Supporting Information

Evaluation of the Nitroaldol Reaction in the Presence of Metal Ion-Crosslinked Alginates

Dennis Kühbeck,‡a Judith Mayr,‡a Marleen Häring,‡a Martin Hofmann,a Françoise Quignardb and David Díaz Díaz*,ac

a Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, 93053 Regensburg, Germany. b Institut Charles Gerhardt Montpellier-UMR 5253 CNRS-UMII-ENSCM-UMI, Matériaux Avancés pour la Catalyse et la Santé, 8 rue de l'École Normale, 34296 Montpellier Cedex 5, France. c IQAC-CSIC, Jordi Girona 18-26, 08034 Barcelona, Spain

David Díaz Díaz: david.diaz@chemie.uni-regensburg.de

‡ These authors contributed equally to this work
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1. Preliminary optimization experiments

**Note:** During the course of our studies we have found that the purity of the aldehydes is very important in order to obtain reliable and reproducible results. For example, 1a purchased from TCI Europe (Cat. number N0559, CAS 555-16-8N0559) provides practically null background reaction (i.e., results of the control experiment in the absence of catalyst). However, samples obtained from other suppliers could contain impurities undetectable by NMR (e.g., metal ions) that cause false positives.

**Table S1.** Influence of the concentration of reactants in the model nitroaldol reaction

| entry | 1a (mmol) | 2a (mmol) | yield 3a (%) \(^b\) |
|-------|-----------|-----------|-------------------|
| 1     | 0.1       | 0.5       | 77                |
| 2     | 0.1       | 1.0       | 88                |
| 3     | 0.3       | 1.0       | 33                |

\(^a\) Reaction conditions: 4-Nitrobenzaldehyde (1a, 1 equiv), nitromethane (2a), Ca\(^{2+}\)-AHG (1 bead, 4 ± 1 mol\% of metal with respect to 1a), DMSO (0.5 mL), room temperature, 24 h. \(^b\) Determined by \(^1\)H NMR analysis of the crude product. Reported values correspond to the average values of at least two independent experiments (STDV = ± 2).

2. Metal loading

**Table S2.** Preparation and main features of M\(^{n+}\)-AHG beads

| entry | M\(^{n+}\)-AHG | dropping height (cm) \(^a\) | dropping rate (drop/s) | qual. M\(^{n+}\) detection | diameter (mm) \(^d\) | metal loading (µmol/bead) \(^e\) |
|-------|---------------|---------------------------|-----------------------|-----------------------------|--------------------|-----------------------------|
| 1     | Ca\(^{2+}\)   | 2.0                       | 1                     | Na\(_2\)CO\(_3\) \(^b\)    | 4.4 ± 0.1          | 4.8 ± 0.2                   |
| 2     | Cu\(^{2+}\)   | 0.5                       | 2                     | NH\(_3\) \(^c\)            | 4.0 ± 0.1          | 3.2 ± 0.2                   |
| 3     | Co\(^{2+}\)   | 1.0                       | 3                     | KSCN                        | 4.1 ± 0.2          | 3.6 ± 0.2                   |
| 4     | Ni\(^{2+}\)   | 1.5                       | 1                     | KCN                         | 3.8 ± 0.2          | 3.0 ± 0.2                   |
| 5     | Zn\(^{2+}\)   | 2.5                       | 1                     | KFeCN                       | 3.6 ± 0.1          | 3.6 ± 0.2                   |
| 6     | Fe\(^{3+}\)   | 1.5                       | 0.5                   | KSCN                        | 4.9 ± 0.3          | 4.3 ± 0.2                   |

\(^a\) Dropping height: distance between the tip of the dropping funnel and the surface of metal-containing solution. \(^b\) Washing solution was combined with a saturated aqueous Na\(_2\)CO\(_3\) solution. \(^c\) Washing solution was combined with a aqueous NH\(_3\) solution (25%). \(^d\) Mean diameter of 20 beads. In all cases, it was determined using a vernier caliper. \(^e\) Metal content of each hydrogel determined by ICP-OES. Sample preparation was performed like previously reported. \(^1\) 20 randomly chosen M\(^{n+}\)-AHG beads were dissolved in conc. HNO\(_3\) in each case.
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Note: The following hydrated salts were used to prepare the beads: CaCl$_2$ × 6H$_2$O, CuCl$_2$ × 2H$_2$O, CoCl$_2$ × 6H$_2$O, NiCl$_2$ × 6H$_2$O, FeCl$_3$ × 6H$_2$O.

**Figure S1.** Correlation between the diameter of the M$^{n+}$-AHG beads diameter (white bars) and the corresponding metal loading (grey bars).

**Figure S2.** Visual appearance of different M$^{n+}$-AHG beads prepared as described in the Experimental Section. The water contents (\% = mass(hydrogel)−mass(xerogel)) estimated were ca. 96 (M = Cu), 96 (M = Co), 95 (M = Ni), 97 (M = Fe) (20 beads in each case were used for calculating average weights. For the xerogels, the beads were dried for two days under vacuum, and additionally in oven for 2 h at 100 °C. From a visual point of view the Cu(II)-, Co(II)- and Ni(II)- beads appeared to be transparent while the Fe(III)-beads were opaque.

3. Leaching study

**Table S3.** Determination of metal leaching of M$^{n+}$-AHG beads in different solvents$^a$

| solvent   | Ca$^{2+}$-AHG | Cu$^{2+}$-AHG | Co$^{2+}$-AHG | Ni$^{2+}$-AHG | Zn$^{2+}$-AHG | Fe$^{3+}$-AHG |
|-----------|---------------|---------------|---------------|---------------|---------------|---------------|
| H$_2$O    | 0.153         | 0.178         | < LOD         | 0.246         | < LOD         | < LOD         |
| EtOH      | 0.070         | 0.143         | < LOD         | < LOD         | < LOD         | < LOD         |
| toluene   | < LOD$^{[b]}$ | < LOD         | < LOD         | < LOD         | < LOD         | < LOD         |
| CH$_2$Cl$_2$ | < LOD    | < LOD         | < LOD         | < LOD         | < LOD         | < LOD         |
| THF       | 0.046         | 0.035         | < LOD         | 0.211         | < LOD         | < LOD         |
| CH$_3$CN  | < LOD         | < LOD         | 0.033         | < LOD         | 0.113         | < LOD         |
| DMSO      | 7.780         | 0.169         | 0.002         | 0.179         | < LOD         | < LOD         |

$^a$ DMSO = dimethyl sulfoxide.
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Conditions: 5 M\textsuperscript{+}-AHG beads were matured in a solvent (2 mL) at room temperature for 48 h. After this time the supernatant solution was filtrated and submitted for ICP-OES analysis. \textsuperscript{b} LOD (limit of detection) = 0.1 mg L\textsuperscript{-1}.

4. Kinetics

TOF values (h\textsuperscript{-1}) for the model reaction between 4-nitrobenzaldehyde (1\textsubscript{a}) and nitromethane (2\textsubscript{a}) in DMSO at room temperature in the presence of different catalysts were estimated as following: Ca\textsuperscript{2+}-2-ethylhexanoate (536.5) > Ca\textsuperscript{2+}-2AHG (0.8) = Ni\textsuperscript{2+}-2AHG (0.8) > Co\textsuperscript{2+}-2AHG (0.6) > Zn\textsuperscript{2+}-2AHG (0.4) > Cu\textsuperscript{2+}-2AHG (0.1) = Fe\textsuperscript{3+}-2AHG (0.1).

Figure S3. Kinetic analysis of the Ca\textsuperscript{2+}-AHG (hydrogel beads; blue circles)- and Ca\textsuperscript{2+}-AAG (aerogel beads; red squares)-catalyzed Henry reaction: \( k_{\text{AHG}} = 0.113\ \text{h}^{-1}, R^2 = 0.993 \); \( k_{\text{AAG}} = 0.121\ \text{h}^{-1}, R^2 = 0.984 \).

Table S4. Model reaction between 1\textsubscript{a} and 2\textsubscript{a} catalyzed by calcium 2-ethylhexanoate\textsuperscript{a}

| entry | time | yield 3\textsubscript{a} (%)\textsuperscript{b} |
|-------|------|----------------|
| 1     | 5 min| 86             |
| 2     | 1 h  | 90             |
| 3     | 3 h  | 90 (100% conversion) |

\textsuperscript{a} Reaction conditions: 4-Nitrobenzaldehyde (1\textsubscript{a}, 0.1 mmol), nitromethane (2\textsubscript{a}, 1.0 mmol), Ca\textsuperscript{2+}-ethylhexanoate (ca. 2.1 mol% with respect to 1\textsubscript{a}), DMSO (0.5 mL), room temperature, 24 h. \textsuperscript{b} Determined by \textsuperscript{1}H NMR analysis of the crude product.
5. FT-IR spectra

**Figure S4.** Comparison of FT-IR spectra: Na\(^+\)-AP (blue line), Ca\(^{2+}\)-AHG bead (black line) and xerogel obtained by freeze-drying (FD) the corresponding Ca\(^{2+}\)-AHG beads (green line).

**Figure S5.** Comparison of FT-IR spectra of M\(^{n+}\)-AHG beads: Ca\(^{2+}\)-AHG (black line), Cu\(^{2+}\)-AHG (turquoise line), Co\(^{2+}\)-AHG (pink line), Ni\(^{2+}\)-AHG (green line), Zn\(^{2+}\)-AHG (grey line) and Fe\(^{3+}\)-AHG (brown line).
Figure S6. Comparison of FT-IR spectra of xerogels obtained by freeze-drying (FD) the corresponding $\text{M}^{n+}$-AHG beads: $\text{Ca}^{2+}$-AHG (FD) (black line), $\text{Cu}^{2+}$-AHG (FD) (turquoise line), $\text{Co}^{3+}$-AHG (FD) (pink line), $\text{Ni}^{2+}$-AHG (FD) (green line), $\text{Zn}^{2+}$-AHG (FD) (grey line) and $\text{Fe}^{3+}$-AHG (FD) (brown line). Average frequencies (cm$^{-1}$): 3313-3261 (-OH, b), 2942-2922 (-C-H, w), 2363-2361 (CO$_2$, w), 1589-1584 (C=O, s), 1413-1404 (C=O, m), 1037-1024 (C-O, s)

6. TGA thermograms

Figure S7. Comparison of TGA curves: $\text{Na}^+$-AP (blue line), $\text{Ca}^{2+}$-AHG (black line), xerogel obtained by freeze-drying (FD) $\text{Ca}^{2+}$-AHG beads (black line), xerogel (FD) from $\text{Cu}^{2+}$-AHG beads (turquoise line), xerogel (FD) from $\text{Co}^{2+}$-AHG beads (pink line), xerogel (FD) from $\text{Ni}^{2+}$-AHG beads (green line), xerogel (FD) from $\text{Zn}^{2+}$-AHG beads (grey line), and xerogel (FD) from $\text{Fe}^{3+}$-AHG beads (brown line).
7. $^1$H NMR spectra

**Table 4, entry 1:** Diphenylmethane was used as internal standard (IS)

**Table 4, entry 2:** Diphenylmethane was used as internal standard (IS)
Table 4, entry 3: Diphenylmethane was used as internal standard (IS)

Table 4, entry 5: N,N-Dimethylacetamide was used as internal standard (IS)
Table 4, entry 6: Diphenylmethane was used as internal standard (IS)

Table 4, entry 7: N,N-Dimethylacetamide was used as internal standard (IS)
Table 4, entry 8: \(^3\) N,N-Dimethylacetamide was used as internal standard (IS)

Table 4, entry 9: \(^5\) N,N-Dimethylacetamide was used as internal standard (IS)
Table 4, entry 10: Diphenylmethane was used as internals standard (IS)

Table 4, entry 12: Diphenylmethane was used as internal standard (IS)
8. HPLC chromatograms

Enantiomeric excess (ee) values were determined by chiral-phase HPLC using a Varian 920-LC Liquid Chromatograph and a column Phenomenex Lux Cellulose-1(2), 4.6 x 250 mm, 5 microm. Eluent: n-heptane:i-PrOH 70:30; flow 1.0 mL min⁻¹, λ = 254 nm.

- Ca²⁺-AHG beads:

- Cu²⁺-AHG beads:
- Co\(^{2+}\)-AHG beads:

![Co\(^{2+}\)-AHG beads](image)

| Index | Name   | Time [Min] | Quantity [% Area] | Height [mAU] | Area [mAU Min] | Area [%]       |
|-------|--------|------------|-------------------|--------------|----------------|----------------|
| 1     | UNKNOWN| 15.25      | 49.94             | 1012.5       | 381.7          | 49.937         |
| 2     | UNKNOWN| 18.25      | 50.06             | 870.2        | 382.6          | 50.063         |
| Total |        |            |                   |              | 764.3          | 100.000        |

- Ni\(^{2+}\)-AHG beads:

![Ni\(^{2+}\)-AHG beads](image)

| Index | Name   | Time [Min] | Quantity [% Area] | Height [mAU] | Area [mAU Min] | Area [%]       |
|-------|--------|------------|-------------------|--------------|----------------|----------------|
| 1     | UNKNOWN| 14.20      | 49.69             | 583.6        | 202.1          | 49.692         |
| 2     | UNKNOWN| 16.72      | 50.31             | 506.8        | 204.6          | 50.308         |
| Total |        |            |                   |              | 406.7          | 100.000        |
9. Additional experiments

**Figure S8.** Effect of modifying the contact surface area of Ca$^{2+}$-AHG beads: A) Whole Ca$^{2+}$-AHG bead is used as catalyst. The reaction can take place either on the surface of the catalyst (path I) or inside the bead based on diffusion of the substrates and subsequent release of the product (path II). A combination of both paths is most likely. B) Two halves of one Ca$^{2+}$-AHG bead, resulting in a slightly larger surface area, is used as catalyst. C) Nanoreactor vs supported catalyst experiment for the model Henry reaction. Reaction conditions: 4-nitrobenzaldehyde (1a, 0.1 mmol), nitromethane (2a, 1.0 mmol), 1 whole or 1 halved Ca$^{2+}$-AHG bead, DMSO (0.5 mL), room temperature. The $^1$H NMR yields of 3a are shown in dependency of time.

**Table S5.** Control experiment: Model reaction between 1a and 2a catalyzed by Mn$^{3+}$-alginate xerogel obtained by air-drying the corresponding hydrogel
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| entry | metal ion | conversion (%) | yield 3a (%)$^b$ |
|-------|-----------|----------------|-------------------|
| 1     | Ca$^{2+}$ | 27             | 1                 |
| 2     | Cu$^{2+}$ | 18             | 1-2               |
| 3     | Co$^{2+}$ | 25             | 2                 |
| 4     | Ni$^{2+}$ | 24             | 1                 |
| 5     | Zn$^{2+}$ | 21             | 2                 |
| 6     | Fe$^{3+}$ | 24             | 1                 |

$^a$ Reaction conditions: 4-Nitrobenzaldehyde (1a, 0.1 mmol), nitromethane (2a, 1.0 mmol), M$^{n+}$-alginate xerogel (1 air-dried hydrogel bead, 4 ± 1 mol% of metal with respect to 1a), DMSO (0.5 mL), room temperature, 24 h. $^b$ Determined by $^1$H NMR analysis of the crude product.

**Table S6.** Control experiment: Model reaction between 1a and 2a catalyzed by M$^{n+}$-alginate xerogel obtained by freeze-drying (lyophilized) the corresponding hydrogel$^a$

| entry | metal ion | conversion (%) | yield 3a (%)$^b$ |
|-------|-----------|----------------|-------------------|
| 1     | Ca$^{2+}$ | 23             | 4                 |
| 2     | Cu$^{2+}$ | 16             | 2                 |
| 3     | Co$^{2+}$ | 25             | 2                 |
| 4     | Ni$^{2+}$ | 18             | 3                 |
| 5     | Zn$^{2+}$ | 23             | 4                 |
| 6     | Fe$^{3+}$ | 19             | 2                 |

$^a$ Reaction conditions: 4-Nitrobenzaldehyde (1a, 0.1 mmol), nitromethane (2a, 1.0 mmol), M$^{n+}$-alginate xerogel (1 lyophilized hydrogel bead, 4 ± 1 mol% of metal with respect to 1a), DMSO (0.5 mL), room temperature, 24 h. $^b$ Determined by $^1$H NMR analysis of the crude product.

**Table S7.** Model reaction between 1a and 2a catalyzed by Ca$^{2+}$-alginate in DMSO/toluene mixtures$^a$

| entry | solvent                  | conversion (%) | yield 3a (%)$^b$ |
|-------|--------------------------|----------------|-------------------|
| 1     | DMSO/toluene 1:1         | 58             | 23 (30°)          |
| 2     | DMSO/toluene 3:1         | 100            | 83 (38°)          |
| 3     | DMSO/toluene 1:3         | 58             | 26 (15°)          |

$^a$ Reaction conditions: 4-Nitrobenzaldehyde (1a, 0.1 mmol), nitromethane (2a, 1.0 mmol), Ca$^{2+}$-AHG (1 bead, 4 ± 1 mol% of metal with respect to 1a), DMSO (0.5 mL), room temperature, 24 h. $^b$ Determined by $^1$H NMR analysis of the crude product. $^c$ One Ca$^{2+}$-AAG bead was used as catalyst.
Table S8. Model reaction between 1a and 2a catalyzed by Ca$^{2+}$-AAG in different solvents$^a$

| entry | solvent | conversion (%) | yield 3a (%)$^b$ |
|-------|---------|----------------|-----------------|
| 1     | Toluene | 13             | 8               |
| 2     | CH$_3$CN | 19             | 14              |
| 3     | Toluene | 68             | 57$^c$          |

$^a$ Reaction conditions: 4-Nitrobenzaldehyde (1a, 0.1 mmol), nitromethane (2a, 1.0 mmol), Ca$^{2+}$-AAG (1 bead, 4 ± 1 mol% of metal with respect to 1a), solvent (0.5 mL), room temperature, 24 h. Note: Additional yields of the expected $\beta$-nitroalcohol product obtained with other substrates: Benzaldehyde (9%); 4-chlorobenzaldehyde (40%). $^b$ Determined by $^1$H NMR analysis of the crude product. $^c$ 10 AAG beads were used.

10. Comparison with other catalysts

Table S9. Comparison with different catalysts

| entry | catalyst | solvent | T (ºC) | time (h) | yield 3a (%) | ee (%) |
|-------|----------|---------|--------|----------|--------------|--------|
| 1$^a$ | Et$_3$N (1 equiv) | H$_2$O | RT | 3 | 86 | - |
| 2$^b$ | D-aminoacylase from *Escherichia Coli* | DMSO | 50 | 0.5 | 99 | - |
| 3$^c$ | Cu(OAc)$_2$-BOX ligand | EtOH | RT | 24 | 85 | 78 |
| 4$^d$ | Ni(OAc)$_2$-Aminoacid-based ligand | THF | 0 | 96 | 58 | 84 |
| 5$^e$ | Ca$^{2+}$-AHG | DMSO | RT | 24 | 88 | - |

$^a$ Reference: C. L. Zhou, Y. Q. Zhou, Z. Y. Wang, *Chin. Chem. Lett.* **2003**, *14*, 355-358. Reaction Conditions: 1a (1.0 mmol), 2a (1.5 mmol), H$_2$O (5 mL), Et$_3$N (1.0 mmol), isolated yield. $^b$ Reference: J.-L. Wang, X. Li, H.-Y. Xie, B.-K. Liu, X.-F. Lin, *J. Biotechnol.* **2010**, *145*, 240-243. Reaction conditions: 1a (1M), 2a (2M), DMSO (1 mL), DA (30 mg), HPLC yield. $^c$ Reference: D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692-12693. Reaction conditions: 1a (1 mmol), 2a (10 mmol), EtOH (1.5 mL), BOX Ligand (0.055 mmol), Cu(OAc)$_2$ × H$_2$O (0.05 mmol), isolated yield. $^d$ Reference: Liu, Y.; Deng, P.; Li, Xiangyang; Xiong, Y.; Zhou, H. *Synlett* **2014**, *25* (12), 1735-1738. Reaction conditions: 4-Chlorobenzaldehyde 1 (0.2 mmol), 2a (2.0 mmol), THF (1 mL), Ni(OAc)$_2$ (20 mol%), $N$-methylmorpholine, isolated yield. $^e$ Reaction conditions: 4-Nitrobenzaldehyde (1a, 0.1 mmol), nitromethane (2a, 1.0 mmol), Ca$^{2+}$-AHG (1 bead, 4 ± 1 mol% of metal with respect to 1a), DMSO (0.5 mL). NMR yield.
11. Mechanistic considerations

Figure S9. Plausible mechanism for the Ca$^{2+}$-AHG-catalyzed Henry reaction. According to the mechanism proposed by Evans and co-workers for the copper acetate-bis(oxazoline)-catalyzed Henry reaction,$^2$ the metallic center probably acts as a Lewis acid activating the nitroalkane towards its deprotonation. Although nitromethane (pK$_a$ 10.2) is a much weaker acid than alginate (pK$_a$ 3-4), the considerable accessibility to nitromethane molecules (10-fold excess with respect to the aldehyde) could make them to participate also in the protonation step of the alcoholate intermediate. In this case, the metal center is embedded within the biopolymer and could be therefore shielded to build a highly ordered transition state required for achieving enantioselectivity.$^2$

12. Additional SEM images

Figure S10. FESEM images: A) Sodium alginate. B) Cu$^{2+}$-alginate xerogel prepared by freeze-drying the corresponding hydrogel. C) Co$^{2+}$-alginate xerogel prepared by air-drying the corresponding hydrogel. D) Ni$^{2+}$-alginate xerogel prepared by air-drying the corresponding hydrogel. E) Zn$^{2+}$-alginate xerogel prepared by freeze-drying the corresponding hydrogel. F) Fe$^{3+}$-alginate xerogel prepared by air-drying the corresponding hydrogel.
### 13. Comparison of solvent properties

Unambiguous correlations could not be drawn between solvent properties and reaction kinetics without clear exceptions, suggesting a complex relationship between these parameters.

**Table S10.** Comparison of solvent properties for the model reaction between 1a and 2a

![Diagram](image)

| solvent (nature) | ε | µ | AN | DN | AS | CS | Hansen’s SP | Kamlet-Taft SP | yield 3a (%) |
|-----------------|---|---|----|----|----|----|-------------|---------------|--------------|
| DMSO (PA)       | 46.7 | 3.96 | 19.3 | 29.8 | 0.34 | 1.08 | 18.4 | 16.4 | 10.2 | 0.00 | 0.76 | 1.00 | 88 |
| H₂O (PP)        | 78.54 | 1.85 | 54.8 | 18 | 1.00 | 1.00 | 15.5 | 16.0 | 42.3 | 1.17 | 0.47 | 1.09 | 16 |
| EtOH (PP)       | 24.6 | 1.69 | 37.9 | 31.5 | 0.66 | 0.45 | 15.8 | 8.8 | 19.4 | 0.86 | 0.75 | 0.54 | 9 |
| CH₃CN (PA)      | 36.64 | 3.92 | 18.9 | 14.1 | 0.37 | 0.86 | 15.3 | 18.0 | 6.1 | 0.19 | 0.40 | 0.75 | < 2 |
| THF (PA)        | 7.52 | 1.75 | 8.0 | 20 | 0.17 | 0.67 | 16.8 | 5.7 | 8.0 | 0.00 | 0.55 | 0.58 | < 2 |
| CH₂Cl₂ (NP)     | 9.1 | 1.60 | 20.4 | 1 | 0.33 | 0.80 | 18.2 | 6.3 | 6.1 | 0.13 | 0.10 | 0.82 | 0 |
| Toluene (NP)    | 2.38 | 0.36 | 8.2 | 0.1 | 0.13 | 0.54 | 18.0 | 1.4 | 2.0 | 0.00 | 0.11 | 0.54 | 0 |

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* Reaction conditions: 4-Nitrobenzaldehyde (1a, 0.1 mmol), nitromethane (2a, 1.0 mmol), Ca²⁺-AHG bead (1 bead, ca. 5 mol% of metal with respect to 1a), solvent (0.5 mL), room temperature, 24 h. 
  b Abbreviations: PA = polar aprotic; PP = polar protic; NP = non-polar. 
  c Dielectric constant (relative permittivity). T = 20 ºC unless specified otherwise. 
  d Measured at 25 ºC. 
  e Dipole moment (debye, D). 
  f Gutmann acceptor number. AN is a quantitative measure of Lewis acidity and it is based on the 31P-NMR chemical shift of triethylphosphine oxide in the solvent. 
  g This value corresponds to benzene. Calculations indicate they are close to toluene (see Taft et al. *J. Org. Chem. 1981*, 3, 663). 
  h Gutmann Gutmann donor number (kcal/mol). DN is a quantitative measure of Lewis basicity and it is based on the heat of reaction between the solvent and SbCl₅ in CH₂Cl₂CH₂Cl. 
  i Anion solvation. 
  j Cation solvation. 
  k Hansen’s solubility parameters (MPa¹/² @ 25°C): δ_D (non-polar, or dispersion interactions), δ_P (polar attraction), and δ_H (hydrogen bonding). 
  l Kamlet-Taft solvent parameters: α (hydrogen bond donor), β (hydrogen bond acceptor), and π* (polarizability). 
  m Yield (%) determined by 1H NMR analysis of the crude product (9.2 µL of DMA was used as internal standard). Reported values correspond to the average values of at least two independent experiments (STDV = ± 2).

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