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Crystallization-Driven Asymmetric Synthesis of Pyridine-β-nitroalcohols via Discovery-Oriented Self-Resolution of a Dynamic System

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The study of dynamic nitroaldol systems aided the discovery of a diastereoselective crystallization process through amplification of 2-nitro-1-(pyridine-4-yl)propan-1-ol. The phenomenon was further developed into an effective procedure for asymmetic synthesis of pyridine-nitroalcohols and several substrates were screened to this end. These results demonstrate how work with larger dynamic systems facilitates and increases the likelihood of serendipitous discoveries.

Introduction

Complex mixtures of molecules generally present a challenge in synthetic chemistry, but these systems can also be used as an advantage in discovery processes. Besides the traditional, and essential, quest of developing high-yielding reactions of single molecules, avoiding the formation of multiple products, discovery-oriented approaches can encompass larger chemical space in single operations. With the recent rapid development of more sophisticated analytical techniques, the field of systems chemistry[1] has emerged as a chemical analogy to the already well established field of systems biology.[1–3] Systems chemistry focuses on the study of complex systems of molecules and their interactions. It is potentially a very broad field ranging from interactions of molecules in the atmosphere, to the primordial soup and "origin of life"-centered research. Systems chemistry provides an overview and a better viewpoint for general understanding of chemical systems. It also embraces complexity and diversity, seeing it as a way of maximizing the likelihood of new discoveries.

Dynamic combinatorial chemistry (DCC) is an expanding part of systems chemistry based on reversible interactions, covalent or supramolecular, between the system components.[4,5] This allows the system to constitutionally evolve according to the laws of thermodynamics. Subsequently, when a thermodynamic driving force, such as a template or a receptor, is applied, it will force the system to produce more of the fittest combinations of building blocks. However, these dynamic systems may also be controlled kinetically. This has been termed dynamic combinatorial resolution[6] and several examples have recently been demonstrated in our laboratory.[6,7] An application that has grown recent interest, is the control of dynamic systems by a phase-change, such as crystallization.[7b,8] This is an area which might help shed light on how nature presently is, and historically was, capable of building advanced functional systems from complex mixtures of molecules. However, it requires "further fundamental and intensive investigation" as suggested by other contributors.[8d,8e]

We have recently demonstrated the nitroaldol (Henry) reaction to be a reversible C–C bond forming reaction, for efficient use in dynamic systems and DCR processes.[6,7b,7c] As shown in these reports, designed systems could be efficiently resolved by enzymes,[6] or an irreversible intramolecular reaction followed by crystallization.[7b,7c] Another important but often neglected advantage of working with larger complex systems is, however, the increased potential of new discoveries. This process, often referred to as serendipitous discovery, is an important part of research as it is free of scientific bias, and also often provides results that would have been difficult to predict.

In this communication, we describe how studies on dynamic nitroaldol systems led to the discovery of interesting crystalline properties of certain pyridine-β-nitroalcohols. The discovery was further expanded into a synthetic procedure and a number of substrates were investigated to this end.

Results and Discussion

A dynamic system consisting of nine aromatic aldehydes **1**–**9** mixed with one equivalent of nitroethane **10** and triethylamine in deuterated chloroform was monitored by ^{1}H-NMR spectroscopy (Figure 1). After being left overnight (t = 17 h), an irregularly large amount of 4-pyridinecarbaldehyde **8** had been consumed (Figure 1, b). On the other

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hand, there was no large amplification of nitroaldol adducts. Upon examination of the actual NMR sample, however, a crystalline solid was observed in the tube. Filtration and subsequent ^{1}H-NMR analyses confirmed the product to be nitroaldol adduct **18**. Furthermore, the isolated crystalline material was obtained in a diastereomeric ratio of 90:10. The identity of the amplified diastereoisomer was determined by X-ray crystallography to be the (*R*,*R*)/(*S*,*S*) isomer, present in a racemic mixture. Due to the fact of working with a complex dynamic system (46 components including isomers), this clear example of packing in solution and consequent diastereoselective crystallization[9] could both be discovered and clearly demonstrated simultaneously.

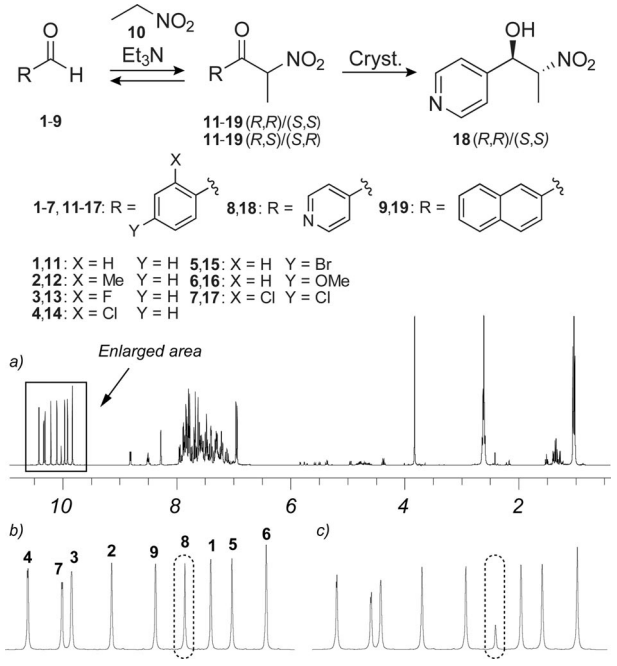
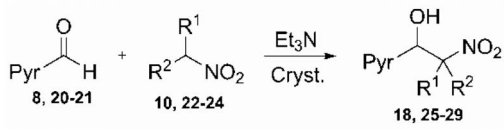


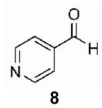
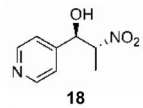
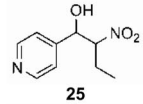
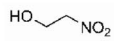
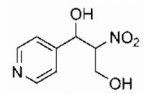
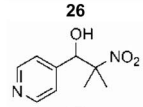
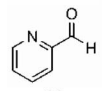
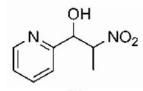
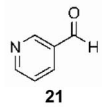
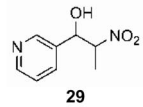
Figure 1. Selected ^{1}H-NMR spectra for the dynamic nitroaldol system. a) Full spectrum, after 17 h. b) The aldehyde region directly after the addition of base ($t \approx t_0$). c) The aldehyde region, after 17 h.

Next, the discovered phenomenon was investigated in single compound synthesis. By increasing the concentration, the conversion of the precipitated nitroaldol product **18** could be increased to over 95%, and diastereoselectivity to more than 96:4, after being left at room temperature overnight. Pure product could then be isolated by simple filtration. At times, however, no crystallization occurred even when the reaction was left for more than a week. ^{1}H-NMR of these samples showed supersaturated mixtures containing **18**, however without diastereomeric preference (see Supporting Information). By adding a small piece of solid, such as broken glass, the precipitation started instantly, again yielding product in close to perfect *dr*. This procedure was then used continuously in the reaction procedure and made precipitation start within seconds after mixing the starting materials.

The reaction was further tested with other pyridinecarbaldehydes **20**–**21** and nitroalkanes **22**–**24** in order to investigate the scope of this crystallization-driven reaction (Table 1). The reaction of 4-pyridinecarbaldehyde **8** with 1-nitropropane **22** (entry 2) resulted in no precipitation, which could be due the fact that the extra methyl group of **25** inhibits close packing, making crystal formation less favorable. The use of 2-nitroethanol **23** as the nitroalkane (entry 3) resulted in the formation of an adhesive gum, and ^{1}H-NMR analysis indicated a complex mixture of several compounds. This variation was more expected because of the introduction of an additional group capable of hydrogen bonding. 2-nitropropane **24** (entry 4), however, worked similarly as the reaction with nitroethane **10** (entry 1), yielding the corresponding β-nitroalcohol **27** in more than 95% conversion as a white powder. Apparently, the increased steric demand of an extra methyl group in this position does not affect crystallization notably. Switching the aldehyde to 2-pyridinecarboxaldehyde **20** and 3-pyridinecarboxaldehyde **21**, again using nitroethane as the nitroalkane (entries 5 and

Table 1. Crystallization-driven synthesis of pyridine-β-nitroalcohols.[a]



Entry	Aldehyde	Nitroalkane	Product	Conv.[b]
1	 **8**	 **10**	 **18**	>95 % (*dr* > 96:4)
2	**8**	 **22**	 **25**	–[c]
3	**8**	 **23**	 **26**	–[d]
4	**8**	 **24**	 **27**	>95 %
5	 **20**	**10**	 **28**	–[c]
6	 **21**	**10**	 **29**	–[c]

[a] Reactions was performed with 1 mmol of each reagent in 0.6 mL of chloroform. [b] Conversions was determined by ^{1}H-NMR analysis of the supernatant after filtration of the product. Filtration yielded pure product. Some loss in yield was experienced upon removal of the precipitation from the reaction flask. [c] No precipitation occurred. [d] An adhesive gum was formed, containing a complex mixture of products.

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6), did not result in any crystallization, most likely because of the positional change of nitrogen in the pyridine structure.

Finally, the crystal structure of adduct **27** was determined and compared to the structure of **18**. Both were packed analogously with hydrogen bonds connecting the pyridine residue in one molecule with the alcohol moiety in the next. More interestingly, although both crystals were of racemic character overall, the molecules formed hydrogen bonds enantiospecifically within the crystal. This made the crystal a collection of chiral chains with a helix-like hydrogen-bonding pattern. The (*S*,*S*)-enantiomer of **18** and the (*S*)-enantiomer of **27** formed right-handed helices, while corresponding (*R*,*R*)- and (*R*)-enantiomers formed left-handed helices (Figure 2 and Supporting Information).

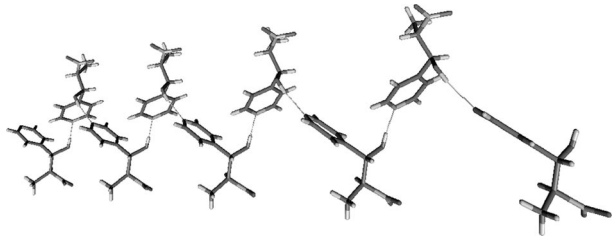

Figure 2. H-bonding of the (*S*,*S*)-enantiomer of nitroaldol adduct **18** in a right-handed helix-like structure.

Conclusions

We have demonstrated how discovery-oriented screening of a dynamic system can facilitate the identification of the asymmetric synthesis of pyridine-β-nitroalcohols. By studying a dynamic nitroaldol system, a strong diastereoselective crystallization effect could be observed for the nitroaldol adduct **18**. This discovery was further developed into an effective single-compound synthesis procedure, which was used to screen several substrates. Crystal structures were also evaluated and displayed enantiospecific packing in chiral strands with helix-like bonding structure.

Experimental Section

General: All commercially available starting materials and solvents were of reagent grade and used as received. ^{1}H and ^{13}C spectra were recorded at 400 (100) MHz and/or 500 (125) MHz, respectively. Spectra were recorded at 298 K in $CDCl_3$ (residual peaks ^{1}H: δ = 7.26 ppm; ^{13}C: δ = 77.16 ppm) or DMSO (residual peaks: ^{1}H: δ = 2.50 ppm; ^{13}C: δ = 39.52 ppm) and were calibrated by the solvent residual peaks.

General Procedure for Dynamic System Generation: Aldehydes **1**–**9** (0.1 mmol each) and nitroethane **10** (0.1 mmol) were dissolved in deuterated chloroform (0.6 mL) and triethylamine (0.1 mmol) was added and the mixture was transferred to an NMR tube. After being left overnight at room temperature (17 h), the formed crystals were filtered and analyzed by ^{1}H NMR ([D_6]DMSO).

General Procedure for Single Compound Synthesis: Pyridinealdehyde (1 mmol) was mixed with the nitroalkane (1 mmol) in chloroform (0.6 mL). Triethylamine (1 mmol) was added and the mixture was left at room temperature overnight (a small piece of solid, such as a piece of broken glass could be added to facilitate precipitation). The formed precipitate was filtered and washed with a small amount of dichloromethane. This yielded analytically pure product as a white powder.

Supporting Information (see also the footnote on the first page of this article): Characterization of new compounds, NMR spectra and crystallographic data.

Acknowledgments

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