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Systematic Studies using 2-(1-Adamantylethynyl)pyrimidine-5-carbaldehyde as a Starting Material in Soai's Asymmetric Autocatalysis

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Abstract: Herein, we present a new substrate for the Soai reaction, which has an adamantylethynyl residue (1g) and exhibits asymmetric autocatalysis, yielding products with enantiomeric excesses above 99%. For the first time, all reactions were performed on a parallel synthesizer system to ensure identical reaction conditions. A detailed systematic study of reaction parameters was performed and we report the highest enhancements of enantiomeric excess reported so far in the Soai reac-

tion in one reaction cycle $(7.2 \rightarrow 94.1\%)$ *ee* or $3.1 \rightarrow 92.1\%$ *ee*). Our results led to a set of reaction parameters that yield reproducible results. Therefore, our new starting material **1g** is suitable for systematic and mechanistic studies on this remarkable reaction. A series

Keywords: asymmetric amplification • autocatalysis • chirality • systems chemistry • organozinc reagents of experiments designed to quantify the amplification of enantiomeric excess demonstrated that the reaction can be used in principle as a tool for the detection of low enantiomeric excesses: under definite conditions, an unknown low enantiomeric excess (0.1-7%) was amplified to a detectable one. A back calculation to the original value offers a new method for the determination of small enantiomeric excesses.

Introduction

The Soai reaction is a remarkable example of asymmetric autocatalysis. In this reaction, which was first discovered by Soai and co-workers in 1990, a pyrimidine-5-carbaldehyde reacts with diisopropylzinc, leading to chiral secondary alcohols (Table 1).^[1a] A substoichiometric addition of the product (itself with only a low enantiomeric excess (*ee*)) as autocatalyst at the beginning of the reaction leads to a significant enhancement of the *ee* during the reaction.^[1b] So far, the best-performing starting material, discovered by Soai's group in 1999, is 2-(*tert*-butylethynyl)pyrimidine-5-carbaldehyde (**1c**), which leads to *ee* values above 99.5% in only a few reaction cycles.^[2a,b] The nonracemic product is also obtained when a chiral compound other than the product is added at the beginning of the reaction. The plethora of suit-

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able chiral initiators includes virtually any class of chiral compounds and also chiral crystals of achiral molecules have been shown to serve as chiral initiators in this reaction.^[3] Soai and co-workers demonstrated unambiguously that even circularly polarized light can induce the formation of nonracemic product.^[4] Without the addition of chiral sources, the reaction shows spontaneous symmetry breaking.^[5] So far, the Soai reaction has proven to be an outstanding example of the incorporation of an asymmetric autocatalytic process into a classical chemical reaction. New findings suggest that such processes might also occur in organocatalytic addol and Mannich reactions.^[6]

Asymmetric autocatalytic processes are a central part of the evolving field of systems chemistry and are believed to play an important role in the origin of homochirality and life. In particular, the self-replication of biological molecules and the amplification of *ee* in the prebiotic environment are favored research topics.^[7] Therefore, the detailed knowledge of a reaction mechanism and the influence of reaction parameters as well as the structure of the starting material on the enhancement of *ee* is important for the discovery and understanding of asymmetric autocatalytic processes.

All previously published substrates that provide a high enhancement of *ee* in this reaction have been synthesized by Soai and co-workers.^[2] In this context, the crucial influence of the residue R in 1 (at the 2-position of the pyrimidine

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ring) on the asymmetric autocatalytic activity has been emphasized in many publications, but has not yet been sufficiently studied.^[8]

In Table 1, the enhancement of ee is summarized for a range of selected substrates and reveals some interesting observations: When R is hydrogen (1a), methyl (1b), or *n*-bu-

Table 1. Different substrates and their asymmetric autocatalytic activity in the Soai reaction. $\ensuremath{^{[8]}}$



[a] Taken from Figure 2 from reference [9a].

tylethynyl (1 f), moderate asymmetric autocatalytic activity is observed, whereas when R is *tert*-butylethynyl (1c) or trimethylsilylethynyl (1d), significantly higher activities are achieved. A triisopropylsilylethynyl group (1e) leads to stagnation of the enhancement. A mechanistic or structural reason for this different behavior is still lacking and no kinetic data for the different substrates under identical conditions are available. Over the last decade only one attempt to synthesize other substrates has been published.^[2c]

Even though several groups have tried to address mechanistic questions, a detailed model of the reaction mechanism and its underlying asymmetric autocatalysis on a molecular level is still incomplete and is the subject of ongoing research.^[9] Ercolani and Schiaffino recently proposed a reaction mechanism for the moderately active substrate **1b**, based on theoretical calculations in the gas phase.^[10] However, the kinetic and mechanistic understanding of the Soai reaction is still not satisfactory. Rate measurements were recorded at -45, -25, and 0°C with substrate **1c**,^[11] at 0°C with substrate **1d**,^[5b] and at +25°C with substrate **1b**.^[9c,d]

All of these substrates show typical autocatalytic behavior. Although the temperature was varied over a range of 70°C in the published measurements, the influence of temperature itself on the reaction rate or the ee has not been studied in detail. Taking into account that substrates 1b, 1c, and 1d exhibit considerable differences in asymmetric autocatalytic activity, it is still not clear whether they (and other substrates) follow the same mechanistic pathway, thus there is still a considerable knowledge gap. Blackmond and Buono published heat-flow measurements with substrate 1b at 25°C and varied reaction parameters in four different experiments, which led to a preliminary result concerning the influence of Zn(iPr)₂ (1.8 vs. 3.6 equiv) and initial ee (6 vs. 22%).^[9a,c] This resulted in an improvement of a previously published rate law proposal by Blackmond and co-workers.^[9d] Considering the limited amount of published data, this suggested rate law is the best so far because the proposed kinetic model predicts the observed time evolution in the experiment.^[9a] The influence of the amount of enantiopure autocatalyst used was investigated by Brown's group for substrate 1d.^[5b] This group also performed extensive NMR spectroscopy studies and DFT calculations, which supported a postulated $\{Zn-O\}_2$ square structure for the resting state and clarifying the necessity of the always used isopropyl group in Zn(iPr)2.^[9b,f,g] In summary, important experiments have been performed and yield a preliminary understanding of this reaction, although a full explanation is still lacking. The use of different conditions and substrates makes it particularly difficult to compare the published data.

To resolve the mechanism of the Soai reaction and to make this reaction valuable for possible applications, further experiments have to be performed. Studies on the influence of reaction parameters such as temperature, molar ratio of added reactants, ee of the added autocatalyst, and variation of substrate structures on both the ee of the newly formed product and on the detailed kinetic behavior of this reaction will lead to reliable data for the elucidation of a mechanism. Since the Soai reaction is sensitive to impurities and slight changes in reaction conditions, systematic studies should be carried out in a reaction setup that ensures reproducibility. Furthermore, repeat determinations of experiments should be performed to determine whether the reaction parameters used have been chosen in such a way as to provide reproducible results or not.^[12] In our opinion, this natural requirement of every scientific experiment demands special mention in the case of the Soai reaction, because this reaction shows bifurcation and chaotic behavior phenomena. Experimental data from previous kinetic studies usually lack explicit information on repeat determinations. Considering the Soai reaction as an ee amplification tool, it should be of interest for practical applications. Possibly it can even be used as a quantitative amplification instrument for the detection of small ee values. Even though it has been shown that the reaction is able to amplify undetectable deviations from racemic mixtures into high ee values, no detailed quantitative experiments have yet been published.

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To address the above open questions, we planned to synthesize a new starting material and to study its behavior in the Soai reaction by varying the reaction conditions in detail. To ensure identical reaction conditions and to make the reaction appropriate for use in applications, we intended to carry out reactions on a parallel synthesizer so that the quantitative behavior of the amplification can be addressed.

Results and Discussion

Synthesis of the adamantyl starting material 1g: We aimed to perform the Soai reaction with 2-(1-adamantylethynyl)-pyrimidine-5-carbaldehyde (**1g**; reaction shown above Table 2). This new compound was synthesized through Sonogashira cross-coupling of the building blocks **3** and **4** followed by subsequent formylation (Scheme 1). A similar sequence was used in the syntheses of most known Soai substrates.^[2] Compound **4** was synthesized in two steps from commercially available 2-hydroxypyrimidine hydrochloride^[13] and **3** was accessible from 1-acetyladamantane by elimination of the corresponding vinyl phosphate.^[14]



Scheme 1. Synthesis of adamantyl starting material **1g**. Reagents and conditions: a) Br₂, H₂O, then POCl₃, *N*,*N*-dimethylaniline; b) HI, CH₂Cl₂, 46% (two steps); c) -78 °C, LDA (1 equiv), CIPO(OEt)₂, -78 °C to RT, -78 °C, LDA (2 equiv), -78 °C to RT, 77%; d) [Pd(PPh₃)₄] (1.7 mol %), CuI (3.4 mol %), (*i*Pr)₂NH (4 equiv), THF, 0 °C, 24 h, 91–99%; e) -110 °C, *n*BuLi (2 equiv), TMEDA (1 equiv), 30 min, then HCO₂Et (1 equiv), 20 min, then HCl in dioxane (3 equiv), THF, -110 °C to RT, 54%. Abbreviations: TMEDA = *N*,*N*,*N*'-tetramethylethylenediamine, LDA = lithium diisopropylamide.

Formylation $(5 \rightarrow 1 g)$ was performed through bromine– lithium exchange at -110 °C followed by the addition of ethyl formate. In our system, these reaction conditions were extensively varied and optimized up to 54% yield. Use of other formylation conditions (Grignard reaction, Pd-catalyzed with CO/H₂, 30 bar) led to lower yields.

Systematic studies on the influence of reaction parameters: Our main goal was to study the influence of reaction parameters such as temperature, equivalents of $Zn(iPr)_2$, and the *ee* and the amount of autocatalyst added at the beginning of the reaction on the *ee* of the newly formed product. Therefore, product **2g** (with a definite *ee*) was used as asymmetric autocatalyst and all reactions were performed in a parallel synthesizer to ensure an identical reaction setup. Random repeat determinations of experiments were performed to examine the reproducibility of the reactions. All reactions were carried out in toluene on a 100 mg scale. It should be noted that all of our experiments were performed by the single addition of reactants and not in multistep procedures consisting of repeating enhancement cycles in one reaction, as used in most studies by Soai.^[15,16]

Influence of reaction temperature: The temperature dependency (-35 to +45 °C) of the *ee* obtained after one reaction cycle is shown in Figure 1a for (S)-2g and in Figure 1b



Figure 1. Influence of reaction temperature on *ee* of product (*S*)-**2g** (a) and (*R*)-**2g** (b). Conditions: $ee_{initial}=7.2\%$ (*S*) (a), 7.4% (*R*) (b), ratio $Zn(iPr)_2/1g/2g=1.5$:1:0.15. For data sets and details see the Supporting Information.

for (*R*)-**2g**, and reveals interesting facts not reported before. Repeat determinations led to reproducible results ($\Delta ee < 3.3\%$). Between -20 and +25°C, no significant change in *ee* was observed (69–74% *ee*, Figure 1a). It is reasonable to assume that higher reaction temperatures shift underlying equilibrium processes or favor an uncatalyzed racemic addition of Zn(*i*Pr)₂, and accordingly, a considerable decrease in *ee* was observed above +25°C (+45°C, 22.5% *ee*, (*S*)-**2g**). Interestingly, a decrease in *ee* was also observed at lower temperatures (-35°C, 45.1% *ee*, (*S*)-**2g**).

A plot of ln(er) against 1/T (er=enantiomeric ratio) exhibited nonlinear Eyring behavior (see the Supporting Information for this plot). Therefore, an explanation involving the isoinversion principle^[17] is not simply applicable also due to the still unknown reaction mechanism. The nonlinear behavior could suggest multiple reaction pathways with

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complex temperature dependencies. Even at -35 °C the reaction proceeded with complete conversion still indicating the presence of catalytic processes but with significantly lower selectivity. Further experiments are required to clarify this temperature influence. The observed temperature dependency is quite challenging for mechanistic and kinetic studies and implies a more complex picture for the Soai reaction. Detailed temperature studies on substrates other than **1g** are lacking. For further studies we propose experiments at the temperatures yielding the highest *ee* values to ensure that the phenomenon of asymmetric autocatalysis is studied at the level of highest activity. In our system, the highest *ee* values were obtained between -15 and +10 °C. Further experiments were conducted at -5 °C.

Influence of amount of low *ee* **autocatalyst added**: Varying the equivalents of autocatalyst **2** used has great influence on the *ee* of newly formed product (Table 2). On addition of large amounts of low *ee* autocatalyst one might expect a decrease in *ee* because a larger amount of the minor enantiomer was added at the beginning of the reaction. Addition of

Table 2. Influence of amount of autocatalyst added on the *ee* of newly formed product 2g.^[a]



[a] Selection of collected data, see Supporting Information for full list of experiments performed. [b] Containing the added catalyst.

lower amounts of autocatalyst results in dispersive ee values as shown by Brown et al. for enantiopure autocatalyst 1d.[5b] A determination of the optimum amount of a low ee autocatalyst required to yield high ee values has not been reported so far and our study shows interesting results for substrate 2g (Table 2): The highest *ee* of the newly formed product (S)-2g was obtained when 2.0 mol% of (S)-2g (7.2% ee) was added at the beginning of the reaction (Table 2, entry 9). This reaction outcome was reproducible in multiple experiments and held also for (R)-2g (Table 2, entry 20). Even 0.2% (S)-2g (7.2% ee) yielded (S)-2g with an ee of 89% (Table 2, entry 5). In summary, we observed that when leaving all other reaction parameters constant, a change in the number of equivalents of autocatalyst added (over two orders of magnitude, 0.2 to 20%) has no crucial influence on the ee of the newly formed product. Further reduction of the amount of (S)-2g added at the beginning of the reaction results in lower ee values, but still with enhancement of the major enantiomer. Even an extremely small amount of (S)-2g is capable of amplifying the ee: the ee value was enhanced to 17 and 40% using just 0.0004 mol% of (S)-2g (Table 2, entries 1 and 2).^[18] Here it seems that statistical effects come to the fore, or the system is very sensitive to small changes. Brown et al. observed this trend using enantiopure (R)-2d at similar amounts of added autocatalyst (~0.002% catalyst).^[5b] Hence, below this concentration, dispersive *ee* values are obtained for both low (7.2%) and high (99%) ee of the autocatalyst used.

About 20 mol% of enantiopure (S)-2g (99.1% ee) is required to maintain or even enhance the ee value up to 99.7% ee. This is consistent with reported results for the substrates 1a-1d.^[2,5b,9b] Blackmond et al. observed higher ee values when 10 mol% of enantiopure 1b was used.^[19] Comparing the enhancement in ee of our substrate 1g with those of 1a-1f, we describe conditions leading to the highest amplification of ee observed so far in the Soai reaction in one reaction cycle (Table 2, entry 9).^[20] Therefore, our starting material 1g is suitable for systematic studies.

Influence of concentration of $Zn(iPr)_2$ and total reaction volume: Blackmond et al. showed that the number of equivalents of $Zn(iPr)_2$ used has no influence on the reaction rate at +25 °C in the Soai reaction of **1b** (1.8 vs. 3.6 equiv).^[9a,c] We only observed small changes in the *ee* of **2g** when the amount of $Zn(iPr)_2$ was varied from one to three equivalents (using 2.5 mol% autocatalyst, Table 3). Lowering the amount of autocatalyst to 0.25 mol% led to differing results. Whereas 1.5 equivalents of $Zn(iPr)_2$ led to reproducible results at both catalyst concentrations (Table 3, entries 1, 2, 7, and 8), the use of two or three equivalents led to dispersive *ee* enhancement at low catalyst concentration, which indicates that these conditions exhibit complex and chaotic behavior in the amplification of *ee*.

The influence of the total reaction volume on *ee* was checked using half, respectively double amount of the otherwise used solvent amount (Table 4). Only small changes in *ee* enhancement were obtained in the concentration range

Table 3. Influence of the amount of $Zn(iPr)_2$ on *ee* (reaction shown above Table 2).

	Chira	additiv			
Entry	Compound	ee [%]	mol %	Zn(iPr) ₂ [equiv]	ee product [%] ^[a]
1	(S)-2g	7.2	2.5	1.5	92.8
2	(S)- 2 g	7.2	2.5	1.5	93.6
3	(S)- 2 g	7.2	2.6	2	84.9
4	(S)- 2 g	7.2	2.5	2	91.4
5	(S)- 2 g	7.2	2.6	3	89.7
6	(S)- 2 g	7.2	0.25	1	73.1
7	(S)-2g	7.2	0.25	1.5	88.8
8	(S)- 2 g	7.2	0.23	1.5	89.4
9	(S)- 2 g	7.2	0.25	2	83.1
10	(S)- 2 g	7.2	0.25	2	11.4
11	(S)- 2 g	7.2	0.25	2	73.0
12	(S)-2g	7.2	0.25	3	62.3
13	(S)- 2 g	7.2	0.25	3	14.9

[a] Containing the added catalyst. All reactions were carried out at -5 °C, see Supporting Information for details.

Table 4. Influence of the total reaction volume on the *ee* (reaction shown above Table 2).

	Chir				
Entry	Compound	ee [%]	$c \ (\mathbf{1g}) \ [mol \ L^{-1}]$	V_{total} (toluene)	ee product [%] ^[a]
1	(R)- 2 g	7.4	0.089	4.2	92.3
2	(R)-2g	7.4	0.089	4.2	88.8
3	(R)-2g	7.4	0.045	8.5	93.4
4	(R)-2g	7.4	0.044	8.5	91.8
5	(R)-2g	7.4	0.022	17	94.8
6	(R)-2g	7.4	0.022	17	95.0

[a] Containing the added catalyst. All reactions were carried out at -5 °C, ratio Zn(*i*Pr)₂/**1g**/**2g** = 1.5:1:0.020, see the Supporting Information for details.

studied to indicate a slightly better enhancement when the initial concentration of 1g was 0.022 M.

Enhancement of low ee catalyst in the Soai reaction: A tool for determination of small ee values: Having established the optimum reaction conditions to yield product 2g with high ee values, we started varying the ee of autocatalyst 2g in the low ee range (Figure 2). Lowering the ee from 7 to 0.1 % led to an almost linear decrease in the ee of the obtained product (in a logarithmic plot). In the range of 1 to 0.1% ee, the results became slightly dispersive ($\Delta ee < 12\%$). Below 0.1 % ee, the results were scattered quite strongly but all still show enhancement and the same handedness. Adding catalyst with 0.001% ee yielded (in two experiments) 40.3 and 84.6% ee. Adding 2 mol% of rac-2g resulted in spontaneous symmetry breaking to give 2g with both R and S configurations.^[21] In summary, we have studied the character of the amplification of small ee values and demonstrated in principle the use of the Soai reaction as a tool for the detection of small ee values. Under definite conditions, an unknown small ee value (ee_x) could be amplified to a detectable one $(ee_{\rm x})$ and a back calculation yields the original value $(ee_{\rm x})$. It



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Figure 2. Amplification of *ee* after addition of low *ee* (*S*)-**2g**. All reactions performed in toluene at -5° C, ratio Zn(*i*Pr)₂/**1g**/**2g**=1.5:1:0.02. See the Supporting Information for details and data.

is evident that repeat determinations are necessary to ensure that the measured probe is within the area of reproducibility (0.1–7% *ee*). A concrete calculation example for a logarithmic fit in the area 0.1–7% *ee* in Figure 2 for a measured *ee* value $ee_{y1} = (75.0 \pm 5.0)$ % affords an original value of $ee_{x1} = (0.35 \pm 0.28)$ %. Compared with the result obtained in our study that an *ee* value of $ee_{x2} = 0.5$ % is amplified to $ee_{y1} = (75.0 \pm 5.0)$ % the determination of *ee* values with $ee_x < 4$ % with the given accuracy is quite remarkable (the model in the given reaction conditions has a lower boundary of 0.1% *ee*). The collection of more data will clearly reduce the error and lead to more accurate results.

Because the Soai reaction is sensitive to various added sources of chirality, the reaction could be used as a general tool for the determination of small *ee* values for other pure compounds under standardized conditions. The determination of whether tuning of the reaction parameters (e.g., higher amount of used catalyst) will lead to reproducible enhancement of still smaller *ee* values will be the subject of future experiments.

We have investigated the ability of chiral initiators to induce chirality in 1g, as studied frequently by Soai et al. for compound $1c.^{[22]}$ Treatment of 1g with $Zn(iPr)_2$ in the presence of (S)-1-phenylethylamine as chiral initiator (21 mol%) yielded (R)-2g with 92% ee. The use of (R)-1phenylethylamine (21 mol%) resulted in an ee of 92% for (S)-2g. By using the chiral bis-sulfoxide (1R,3R)-2-benzylidene-[1,3]dithian-1,3-dioxide^[23] (20 mol%) as chiral initiator yielded (S)-2g with an ee of 77%. Sulfoxides have not previously been tested as chiral initiators and we hereby show that they also serve as excellent molecules for this purpose. Again, our implementation in a parallel synthesizer system yielded reproducible results in repeat determinations ($\Delta ee <$ 3%). Compared with the laborious multistep reaction setup used by Soai's group for their studies with chiral initiators,^[16] our procedure (consisting of mixing reagents, adding $Zn(iPr)_2$, and stirring) to yield high *ee* values is quite a simple approach. An expansion of our work would be to attempt to transfer the determination of small ee values of 2g to the determination of small ee values of any chiral compound, and this will be a challenging subject of our further research.

Conclusions

The Soai reaction offers a chance to study the phenomenon of asymmetric autocatalysis in the form of a chemical reaction. To perform detailed studies, a setup that ensures identical reaction conditions was necessary. This was accomplished by performing the reaction in a parallel synthesizer system. We present a new starting material 1g for the Soai reaction, which shows high asymmetric autocatalytic activity, together with a detailed study that led to the highest enhancement of ee reported so far in the Soai reaction in one reaction cycle $(3.1 \rightarrow 92.1\%)$. We emphasize the important influence of the residue at the 2-position in 1 for the asymmetric autocatalytic activity. Comparative studies of the different substrates are not yet available and should be useful for mechanistic investigations. Compound 1g exhibits typical behavior in the Soai reaction as observed for other starting materials 1a-1f. It was shown that high ee values can be induced by different chiral initiators and in the absence of a chiral source the reaction shows spontaneous symmetry breaking. Beyond the confirmation of known facts, we have demonstrated that the reaction parameters have to be chosen carefully to yield reproducible results. On the other hand, the parameters can be tuned in such a way that definitely scattered ee values are obtained. The consideration of this boundary between reproducible and scattered results is important for all mechanistic studies. The influence of the reaction temperature on ee amplification reveals a decrease at lower temperatures, indicating a still more complex mechanism for the Soai reaction. The transfer of our findings to an application as a general tool for the determination of small ee values of any chiral compound might be possible and will be the subject of further investigations.

The Soai reaction is one of the most successful asymmetric autocatalytic reactions. Our present study on the new substrate **1g** expands our understanding of this remarkable reaction and offers a means for possible application of the reaction. Our work should therefore stimulate further research in this field.

Experimental Section

General: Toluene, pentane, tetrahydrofuran, and diisopropylamine were freshly distilled over sodium/benzophenone ketyl before use. Syntheses of $3^{[14]}$ and $4^{[13]}$ are published elsewhere, and $Zn(iPr)_2$ was prepared according to Knochel's protocol.^[24] A solution of $Zn(iPr)_2$ (c=0.5-2.0 M) was prepared by diluting freshly distilled $Zn(iPr)_2$ in toluene. Concentration was determined by titration versus iodine in a LiCl solution (0.5 M in THF) until the violet color vanished (mean value over three independent titrations).^[25] The concentrations of commercial *n*BuLi (Sigma–Aldrich) solutions were determined by performing titration with diphenylacetic acid or salicyl aldehyde phenylhydrazone.^[26] All moisture-sensitive reactions were carried out under oxygen-free argon using heat-gun-dried glassware and a vacuum line. Flash column chromatography^[27] was carried out by using Merck silica gel 60 (230-400 mesh) and TLC was carried out by using commercially available Merck F254 pre-coated sheets. ¹H and ¹³C NMR spectra were recorded on Bruker Cryospek WM-250, AM-400, and DRX 500 spectrometers. The spectra were measured at room temperature unless noted otherwise. Chemical shifts are given in ppm downfield of tetramethylsilane or calibrated to the CHCl₃ solvent signal. ¹³C NMR spectra were recorded with broadband proton decoupling and were assigned using DEPT experiments. Melting points were measured on a Büchi 530 melting point apparatus and are not corrected. IR spectra were recorded on a Bruker IFS-88 spectrophotometer. Elemental analyses were performed on an Elementar Vario MICRO instrument. Electron-ionization and high-resolution mass spectra were recorded on a Finnigan MAT-90 spectrometer. Determination of ee values by HPLC was performed using a Chiralcel OD-H column and hexane/2propanol as solvent (HPLC-grade quality, Fisher scientific). Flow rate, solvent ratio, and retention time are given in the particular procedures. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter and specific optical rotations $[\alpha]^{20}_{\rm D}$ are given in units of $10^{-1}\, \mbox{deg}\,\mbox{cm}^2\,\mbox{g}^{-1}.$ The Soai reactions were performed in a Heidolph Synthesis Liquid 16 parallel synthesizer. Temperature tuning was achieved by connecting the parallel synthesizer to a Lauda PROLINE RP890 cryostat.

Synthesis of 5: THF (140 mL) and diisopropylamine (16.7 mL, 119 mmol) were added to a heat-gun-dried Schlenk tube charged with 4 (8.47 g. 29.7 mmol). tetrakis(triphenylphosphane)palladium (584 mg, 0.505 mmol), and CuI (192 mg, 1.01 mmol). The resulting milky solution was degassed (three freeze-thaw cycles with liquid nitrogen under vacuum). Compound 3 (5.00 g, 31.2 mmol) was added at 0°C and the reaction mixture was stirred at 0 °C until complete conversion was observed (typically 24 to 48 h reaction time; 0.1 mL samples of the reaction mixture were removed, filtered over Celite, and analyzed by ¹H NMR). After filtration through Celite, the solvents were removed in vacuo and the residue was purified by column chromatography (cyclohexane/EtOAc 20:1) to yield **5** as a white crystalline solid (8.54 g, 26.9 mmol, 91 %). $R_{\rm f}$ = 0.55 (hexanes/EtOAc 5:1); m.p. 175-176 °C; ¹H NMR (400 MHz, CDCl₃, TMS): $\delta = 1.65$ (s, 6H), 1.94 (s, 9H), 8.65 ppm (s, 2H; aromatic-H); ¹³C NMR (101 MHz, CDCl₃, TMS): $\delta = 27.5$ (d), 29.9 (s), 36.0 (t), 41.7 (t), 78.1 (s), 99.0 (s), 118.3 (s), 151.1 (s), 157.6 ppm (d); IR (KBr): $\tilde{\nu} = 3026$, 2927, 2900, 2853, 2220 (alkyne), 1526, 1417, 1368, 1239, 1109, 1013, 933, 790, 653, 542 cm⁻¹; MS (EI, 70 eV): m/z (%): 316 (100) [M^+], 301 (3), 275 (12), 261 (15), 55 (23), 41 (56); HRMS (EI): m/z calcd for C16H17BrN2: 316.0575; found 316.0578; elemental analysis calcd (%) for C₁₆H₁₇BrN₂: C 60.58, H 5.40, N 8.83; found: C 60.30, H 5.59, N 8.74.

Synthesis of 1g: nBuLi (11.8 mL of a 1.60 M solution in hexane, 18.9 mmol) was added over 20 min using a syringe pump to a solution of (3.00 g, 9.46 mmol) and N, N, N', N'-tetramethylethylenediamine 5 (1.45 mL, 9.46 mmol) in THF (150 mL) at -110 °C (temperature of the ethanol/N2 (l) cooling bath). After complete addition the yellow solution was stirred for 30 min at -110°C. At this time the bromine-lithium exchange is complete as shown by TLC or GC-MS. Then, a solution of ethyl formate (1.52 mL in 5 mL THF, 18.9 mmol) was added dropwise over 5 min by using a syringe pump. After 15 min of stirring at -110°C a solution of HCl in dioxane (7.03 mL, 4.03 M, 28.4 mmol) was added dropwise within 5 min, the cooling bath was removed, and the solution was allowed to warm to 0°C. Water (40 mL) and a saturated aqueous solution of NaHCO₃ (40 mL) were added followed by extraction with EtOAc ($3 \times$ 70 mL). The combined organic extracts were dried over Na₂SO₄, filtered through Celite, and the solvents were removed in vacuo. The crude yellow product was subjected to column chromatography (cyclohexane/ EtOAc 20:1) to yield 1g as a white to slight yellowish solid, which was sometimes contaminated with a side product (2-(1-adamantylethynyl)pyrimidine). Recrystallization from hot cyclohexane yielded pure 1g as a white crystalline solid (1.35 g, 5.07 mmol, 54%). $R_{\rm f}$ = 0.50 (hexane/EtOAc 2:1); m.p. 160–162 °C; ¹H NMR (400 MHz, CDCl₃, TMS): $\delta = 1.69$ (s, 6H), 1.99 (s, 9H), 9.06 (s, 2H; aromatic-H), 10.08 ppm (s, 1H; -CHO); ¹³C NMR (101 MHz, CDCl₃, TMS): $\delta = 27.5$ (d), 30.2 (s), 36.0 (t), 41.7 (t), 79.3 (s), 102.6 (s), 126.1 (s), 156.4 (s), 158.1 (d), 188.2 ppm (d); IR (KBr): $\tilde{v} = 2931$, 2854, 2215 (alkyne), 1710 (aldehyde), 1579, 1542, 1423, 1367, 1344, 1216, 797 cm⁻¹; MS (EI, 70 eV): m/z (%): 266 [M^+] (14), 58 (38), 43 (100); HRMS (EI): *m/z* calcd for C₁₇H₁₈N₂O: 266.1419 [*M*⁺]; found:

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266.1417; elemental analysis calcd (%) for $C_{17}H_{18}N_2O$: C 76.66, H 6.81, N 10.52; found: C 76.26, H 6.91, N 10.37.

Representative experimental procedure for a Soai reaction in a parallel synthesizer: Full experimental details of all runs can be found in the Supporting Information. An oven-dried Heidolph Synthesis Liquid-16 tube was charged with 1g (100 mg). A chiral initiator can be added now as a solid or later in the form of a stock solution (noted for each experiment in the Supporting Information). The tube containing all solids was evacuated and flushed with argon (three times) followed by the addition of freshly distilled toluene in an amount such that the final reaction volume (including the $Zn(iPr)_2$ solution to be added later) is 8.5 mL. The reaction was carried out at -5°C (unless noted otherwise). The temperature tuning with the connected cryostat took about one hour. Upon reaching the exact temperature (measured with a temperature sensor inside the reaction vessel) the required amount of $Zn(iPr)_2$ (c=0.5-2.0 M in toluene) was added by syringe in a single shot into the shaking reaction mixture. The reaction was performed for 12-15 h at -5°C under vigorous shaking. The solution was quenched by addition of a 1 M aqueous solution of HCl (7 mL) followed by careful addition of an ice-cold saturated solution of NaHCO₃ (20 mL), and extraction with EtOAc (2×20 mL). The combined organic phases were dried over Na2SO4 and filtered over Celite. The solvents were removed in vacuo and the crude product was obtained as a pale-yellowish solid. The ee value was determined by using chiral HPLC of the crude reaction product (retention time (-)-(S)-2g 13 min, (+)-(R)-2g 26 min, hexane/isopropyl alcohol (93:7) 1.5 mL min⁻¹). For determination of the absolute configuration of the product, compound (S)-2g was synthesized through asymmetric addition of $Zn(iPr)_2$ to 1g in the presence of (1S,2R)-(-)-2-(dibutylamino)-1-phenyl-1-propanol ((-)-DBNE), which then allowed an assignment of HPLC peaks to the absolute configuration of 2g.^[28] All reactions proceeded with complete consumption of the starting material and yielded pure product (purity checked by HPLC analysis of the crude product with the integrated chromatogram 240-261 nm; in the majority of the runs the sum of the peak areas of both enantiomers was in the range 95-99.5%; details are given in the complete list of all runs in the Supporting Information).

(S)-2g: $R_{\rm f}$ =0.46 (hexanes/EtOAc 1:1); m.p. 176–178°C; $[\alpha]_D^{20}$ =–27.4 (*c*=1.01 in CHCl₃); ¹H NMR (400 MHz, CDCl₃, TMS): δ =0.84 (d, *J*= 6.8 Hz, 3H), 0.91 (d, *J*=6.7 Hz, 3H), 1.68 (s, 6H), 1.97 (s, 9H), 1.89–2.00 (m, 1H), 3.17 (s, 1H), 4.47 (d, *J*=5.5 Hz, 1H), 8.54 ppm (s, 2H); ¹³C NMR (101 MHz, CDCl₃, TMS): δ =17.4 (q), 18.3 (q), 27.7 (d), 29.9 (s), 35.1 (d), 36.1 (t), 42.0 (t), 75.0 (d), 78.7 (s), 97.5 (s), 134.4 (s), 152.0 (s), 155.5 ppm (d); IR (KBr): $\tilde{\nu}$ =3300, 2906, 2851, 2221 (alkyne), 1543, 1427, 1019, 809, 666 cm⁻¹; MS (FAB): *m*/*z*: 311 [*M*+H⁺]; HRMS (FAB): *m*/*z* calcd for C₂₀H₂₇ON₂: 311.2123 [*M*+H⁺]; found: 311.2120; elemental analysis calcd (%) for C₂₀H₂₇ON₂: C 77.38, H 8.44, N 9.02; found: C 77.10; H 8.12, N 8.92.

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