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Journal

Journal of the American Chemical Society, 142(2)

ISSN

0002-7863

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Publication Date

2020-01-15

DOI

10.1021/jacs.9b13177

Peer reviewed

A Nanovessel-Catalyzed Three Component Aza-Darzens Reaction

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ABSTRACT: It has been previous demonstrated that nanovessels can be highly competent catalysts providing large rate accelerations and unique selectivity to the organic transformations which they mediate. However, for supramolecular assemblies to be considered a standard reagent in organic synthesis they must first demonstrate the ability to catalyze increasingly complex transformations. Herein we report a three component Aza-Darzens reaction that generates N-phenylaziridines, catalyzed by a supramolecular host, that provides the stereoisomer opposite to the one generated in bulk solution (*trans* vs. *cis*). This transformation constitutes a rare catalytic three component coupling within a supramolecular assembly, providing a supramolecular solution to a synthetically challenging transformation.

Control of reactions at the macroscopic level can be achieved through the manipulation of standard parameters such as temperature, solvent, and exclusion of deleterious components such as oxygen or water. Alternatively, container molecules and supramolecular assemblies ("nanovessels") provide the opportunity for microscopic control of reactions beyond the bounds of the flask. This possibility has inspired the preparation of a variety of self-assembled nanovessels,[1-8] that provide disparate selectivity from bulk reactions, often in a stoichiometric sense, but increasingly catalytically.[9-16] The reactivity of such container molecules has been attributed to the unique environment within their cores, which are often compared to the active sites of enzymes.[17-19] Within this internal space, the supramolecular host provides a reaction environment, distinct from that of bulk solvent, that enables recognition and energetic stabilization of molecules and transition states.

The Raymond tetrahedron (**1**) has been investigated as a catalyst for a number of organic and organometallic transformations, due to the unique microenvironment generated by its internal cavity. This host contains a hydrophobic binding site while its overall dodecanionic charge enables solubility in polar solvents, such as water.[20] The hydrophobic interior allows recognition and binding of lipophilic substrates in water, and the overall anionic charge permits strong binding of cationic species.[21,22] In addition, nitrogenous and phosphorous bases experience a pKa shift of up to 4-5 units, due to stabilization of their protonated form within the host.[23] Also solvent exclusion and charge stabilization by the cavity of **1** enables the encapsulation and stabilization of hydrolytically unstable iminium ions within the host, despite water as solvent.[24]

The properties imposed by the cavity of **1** on its guests have led to the discovery of a variety of catalytic transformation that occur within its binding site.[25-28] For example, we have previously shown that host **1** catalyzes the Aza-Prins reaction *via* stabilization of an *in situ* generated iminium ion, that cyclizes upon encapsulation. This reaction, and the prevalence of iminium intermediates in multicomponent reactions and in supramolecular catalysis,[29-30] inspired us to investigate whether the iminium-stabilizing property of **1** could enable multicomponent reactions involving that species within the nanovessel cavity. While multicomponent reaction present inherent challenges, catalysis of these transformations by supramolecular assemblies raises the unique question of whether multiple guests can be accommodated in their constrained environment; if so, will the reactivity and selectivity differ from the coupling in bulk solvent. More specifically, we wondered whether the Aza-Darzens synthesis of *N*-substituted aziridines from imines, which is typically Bronsted or Lewis acidic catalyzed,[31-35] would be amenable to supramolecular catalysis. Herein, we report the development of a diastereoselective three-component Aza-Darzens reaction of anilines, aldehydes, and α-diazo esters catalyzed by supramolecular assembly **1**. Three component coupling of this type have been seldom promoted by

supramolecular hosts,[36-38] and are an exceedingly rare within a self-assembled container molecule.

Scheme 1: General reactivity for three-component Aza-Darzens reaction within the Raymond Tetrahedron
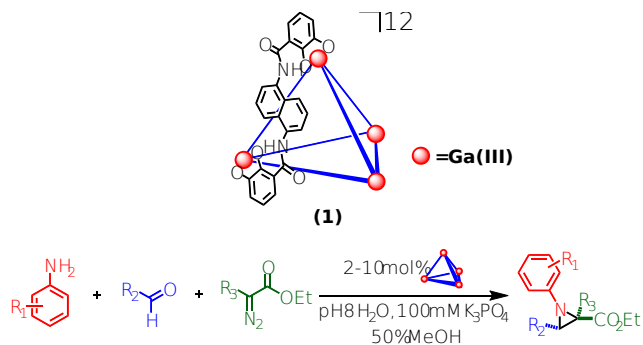

Given our previous results employing iminium intermediates in reactions catalyzed by **1**, we first sought to identify a nucleophile that would be compatible with the host and the reaction conditions, and which could be employed in a multicomponent reaction. These efforts identified ethyl-diazoacetate (EDA) as a nucleophile that met these requirements and showed a propensity to bind to host **1**. Next, we examined the amine component required for formation of the electrophilic iminium component with formaldehyde, in the presence of **1** and EDA. While basic amines (BnNH$_2$ and IPrNH$_2$) and amides (AcNH$_2$) did not afford any desired aziridine, we found that aniline and aqueous formaldehyde (37 wt. %) coupled with EDA to form to N-phenylaziridine **2a** in an aza-Darzens reaction, promoted by catalytic amounts of host **1**, (Scheme 2a). Building on this initial result, we sought to find optimal reaction conditions and explore the scope of this reaction. While poor solubility of the reaction components precluded reactivity in water, and pure methanol gave poor reactivity due to the lack of a hydrophobic driving force for the encapsulation of reagents within the host, using a 50% (v/v) methanol/pH 8 water mixture, N-phenylaziridine (**2a**) was isolated in good yield and at low catalyst loading (82%, Scheme 2b). Substitution on the aniline ring was tolerated for both electron-withdrawing and -donating groups at both the para (**2b,c**) and meta positions (**2d,e**), providing the corresponding N-phenylaziridines in moderate yield. As a control experiment, the cavity of **1** was blocked with an equivalent of tetraethylammonium chloride, a strongly binding guest, which lowered the yield of the reaction to 10% after 24 hours. This result demonstrates the necessity of the host cavity for the reaction to proceed efficiently (Scheme 2c).

Scheme 2: (a) Initial screening for multicomponent Aza-Darzens reaction, (b) scope of monosubstituted aziridines (reported as isolated yields) and (c) blocked host control (reported as NMR yield).

R$_1$	R$_2$	H$_2$O:MeOH	aziridine conversion
-H	-Ph	16:84	20%
-H	-Ph	33:67	64%
-H	-Ph	50:50	99%
-H	-Ph	67:33	heterogeneous
-H	-Bn	50:50	<5%
-H	-iPr	50:50	<5%
-H	-COMe	50:50	<5%

b)

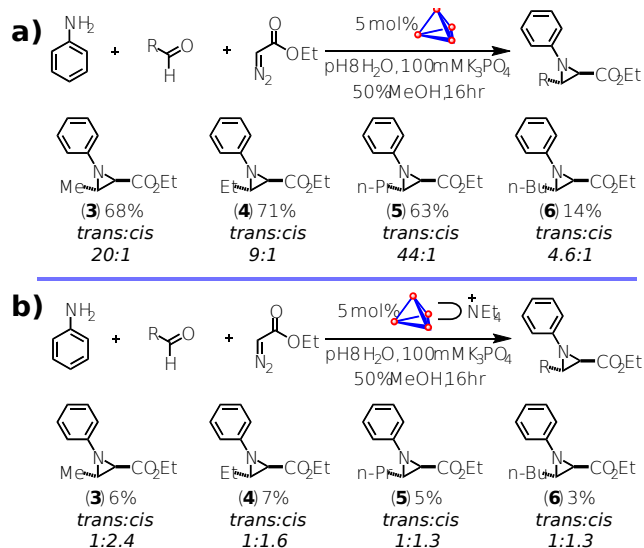(**2a** 82%)   (**2b** 33%)   (**2c** 29%)   (**2d** 68%)   (**2e** 39%)

c)

10%
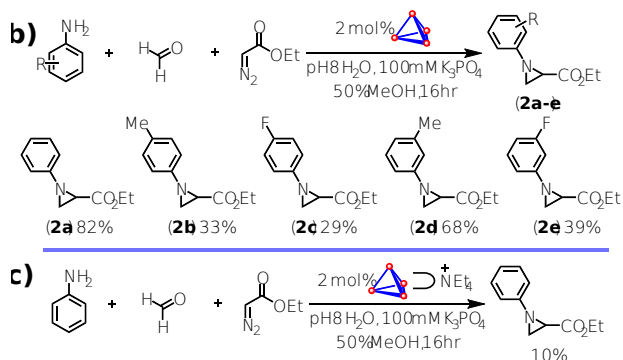
These initial results encouraged us to explore the generation of more complex products where diastereomeric selectivity could be investigated. Acetaldehyde was first selected as a coupling partner, which could undergo the reaction with aniline and EDA to provide disubstituted N-phenylaziridines where the formation of both *cis*- and *trans*-aziridines would be possible (Scheme 3a). The presence of 5 mol% **1** with aniline, acetaldehyde, and EDA gave the N-phenyl *trans*-aziridine (**3**) as the major diastereomer (20:1, ^{1}H NMR) in 68% yield. This selectivity for the *trans* diastereomer was maintained for propanal (**4**) and butanal (**5**); however, yields and selectivity for the *trans* product diminished when pentanal (**6**) was employed. Lack of reactivity with pentanal was attributed to the increased size of this substrate preventing co-encapsulation within **1** and subsequent reactivity. The high selectivity (20:1) for the *trans*-aziridine in this Aza-Darzens reaction catalyzed by **1** was surprising as literature examples for this reaction typically provide the *cis*-aziridine as the major isomer when α-diazo esters are employed as nucleophiles.[31]

In contrast, when the reaction was performed with Et$_4$N$^+$-blocked **1**, only minor background conversion (ca 7%) to the aziridine product was observed (Scheme 3b). Further investigation of the product revealed that the *cis*-aziridine was formed in the uncatalyzed process as opposed to the *trans*-aziridine generated when the host cavity was not blocked. This reversal in selectivity between the host-catalyzed and background reactions demonstrates that the confined interior of the host not only accelerates the reaction but also overrides
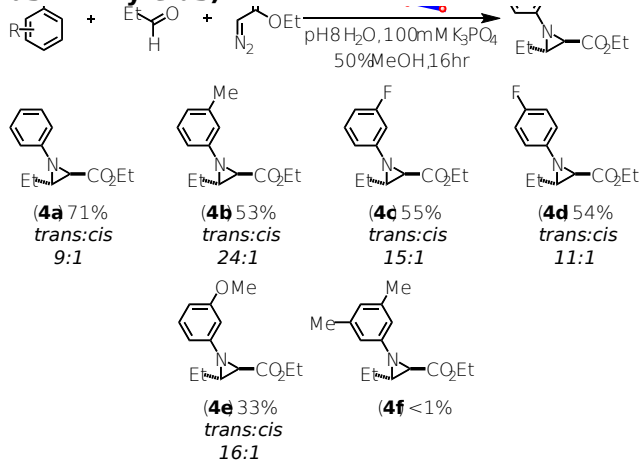
the inherent diastereoselectivity of the uncatalyzed process.

Scheme 3: (a) Effect of n-aldehyde substituent on reactivity and (b) blocked host control (reported as NMR yields)

a)

(**3**) 68%	(**4**) 71%	(**5**) 63%	(**6**) 14%
trans:cis	*trans:cis*	*trans:cis*	*trans:cis*
20:1	9:1	44:1	4.6:1

b)

| (**3**) 6%	(**4**) 7%	(**5**) 5%	(**6**) 3%
trans:cis	*trans:cis*	*trans:cis*	*trans:cis*
1:2.4	1:1.6	1:1.3	1:1.3

Several substitutions on the aniline ring were tolerated at the meta and para positions, all of which were selective for the disubstituted N-phenyl *trans*-aziridine (Scheme 4). Both electron-rich and -deficient rings were reactive and there was no major effect on selectivity. As previously observed when pentanal was used as a coupling partner, size exclusion also appears to play a role in the aniline component. For example, the formation of 3-methylaniline-derived *trans*-aziridine occurred in 53% yield in 24:1 *trans* selectivity (**4b**), while minimal reactivity was observed in the host-catalyzed reaction of 3,5-dimethylaniline (**4f**).

Scheme 4: Effect of aryl substitution on disubstituted aziridine synthesis (reported as NMR yields)

(**4a**) 71%	(**4b**) 53%	(**4c**) 55%	(**4d**) 54%
trans:cis	*trans:cis*	*trans:cis*	*trans:cis*
9:1	24:1	15:1	11:1

| (**4e**) 33%	(**4f**) <1%
trans:cis	
16:1	

The experiments with 3,5 dimethylaniline (Scheme 4, **4f**) and pentanal (Scheme 3b, **6**) are consistent with the hypothesis that the iminium must be small enough to fit within the host for the reaction to proceed efficiently. Therefore, the size limitation of the third component, the α-diazo ester, was examined using a larger *t*-butyl ester as the nucleophilic component of the Aza-Darzens reaction. (Scheme 5a). This larger α-diazo ester gave only 11% yield of the disubstituted *N*-phenylaziridine (**7**); moreover, in the presence of a stoichiometric amount of tetraethylammonium as an inhibitor, 7% yield of the aziridine was obtained (Scheme 5b). Taken together, these observations suggest that for the reaction to proceed efficiently, and with high selectivity for the *trans*-aziridine, all three components of this transformation must fit within the cavity of the supramolecular host.

Scheme 5: (a) Effect of bulky ester on Aza-Darzens reaction and (b) blocked host control (reported as NMR yields)

a)

(**7**), 11%
trans:cis
1.1:1

b)

(**7**), 7%
trans:cis
1:2.6
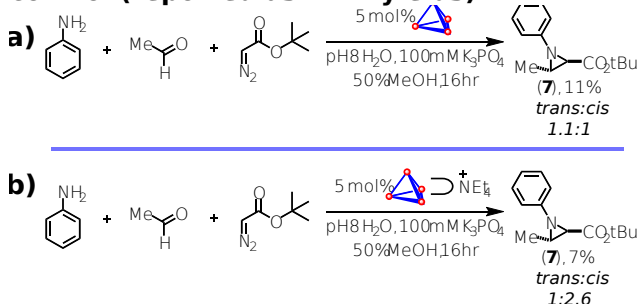
To further explore the synthetic applications of this transformation, the formation of trisubstituted aziridines from substituted α-diazo esters was investigated. The reaction of α-ethyl substituted α-diazo ester, acetaldehyde, and aniline, catalyzed by **1** gave the trisubstituted *N*-phenylaziridine in 70% yield, with excellent selectivity for the *trans*-diastereomer as determined by 1D NOE correlation (Scheme 6, **8b**). Further substitution of the α-diazo ester was tolerated to some degree; however, yields diminished when the longer α-propyl substituted α-diazo ester was employed (**8e**), again demonstrating the impact of the nucleophile's size on this transformation.

Scheme 6: Trisubstituted aziridine synthesis (reported as NMR yields

(**8a-e**)

(**8a**) 63%	(**8b**) 70%	(**8c**) 92%	(**8d**) 60%	(**8e**) 20%
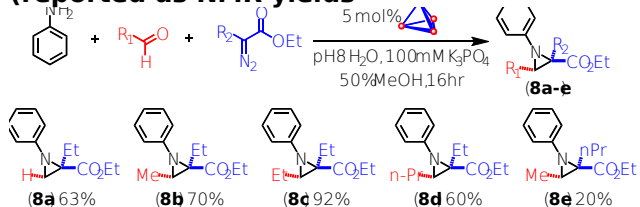
In order to gain insight into the mechanism of the three-component coupling, a series of *in situ* NMR experiments were conducted. First, we examined

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the binding of the separate components with the supramolecular host **1**. Thus, a mixture of aniline, aldehyde and **1** showed only an equilibrium between the aniline/aldehyde and the corresponding hemiaminal, without observable signals for imine either in solution or within the cavity of the host. While it might be anticipated that encapsulation of a cationic protonated imine/aniline might be favorable in the dodecanionic host, the low basicity of the aniline and the unfavorable equilibrium for imine formation in water are apparently not overcome by this association. In contrast, a mixture of **1** and α-diazo ester resulted in noticeable broadening of the signals associated with the α-diazo ester, consistent with a rapid and reversible, on the NMR time scale, binding of this guest. Second, kinetic analysis was performed to examine the kinetic profile of the components (see supporting information). The reaction showed first order kinetics in aldehyde and saturation kinetics in α-diazo ester. Saturation kinetics in α-diazo ester is consistent with a preequilibrium host-guest complex, while the first order kinetics in aldehyde suggests that preequilibrium for iminium ion encapsulation is not relevant to the functioning catalytic processes. On the basis of these experiments, we propose that the Aza-Darzens reaction catalyzed by **1** proceeds *via* initial encapsulation of the α-diazo ester within the cavity of **1** (Scheme 7). This initial binding equilibrium is followed by rate determining encapsulation of an equivalent of *in situ* generated iminium ion, driven by the anionic charge of **1,** to provide intermediate **III**. Inside the assembly the α-diazo ester undergoes nucleophilic addition to the iminium ion, followed by intramolecular nucleophilic displacement of an equivalent of nitrogen, to yield the protonated aziridine **V**. It is then proposed that the aziridine leaves the host, and is deprotonated in the bulk pH 8 solution, regenerating the catalyst.

Scheme 7: Proposed mechanism for Aza-Darzen reaction within the Raymond tetrahedron
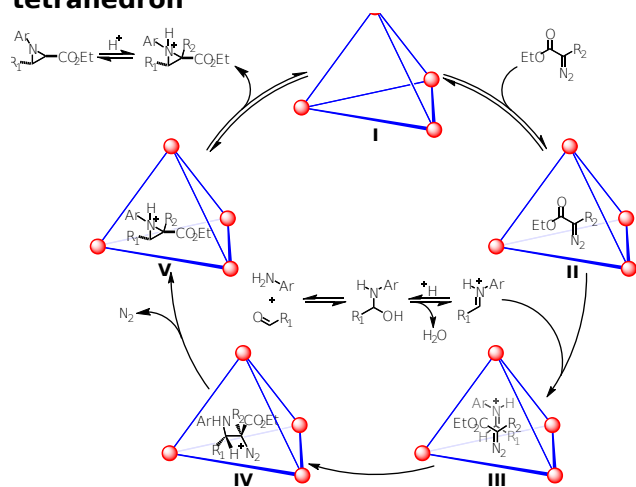
In conclusion, a rare example of a three-component reaction within a supramolecular host is reported. This Aza-Darzens reaction within **1** displays divergent reactivity from the uncatalyzed background reaction, giving the *trans* isomer of the disubstituted *N*-phenylaziridine. The reaction proceeds with low yield when the host cavity is blocked, and larger substrates proceed with minimal conversion, providing evidence that the cavity of this supramolecular assembly is essential for the multicomponent reaction observed. We envision that this reaction could inspire the development of more complex reactions with supramolecular assemblies to enable the unique secondary environment of these hosts to dictate selectivity as well as take advantage of chemistry in aqueous media.

ASSOCIATED CONTENT

Supporting Information

General synthetic procedures and characterization of new compounds are available in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interests.

ACKNOWLEDGMENT

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■ -Mono-, di, and trisubstited aziridines accessible