nos. CCDC-156104 (**7**) and -156105 (**7**-H · PF_6). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[29] Previous syntheses of rotaxanes based on dialkylammonium ions under thermodynamic control, either by the threading-followed-by-stoppering (see ref. [9]) or slippage (see ref. [10]) approaches, have not been template-directed ones. Rather, they have afforded products in yields that reflect the association constants of their intermediates.

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Precipitons—Functional Protecting Groups to Facilitate Product Separation: Applications in Isoxazoline Synthesis

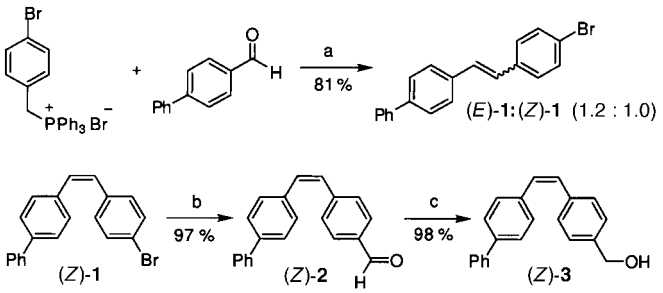
Todd Bosanac, Jaemoon Yang, and Craig S. Wilcox*

Dedicated to Prof. Dr. Ronald Breslow on the occasion of his 70th birthday symposium

Automated solid-phase organic synthesis (SPOS) has emerged as an important tool in organic synthesis and medicinal chemistry.[1] One of the advantages of SPOS is that the technique allows a large excess of reagents or co-reactants to be employed to ensure that a reaction reaches completion, and these reaction components can then be easily separated from resin-bound products by simple filtration. Although the insoluble nature of the resin is an advantage at the purification stage, it is often a liability at the reaction stage. For example, heterogeneous reaction conditions can complicate monitoring the progress of a reaction by classical methods, and tedious optimization of reaction protocols is sometimes required to obtain good yields in solid-phase reactions. In response to these limitations several research groups have introduced alternatives to SPOS. The new methods (fluorous synthesis,[2] soluble polymer-supported organic synthesis (SPSOS),[3] dendrimer-supported organic synthesis,[4] and new approaches to acid-base-induced isolation[5]) begin with a step in which reactant molecules are attached to "phase-tags",[2b] which are molecular fragments that have special physical properties that facilitate product isolation. These alternatives to solid-phase synthesis share two features: they allow reactions to be carried out under homogeneous conditions, and, after the reaction stage, the product can be isolated by a phase-transfer event (precipitation or liquid–liquid partition) that is induced by the addition of a solvent or by the addition of new co-solutes or reactants.

We envisioned a separation process enabled by a change in solubility that would be caused *not* by a change in solvent or environment, but by structural isomerization of an ancillary portion of the desired product. We define a "precipiton" as a group of atoms (molecular fragment) that is purposefully attached to a reactant molecule and can be isomerized after the reaction to facilitate precipitation or phase transfer of the attached product. One class of precipitons would include molecular fragments that can exist in two isomeric forms: one form freely soluble in a given organic solvent and the other form quite insoluble in that solvent. A product attached to such a molecular fragment could be isolated directly from a reaction mixture by isomerization of the ancillary group to generate the insoluble isomer of the product. The precipitated product would then be isolated by filtration or centrifugation. In the ideal example of this concept of controlled changes in solubility, only products or reagents labeled with the precipiton group would precipitate. Therefore, as in SPOS, excess reagents and co-reactants that might be required to provide good reaction efficiency could be easily removed by filtration.

Our search for such precipitons began with a study of stilbene analogues because *cis*-stilbenes can be more soluble than *trans*-stilbenes.[6, 7] The biphenyl-derived alkenes (*Z*)-**3** and (*E*)-**3** were prepared by a Wittig reaction (Scheme 1).



Scheme 1. Synthesis of precipiton (*Z*)-**3**. a) KHMDS, THF, −78 °C, 81 %; b) 1. *t*BuLi, THF, −78 °C; 2. DMF, −78 → 0 °C, 97 %; c) $NaBH_4$, EtOH, 0 °C, 98 %. KHMDS = potassium 1,1,1,3,3,3-hexamethyldisilazane.

Alkene (*Z*)-**3** was freely soluble (saturated solutions exceeded 0.2 M) in common organic solvents such as EtOAc, THF, Et_2O, CH_2Cl_2, $CHCl_3$, and $C_6H_5CH_3$. The solubility of (*E*)-**3** in the same solvents were determined by UV/Vis spectroscopic analysis of saturated solutions.[7, 8] Isomer (*E*)-**3** was virtually insoluble in all solvents examined (Table 1, entry 1). We prepared dodecyl ether (*E*)-**4** and β-ketoester (*E*)-**5** and measured their solubilities in common organic solvents by the same methods used for (*E*)-**3** (Table 1, entries 2 and 3) to assess the effect that attached productlike groups might have

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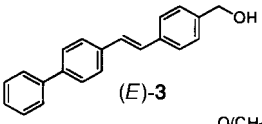
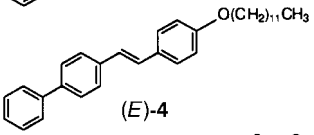
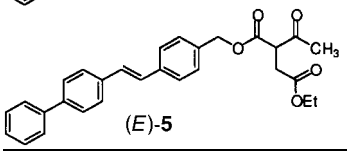
Table 1. Solubilities of precipitons (*E*)-**3**, (*E*)-**4**, and (*E*)-**5** in common organic solvents.

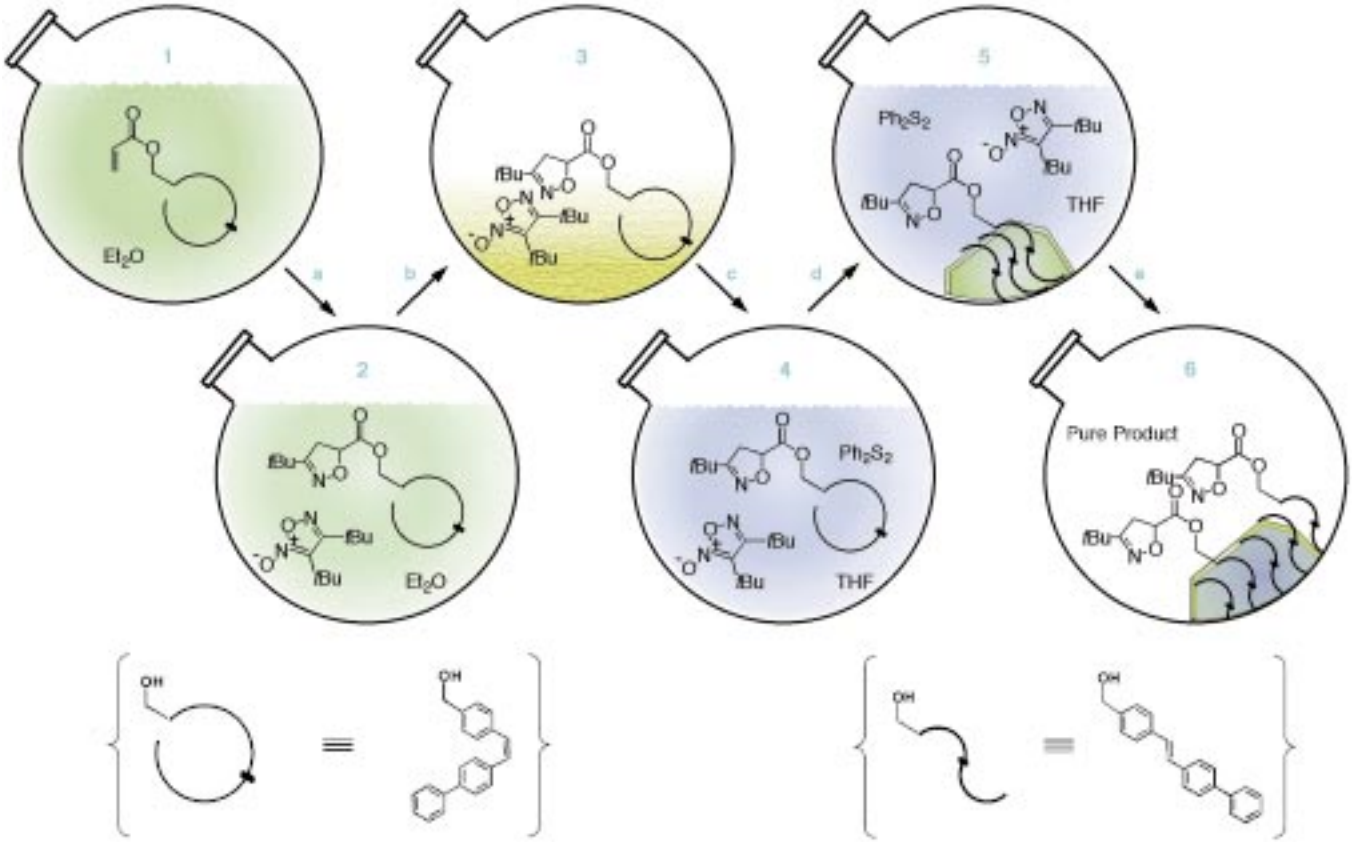
Compound	Solubility [mg mL^{-1}/mM] EtOAc	THF	Et_2O	MeOH	Hexanes
 (*E*)-**3**	0.8/2.9	4.0/14	0.4/1.3	0.2/0.7	0.0/0.0
 (*E*)-**4**	< 0.1/ < 0.2	1.3/3.0	0.1/0.2	0.0/0.0	0.0/0.0
 (*E*)-**5**	> 11/ > 24	> 13/ > 29	2.9/6.4	0.7/1.6	0.1/0.2

on the solubility of the precipiton. The dodecyl group had no measurable effect on the solubility of the *E* isomer, but the β-ketoester functionality increased the solubility of the *E* isomer in EtOAc and THF. Fortunately, regardless of the nature of the appended fragment, the *E* isomers remained virtually insoluble in Et_2O, hexanes, and MeOH.

Before using auxiliary groups similar to **3** for isolating products we examined several isomerization conditions that might effect the conversion of the high solubility (*Z*) form of **3** into the low solubility (*E*) form. Photochemical methods (with and without sensitization[9]) were examined, but these methods were not satisfactory because the reactions were slow and side products arose. However, the use of diphenyl disulfide[10] in THF at reflux (18 h) or iodine with benzoyl peroxide[11] under illumination by a sunlamp (1 h) were very effective and afforded excellent yields of precipitated product.

To evaluate the effectiveness of our method we prepared a family of Δ^2-isoxazolines. Usually these compounds are generated by [3+2] cycloaddition reactions between alkenes and nitrile oxides.[12–14] Furoxans, formed by dimerization of nitrile oxides, are troublesome by-products of such cycloadditions. Canonical methods require purification of the desired isoxazoline products by flash chromatography to remove this by-product. The problem is exacerbated when an excess of the nitrile oxide is required. Solid-phase[15] and fluorous[16] techniques for isolation of the nitrile oxide cycloaddition product have been developed in efforts to simplify removal of the furoxan.

We hypothesized that the precipiton approach to product isolation would allow nitrile oxide cycloaddition products to be separated from reaction by-products (Scheme 2). To test this hypothesis, several alkenoates were attached to precipiton (*Z*)-**3** by an ester linkage (Scheme 3) and subjected to



Scheme 2. Illustration of the "precipiton" process for isoxazoline isolation. a) A solution of *tert*-butylnitrile oxide is added to an ethereal solution of acrylate (*Z*)-**4**. b) The Et_2O is removed to afford a crude residue. c) The crude residue is diluted with THF and one equivalent of diphenyl disulfide is added. d) The solution is heated at reflux to cause isomerization and product precipitation. e) The THF is removed and the solid is washed with hexanes, Et_2O, or methanol to afford clean solid.

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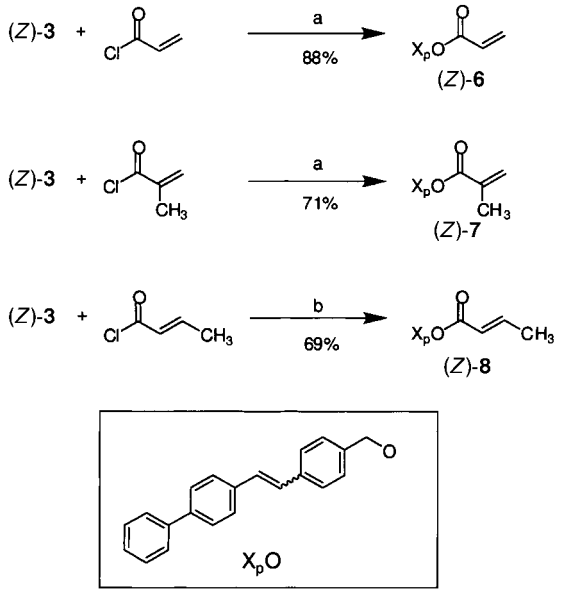


Scheme 3. Synthesis of alkene substrates for cycloaddition with nitrile oxide. a) TEA, CH_2Cl_2, 0 °C; b) Pyridine, CH_2Cl_2, 0 °C.

cycloaddition with nitrile oxides in diethyl ether. The nitrile oxides were generated by the method of Christl and Huisgen.[14] The iminoyl chloride precursors to the nitrile oxides were prepared from the appropriate hydroxylamines.[17] After the reaction, the reaction mixture was washed with water and the volatile components were removed. The precipiton approach allowed pure isoxazolines to be isolated from this crude product. To accomplish this the residue was dissolved in THF and *Z*/*E* isomerization of the precipiton auxiliary was induced by adding diphenyl disulfide and heating the solution. The solvent was removed after isomerization, the crude residue was washed with Et_2O, MeOH, or hexanes to remove any by-products, and the sparingly soluble pure product was isolated by filtration. The desired products were attached to the *trans*-precipiton and hence they were nearly insoluble in these solvents, and all by-products (including the furoxan) could be removed during this trituration.

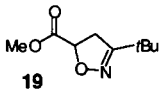
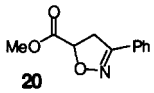
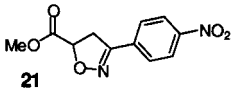
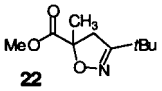
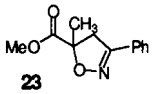
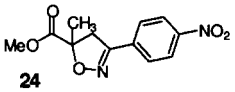
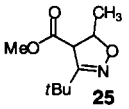
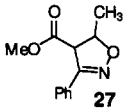
Precipiton-bound isoxazolines were isolated in good yields and high purity (Table 2). As expected, two regioisomers were observed in the cycloadditions of crotonate (*Z*)-**8** with either *tert*-butylnitrile oxide or benzonitrile oxide (Table 2, entries 7

Table 2. The use of the precipiton method in nitrile oxide cycloaddition reactions.

Entry	Alkene	Nitrile oxide	Major product	Minor product	Yield [%]	Regioselectivity[a]
1	(*Z*)-**6**	*t*Bu	(*E*)-**9**		88	
2	(*Z*)-**6**	Ph	(*E*)-**10**		81	
3	(*Z*)-**6**	O_2N	(*E*)-**11**		90	
4	(*Z*)-**7**	*t*Bu	(*E*)-**12**		74	
5	(*Z*)-**7**	Ph	(*E*)-**13**		74	
6	(*Z*)-**7**	O_2N	(*E*)-**14**		87	
7	(*Z*)-**8**	*t*Bu	(*E*)-**15**	(*E*)-**16**	75	5:1
8	(*Z*)-**8**	Ph	(*E*)-**17**	(*E*)-**18**	74	13:3[b]

[a] Regioselectivity was determined by comparison of the ^1H NMR data for these products with data for the reported methyl esters. [b] Both diastereomers of the major regioisomer were observed.

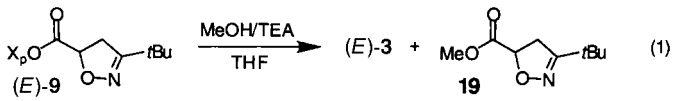
Table 3. Cleavage of the precipiton auxiliary from the isoxazolines.

Entry	Starting material	Yield of (*E*)-**3** [%]	Isoxazoline product	Yield [%]	Purity[a]
1	(*E*)-**9**	84	 **19**	90	95
2	(*E*)-**10**	87	 **20**	79	95
3	(*E*)-**11**	88	 **21**	79	91
4	(*E*)-**12**	84	 **22**	73	95
5	(*E*)-**13**	88	 **23**	74	95
6	(*E*)-**14**	89	 **24**	82	95
7	(*E*)-**15**, (*E*)-**16**	89	 **25** (major shown) and **26**	73	88
8	(*E*)-**17**, (*E*)-**18**	92	 **27** (major shown) and **28**	84	95

[a] The only impurity detected by NMR spectroscopy was a small amount of (*E*)-**3**. The amount of this contaminant was usually less than 5% and was determined by NMR analysis.

and 8), and in the case of benzonitrile oxide both diastereomers of the major regioisomer were observed. All of the products were fully characterized and obtained in greater than 95% purity as determined by ^{1}H NMR spectroscopy.

The *trans*-precipiton-bound products are sufficiently soluble in THF to allow cleavage of the precipiton from the products by methanolytic transesterification in THF by methanol/triethylamine (MeOH/TEA) [Eq. (1)].[4a] After removal of the volatile components from the reaction mixture, the desired methyl esters were separated from the insoluble benzyl alcohol precipiton (*E*)-**3** by extraction with Et_2O or MeOH. Removal of solvents from the extract afforded methyl ester isoxazolines **19**–**28** in good yields and purities (Table 3). The purity was determined by ^{1}H NMR spectroscopy. The only detectable impurity was alcohol (*E*)-**3** (typically present in <5%). Some epimerization at the carbon atom adjacent to the ester functionality occurred during methanolysis of the isoxazoline mixtures (*E*)-**15**/(*E*)-**16** and (*E*)-**17**/(*E*)-**18**, and this resulted in mixtures of diastereomers (Table 3, entries 7 and 8).



(1)

These experiments demonstrate a promising new approach to product isolation. Control of the solubility properties in this initial class of precipitons was achieved by isomerization from the soluble *Z* form of a biphenyl stilbene analogue to the insoluble *E* form. Significant features of this approach are: 1) it allows reactions to be performed under homogenous conditions; 2) the reactions may be monitored by standard methods; 3) loading capacities for this precipiton phase tag are high (3–4 mmol g^{-1}); 4) very little solvent is used during the isolation stage of the synthesis; 5) the process can be applied to large- or small-scale syntheses; and 6) the process may be automated. Reactions using this strategy have been conducted on a 5–600 milligram scale and the method could well be used to produce kilogram quantities of material. These stilbene-based precipitons are being evaluated for use with other reactions. It is not yet possible to efficiently regenerate the high-solubility form of the precipiton. We are examining more cost-effective approaches to this class of precipitons and the development of precipitons that can be recycled.

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[8] Saturated solutions were prepared by stirring excess *E* isomers in each given solvent for 72 h at 23 °C. Undissolved solid was removed from these suspensions by microfiltration. The filtrate was diluted in THF and the absorbance of the resulting solution was used to determine the amount of the solute present.

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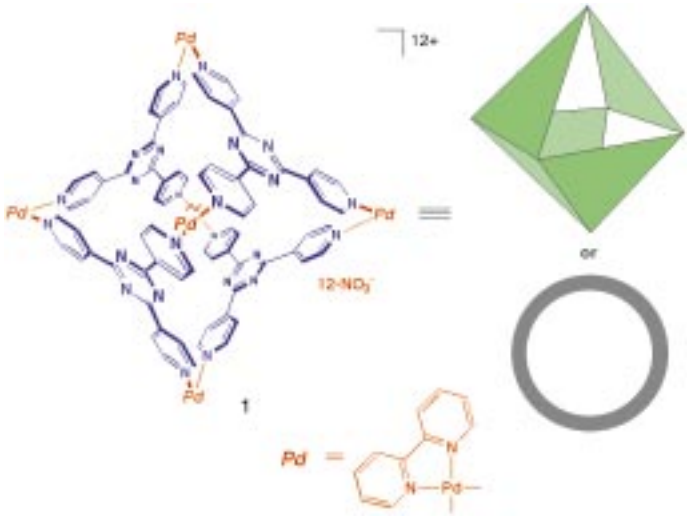
Probing Guest Geometry and Dynamics through Host – Guest Interactions**

Takahiro Kusukawa, Michito Yoshizawa, and Makoto Fujita*

Conformational freedom of molecules is restricted when they are enclathrated within the limited interior space of hollow compounds.[1] Analysis of the inclusion geometry of guest molecules is important because molecules in a specific geometry or aggregation are expected to show unique properties and reactivities which do not appear when they are in solution. The restricted conformations are in general analyzed by observing guest molecules themselves. On the other hand, information on the geometry of guests can be read out by the spectroscopic analysis of host frameworks provided the host and the guest communicate with each other through subtle host – guest interactions. Several reports have dealt with the conformational analysis of guests by the observation of host frameworks.[2, 3] However, the observed spectra of the hosts are often not sufficiently simple to analyze details.

Coordination nanocage **1** has recently been shown to strongly bind a variety of neutral substrates within its nanosized cavity.[4] As a result of the high symmetry of cage



1 (T_d) the twelve pyridine rings in **1** are all equivalent, and the NMR spectrum of the empty cage displays only a set of pyridine protons at $\delta = 9.47$ (PyH^{α}) and 8.92 (PyH^{β}) (Figure 1a). When the cage accommodates guest molecule(s) with lower symmetry the T_d symmetry of the cage is desymmetrized and the symmetry of the entity follows that of the guest(s) if the cage and the guest(s) strongly interact. For example, if the guest has C_1 symmetry then 48 pyridine protons of **1** become inequivalent and, in principle, 48 independent pyridine protons should be observed in the ^{1}H NMR spectrum. Scheme 1 summarizes the relationship between the guest symmetry and the maximum number of pyridine protons which should appear in the NMR spectra. Thus, an analysis of the symmetry of the cage probes how guests are accommodated in the cavity. We show in the following discussions some examples of probing the guest geometry by NMR analysis of the host symmetry, where all predicted structures have been confirmed by X-ray analyses. The analysis of the symmetry by NMR spectroscopic analysis also elucidates the dynamic motion of included guests.

The 1:2 complexation of cage **1** with 4,4′-dimethoxydibenzoyl (**2a**) provides a fine example. The 1:2 inclusion complex $(\mathbf{2a})_2 \subset \mathbf{1}$ was easily prepared by mixing a solution of **2a** in hexane (saturated, 1 mL) and a solution of **1** in D_2O (5.3 mM, 2 mL), and stirring the mixture at 80 °C for 0.5 h. After

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