOTE.** Organolithiums were handled under an inert atmosphere (Schlenk techniques) until the point at which they were mixed with a solution of the substrate in CPME, 2-MeTHF and 4-MeTHP under an air atmosphere and with vigorous magnetic stirring. No problems were experienced during the addition. Organolithiums, however, are notoriously prone to ignition in air, and caution should be exercised in adopting the recommended procedure, especially on a larger scale.

**Preparation of lithium 2,2,6,6-tetramethylpiperidine (LiTMP) solution in 2-MeTHF (1 M) or in 4-MeTHP (0.5 M).** In a Schlenk tube under a positive argon pressure, *n*-BuLi (2.5 M in hexanes, 4.0 mmol, 1.0 eq.) was added to a precooled (0 °C) stirred solution of 2,2,6,6-tetramethylpiperidine (TMP) (4.4 mmol, 1.1 eq., 0.75 mL) in dry 2-MeTHF (1.65 mL) or dry 4-MeTHP (5.65 mL). The mixture was stirred at 0 °C for 10 min to yield a clear yellowish solution of LiTMP that was used without further purification.

**General procedure for the gram-scale synthesis of 2a-b by anionic ortho-Fries rearrangement of 1a-b.** Reactions were performed under air at room temperature. In a round bottom flask, the appropriate carbamate **1a-b** (2 mmol, 1 eq.) was dissolved in 4-MeTHP (10 mL, 0.2 M) and the mixture was vigorously stirred for 5 minutes. LiTMP (12 mmol, 1 M in 2-MeTHF, 12 mL, 6 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring for 1 h and then quenched with aqueous 1 M HCl. The mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

### Recycle of 4-MeTHP and 2,2,6,6-tetramethylpiperidine (TMP).

Reactions were performed under air at room temperature. A 0.2 M solution of **1a** (1.0 mmol, 540 mg) in 4-MeTHP (5 mL) was treated with a freshly prepared solution of LiTMP in 4-MeTHP (0.5 M, 6 mmol, 12 mL, 6 eq.) under the optimized reaction conditions. After 1 h the reaction was quenched with aqueous 1 M HCl. The crude mixture was extracted with 4-MeTHP (3 x 10 mL) and the combined organic extracts (**A**) were dried over Na<sub>2</sub>SO<sub>4</sub>. The acidic aqueous layer, containing 2,2,6,6-tetramethylpiperidine hydrochloride, was treated with aqueous 1 M NaOH solution until pH = 10, and then extracted with 4-MeTHP (3 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> (**B**). The dried organic extracts **A** were transferred to a Claisen distillation apparatus fitted with a 20 cm Vigreux column and fractionally distilled at 760 mmHg. This allows the recovery of the 4-MeTHP fraction without contamination of *n*-hexanes. The residual non-volatile fraction recovered from the distillation apparatus, containing the racemic BINOL derivative **2a**, was directly purified by flash column chromatography to give pure **2a** in 98% yield (529 mg). The dried organic extracts **B** were transferred to a Claisen distillation apparatus fitted with a 20 cm Vigreux column and fractionally distilled at 760 mmHg. This allows the recovery of the 4-MeTHP fraction and the pure 2,2,6,6-tetramethylpiperidine (TMP) as pale-yellow liquid (661 mg, 78%).

### General procedure for the enantioselective addition of diethylzinc to aldehydes.

Reactions were performed under air at 0 °C. A solution of (*R*)-(+)-**2a** (27 mg, 0.05 mmol, 0.1 eq.) in 4-MeTHP (2 mL) was stirred in an open screw cap vial. Et<sub>2</sub>Zn (1.0 M in hexanes, 1 mmol, 1 mL, 2 eq.) was added to the solution and the mixture was stirred for 30 min. A solution of the appropriate aldehyde **3** (0.5 mmol, 1 eq.) in 4-MeTHP (1.3 mL) was then added. The resulting mixture was stirred for 24 h. After quenching with satd. NH<sub>4</sub>Cl aqueous solution, the product was extracted with diethyl ether (3 x 10 mL), the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent removed under reduced pressure. The crude products **4** were purified by flash column chromatography on silica gel. The enantiomeric ratios were determined by analytical HPLC on chiral column.

## Supporting Information

The authors have cited additional references within the Supporting Information.<sup>[35-50]</sup>

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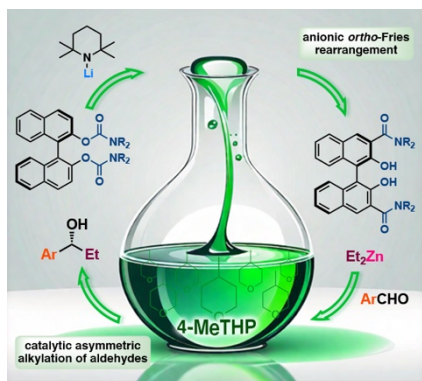
**Keywords:** 4-methyltetrahydropyran • Fries rearrangement • alkali metal • BINOL • asymmetric alkylation

- [1] P. T. Anastas, J. C. Warner, Oxford University Press, **2000**.
- [2] S. Kar, H. Sanderson, K. Roy, E. Benfenati, J. Leszczynski, *Chem. Rev.* **2022**, *122*, 3637-3710.
- [3] M. Miele, V. Pillari, V. Pace, A. R. Alcántara, G. de Gonzalo, *Molecules* **2022**, *27*, 6701.
- [4] a) L. Song, Y. Meng, T. Zhao, L. Liu, X. Pan, B. Huang, H. Yao, R. Lin, R. Tong, *Green Chem.* **2024**, *26*, 428-438; b) M. R. Mutra, T. L.



- Chandana, Y.-J. Wang, J.-J. Wang, *Green Chem.* **2023**, *25*, 8124-8133; c) L. Liang, L.-D. Guo, R. Tong, *Acc. Chem. Res.* **2022**, *55*, 2326-2340.
- [5] M.-O. Simon, C.-J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415-1427.
- [6] a) A. Mannu, M. Blangetti, S. Baldino, C. Prandi, *Materials* **2021**, *14*, 2494; b) B. B. Hansen, S. Spittle, B. Chen, D. Poe, Y. Zhang, J. M. Klein, A. Horton, L. Adhikari, T. Zelovich, B. W. Doherty, B. Gurkan, E. J. Maginn, A. Ragauskas, M. Dadmun, T. A. Zawodzinski, G. A. Baker, M. E. Tuckerman, R. F. Savinell, J. R. Sangoro, *Chem. Rev.* **2021**, *121*, 1232-1285.
- [7] V. Pace, P. Hoyos, L. Castoldi, P. Domínguez de María, A. R. Alcántara, *ChemSusChem* **2012**, *5*, 1369-1379.
- [8] U. Azzena, M. Carraro, L. Pisano, S. Monticelli, R. Bartolotta, V. Pace, *ChemSusChem* **2019**, *12*, 40-70.
- [9] a) R. Bijoy, P. Agarwala, L. Roy, B. N. Thorat, *Org. Process Res. Dev.* **2022**, *26*, 480-492; b) A. Jordan, C. G. J. Hall, L. R. Thorp, H. F. Sneddon, *Chem. Rev.* **2022**, *122*, 6749-6794.
- [10] S. Kobayashi, T. Tamura, S. Yoshimoto, T. Kawakami, A. Masuyama, *Chem. Asian J.* **2019**, *14*, 3921-3937.
- [11] T. Nienaltowski, P. Krzesiński, M. E. Baumert, A. Skoczeń, E. Suska-Kauf, J. Pawłowska, A. Kajetanowicz, K. Greła, *ACS Sustainable Chem. Eng.* **2020**, *8*, 18215-18223.
- [12] a) H. Mizoguchi, H. Kamada, K. Morimoto, R. Yoshida, A. Sakakura, *Chem. Sci.* **2022**, *13*, 9580-9585; b) J. Zhang, K. Suzuki, K. Ohmori, *Org. Lett.* **2023**, *25*, 9036-9040.
- [13] M. Korb, H. Lang, *Chem. Soc. Rev.* **2019**, *48*, 2829-2882.
- [14] a) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047-9153; b) J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857-898.
- [15] a) H. Kitajima, K. Ito, Y. Aoki, T. Katsuki, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207-217; b) K. Ito, Y. Tomita, T. Katsuki, *Tetrahedron Lett.* **2005**, *46*, 6083-6086.
- [16] M. R. Dennis, S. Woodward, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1081-1086.
- [17] E. M. da Silva, H. D. Vidal, M. A. Januário, A. G. Corrêa, *Molecules* **2023**, *28*, 12.
- [18] a) S. Ghinato, D. Territo, A. Maranzana, V. Capriati, M. Blangetti, C. Prandi, *Chem. Eur. J.* **2021**, *27*, 2868-2874; b) S. Ghinato, G. Dilauro, F. M. Perna, V. Capriati, M. Blangetti, C. Prandi, *Chem. Commun.* **2019**, *55*, 7741-7744; c) D. Arnodo, S. Ghinato, S. Nejrrotti, M. Blangetti, C. Prandi, *Chem. Commun.* **2020**, *56*, 2391-2394; d) S. Ghinato, C. Meazzo, F. De Nardi, A. Maranzana, M. Blangetti, C. Prandi, *Org. Lett.* **2023**, *25*, 3904-3909.
- [19] S. Ghinato, F. De Nardi, P. Bolzoni, A. Antenucci, M. Blangetti, C. Prandi, *Chem. Eur. J.* **2022**, *28*, e202201154.
- [20] a) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757-824; b) L. Pu, *Acc. Chem. Res.* **2014**, *47*, 1523-1535.
- [21] J. Clayden, Y. J. Y. Foricher, H. K. Lam, *Eur. J. Org. Chem.* **2002**, *2002*, 3558-3565.
- [22] F. F. Mulks, L. J. Bole, L. Davin, A. Hernán-Gómez, A. Kennedy, J. García-Álvarez, E. Hevia, *Angew. Chem. Int. Ed.* **2020**, *59*, 19021-19026.
- [23] The anionic *ortho*-Fries rearrangement of carbamates **1a-b** under classical Schlenk conditions, using *s*-BuLi/TMEDA at -80 °C in THF as solvent, affords **2a** and **2b** in 80% and 42% yield, respectively. See ref. [16].
- [24] Attempts to prepare a 1 M solution of LiTMP in 4-MeTHP result in the almost instantaneous precipitation of the lithium amide upon addition of *n*-BuLi at 0 °C.
- [25] Deposition numbers 2327648 (for **2a**), and 2327647 (for **2b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe. [Access Structures service.](#)
- [26] Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155-3212.
- [27] a) M. Mori, T. Nakai, *Tetrahedron Lett.* **1997**, *38*, 6233-6236; b) H. Kodama, J. Ito, A. Nagaki, T. Ohta, I. Furukawa, *Appl. Organomet. Chem.* **2000**, *14*, 709-714; c) W.-S. Huang, Q.-S. Hu, L. Pu, *J. Org. Chem.* **1999**, *64*, 7940-7956; d) W.-S. Huang, Q.-S. Hu, L. Pu, *J. Org. Chem.* **1998**, *63*, 1364-1365.
- [28] a) Z. Fu-Yao, A. S. C. Chan, *Tetrahedron: Asymmetry* **1997**, *8*, 3651-3655; b) F.-Y. Zhang, C.-W. Yip, R. Cao, A. S. C. Chan, *Tetrahedron: Asymmetry* **1997**, *8*, 585-589; c) Y. Chen, S. Yekta, L. J. P. Martyn, J. Zheng, A. K. Yudin, *Org. Lett.* **2000**, *2*, 3433-3436.
- [29] This might be ascribed to the combination between steric factors and the presence of  $\pi$ - $\pi$  interactions among the catalysts and the aldehyde. However, further studies are necessary to unveil the observed poor enantioselectivity. See ref. [33].
- [30] Similar results in terms of yield and enantioselectivity for the catalytic alkylation of *trans*-cinnamaldehyde, using diethylzinc and chiral BINOL catalysts under Schlenk-type conditions, have been reported in the literature. See refs [15a] and [33].
- [31] These results are consistent with those reported by Katsuki and co-workers using this class of BINOL ligands under Schlenk-type conditions. In this case the formation of aldol-type products with low stereoselectivity was observed. See ref. [15a].
- [32] M. Fairley, L. J. Bole, F. F. Mulks, L. Main, A. R. Kennedy, C. T. O'Hara, J. García-Álvarez, E. Hevia, *Chem. Sci.* **2020**, *11*, 6500-6509.
- [33] M. Hatano, T. Miyamoto, K. Ishihara, *J. Org. Chem.* **2006**, *71*, 6474-6484.
- [34] Dipole moment, dielectric constant, solubility in water, and log P values for 4-MeTHP and CPME are nearly identical. See ref. [10].
- [35] a) W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879-1880; b) E. Juaristi, A. Martínez-Richa, A. García-Rivera, J. S. Cruz-Sánchez, *J. Org. Chem.* **1983**, *48*, 2603-2606; c) A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281-283.
- [36] V. Pace, L. Castoldi, A. R. Alcántara, W. Holzer, *Green Chem.* **2012**, *14*, 1859-1863.
- [37] Y. Sato, A. Osada, N. Ogawa, Y. Kobayashi, *Eur. J. Org. Chem.* **2023**, *26*, e202300403.
- [38] S. Lauzon, T. Ollevier, *Chem. Commun.* **2021**, *57*, 11025-11028.
- [39] J. B. Reigada, C. M. Tcacenco, L. H. Andrade, M. J. Kato, A. L. M. Porto, J. H. G. Lago, *Tetrahedron: Asymmetry* **2007**, *18*, 1054-1058.
- [40] A. Joncour, A. Décor, S. Thoret, A. Chiaroni, O. Baudoin, *Angew. Chem. Int. Ed.* **2006**, *45*, 4149-4152.
- [41] G. Xu, Z. Z. Liu, *Chin. Chem. Lett.* **2010**, *21*, 309-311.
- [42] R. P. Tanpure, A. R. Harkrider, T. E. Strecker, E. Hamel, M. L. Trawick, K. G. Pinney, *Biorg. Med. Chem.* **2009**, *17*, 6993-7001.
- [43] Ö. Dilek, M. A. Tezeren, T. Tilki, E. Ertürk, *Tetrahedron* **2018**, *74*, 268-286.
- [44] T. Werner, A. M. Riahi, H. Schramm, *Synthesis* **2011**, *2011*, 3482-3490.
- [45] C. Yao, P. Wu, Y. Huang, Y. Chen, L. Li, Y.-M. Li, *Org. Biomol. Chem.* **2020**, *18*, 9712-9725.
- [46] Q. Wang, S. Li, C.-J. Hou, T.-T. Chu, X.-P. Hu, *Appl. Organomet. Chem.* **2019**, *33*, e5108.
- [47] J. Varma Nallaparaju, T. Nikonovich, T. Jarg, D. Merzhyevskiy, R. Aav, D. G. Kananovich, *Angew. Chem. Int. Ed.* **2023**, *62*, e202305775.
- [48] S. Beckendorf, O. G. Mancheño, *Synthesis* **2012**, *44*, 2162-2172.
- [49] M. Agnes, A. Sorrenti, D. Pasini, K. Wurst, D. B. Amabilino, *CrystEngComm* **2014**, *16*, 10131-10138.
- [50] L. Pérez-García, D. B. Amabilino, *Chem. Soc. Rev.* **2007**, *36*, 941-967.

## Entry for the Table of Contents



The beneficial effects of 4-methyltetrahydropyran (4-MeTHP) as reaction media have been highlighted in two organometallic-mediated transformations performed under bench-type aerobic conditions. The use of 4-MeTHP induces a remarkable stability of the organolithium species involved in the anionic Fries rearrangement of binaphthol (BINOL)-carbamates, and superior performances of 4-MeTHP than other sustainable solvents have been disclosed in the asymmetric addition of organozinc reagents to aldehydes catalyzed by BINOL-(bis)carboxamide derivatives.

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