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SHORT COMMUNICATION

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One-Pot Synthesis, Crystallization and Deracemization of Isoindolinones from Achiral Reactants

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The synthesis, crystallization, and complete solid-state deracemization of isoindolinones was realized in one pot simply by grinding achiral reaction components in a suitable solvent with an achiral catalyst. Previously, this concept was applied to a reversible reaction, but herein we showed that it could also be used in combination with reactions in which product formation is irreversible. A controlled final configuration of the product was obtained by using small amounts of chiral additives or seed crystals of the product.

Introduction

Enantiopure compounds in nature emerged under seemingly simple prebiotic conditions, yet creating them in the laboratory under achiral circumstances still remains a formidable challenge to date. This challenge affects the chemical industry, which has to produce vast amounts of enantiopure building blocks for application in food and pharma products. The number of enantiopure drugs being launched is steadily increasing, so the development of novel methods to obtain enantiopure compounds is of paramount interest.[1] The chirality of the solid state can be used as a tool for asymmetric synthesis. Achiral molecules that form chiral crystals can be subjected to solid-state reactions to deliver enantiomerically enriched products.[2] Moreover, a number of chiral molecules that undergo racemization in solution can undergo enantioselective autocatalysis upon crystallization.[3] This latter approach can also be combined with a reversible reaction, in which the chiral product undergoes racemization through its achiral precursors. Reversible Mannich[4] and reversible aldol[5] reactions were previously used to obtain enantiopure products. However, these examples only work if there is a rather large initial enantiomeric excess (*ee*) present from the beginning. Single chirality can also emerge from an initial mixture of achiral reactants and seed crystals of the product. This way, only one chiral form of an oxorhenium(V) complex, in which the final configuration depended on the seed crystals, was obtained.[6]

We recently showed that an enantiopure (100% *ee*) intrinsically chiral product [i.e., molecules that contain a tetrahedral stereocentre, being either (*S*) or (*R*)] could be obtained from its corresponding achiral precursors in high yield without any preadded chiral agents (Figure 1).[7] During this process, the achiral enone and *p*-anisidine undergo a reversible aza-Michael addition in solution to give both enantiomeric β-amino ketones, which rapidly crystallize as racemic conglomerate crystals. These crystals repeatedly dissolve, racemize in solution, and grow under grinding conditions and, as such, undergo deracemization through Viedma ripening.[8] Overall, this procedure encompasses a one-pot transformation involving three steps: (1) synthesis of the product from achiral reactants, (2) crystallization, and (3) solid-state deracemization of the product under grinding conditions, after which the enantiopure product can simply be filtered from the solution. Such a one-pot multistep conversion, in which a combination of processes occur without intermediate recovery steps, reduces the number of unit operations, which thereby makes this pro-

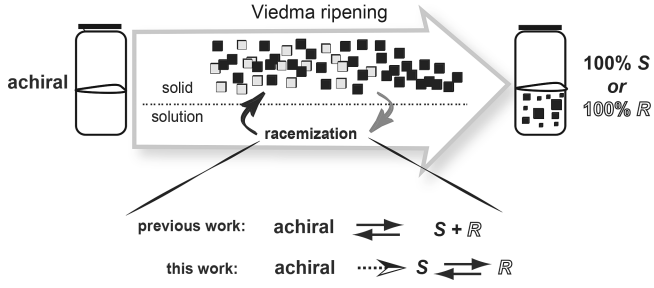

Figure 1. One-pot synthesis of enantiopure solids from achiral molecules. The previously reported racemization step involved only the reverse reaction.[7] This work involves two reactions: (1) irreversible product formation and (2) a racemization reaction of the product.

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cess economical and sustainable.[9] Moreover, in situ product precipitation can offer many advantages, for instance, during continuous crystallization,[10] an approach that already has led to the continuous resolution of crystals of threonine.[11]

Key in the previous one-pot deracemization procedure is a reversible aza-Michael reaction, in which the combination and elimination of *p*-anisidine with an enone proceed under the same conditions, which causes continuous solution-phase racemization. A single reversible reaction thus leads to product formation as well as racemization in solution. More recently, the synthesis of an enantiomerically enriched α-aminonitrile from its achiral precursors was realized through crystallization-induced asymmetric synthesis.[12] Although the yield and *ee* were somewhat moderate, this latter example demonstrates the clear implication of this one-pot deracemization approach to studies on the origin of chirality.

In this work, we used an irreversible reaction to make a chiral product and a reversible ring-opening and ring-closure reaction to induce racemization in solution. The irreversible reaction involves the formation of isoindolinones, a building block that might be used in the synthesis of a number of pharmaceutical drugs.[13] This one-way addition of achiral amines to achiral acid chlorides proceeds rapidly, which leads to a racemic mixture of enantiomers. The isoindolinone products are not in equilibrium with the achiral precursors but racemize in solution through an equilibrium of the N,O-acetal with the ring-opened form. After precipitation of the product, the crystals undergo deracemization through Viedma ripening. This way, three different isoindolinones could be obtained in good yields and in enantiopure solid form under initially achiral conditions.

Results and Discussion

Isoindolinones **1**–**3** (Figure 2) crystallize as separate enantiopure crystals (i.e., racemic conglomerate crystals).[14] Conglomerate crystal formation is required for the crystalline product to undergo deracemization. In solution, the synthesis of isoindolinones **1**–**3** proceeds through the irreversible reaction of acid chloride **4** with the corresponding amine (Figure 2a). We found that this reaction could be promoted by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Moreover, molecules **1**–**3** undergo racemization in solution through a ring-opening and -closing mechanism, which can be induced by catalytic amounts of the same DBU.[14]

The combination of conglomerate crystallization and racemization in solution allows for the complete deracemization of isoindolinones **1**–**3** through total spontaneous resolution[14] or Viedma ripening (Figure 2b).[15] The synthesis of the isoindolinones from the corresponding precursors proceeds smoothly in THF, in which the reactants and products readily dissolve. However, to combine the synthesis and deracemization of isoindolinones **1**–**3** in one pot, precipitation of the product is required. Therefore, water was added prior to the experiment to enable precipitation of the product during the reaction. A typical experiment involves mixing of all the required achiral components (i.e., acid chloride **4**, the amine, glass beads, DBU, the solvents THF and water, and a stirring bar) into a round-bottomed flask. Once combined, the solution was stirred at full speed, after which precipitation of the product started. The *ee* of the solids was monitored over time to show that an enantiopure solid state was obtained within 2 d for all three isoindolinones (Figure 3).

To date, these isoindolinones were typically acquired through a homogeneous solution-phase reaction, after which quenching, multiple extractions, washing steps, drying, filtering, solvent removal, and solid-state deracemization were needed to arrive at an enantiopure product.[14] With the herein reported protocol, these typical workup procedures can be avoided, as the enantiopure product can simply be isolated through filtration from the flask in which the reaction took place.

The experiments reproducibly resulted in the complete transformation of achiral starting materials into the

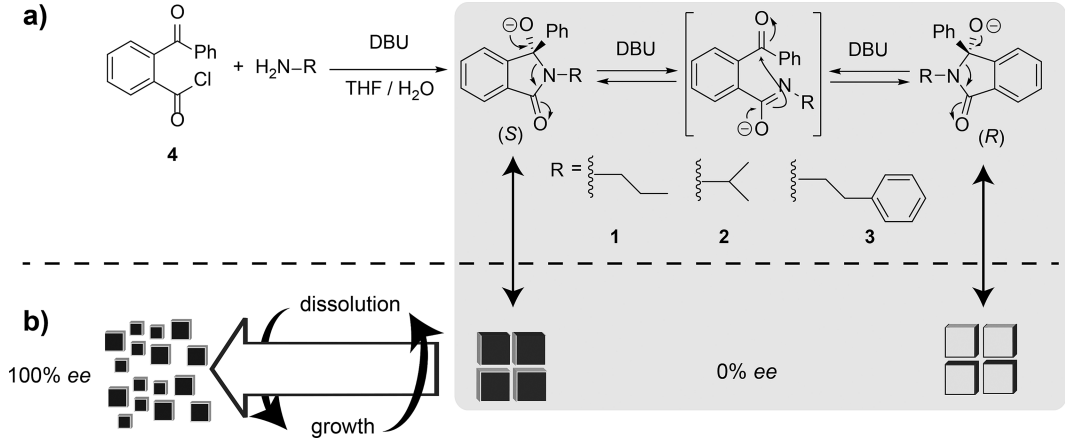

Figure 2. One-pot transformation of achiral reactants into enantiopure isoindolinone crystals. (a) In solution, achiral precursor **4** reacts with the appropriate amine (H_2NR) to give isoindolinones **1**, **2**, and **3**, which racemize through an achiral intermediate. (b) Both enantiomers crystallize and undergo complete deracemization through Viedma ripening.

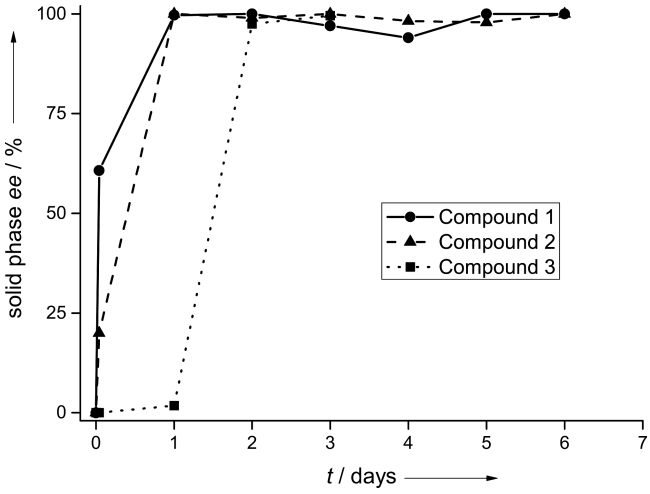

Figure 3. Evolution of the solid-phase *ee* over time for all three isoindolinones.

enantiopure products (Table 1). As these experiments start under achiral conditions, it is expected that the final configuration of the product is either (*R*) or (*S*) with equal probability. We found that enantiopure isoindolinone **1** was obtained 4× (*R*) and 2× (*S*) (Table 1, Entry 1). On the other hand, enantiopure isoindolinone **2** was more often obtained with a final (*S*) configuration (Table 1, Entry 2). The transformation of achiral reactants into enantiopure isoindolinone **3** proceeded to give 6× (*R*)-**3** and 5× (*S*)-**3**.

Table 1. Final configuration of the product depending on the presence or absence of additives or seed crystals.

Entry	Isoindolinone	Additive/seed	Final configuration of product[a]
1	**1**	–	4× (*R*); 2× (*S*)
2	**2**	–	2× (*R*); 6× (*S*)
3	**3**	–	6× (*R*); 5× (*S*)
4	**2**	(*S*)-**1**[b]	4× (*R*); 1 × (*S*)
5	**1**	(*S*)-**1**[c]	5× (*S*)
6	**3**	(*R*)-**3**[c]	5× (*R*)

[a] The *ee* of the samples in each experiment was >99.9%. [b] Additive (1.3 mol-%) was added right before stirring. [c] Seed crystals (2.5 mol-%) were added right before stirring.

A nonstochastic outcome can be explained by the presence of chiral impurities that affect the crystal growth of one of the enantiomers.[16] The effect of chiral impurities can be overruled by using chiral additives that closely resemble the molecule that undergoes deracemization.[16] Isoindolinone **1** would be a suitable additive for the deracemization of isoindolinone **2**, as these molecules crystallize in the same space group (i.e., $P2_12_12_1$)[14] and are structurally similar. We indeed found that the addition of (*S*)-**1** (1.3 mol-%) gave (*R*)-**2** in most experiments, following Lahav's rule of reversal[17] (Table 1, Entry 4). In a different way, (*S*)-**1** was reproducibly obtained by using seed crystals of the same (*S*)-**1** (Table 1, Entry 5). Owing to fast precipitation of the product, most likely the unwanted enantiomeric form also precipitated, as was observed in previous studies for different reactions.[9b,18] The subsequently applied Viedma ripening conditions ensure in all cases that the enantiopure product was obtained with the same configuration as that of the seed crystals. The final configuration of isoindolinone **3** could also be controlled by using seed crystals of the same product (Table 1, Entry 6).

After filtration, white crystals of the product were obtained in about 55–74% yield with 97% *ee*. (see the Supporting Information). DBU likely incorporates into the crystal structure of the product, which results in trace amounts of DBU in the solid phase that can easily be removed by recrystallization. The mother liquor consisted of only the product and DBU, which shows that no side reactions were involved during the experiments.

Conclusions

We herein showed that the concept of crystallization-induced asymmetric synthesis of enantiopure products from achiral precursors can be extended to irreversible reactions. Our proof of concept involves the synthesis of three different enantiopure isoindolinones from the general reaction between an achiral acid chloride and an achiral amine. This one-pot procedure was developed to allow racemization in solution and formation of conglomerate crystals, two requirements that enable complete deracemization of the solid state through Viedma ripening. The final configuration of the product could be controlled by enantiopure additives or, more efficiently, by using seed crystals of the desired product. Isolation of the product was simply achieved through filtration, which avoided the many workup steps that are otherwise required for this type of reaction.

Experimental Section

Typical Procedure for the Synthesis of Enantiopure Isoindolinones from Achiral Reactants in One Pot: Benzoyl chloride derivative **4** (1.25 mmol) was dissolved in THF (0.5 mL) in a round-bottomed flask (25.0 mL) that was filled with glass beads (7 g) and an octahedral stirring bar. The solubility of isoindolinone **3** was significantly lower than the solubility of isoindolinones **1** and **2**,[15] and therefore, a larger amount of THF (1.3 mL) was used for the synthesis of compound **3**. The solution was cooled by using an ice bath, and the appropriate amine (1.25 mmol), DBU (1.50 mmol), and water (1.0 mL) were added to the flask. The resulting mixture was stirred at 600 rpm at room temperature; samples of the solids were collected by filtration, and the *ee* was measured by using HPLC on a chiral stationary phase.

Supporting Information (see footnote on the first page of this article): Description of the remaining methodology as well as spectra of all three isoindolinones.

Acknowledgments

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