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SHORT COMMUNICATION

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Asymmetric Amplification Coupling Enantioselective Autocatalysis and Asymmetric Induction for Alkylation of Azaaryl Aldehydes

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Dedicated to the memory of Professor Per Ahlberg

Keywords: Asymmetric synthesis / Alkylation / Autocatalysis / Chirality

Herein, we describe a chemical system combining asymmetric amplification of Soai's autocatalyst alongside a catalytic addition of $Zn(iPr)_2$ to azaaryl aldehydes. Thus, Soai autocatalyst is amplified in situ from 11 to > 98 % *ee* and concomitantly catalyzes the alkylation of pyridine aldehydes to provide alkanols with up to 99 % *ee*. Also, exceptional amplifications of *ee* in one cycle are observed for both compounds produced throughout the reaction, probably as a result of interactions in a reaction network coupling enantioselective autocatalysis and asymmetric induction.

Introduction

Research has been intensive to develop methods for catalytic asymmetric synthesis of highly enantioenriched compounds with enzyme-like chemo- and stereoselectivity. These strategies make use of optically pure catalysts only available from the chiral pool. In parallel, low *ee* catalysts are believed to be of limited interest in asymmetric synthesis, since a linear relationship of the *ee* values between the chiral catalyst and the product is expected.

The pioneering work of Soai on a practically perfect asymmetric amplification in the asymmetric autocatalysis of (5-pyrimidyl)alkanol **2** by addition of $Zn(iPr)_2$ to (5-pyrimidyl)aldehyde **1**,[1] introduced a new entry into optically pure compounds.[2] Despite the structure requisite of a rigid γ-imino aldehyde, the extreme sensitivity of this reaction to any variation in chirality made it the perfect tool for the detection of minute imbalance of asymmetry.[3]

Because autocatalysis may contribute to understanding the origins of homochirality, several groups have investigated the chemical mechanism of the Soai reaction.[4] While the exact details remain under investigation, results obtained in kinetic studies proposed the involvement of homo- and heterochiral dimers of Zn-**2**.[5] However, this chemical model alone cannot rationalize such marked *ee* amplification as in the Soai reaction.

An interesting and more integrative model describes the Soai reaction as Frank-like reaction network operating in a closed system to give rise to absolute asymmetric synthesis under kinetic control. Such a system requires an efficient irreversible enantioselective autocatalysis and a fast heterodimerization, which are key for the observed non-linear amplification of *ee*.[6]

Thus, asymmetric autocatalytic amplification, if coupled to asymmetric induction, might become a powerful process to access chiral molecules in the future.

Also, inspired by the work of Soai et al., we herein report on a reaction network combining simultaneous enantioselective autocatalysis with asymmetric induction in the alkylation of azaaryl substrates, which are unable of such asymmetric amplification on their own.

Results and Discussions

We describe a process whereby asymmetric autocatalytic amplification of **2** operates in one single cycle alongside enantioselective addition of $Zn(iPr)_2$ to azaaryl aldehydes. We also demonstrate that high enantiopurity through asymmetric amplification of **2** is not a prerequisite for high enantioselctivity in the asymmetric catalysis.

Scheme 1 introduces the proposed catalytic process consisting of an asymmetric autocatalytic loop where the low *ee* pyrimidyl alcohol **2** undergo a self-replication process with amplification of *ee*, and a second loop with asymmetric catalysis where **2** should act as the catalyst for the dialkylzinc addition to a different set of pyridine-3-carbaldehydes.

Interestingly, Soai reported an elegant and efficient one-pot asymmetric alkylation method where a chiral catalyst self improves its *ee* by asymmetric autocatalysis and then acts as a chiral catalyst to give very high *ee* products.[7]

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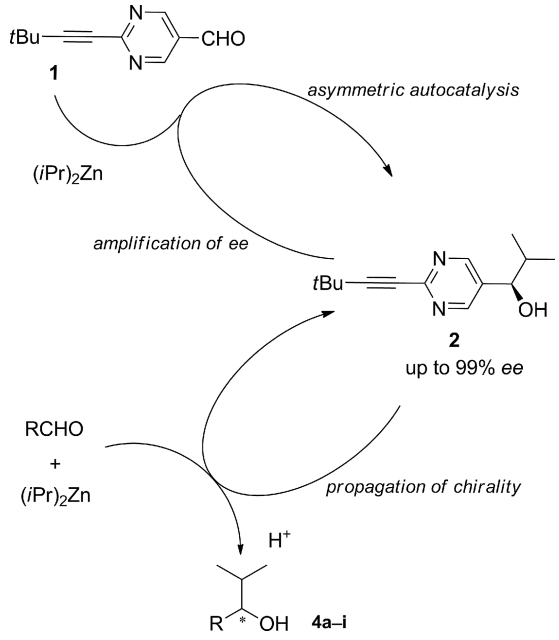


Scheme 1. Asymmetric autocatalysis with amplification of *ee* of the pyrimidyl alcohol and its use as a chiral catalyst.

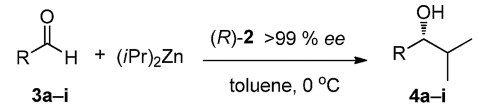
However, the use of autocatalyst **2** required a self-improvement to high *ee* prior to its use in a subsequent asymmetric reaction.

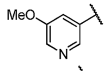
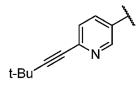
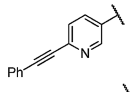
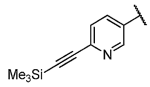
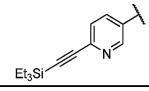
Besides, two substrates reported by Soai, namely quinoline-3-carbaldehyde and 5-(diisopropylcarbamoyl)pyridine-3-carbaldehyde are capable of autocatalytic amplification of *ee* in their alkylation with $Zn(iPr)_2$.[8,9] Therefore it is not clear whether the high *ee* of the product is due to the catalytic effect of autocatalyst **2** or to own amplification of compound **4**. It is also conceivable to attribute this amplification of *ee* to a combined effect of **2** and **4**.

Surprisingly, this new concept of asymmetric catalysis went overlooked and no further studies on the subject have been published since. Moving in this direction, we also applied this concept to the asymmetric alkynylation of azaaryl aldehydes.[10]

To test our approach, we began our survey by evaluating the reactivity of a series of azaaryl aldehydes as substrates in the presence of highly enantioenriched (*R*)-1-(2-*tert*-butylethynyl-5-pyrimidyl)-2-methylpropanol (*R*)-**2**, following experimental conditions originally reported by Soai. The synthesis of chiral pyrimidyl alcohol (*R*)-**2** was achieved in high yield and > 98% *ee* by autocatalytic asymmetric amplification as described previously by Soai and subsequently used to catalyse the asymmetric addition of $Zn(iPr)_2$ to different azaaryl aldehydes **3**.[11] The zinc alkoxide of (*R*)-**2** was generated by premixing autocatalyst (*R*)-**2** (10 mol-%) with $Zn(iPr)_2$ (2.2 equiv.) and subsequently followed by slow addition of aldehyde **3** (Table 1). The current limitation lies with the high reactivity of 2- and 4-pyridine aldehydes which exhibited extremely fast and non-enantioselective reactions to produce racemic mixtures of alkanols. For example, nicotinaldehyde reacted with dialkylzinc in few seconds even in absence of any ligand. Thus, a range of 3-pyridine derived carbaldehydes with various electron-rich and -deficient substituents were investigated as depicted in Table 1.[8]

Table 1. Enantioselective addition of $Zn(iPr)_2$ to aldehydes using (*R*)-pyrimidyl alcohol **2** as chiral catalyst.



Entry[a]		R	Prod.	Yield %[b]	*ee* %[c]
1	**3a**		**4a**	58	20
2	**3b**		**4b**	71	68
3	**3c**		**4c**	65	68
4	**3d**		**4d**	61	16
5	**3e**		**4e**	57	26
6	**3f**		**4f**	92	89
7	**3g**		**4g**	82	82
8	**3h**		**4h**	85	91
9	**3i**		**4i**	83	93

[a] Reactions were performed under nitrogen at 0 °C using 2.2 equiv. of $(iPr)_2Zn$ and 10 mol-% of (*R*)-**2**. [b] Isolated product after column chromatography. [c] *ee* were determined by HPLC and/or GC analysis on chiral stationary phases.

Even if certain levels of *ee* were reached with all substrates studied, the reaction proved to be clearly sensitive to substituent effect. Substitution at 4- and 5-positions provided poor to moderate enantioselectivity although good yields could be obtained (Table 1, entries 1–3). For example, the enantioselectivity increased drastically from 20% *ee* with (*R*)-**4a** to 68% *ee* for (*R*)-**4b** (Table 1, enty1 vs. 2). A MeO at 5-position delivered alkanol (*R*)-**4c** with 68% *ee* (Table 1, entry 3). Remarkably, the nature of the substituent at the 6-position on the pyridine ring proved to have a more profound influence on the enantioselectivity. While methyl and phenyl groups gave poor *ee* for alkanols (*R*)-**4d**,**e**, substituted alkynyls all provided excellent *ee*. Whether the alkynyl provides an electronic effect or only acts as a spatial stretch to avoid an excessive strain of the complex is still unclear.

It is important to note that control reactions showed that substrates such as **3a**, **3b** and **3f** can undergo autocatalysis but with a pronounced loss of *ee* (Supporting Information,

Table S1). This confirms the influence of the Zn-alkoxide (*R*)-**2**-Zn in the asymmetric alkylation of aldehydes **3**.

Among the substrates investigated we paid a particular attention to the behavior of compound (*R*)-**4f**, a pyridine reminiscence of the Soai's autocatalyst **2**. Reaction of aldehyde **3f** in presence of autocatalyst (*R*)-**2** provided very high yield of alkanol (*R*)-**4f** with 89% *ee* (Table 1, entry 6). In contrast, when alkanol (*R*)-**4f**, with initial *ee* of 92%, was used to perform an autocatalytic reaction, the *ee* of the final product dropped to 33% (Supporting Information, Table S1). This represents a very significant observation with regard to the structure similarity of **3f** and **2**. This result clearly shows the beneficial contribution of autocatalyst **2** to achieve high *ee* in systems unable themselves of amplification of *ee*.

After these preliminary results, aldehyde **3f** was then chosen as a model for some systematic studies regarding this procedure.

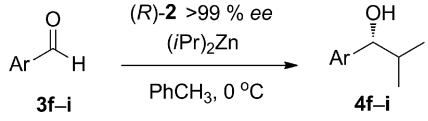
Early studies demonstrated the influence of the temperature on the enantioselectivity in the Soai reaction.[12] Naturally, we wondered whether the temperature influenced the enantioselectivity induced by **2** in the addition of Zn(*i*Pr)$_2$ to other azaaryl aldehydes. These experiments show the temperature dependency of the *ee* of product (*R*)-**4f** in the alkylation reaction of **3f** (Supporting Information, Figure S1), and the system reveals a dramatic erosion of *ee* just above 0 °C (+10 °C, 22% *ee*). The plot shows retention of high *ee* at 82–89% over a wide range of low temperatures (–30 °C, 82% *ee*). It is therefore reasonable to assume that the temperature is a critical factor in the formation of the intermediate complexes that are responsible for the enantioselectivity of the reaction. Although uncatalyzed racemic alkylation that would resolve into a great loss of *ee* remain plausible, this behaviour may also stem from an improved stability for the active species favouring the catalytic step at lower temperature.

Another interesting aspect is the strong amplification observed when (*R*)-**4f** is generated under a reverse mode of addition of Zn(*i*Pr)$_2$ to aldehyde **3f**. Thus, Zn-alkoxide was generated by mixing (*R*)-**2** (10 mol-%) in 99% *ee* and Zn(*i*Pr)$_2$ (10 mol-%) at 0 °C for 30 min. Then, aldehyde **3f** was added in a single portion, followed by slow addition of Zn(*i*Pr)$_2$ (2.1 equiv.) at 0 °C over 3 h. Under these conditions, which are different from those usually employed by Soai et al., (*R*)-**4f** was obtained with 98% *ee*. Furthermore, this strong amplification is retained when Zn(*i*Pr)$_2$ was added over 3 h to a mixture of (*R*)-**2** (10 mol-%) in 99% *ee* and aldehyde **3f** at 0 °C. Except for compound **4h**, alkanols **4f**,**g**,**i** show a significant amplification of *ee* in the range of 95–99%, as shown in Table 2.

This might suggest that (*R*)-**2**, when generated in situ, is a much better catalyst for the alkylation of **3**. Also, notice that the slow addition of Zn(*i*Pr)$_2$ may contribute to suppress a possibly competing background and non-enantioselective alkylation of **3**.

Because of the structural similarity of (*R*)-**2** and alkylation product **4f**, together with such a remarkable asymmetric amplification, we became intrigued by the potentially relevant interaction between autocatalysts (*R*)-**2** and (*R*)-**4**. Indeed, while (*R*)-**2** is a catalyst for the formation of (*R*)-**4** – as we originally assumed – the newly formed (*R*)-**4** might interfere with the reactivity of (*R*)-**2** and become a concern for the overall outcome of the reaction. Thus, if (*R*)-**2** and (*R*)-**4** are generated in the reaction without prior amplification of (*R*)-**2**, the process of coupling asymmetric autocatalysis with asymmetric induction would become of major interest. To evaluate such an opportunity, we set out to investigate a system combining asymmetric amplification of autocatalyst (*R*)-**2** alongside a catalytic addition of Zn(*i*Pr)$_2$ to aldehydes **3**. The results are shown in Table 3.

Table 2. Enantioselective addition (reverse mode) of Zn(*i*Pr)$_2$ to aldehydes with (*R*)-pyrimidyl alcohol **2**.



3f–i **4f–i**

Entry[a]	Aldehyde	Prod.	Yield [%][b]	*ee* [%][c]
1	**3f**	**4f**	88	98
2	**3g**	**4g**	91	95
3	**3h**	**4h**	93	91
4	**3i**	**4i**	95	99

[a] Reactions were performed under nitrogen at 0 °C using 2.2 equiv. of (*i*Pr)$_2$Zn, 10 mol-% of (*R*)-2 (99% *ee*). [b] Yield determined by ^{1}H NMR spectroscopy. [c] *ee* were determined by HPLC analysis on chiral stationary phases.

Table 3. One-pot asymmetric autocatalysis and enantioselective addition of Zn(*i*Pr)$_2$ to aldehydes using low *ee* (*R*)-pyrimidyl alcohol **2** as chiral catalyst.

Entry[a]	Aldehyde	Cat. (*R*)-**2** [%] *ee* initial	(*R*)-**2** [%] *ee* final		Product (*R*)-**4** yield[b] [%]	*ee*[c] [%]
1	**3a**	15	–[d]	**4a**	47	3
2	**3b**	15	40	**4b**	65	15
3	**3c**	11	42	**4c**	59	30
4	**3d**	11	41	**4d**	60	12
5	**3e**	11	39	**4e**	62	26
6	**3f**	11	97	**4f**	81	98
7	**3g**	11	80	**4g**	96	95
8	**3h**	11	84	**4h**	93	82
9	**3i**	11	96	**4i**	92	98

[a] Reactions were performed under nitrogen at 0 °C using 2.2 equiv. of (*i*Pr)$_2$Zn, 10 mol-% of aldehyde **1** and 1 mol-% (*R*)-**2**. [b] Yield determined by ^{1}H NMR. [c] *ee* values were determined by HPLC and/or GC analysis on chiral stationary phases. [d] The soai alcohol **2** could not be isolated.

In a first attempt, to a mixture containing alkanol (*R*)-**2** (1 mol-%.) with an initial 53% *ee* and aldehydes **1** (10 mol-%) and **3f** in toluene was added dialkylzinc slowly over 3 h. To our surprise, we observed the formation of alkanol (*R*)-**4f** in > 98% *ee* and in good yield. Moreover, under these conditions (*R*)-**2** showed high autocatalytic activity and was amplified to a final 98% *ee*. This suggests that compound **2** is not operating just as an autocatalyst, but might be part of an improved catalytic system.

Next, we decided to evaluate the performance of this combination starting from a lower enantiopurity. Under similar conditions, even (*R*)-**2** (1 mol-%.) with initially only 11% *ee* was still able to perform with high asymmetric amplification. The reaction could deliver high yields of (*R*)-**2** in a final > 97% *ee* together with (*R*)-**4f** in >98% *ee*. The results indicate that autocatalyst (*R*)-**2** had also achieved a high asymmetric amplification in-situ in one cycle.

This transformation was also applicable to a series of azaaryl aldehydes even when Soai autocatalyst (*R*)-**2** was employed initially with only 11% *ee* as shown in Table 3.

Aldehydes **3a**–**e** do not seem to have the necessary electronic or steric properties to interact with the autocatalysis of (*R*)-**2**, and thus have failed to exhibit the expected amplification of *ee*. Although we observe clearly that (*R*)-**2** was generated with asymmetric amplification from 11% to about 39–42% *ee*, this resulted in poor final *ee* for products **4a**–**e** (Table 3, entries 1–5). With a striking difference, substrates **3f**–**i** reacted efficiently to afford high yields of **4f**–**i**, and exhibited remarkable amplification of *ee*. Again, overexpression of autocatalyst (*R*)-**2** reached high values of 80–95% *ee* after just one cycle (Table 3, entries 6–9). Compounds (*R*)-**4g**–**i** were isolated in up to 98% *ee*. More interestingly, alkanol (*R*)-**4g** is isolated with 95% *ee* though (*R*)-**2** had only reached a final 80% *ee*.

These findings prompted us to get more insight into the amplification of *ee*. For this purpose, we started continuous monitoring over time of *ee* progress in the formation of **2** and **4f**. Examination of the correlation between the *ee* of the catalyst derived from (*R*)-**2** and *ee* of product (*R*)-**4f** revealed clear time dependence and pronounced asymmetric amplification. As depicted in Figure 1 (a), the enantiomeric excess of autocatalyst (*R*)-**2** increased steadily to > 90% *ee* from the initial condition (53% *ee*) in ca 45 minutes, reaching the maximum value of > 98% after 2 hours (a plot of *ee*/conv. is also provided, see Supporting Information, Figure S2). For autocatalyst (*R*)-**2** with low initial 11% *ee*, the plot shows a similar trend but with a stronger amplification of *ee* (Figure 1, b).

Surprisingly, both plots show a rapid increase of the enantiomeric excess of the newly forming alkanol (*R*)-**4f** to its maximum of 98% *ee* (Figure 1), instead of increasing slowly, as it would be expected, following the amplification of the catalyst (*R*)-**2**. Intriguingly, a strong amplification of (*R*)-**4f** could be observed already in the early amounts of product.

In addition, the progress of the reaction exhibits an unusual amplification-time profile,[13] and suggests two strong NLE for both autocatalysts (*R*)-**2** and (*R*)-**4f** in interdependent relationship. Also, to the best of our knowledge, no case of such two NLE that operate in parallel has been reported to date.

Although tempting, the observed non-linear asymmetric amplification cannot be attribute solely to the formation of dimeric or oligomeric catalytic species as described in previous reports.[5]

Such behaviour could be rationalized by a kinetically controlled amplification that leads to high *ee* for (*R*)-**2** and

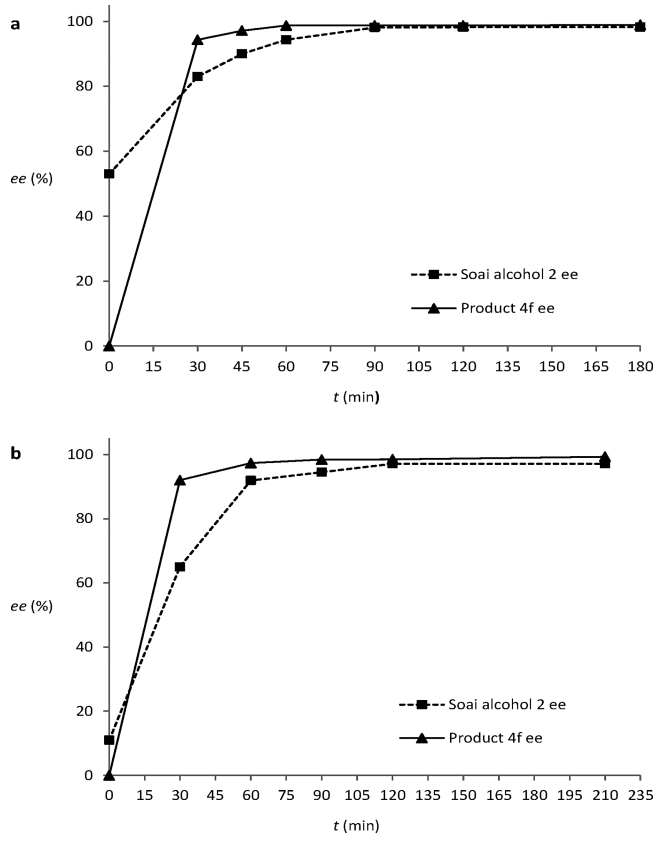


Figure 1. Variation of *ee* of product (*R*)-**4f** and Soai alcohol (*R*)-**2** as a function of time. Reactions were performed under nitrogen at 0 °C using experimental conditions as above (Table 3, entry 6). *ee* were measured by HPLC analysis using chiral stationary phases. The *ee* values for Soai alcohol (*R*)-**2** are reported as measured from the HPLC traces and include the initial catalyst.

(*R*)-**4f** in a single reaction step, which is a breach to the essential feature of the Soai reaction, i.e. a sequential procedure of 3–4 reactions.

This behaviour could be attributed to a process whereby (*R*)-**2** and (*R*)-**4f** promote a reaction network of enantioselective autocatalysis coupled to asymmetric induction. It is also reasonable to assume the presence in this network of a fast equilibrium of heterodimers of **2** and **4f**, which can be seen as mutual enantiomeric inhibition.[6a–6c] If faster than enantioselective autocatalysis, this equilibrium may lead to the generation of non-linear effect in catalysis. Also, the eventuality of a cross catalysis must not be disregarded and this is the subject of further investigations. Nevertheless, these findings support our assumption of a potential interaction between the Soai autocatalyst and pyridinyl-alkanol products. This is confirmed by recalling the inhibition of asymmetric amplification of (*R*)-**2** during formation of products **4a**–**e** (Table 3, entries 1–5).

Of course, it remains very intriguing that this new approach gave great results for pyridine systems, which closely resemble the structure of the Soai autocatalyst, but unable of such performance on their own. In particular the bulky alkynyl moiety in the 6-position seems to be a key feature, crucial to form a new complex, which exhibits a higher

catalytic activity responsible for this unexpected behaviour. Such profound effect can be illustrated by considering the striking asymmetric amplification for compound (*R*)-**4f** when compared to (*R*)-**4e** under identical reaction conditions (Table 3, entries 5,6).

Conclusions

In summary, we have presented a new chemical system combining asymmetric amplification of autocatalyst **2** alongside a catalytic addition of $Zn(iPr)_2$ to aldehydes **3**. Probably most important, even starting from very low enantiopurity, autocatalysts (*R*)-**2** and (*R*)-**4** exhibit efficient cooperation and reveal a strong non-linear relationship. Also, this catalytic system provides exceptional amplification up to >98% *ee* in one reaction cycle for both compounds (*R*)-**2** and (*R*)-**4**, which adds complexity to the Soai reaction when it is coupled to asymmetric induction, and suggests a more advanced reaction network. Currently we are conducting further investigations to delineate the nature and the key role of reactive species in such a novel reaction network.

Experimental Section

General Procedures for the Asymmetric Alkylation: Standard procedures for the asymmetric alkylation catalysed by 2 in two step one-pot: In an oven dried flask (*R*)-1-[2-(3,3-dimethylbut-1-yn-1-yl)pyrimidin-5-yl]-2-methylpropan-1-ol (*R*)-**2** (0.027 mmol, 99% *ee*), is dissolved in 0.4 mL of dry toluene under nitrogen and diisopropylzinc 1 M (0.583 mmol) is added drop wise at 0 °C and stirred for 30 min. The pyrimidyl aldehyde **3** (0.265 mmol) is dissolved in 1.6 mL of dry toluene and added slowly over three hours at 0 °C to the reaction mixture. The advancement of the reaction is monitored by HPLC. The reaction is quenched by the addition of HCl 1 M in dioxane (0.265 mmol) and neutralized with saturated aqueous $NaHCO_3$. The mixture is extracted with ethyl acetate, dried with anhydrous Na_2SO_4 and the solvents evaporated to dryness under reduced pressure. The crude is further purified by flash chromatography on silica gel to give the pure alcohol **4**.

Standard Procedure for the One-pot Asymmetric Autocatalysis of 2 and Asymmetric Alkylation: In an oven dried flask soai alcohol (*R*)-**2** (0.002 mmol, 11% *ee*), soai aldehyde **1** (0.02 mmol) and aldehyde **3** (0.200 mmol) are dissolved in 2 mL of dry toluene under nitrogen atmosphere. A solution of diisopropylzinc 1 M in toluene (0.51 mL, 0.51 mmol) is added slowly over 3 h to the mixture, and is monitored by TLC. The reaction is quenched by the addition of HCl 1 M in dioxane (0.210 mmol) and neutralized with saturated aqueous $NaHCO_3$. The mixture is extracted with ethyl acetate, dried with anhydrous Na_2SO_4 and the solvents evaporated to dryness under reduced pressure. The crude was further purified by flash chromatography on silica gel to give the pure alcohol **4**.

Acknowledgments

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