### Feature

# Zeolites Catalyze the Nazarov Reaction and the *tert*-Butylation of Alcohols by Stabilization of Carboxonium Intermediates

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**Abstract** Zeolites are the most used catalysts worldwide in petrochemistry processes, with particular ability to stabilize carbocations. However, the use of zeolites in organic synthesis is still scarce. We show here that representative carboxonium-mediated organic reactions, such as the Nazarov cyclization and the *tert*-butylation of alcohols with *tert*-butyl acetate, typically performed with very strong acid catalysts in solution such as triflic acid, can be catalyzed by simple zeolites with high yield and selectivity. The aluminosilicate framework stabilizes the intermediate carboxonium species and overrides the need for superacid protons in solution.

Key words zeolites, solid catalyst, Nazarov reaction, *tert*-butylation reaction, carboxonium, heterogeneous catalysis

Organic reactions catalyzed by very strong acids in solution, either Brønsted acids composed of protons loosely bound to low-coordinating anions, such as sulfuric acid  $(H_2SO_4)$ , phosphoric acid  $(H_3PO_4)$ , and triflic acid (TfOH), or Lewis acids, such BF<sub>3</sub> and AlCl<sub>3</sub>, are recurrent in organic synthesis.<sup>1</sup> In many cases, the substrates evolve to carbocations and carboxoniums (if the positive charge is stabilized and can delocalize into an adjacent oxygen atom) after the initial protonation, and these charged intermediates are often the key intermediate of the reaction.<sup>2</sup> Thus, one must accept that the strong acid in solution not only triggers the reaction, but also stabilizes intermediate (oxo)carbocations with the low-coordinating anion left behind, which makes them, on the one hand, very efficient and somewhat unique for certain organic reactions while, on the other hand, unsuitable to provide mild reaction conditions.

The catalytic and stabilizing effect of strong acids in solution for (oxo)carbocations can be somehow mimicked by simple solid acids (Scheme 1A), despite the fact that acidity of the latter is orders of magnitude lower.<sup>3</sup> This hap-

pens when the success of the organic reaction not only relies on the first protonation of the substrate, but also on the lifetime of the positively charged intermediates.<sup>4</sup> If so, a solid having a negatively charged, highly delocalized framework, can readily interact with the flourishing (oxo)carbocation intermediate and catalyze the reaction to the final product under much milder reaction conditions than soluble superacids.

Zeolites are crystalline microporous aluminosilicates with the general formula shown in Figure 1.<sup>5</sup> The isomorphic substitution of Si<sup>4+</sup> by Al<sup>3+</sup> atoms, generates a defect of positive charges in the framework that must be balanced with external cations, and if these cations are protons, the zeolite shows Brönsted acidity. The negatively charged zeolite framework acts as a very diffuse macroanion, in analogy with low-coordinating anions in solution. Thus, a zeolite may be active as acid catalyst in relatively complex organic reactions involving positively charged intermediates, and substitute very strong soluble acids. Indeed, this strategy has proved efficient in organic reactions involving highly delocalized aromatic carbocations.<sup>4,6</sup> However, it is difficult to find in the literature simple solid acids that catalyze relatively complex organic reactions involving carboxonium intermediates.7

Two representative organic reactions involving carboxonium intermediates are the Nazarov cyclization (Scheme 1B)<sup>8</sup> and the *tert*-butylation of alcohols (Scheme 1C).<sup>9</sup> The former is typically catalyzed by very strong soluble acids, for instance TfOH,<sup>10</sup> and starts with the protonation of a dienone in *trans-trans* configuration, which after several delocalizations of the positive charge evolves to the cyclized product. The very strong acid catalyst not only triggers the reaction, but also may isomerize the starting dienone into other conformations than the required *trans-trans* configuration.<sup>11</sup> While a zeolite will not trigger so efficiently the reaction, it may stabilize the different positively charged

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intermediate species formed during reaction, in such a way to perform the cyclization efficiently.<sup>12</sup>

### M<sub>2/n</sub>O·Al<sub>2</sub>O<sub>3</sub>·xSiO<sub>2</sub>·yH<sub>2</sub>O

**Figure 1** General formula for zeolites; M = hydrogen, alkali metal, or alkaline earth atom, n = charge of that atom, x = ratio of SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub>, and <math>y = number of water molecules.

### **Biographical Sketches**



Maria Tejeda-Serrano defended her master thesis in 2015 focused on the synthesis of ionic liquids as sustainable organic catalysts. Then she moved to Instituto de Tecnología Química (UPV-CSIC) in Valencia for a Ph.D. in Sustainable Chemistry under the supervision of Dr. Antonio Leyva-Pérez, focused on the substitution of homogeneous catalysts for heterogeneous catalysts in organic reactions of industrial interest. Furthermore, she worked on a RETOS Collaboration project between ITQ and a multinational company, Schimmer & Schwarz, supervised by Dr. Antonio Leyva-Pérez. Currently, she is a postdoc at the ETH Zurich under the supervision of Prof. Christophe Copéret.



Sergio Sanz Navarro was born in Valencia (Spain). He obtained a Bachelor's degree in Chemistry and a Master's degree in Organic Chemistry at the University of Valencia. He developed his degree and Master's degree projects under the supervision of Dr. Carlos del Pozo in the Organic Chemistry Department of the University of Valencia, working on the asymmetric synthesis of pharmacological compounds. Currently he is carrying out a Ph.D. on heterogeneous catalysis under the supervision of Dr. Antonio Leyva-Pérez at the Universitat Politècnica de València.



Finn Blake grew up in Aberdeen, Scotland. He graduated from the University of Strathclyde with a Master's degree in Chemical and Process Engineering in 2017. As part of his university studies he received the opportunity through the Erasmus program to spend a semester studying at the Universitat Politècnica de València, working at the Instituto de Tecnología Química under the stewardship of Dr. Antonio Leyva-Perez and Dr. Maria Tejeda to complete his master's thesis. Since completing his studies Finn has spent the last 2 years working as a Process Engineer in the energy industry.



Antonio Leyva-Pérez was born and grew up in Seville (Spain). He carried out his Ph.D. research on heterogeneous catalysis under the supervision of Prof. Hermenegildo García at the Universitat Politècnica de València. After a short stay at M.I.T. in Prof. Steven L. Buchwald's laboratories, working in organometallics, he did post-doctoral studies in the Chemistry Department of the University of Cambridge in Prof. Steven Ley's group, working on the total synthesis of the complex natural products bongkrekic and isobongkrekic acids and epyriculol. In 2008, he returned to the ITQ to work with Prof. Avelino Corma. After receiving a Ramon y Cajal research contract in 2014 and a Distinguished Research permanent position in 2016, he started the Catalysis for Sustainable Organic Synthesis at CSIC, which he currently leads.

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Catalytic results for the Nazarov cyclization with H-USY zeolite (commercially available as CBV-720), a standard acid zeolite of Si/Al ratio = 15, pore diameter of ~10 Å, and acidity of 444.5 µmol H<sup>+</sup>/g according to amine-probe titrations are given in Scheme 2 and Table S1.<sup>4,13a</sup> It can be seen that dienones **2a–c** cyclize in high yields with just 0.5 mol% solid acid sites (10 wt% in zeolite) after 2 h reaction time at 75 °C



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(see comments for products **2d,e** below). Remarkably, the *cis-cis* isomer was obtained as the major product, since kinetic results by gas chromatography coupled to mass spectrometry (GC-MS) show that the other isomers appear at the very beginning of the reaction, but evolve progressively to the *cis-cis* isomer, as assessed with independently synthesized pure samples of the product.<sup>11</sup> It must be recog-



nized that the substrate scope is quite narrow, however, not

**Scheme 2** Nazarov cyclization catalyzed by H-USY zeolite under the reaction conditions indicated; GC yields. Only the *cis-cis* product is shown, since it typically accounts for >90% of the total isomeric mixture.

Figure 2 shows a plot where the activation energy ( $E_a$ ) for the Nazarov cyclization of dienone **1a** is represented vs. the acidity (tabulated  $pK_a$  values) of different soluble and solid acids.<sup>4,6c</sup> The activation energy was calculated from the initial rate of the cyclization at different temperatures, which was obtained by linear regression of the first points of the corresponding kinetics (Figure S1), then applying the Arrhenius equation. The results clearly show that, for soluble acids, the activation energy correlates linearly with the  $pK_a$  of the acid, as it would be expected for general acid catalysis where the protonation step is the limiting step of the reaction (see Scheme 1A). In striking contrast, different



**Figure 2** Activation energy ( $E_a$ ) for the Nazarov cyclization of dienone **1a** as a function of the acidity ( $pK_a$ ) of different soluble and solid acids. The Si/Al ratios for the different zeolites are: HY-720, beta-H, and ZSM-5 ~15, HY-740 ~20, and HY-760 ~30. Error bars account for a 5% uncertainty.

zeolites show much lower activation energy than that expected from their corresponding  $pK_a$  values, at least 40 kcal lower. This decrease in activation energy is more pronounced as the acid strength of the zeolite increases (i.e., compare H-USY 720 with 760) and it does not depend on zeolite pore size or topology, since the beta-H and ZSM-5-H zeolites also catalyze the cyclization.

When the activation energy is decoupled into the enthalpic and entropic contributions (Figures S2 and S3), it can be seen that the decrease in the activation energy is enthalpic in nature.<sup>14</sup> Comparison of the activation energies for **1a-c**, with different zeolites (Figures S4–S7), shows an increase with the electron-withdrawing nature of the substituents, in other words, the more delocalized dienones react worse. This can be the reason why dienones 1d.e did not cyclize significantly under all conditions tested. Single crystal X-ray crystallography of dienone 1e (Figure S8) did not show any particular structural issue to justify such a huge difference in reactivity, and the use of the aluminosilicate MCM-22 as a catalyst (the non-porous analogue of H-USY) did not improve the vield of **2d** (Figure S9). These results confirm that the catalytic action of the zeolites for the Nazarov reaction depends on electronics rather than sterics, and that very subtle changes in the electronics of the dienone dramatically changes the cyclization outcome. Indeed, in the case of 1d, only the isomerization of the starting dienone to non-productive isomers, was found, and calculation of the dynamic radii by molecular mechanics (MM2) at minimized energy for this and other dienone isomers, gives values of ~15 Å, nearly one and a half times higher than the pore diameter of H-USY zeolite (Figure S9). Thus, the Nazarov cyclization must occur outside the pores, on the outer surface of the microporous of the zeolite. To check this, the aluminosilicate MCM-22 was used as a catalyst for **1a**, and a similar activation energy to H-USY was obtained. These results strongly support that the Nazarov cyclization is catalyzed on the negatively charged surface of the zeolite by electronic stabilization of the carboxonium and carbocations intermediates during reaction, and not to confinement effects within the pores.<sup>15</sup>

The catalytic zeolite was recovered and recycled after the Nazarov cyclization of **1a** (Figure S10). Thermogravimetric analysis of the used solid catalyst showed a significant amount (~8%) of non-volatile carbonaceous substances retained in the zeolite, even after extensive washings (Figure S11), and Fourier-transformed infrared spectroscopy (FT–IR, Figure S12) of the used catalyst showed the appearance of new signals around 1650–1700 cm<sup>-1</sup>, which corresponds to entrapped aromatic organic compounds.<sup>16</sup> These results, together, indicate the strong adsorption of colored aromatic intermediates, most probably positively charged species, on the zeolitic surface.

A one-pot Friedel–Crafts/Nazarov cyclization<sup>17</sup> catalyzed by the most active H-USY zeolite (CBV740), where the dihydroxylation of propargyl alcohols **3a–c** with mesitylene (**4**) gives directly the all-carbon products, indenes **6a**-**c**, in 42–69% yields, without the need to isolate intermediates **5** is shown in Scheme 3.<sup>6a,18</sup> These results illustrate the potential of zeolites as catalysts for the Nazarov reaction. However, it must be noticed that, while intermediate **5a** is formed with just 1 mol% of acid zeolitic sites in 78% under similar reaction conditions,<sup>19</sup> the cyclization needs 10 mol% of zeolite to convert ~80% of this intermediate, even with the more active H-USY (Si/Al = 20) zeolite.



**Scheme 3** One-pot Friedel–Crafts/Nazarov cyclization of propargyl alcohols **3a–c** to indenes **6a–c** catalyzed by H-USY zeolite (CBV740). GC yields.

The *tert*-butylation of benzyl alcohols **7a–j** with *tert*butyl acetate (**8**), another representative carboxoniummediated organic reaction (see Figure 1C), was then attempted with zeolite catalysts (Scheme 4).<sup>9</sup> Different benzyl alcohols give a variety of *tert*-butylated products containing halide (**9b–g**), trifluoromethyl (**9b**), alcohol (**9d**), thioether (**9h**), and cyano (**9j**) functional groups, in different positions of the aromatic ring in good yields, when a H-USY catalyst was employed; 2-thienylmethanol also gave the corresponding product **9i**. Not only that, alkyl (products **9k–o**) and homobenzyl (products **9p–s**) alcohols also engage in the reaction, although the latter provided somewhat lower yields due to extensive dehydration to the corresponding styrene derivatives, under the indicated reaction conditions.

Figure 3 shows a plot with the calculated activation energies for the *tert*-butylation of benzyl alcohol (**7a**) with *tert*-butyl acetate (**8**), in the presence of different soluble and solid acids. As for the Nazarov reaction, the solid acids show a significant decrease in the activation energy compared to soluble acids, the latter showing a linear correlation. As it occurs in the Nazarov reaction, not only zeolites, but also other aluminosilicates, such as MCM-22 and the

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Scheme 4 tert-Butylation of benzyl, alkyl, and homobenzyl alcohols 7a-s with tert-butyl acetate (8) catalyzed by H-USY zeolite (CBV740).

mesoporous material MCM-41, efficiently catalyze the reaction, which suggests that the reaction occurs on the external surface of the zeolite.

In conclusion, carboxonium and carbocation-mediated reactions are efficiently catalyzed by acid aluminosilicates, particularly zeolites, under relatively mild conditions. The



**Figure 3** Correlation between the activation energy ( $E_a$ ) and the acidity ( $pK_a$ ) of different soluble and solid acids for the *tert*-butylation of benzyl alcohol (**7a**) with *tert*-butyl acetate (**8**) to give the ether product **9a**. Error bars account for a 5% uncertainty.

catalysis occurs on the surface of the zeolite, thus molecular size is not a restriction and the most important factor governing the reactions is the electronics of the substrate. These results open new opportunities in the design of organic reactions based on cheap, widely available, and environmentally friendly solid catalysts to substitute corrosive soluble acids.<sup>20</sup>

All chemicals were of reagent grade quality. They were purchased from commercial sources and used as received. Gas chromatographic analyses were performed in an instrument equipped with a 25-m capillary column of 5% phenylmethylsilicone. *n*-Dodecane was used as an external standard. GC/MS analyses were performed on a spectrometer equipped with the same column as the GC and operated under the same conditions. <sup>1</sup>H, <sup>13</sup>C, and DEPT NMR spectra were recorded at r.t. on a Bruker AC 300 using the appropriate solvent containing TMS as an internal standard. FT-IR spectra were recorded on a Perkin-Elmer 882 spectrophotometer as KBr pellets or on a Thermo Nicolet iS10 after deposition and evaporation of a solution of the compound over a germanium wafer. Absorption spectra were recorded on a Cary 300 UV-Vis spectrophotometer (Varian). The thermogravimetric analyses were performed under a dry N<sub>2</sub> atmosphere with a Mettler

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Toledo TGA/STDA851e thermobalance operating at a heating rate of 10 °C min<sup>-1</sup>. CCDC 1981152 contains the supplementary crystallographic data for **1e** for this paper. The data can be obtained free of charged from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

# 1,5-Disubstituted 2,4-Dimethylpenta-1,4-dien-3-ones 1a-e; General Procedure<sup>13b,20c</sup>

To distilled water (20 mL) in a beaker was slowly added KOH pellets (6.9 g); the mixture was stirred to dissolve the KOH. This solution was added to a second flask equipped with a magnetic stirrer and containing MeOH (40 mL), pentan-3-one (6.15 mL), and aldehyde (122 mmol). The conical flask was then placed into a silicone bath set at 100 °C and connected to a condenser to achieve reflux. The reaction was refluxed overnight and allowed to cool. The solution was neutralized by slow addition of 2 M HCl (61 mL). After neutralization, the solution was poured into a separatory funnel along with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and shaken to allow the phases to mix. The aqueous phase was discarded, the process was repeated (2 ×), and also with aq NaHCO<sub>3</sub> soln (20 mL), water (40 mL), and finally brine (20 mL). The final organic solution was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under vacuum. The product was purified by crystallization (MeOH, cool overnight). The pure crystals examined by GC using a general 10-min method with single injection of 3 µL. The products were characterized by <sup>1</sup>H and <sup>13</sup>C NMR, MS, and analysis.

### 2,4-Dimethyl-1,5-diphenylpenta-1,4-dien-3-one (1a)

White solid.

IR: 1606, 1441 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.46–7.32 (m, 10 H), 7.23 (s, 2 H), 2.23 (s, 6 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 202.14, 139.09, 137.04, 136.10, 129.74, 128.58, 128.40, 15.04.

MS: *m*/*z* (%) = 262 (M<sup>+</sup>, 60), 116 (100).

Anal. Calcd for C<sub>19</sub>H<sub>18</sub>O: C, 85.67; H, 8.32. Found: C, 85.85; H, 6.82.

# **1,5-Bis(2-chlorophenyl)-2,4-dimethylpenta-1,4-dien-3-one (1c)** White solid.

IR: 1635, 1470, 1435 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 7.35 (t, *J* = 9.8 Hz, 6 H), 7.24–7.18 (m, 4 H), 2.00 (s, 6 H).

 $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  = 201.54, 138.87, 136.87, 135.10, 134.61, 130.88, 130.15, 129.91, 127.05, 15.12.

MS: *m*/*z* (%) = 330 (M<sup>+</sup>, 3), 295 (45), 150 (70).

Anal. Calcd for C<sub>19</sub>H<sub>16</sub>Cl<sub>2</sub>O: C, 68.07; H, 6.01. Found: C, 69.01; H, 4.78.

# 1,5-Bis(2,6-dichlorophenyl)-2,4-dimethylpenta-1,4-dien-3-one (1d)

White solid.

IR: 1718, 1642, 1423 cm<sup>-1</sup>.

 $^{1}\text{H}$  NMR (CDCl\_3, 300 MHz):  $\delta$  = 7.31 (s, 1 H), 7.29 (s, 2 H), 7.20–7.12 (m, 5 H), 1.79 (s, 6 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 199.39, 141.10, 134.49, 134.40, 134.29, 129.55, 128.09, 14.80.

MS: m/z (%) = 400 (M<sup>+</sup>, 2), 277 (100), 199 (50).

Anal. Calcd for C<sub>19</sub>H<sub>14</sub>Cl<sub>4</sub>O: C, 56.47; H, 4.49. Found: C, 57.10; H, 3.28.

# **1,5-Bis(4-chlorophenyl)-2,4-dimethylpenta-1,4-dien-3-one (1e)** White solid.

IR: 1678, 1622, 1487 cm<sup>-1</sup>.

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<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 7.37 (s, 8 H), 7.12 (s, 2 H), 2.18 (s, 6 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  = 201.49, 137.70, 137.50, 137.42, 134.38, 130.97, 128.84, 15.05.

MS: m/z (%) = 330 (M<sup>+</sup>, 3), 295 (45), 150 (70), 115 (100).

Anal. Calcd for C<sub>19</sub>H<sub>16</sub>Cl<sub>2</sub>O: C, 68.07; H, 6.01. Found: C, 69.01; H, 4.78.

#### Zeolite-Catalyzed Nazarov Cyclization

The corresponding amount of dienone **1a–e** (0.2 mmol) was weighed and diluted with DCE (1 mL) in a test tube. A 50 µL sample was taken as the zero-time sample and diluted in a vial with EtOAc (1 mL) to be analyzed using GC with *n*-dodecane (22 µL, 0.1 mmol) as the external standard. The substrate and DCE were then added to a vial containing 0.5 mol% H<sup>+</sup> of the zeolite (5 wt% for **1a**) and a magnetic stirrer. The vial was placed in a silicone bath at the required reaction temperature, ranging from 25 to 75 °C. The reaction was typically run for 120 min and 50 µL samples were taken throughout the reaction, and each was added to a vial containing EtOAc (1 mL). Each sample was then filtered to remove any solid catalyst in the sample, and then analyzed by GC with *n*-dodecane (22 µL, 0.1 mmol) as an internal standard. All the products are reported and characterized in the literature: **2a–d**,<sup>13b</sup>

#### **Recovery and Reuse of the Catalyst**

The Nazarov cyclization was performed using the same method as above except with double the amount of catalyst (1 mol%, 10 wt%) to ensure a good recovery. The reaction chosen to test the reusability of the catalyst was the cyclization of **2c** at 75 °C. After 60 min, the reaction was stopped and the zeolite separated from the solution using a centrifuge at 6000 rpm. After separation, the zeolite was cleaned with a solvent and separated again in the centrifuge. The process was repeated twice. Then, the zeolite was left to dry overnight, weighed and used again in reaction, adjusting the mass of substrate and volume of DCE to keep the same final concentration.

### Zeolite-Catalyzed One-Pot Friedel–Crafts/Nazarov Cyclization

Alcohol **3** (32 mg, 0.125 mmol) was weighed into a 2-mL vial and diluted with mesitylene (**4**; 1 mL). The corresponding zeolite (10 mol%, 100 wt%) was added and the vial was capped and placed in a steel heat block at 130 °C. A 50  $\mu$ L sample was taken after 30, 60, and 90 min and then the reaction was left to run overnight. The samples were diluted with DCE (1 mL), filtered to remove any solid catalyst in the sample and analyzed by GC after addition of *n*-dodecane (22  $\mu$ L, 0.1 mmol) as an internal standard. All the products are reported and characterized in the literature: **6a–c.**<sup>17c</sup>

#### Zeolite-Catalyzed tert-Butylation Of Alcohols

Alcohol **7a-s** (0.4 mmol) was weighed in a test tube, then the corresponding amount of *tert*-butyl acetate (**8**; 68  $\mu$ L, 0.5 mmol) and toluene (0.5 mL) were added. A 20  $\mu$ L sample was taken as the zero-time sample and diluted in a vial with EtOAc (1 mL) to be analyzed using GC, with *n*-dodecane (22  $\mu$ L, 0.1 mmol) as an internal standard. The mixture was then added to a vial containing 5 mol% H<sup>+</sup> of the zeolite (50 wt% for **7a**) and a magnetic stirrer. The vial was placed in a silicone bath at 75 °C. The reaction was typically run for 240 min and 20  $\mu$ L samples were taken throughout the reaction, and each was placed in a vial with EtOAc (1 mL). Each sample was then filtered to remove

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any solid catalyst in the sample, and then analyzed by GC with *n*-dodecane (22 mL, 0.1 mmol) as an external standard. Most of the products are reported and characterized in the literature: **9a**,<sup>21b</sup> **9g**,<sup>21c</sup> **9h**,<sup>21d</sup> **9i**,<sup>21e</sup> **9k–1**,**n**,<sup>21f</sup> **9m**,<sup>21g</sup> **9o**,<sup>21h</sup> **9p**,<sup>52li</sup> **9q**,<sup>21j</sup> **9r**.<sup>21k</sup>

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### **Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690896.

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