A High-Throughput Screening Approach for the Determination of Additive Effects in Organozinc Addition Reactions to Aldehydes

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Abstract: The effects of additives in phenylzinc addition reactions to an aldehyde have been studied using an automated high-throughput screening approach. With 2-bromobenzaldehyde as test substrate and *N*,*N*-dibutylnorephedrine (dbne) as chiral ligand, an improvement of 20% ee over the catalyzed reaction in the absence of the additive was observed. The described results enable a novel access towards chiral diarylmethanols using commercially available substrates, reagents and ligands as well as fast, automated techniques.

Keywords: additives; asymmetric catalysis; combinatorial catalysis; high-throughput screening; organozinc reagents

Introduction

Asymmetric catalysis is mostly regarded as a discipline, which is driven by mindful planning of substrates, reagents and chiral catalysts.[1] Furthermore, theoretical approaches are followed with the hope of gaining a better mechanistic understanding of catalytic reactions and of improving important parameters such as ligand structures.[2]

Despite the efforts to achieve a rational access to catalytic reactions, the development of most processes is nowadays still accompanied by massive experimental expenditure. Reaction conditions, solvents and additives are as important for the (enantio)-selectivity and catalytic turnover as is the choice of the right chiral ligand or catalyst. Additives have also been found to have a dramatic effect in catalysis.[3] One of the most prominent examples in that respect is the production process of Metolachlor by asymmetric hydrogenation, where the use of additives such as an acid and iodine is required for achieving turnover number of over 1 million![4] The downside of this approach is equally clear in this example: the effect of the additive is often hard to rationalize and mostly unpredictable.

An indispensable tool of modern catalysis is high-throughput screening.[5] State of the art automation equipment enables the testing of hundreds of reactions per day. Such automation techniques are usually referred to as combinatorial catalysis. These screening techniques are an ideal way to test additive effects in (asymmetric) catalysis.

In Lewis-acid/Lewis-base catalyzed reactions such as the addition of diethylzinc to aldehydes,[6] the effect of additives has been described in numerous publications over the past years.[7] As the diethylzinc addition to benzaldehyde as the standard test substrate has nearly no background reaction, in almost all cases Lewis-acidic additives were applied in order to improve the reactivity (and selectivity) of the chiral ligands or catalysts. Alkenyl-, aryl-, and alkynylzinc reagents, however, are much more reactive towards aldehydes.[6] The addition processes of such reagents inherit considerably fast background reactions and therefore require a thorough reaction optimization. Sometimes, relatively high catalyst loadings (e.g. = 10 mol %) are required in order to reach high enantiomeric excesses. However, unlike in several other Lewis acid-catalyzed reactions, where large quantities of catalysts are needed for increasing the reactivity of the catalyst system, the high catalyst loadings here are mostly required for lowering the impact of the fast background reaction, which diminishes the enantioselectivity. A primary goal in these processes is therefore to let more of the reaction proceed by the catalyzed (stereoselective) pathway relative to the "uncatalyzed" (non-stereoselective) background reaction.[8] One way to achieve this is by finding faster catalysts. Alternatively, the background reaction must be slowed down by modifying the reagents. Noteworthy is the fact that in most Lewis acid(/Lewis base)-catalyzed reactions, trace impurities of (achiral) Lewis acidic compounds raise the contribution of the background reaction. In the aforementioned organozinc additions, the zinc reagents themselves can

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usually be ruled out for such effects. Zinc carboxylates and zinc halides, however, are more Lewis acidic than the catalytically active ligand-zinc complex and they can therefore lead to a reduced ee of the product.

We have recently described that additives have considerable effects in organozinc chemistry.[9] Here we report a systematic study of additive effects in the reaction between phenylzinc reagents and aldehydes. In this investigation high-throughput screening techniques were utilized.

Results and Discussion

The addition of phenylzinc to 2-bromobenzaldehyde (**1**) in the presence of commercially available *N*,*N*-dibutylnorephedrine (dbne, **2**) was chosen as test reaction (Scheme 1). The phenylzinc reagent was prepared *in situ* from triphenylborane and diethylzinc. Under those conditions, the active species is believed to be a mixed phenyl-ethyl-zinc formed by transmetallation from the borane. Presently, this protocol is the most economical way of preparing an active phenylzinc reagent suitable for this asymmetric catalysis.[10] The reaction conditions for the high-throughput screening were derived from previous studies.[9a,11,12] The ee of **3** was then determined by conventional HPLC using a chiral stationary phase.[13]

The reactions were carried out on *cynora's* high-throughput screening system based on a Tecan Genesis Freedom 200 robot equipped with a reaction block capable of 96 reactions. Reaction vessels were individually sealed by septa, agitated with magnetic stirring and flushed with argon using the pipetting arm of the robot. All reactions were run at a concentration of 0.25 mmol · mL^{-1} at 10 °C. Additives were either directly weighed in the reaction vessel prior to flushing with argon, or dispensed using stock solutions. Reagents and ligand were employed as stock solutions as well.

Prior to the full additive screening, we conducted a kinetic study to determine the reaction rate and optimal reaction times. Two additives, methanol and polyethylene glycol dimethyl ether (DiMPEG, MW 2500), which have previously been found to be suitable for the test reaction[9a,14] were used in different amounts. Samples were taken simultaneously after 10, 30, 90, and 360 minutes. The conversion was determined using a calibrated HPLC method, leading to the results depicted in Figure 1.

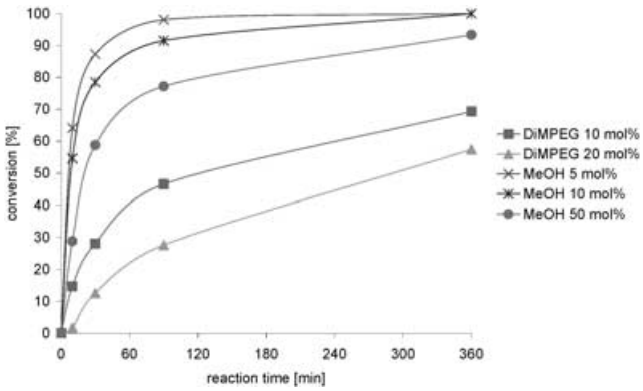
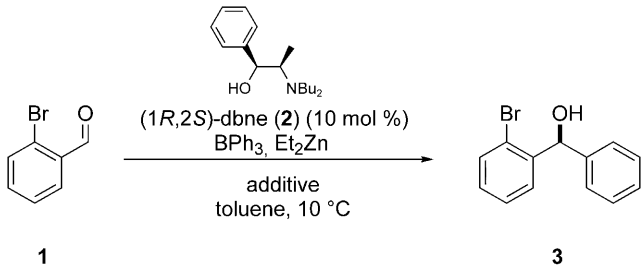


Figure 1. Kinetic study for phenyl transfer reactions in the presence of DiMPEG (MW 2000) and methanol.

The reaction without additive is rather fast and virtually complete within 60 to 90 minutes.[15] This behaviour is best reflected by the results with small amounts of methanol as additive. Upon addition of 5, 10, 50 mol % of methanol, the reaction becomes (slightly) slower, although the initial rate is not drastically decreased. The effect of DiMPEG is different. The initial rate is drastically diminished. The addition of, e.g., 10 mol % of DiMPEG reduces the initial reaction rate by more than 50%.

Given the primary kinetic results, a reaction time of 16 h was chosen to guarantee complete conversion for all additives. We chose a set of (Lewis basic) additives consisting mainly of alcohols, polyethylene glycol derivatives, ethers, and nitrogen-containing compounds. Lewis acidic compounds were neglected due to the initially mentioned considerations. The additives are listed in Table 1, and they were employed in amounts varying from 1 to 200 mol % depending on the additive. A complete list of reactions can be found in the Experimental Section.

The results of this additive screening are visualized using a 3-dimensional representation of *ee vs.* additive and additive amount (Figure 2). This representation helps in finding the best absolute results but also gives a first impression of possible correlations of additive (classes) and amounts. The blue "water-level" in Figure 2 represents the ee that can be achieved by the catalyst dbne in the absence of an additive under the chosen conditions (68% ee as an average of several runs). The colour of the spheres reflects the ee (red: highest ee). As can be clearly seen on first glance, several additives can improve the ee while others drastically diminish the ee. The best result is obtained with DiMPEG 2000 in an amount of 10 mol %. Using this additive, 88% ee are



Scheme 1. Addition of phenylzinc to 2-bromobenzaldehyde (**1**).

Table 1. List of selected additives.

Additive	Abbreviation in Figure 2
21-Crown-7	21c7
2-Propanol	*i*-PrOH
Ascorbic acid	ascorbic acid
Dioxane	Dioxan
Imidazole	IMI
Methanol	MeOH
Molecular sieves 4 Å	MS
N-Methylimidazole	NMIM
Phenol	Phenol
Polyethylene glycol MW 350	PEG
Polyethylene glycol dimethyl ether MW 2000	DiMPEG
Polyethylene glycol monomethyl ether MW 2000	MeOPEG 2000
Polyethylene glycol monomethyl ether MW 750	MeOPEG 750
Polyethylene glycol monomethyl ether MW 350	MeOPEG 350
Polyvinyl alcohol	PVA
Pyridine	Pyridin
tert-Butyl alcohol	*t*-BuOH
Tetrahydrofuran	THF
Tetrahydrofurfuranol	THFOH
Tetramethylethylenediamine	TMEDA

achieved, which reflects an improvement of 20% ee without changing catalyst or conditions! For most additives, the conversion of aldehyde was complete. Some examples – especially those with over-stoichiometric amounts of alcohols, as well as TMEDA – show low or no conversion of the aldehyde (see Experimental Section for details).

Apparently, the amount of additive and the chain length of the polyethylene glycol (PEG) derivatives have an influence on the selectivity. PEGs with longer chains tend to give better results than the shorter chain derivatives. Also, the dimethyl ethers are apparently superior to the monomethyl ether derivatives.[16] Other oxygen donor-containing additives that have complexing abilities do not improve the enantioselectivity. Dioxane and THF, for instance, drastically diminish the selectivity. This effect has often been observed in organozinc additions.[6] For coordinating polyethylene glycol derivatives, we attribute the additive effect to a complexation (and in some cases visible precipitation) of highly Lewis acidic zinc salts which can be present in the reaction mixture.[17] As discussed above, these would diminish the enantioselectivity by boosting the undirected background reaction.

Several other additives have considerable effects, which require closer examination. Figure 2 shows the dependency of ee *vs.* additive amount for 2-propanol. Alcohols such as methanol, 2-propanol, *tert*-butyl alcohol, tetrahydrofuranol and phenol are deprotonated by zinc reagents and lead to the formation of alkoxyaryl-zinc species, which have previously been shown to add to aldehydes.[14] Among the tested alcohols, 2-propanol gave the best results.

Figure 3 demonstrates that the amount of added alcohol is decisive for the outcome of the reaction. When 100 mol % of 2-propanol (with regard to the zinc reagent) is added, the highest ee of 80% is achieved. Lower amounts of alcohol do not significantly improve the selectivity because the remaining ethyl-phenyl-zinc reagent is more reactive than the alkoxide. When 200 mol % of alcohol is added, no product can be obtained due to the complete quenching of the reagent.

Most of the employed nitrogen donor additives have only complexing ability and cannot be deprotonated. The addition of TMEDA in substoichiometric amounts is beneficial. Stoichiometric quantities diminish the ee (and the yield). Pyridine is tolerated up to stoichiometric level (Figure 4). Over-stoichiometric amounts drastically diminish the selectivity. *N*-Methylimidazole improves the selectivity when stoichiometric amounts are employed. The selectivity drops when 150 mol % are used and rises again to 73% ee when 200 mol % are employed. This behaviour can be explained by the formation of phenylzinc complexes inheriting either one or two *N*-methylimidazole ligands.

The most interesting case is the reaction with the additive imidazole, representing the only N–H compound, which could be deprotonated by the zinc reagent. As shown in Figure 5, the direction of induction can be reversed, when one equivalent of imidazole is employed. Presumably, an imidazolyl-phenyl-zinc reagent is formed which favours a different transition state in the catalytic addition step.[18,19] These assumptions, however, could not be rationalized by preliminary B3LYP/LACVP* calculations employing a simple *N*,*N*-dimethylaminoethanol model.

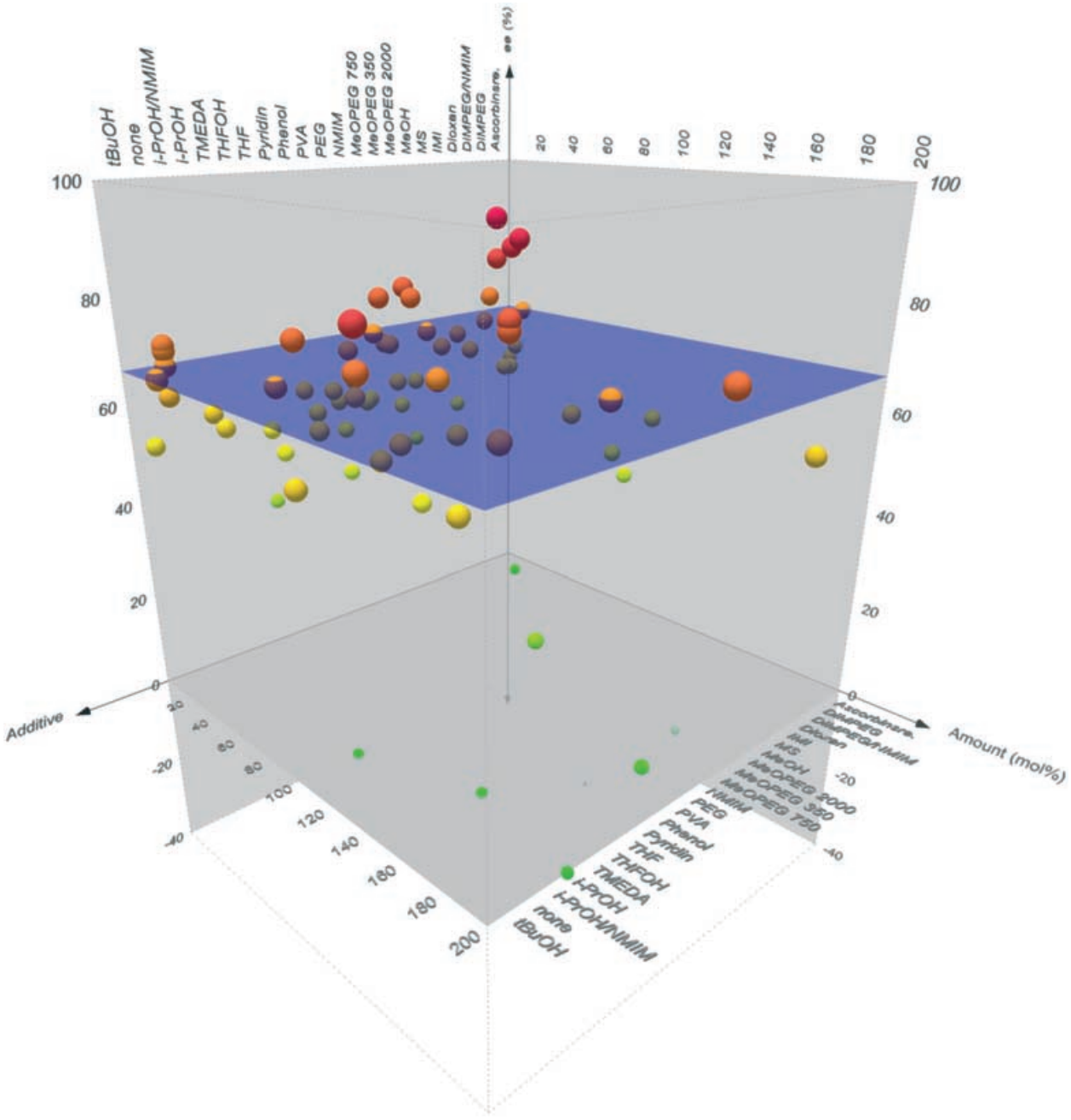


Figure 2. High-throughput screening of additives.

Unfortunately, the beneficial effects of the single additives cannot be combined. The addition of, e.g., 100 mol % of 2-propanol with 100 mol % of *N*-methylimidazole gives no product at all. Combining DiMPEG (10 mol %) and *N*-methylimidazole (100 mol %) gives the product in a disappointing 38% ee.

Conclusion

In an additive screening using automation techniques we demonstrated that several additives have positive effects in the phenylzinc addition to 2-bromobenzaldehyde (**1**). It also became apparent that the additive amount is (depending on the type of additive) equally important. Polyethylene glycol derivatives generally improve the enantioselectivity, presumably by complexing zinc salts and thereby reducing the importance of the background reaction. Alcohols, in contrast, react with the zinc reagent and influence the selectivity by formation of phenylzinc alkoxides. Most interesting (though not the best) results were obtained with imidazole as additive, which led to a reversal in enantioselectivity. Overall, DiMPEG 2000 proved to be the best additive, giving

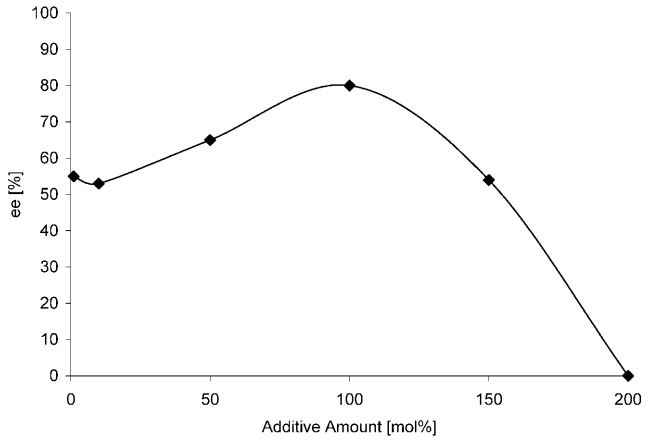


Figure 3. The ee value of **3** *versus* the amount of 2-propanol as additive.

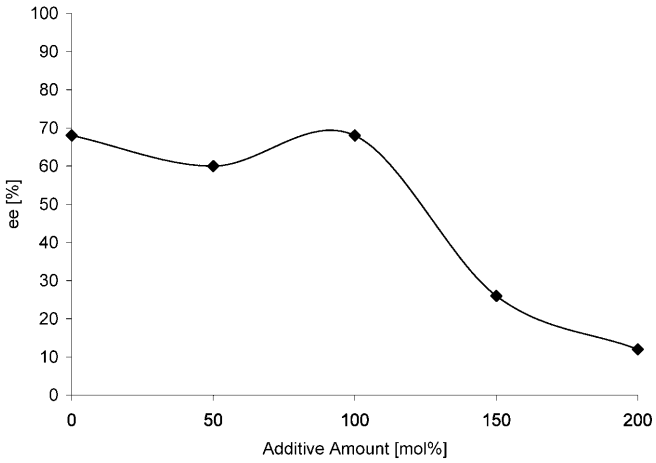


Figure 4. The *ee* value of **3** versus the amount of pyridine as additive.

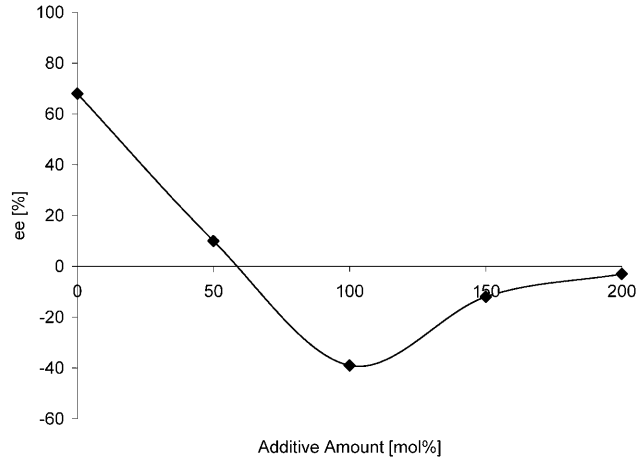


Figure 5. The ee value of **3** *versus* amount of imidazole as additive.

an improvement of about 20% ee (88% ee for the chosen test substrate 2-bromobenzaldehyde) compared to the catalyzed reaction without additive.

Experimental Section

General Methods

All reactions involving organometallic reagents were carried out under an atmosphere of argon in argon-flushed vials. Toluene was distilled over sodium under an atmosphere of nitrogen. All other chemicals were obtained from commercial sources and used without further purification. HPLC measurements were conducted on an Agilent 1100 Series instrument using a well-plate autosampler. The screening experiments were carried out on a Tecan Genesis Freedom 200 pipetting robot equipped with an H + P Variomag magnetically stirred reaction block with 96 individual reaction vessels. The Tecan robot was equipped with 8 coaxial pipetting needles capable of rinsing the reaction vessels, which were individually closed by septa, with argon and handling all sensitive reagents under a protective atmosphere.

Screening Protocol

All pipetting jobs were conducted by the Tecan robot. Solid additives were weighed into the reaction vessels prior to flushing with argon (2 minutes for each vessel, 8 vessels simultaneously). The liquid additives were added as stock solutions in toluene. Toluene (1 mL) was added to each reaction vial. A mixture of triphenylborane (1 equiv.) and diethylzinc (3 equivs., diethylzinc employed as a 15% solution in hexane; 1.0 mL, 0.25 M in toluene based on Ph_3B, 0.25 mmol) was added and the reaction block was brought to 10 °C (internal, PT100 probe inside one test vial). The amino alcohol (1*R*,2*S*)-dbne (**2**) was added as a stock solution in toluene (1.0 mL, 0.025 M in toluene, 0.025 mmol, 10 mol %) and the mixture was stirred for 30 minutes. The reaction was started by addition of a solution of 2-bromobenzaldehyde (**1**, 1 mL, 0.25 M in toluene, 0.25 mmol). The total amount of solvent in each vial was 4 mL. The reaction mixtures were agitated by magnetic stir bars at 1000 rpm for 12 h at 10 °C. The reactions were quenched by addition of a minimum amount of 1 M HCl (100 μL). The stirring was stopped in order to facilitate the deposition of formed zinc salts. Of the clear supernatant solutions, a sample of 0.5 mL was taken and vacuum-filtered over 0.5 cm of $MgSO_4$ into a 96-well deep well plate (2.0 mL volume for each cavity). The $MgSO_4$ was washed with 0.5 mL of MTBE resulting in a total amount of 1.0 mL for each cavity of the deep-well plate.

HPLC Method for Compound 3

Analytical data for product alcohol **3** have been reported in the literature.[9–11] The ees of the individual reactions were determined by conventional HPLC analyses on a chiral stationary phase directly from the quenched reaction mixtures as obtained by the above protocol. Enantiomer separation was performed on a Chiralcel OD, 20 °C, 230 nm, heptane/*i*-PrOH

Table 2. Screening of additives according to Scheme 1 and Figure 1.

Additive	Abbreviation	Additive amount [mol %]	ee [%]
21-Crown-7	21c7	1	54
21-Crown-7	21c7	5	57
21-Crown-7	21c7	10	66
Ascorbic acid	Ascorbinsre.	10	53
Ascorbic acid	Ascorbinsre.	100	49
DiMPEG 2000	DiMPEG	1	64
DiMPEG 2000	DiMPEG	5	70
DiMPEG 2000	DiMPEG	10	79
DiMPEG 2000	DiMPEG	10	88
DiMPEG 2000	DiMPEG	15	54
DiMPEG 2000	DiMPEG	20	82
DiMPEG 2000	DiMPEG	25	84
DiMPEG 2000/*N*-methylimidazole	DiMPEG/NMIM	100	38
Dioxane	Dioxane	1	62
Dioxane	Dioxane	10	59
Dioxane	Dioxane	100	44
Dioxane	Dioxane	1000	45
Imidazole	IMI	50	10
Imidazole	IMI	100	−39
Imidazole	IMI	150	−12
Imidazole	IMI	200	−3
i-PrOH	*i*-PrOH	1	55
i-PrOH	*i*-PrOH	10	53
i-PrOH	*i*-PrOH	50	65
i-PrOH	*i*-PrOH	100	80
i-PrOH	*i*-PrOH	100	72
i-PrOH	*i*-PrOH	150	54
i-PrOH	*i*-PrOH	200	0[a]
i-PrOH/*N*-methylimidazole	*i*-PrOH/NMIM	100	0
MeOH	MeOH	1	53
MeOH	MeOH	10	65
MeOH	MeOH	100	55
MeOH	MeOH	1000	39
MeOPEG 350	MeOPEG 350	1	63
MeOPEG 350	MeOPEG 350	5	63
MeOPEG 350	MeOPEG 350	10	55
MeOPEG 750	MeOPEG 750	1	51
MeOPEG 750	MeOPEG 750	5	66
MeOPEG 750	MeOPEG 750	10	74
MeOPEG 2000	MeOPEG 2000	1	48
MeOPEG 2000	MeOPEG 2000	5	75
MeOPEG 2000	MeOPEG 2000	10	73
Molecular sieves 4 Å	MS	10	61
N-Methylimidazole	NMIM	1	56
N-Methylimidazole	NMIM	10	52
N-Methylimidazole	NMIM	100	74
N-Methylimidazole	NMIM	100	76
N-Methylimidazole	NMIM	150	66
N-Methylimidazole	NMIM	200	73
Polyethylene glycol	PEG	1	52
Polyethylene glycol	PEG	5	46
Polyethylene glycol	PEG	10	64
Phenol	Phenol	1	56
Phenol	Phenol	10	52
Phenol	Phenol	100	57[b]
Polyvinyl alcohol	PVA	10	56
Polyvinyl alcohol	PVA	20	39
Pyridine	Pyridine	50	60
Pyridine	Pyridine	100	68

Table 2 (cont.)

Additive	Abbreviation	Additive amount [mol %]	ee [%]
Pyridine	Pyridine	150	26
Pyridine	Pyridine	200	12
t-BuOH	*t*-BuOH	1	51
t-BuOH	*t*-BuOH	10	65[a]
t-BuOH	*t*-BuOH	100	55[a]
THF	THF	1	49
THF	THF	10	45
THF	THF	100	46
THF	THF	1000	33
Tetrahydrofuranol	THFOH	50	55
Tetrahydrofuranol	THFOH	100	58
Tetrahydrofuranol	THFOH	150	64
TMEDA	TMEDA	50	73
TMEDA	TMEDA	100	56[a]
TMEDA	TMEDA	150	0[a]

[a] $<10\%$ conversion.
[b] $<30\%$ conversion.

88:12, 1.1 mL·min^{-1}, $t_R = 7.5$ min (*R*), 10.6 min (*S*), total length of method 12.5 min.

Listing of Individual Results

The individual results of the additive screening as depicted in Figure 2 are given in Table 2. The blank runs without additive are omitted. The average ee of 5 runs without additive was calculated to be 68% under the chosen reaction conditions. Positive ee values correspond to an (*R*)-configuration of the final product alcohol **3**, when the (1*R*,2*S*)-enantiomer of dbne is used.

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[16] These findings are not in accord to our initial findings (ref.[9b]) and might be correlated to the chosen substrate or catalyst.

[17] Commercially available diethylzinc solution can contain considerable amounts of zinc salts. Usually their effect becomes only apparent, when highly active zinc reagents such as phenylzincs or alkynylzincs are used.

[18] For the transition state description of the phenyl transfer to aldehydes, see: a) J. Rudolph, T. Rasmussen, C. Bolm, P.-O. Norrby, *Angew. Chem. Int. Ed.* **2003**, *42*, 3002; b) J. Rudolph, P.-O. Norrby, C. Bolm, *J. Am. Chem. Soc.* **2005**, *127,* 1548.

[19] This effect could only be observed with phenylzinc obtained by the BPh_3/diethylzinc protocol. In the diethylzinc addition to aldehydes no effect of imidazole was observed. In this reaction, imidazole does not seem to be deprotonated by diethylzinc. Hence formation of a mixed imidazolyl-aryl-zinc reagent can only be achieved by the more basic phenylzinc.

