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Magnetic Superbasic Proton Sponges Are Readily Removed and Permit Direct Product Isolation

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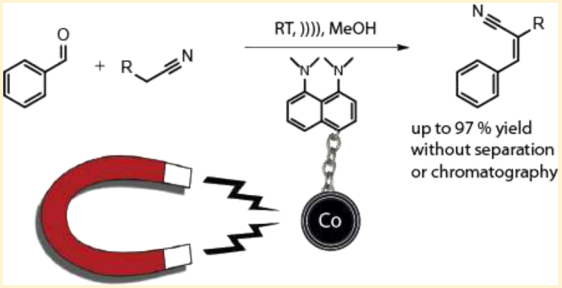
Supporting Information

ABSTRACT: Workup in organic synthesis can be very time-consuming, particularly when using reagents with both a solubility similar to that of the desired products and a tendency not to crystallize. In this respect, reactions involving organic bases would strongly benefit from a tremendously simplified separation process. Therefore, we synthesized a derivative of the superbasic proton sponge 1,8-bis(dimethylamino)naphthalene (DMAN) and covalently linked it to the strongest currently available nanomagnets based on carbon-coated cobalt metal nanoparticles. The immobilized magnetic superbase reagent was tested in Knoevenagel- and Claisen−Schmidt-type condensations and showed conversions of up to 99%. High yields of up to 97% isolated product could be obtained by simple recrystallization without using column chromatography. Recycling the catalyst was simple and fast with an insignificant decrease in catalytic activity.



INTRODUCTION

Organosuperbases, such as the classic proton sponge 1,8-bis(dimethylamino)naphthalene (DMAN),[4] Verkade's base (proazaphosphatrane), and 1,8-bis(tetramethylguanidino)-naphthalene (TMGN) have become very important reagents in organic chemistry in past years.[7] Their exceptional basicity is associated with high levels of kinetic activity in proton-exchange reactions. These properties are often manifested by low nucleophilicity, making this kind of compound interesting for a wide scope of reactions,[8−11] and even heterogeneous cases are known.[1,2] However, the workup of such reactions on the laboratory level can be difficult, time-consuming, and expensive. Similarly, in industry, a broad variety of condensation reactions are applied. At present, free bases, such as sodium hydroxide, potassium hydroxide, and various organic bases, are the most commonly used, and they often lead to corrosion, significant waste production, and difficult workup. Thus, a chemically stable magnetic base with the attributes necessary for rapid quantitative separation would be very useful for industrial applications, resulting in significant solvent savings, a reduced amount of time spent, a decreased need for expensive equipment, and reusability of the separation reagent. Moreover, a ready-to-separate reagent is interesting for its potential use in the synthesis of high-quality products, where impurity carryover defines product performance. Magnetic nanoparticles have fascinated scientists for several decades and have been used in a plethora of applications,[14] such as for drug delivery,[15] in cancer treatments,[16] and as contrast agents for magnetic resonance imaging.[17] In chemical synthesis, magnetic nanoparticles have recently gained attention in the field of catalysis[18] because they combine a large surface area with the potential for a simple separation process. However, many magnetic reagents and surface linkers for reagent attachment are unstable in acidic-, basic-, or organic-solvent-containing reaction media. The exceptional chemical stability of carbon-coated metal nanoparticles[19] is based on a crystalline, graphene-like carbon surface that effectively prevents core oxidation. The all-carbon surface further allows covalent functionalization of the particle surface by using commercially available aryl diazonium salts.[20] At present, a number of promising recyclable, stable, metal-based magnetic catalysts have been proposed.[21−31] Most recently, alkene hydrogenation palladium catalysts[32,33] (so-called "catch-and-release" systems[34]) have been developed. In this work, we present an organic superbase, coupled to magnetic nanoparticles, with stability amenable for use under such challenging reaction conditions. We also show that such an easy-to-separate reagent is useful in a number of condensation reactions and simplifies workup and product isolation.

RESULTS AND DISCUSSION

Preparation and Characterization of the Magnetic Base. Magnetic, nanosized DMAN was prepared from chemically modified magnetic nanoparticles, a linker, and a derivative of DMAN. For covalent attachment of the base to the magnetic particle (**1**), the bifunctional linker hexamethylene diisocyanate (**4**) was first reacted with the primary amine of 4′-

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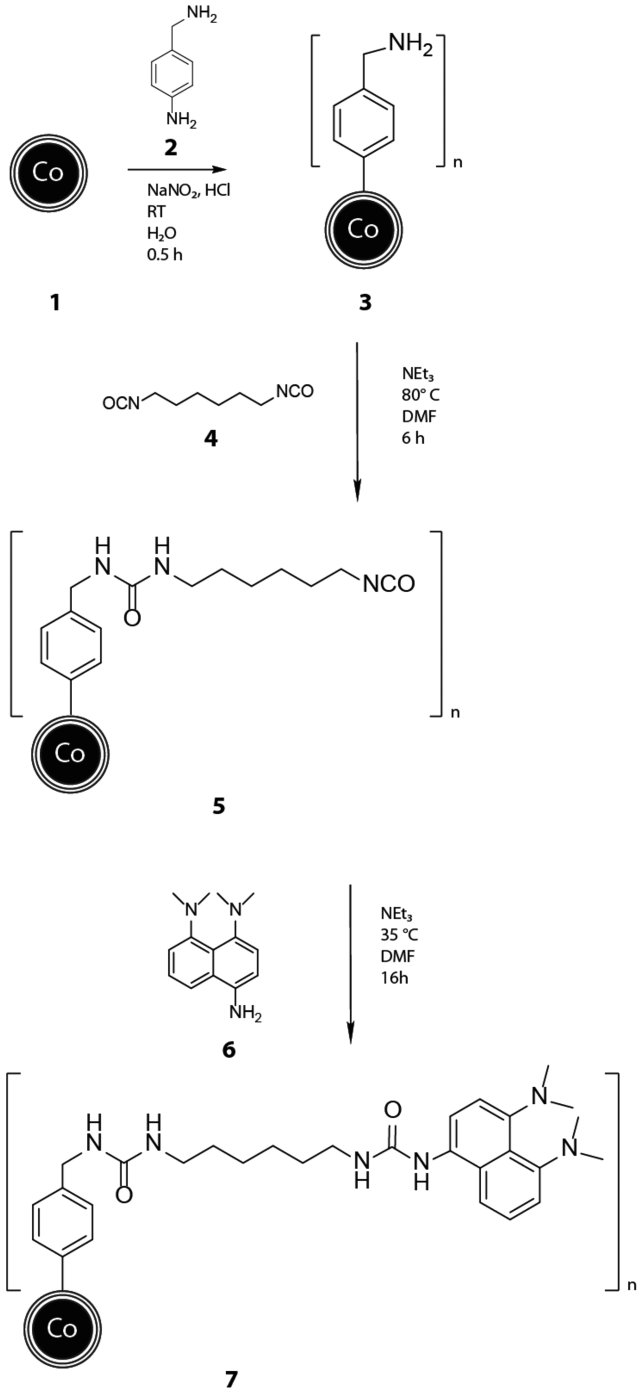
benzylamine-derivatized, graphene-coated metal nanoparticles (C/Co@amine) (**3**) to yield C/Co@hexamethyleneisocyanate (**5**). This intermediate contains a stable *N*-alkylurea bond and an active isocyanate moiety. Subsequently, C/Co@hexamethyleneisocyanate (**5**) was reacted in situ with 4-amino-1,8-bis(dimethylamino)naphthalene (DMAN-NH_2, **6**), which was prepared according to the literature.[35] This afforded a magnetic, covalently bound DMAN (C/Co@DMAN (**7**)) in proper yield with a base capacity of 0.11 ± 0.01 mmol g^{-1}. For an illustration of the synthesis, see Scheme 1. The chemical identity of the herein synthesized reagent C/Co@DMAN (**7**) was proven by diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) and elemental microanalysis (C, H, N; Figure S1 and Table S1). The fairly strong urea-stretching vibration at 1690 cm^{-1} clearly confirms urea formation in the case of C/Co@hexamethyleneisocyanate (**5**). The successful attachment of DMAN to the isocyanate linker of C/Co@hexamethyleneisocyanate (**5**) was investigated with IR spectroscopy and elemental microanalysis (Table S1). A substantial increase in nitrogen content (ΔN = 0.82%) as well as an increase in carbon content (ΔC = 3.43%) is in line with successful functionalization. Vibrating sample magnetometry (VSM) measurements (at room temperature) showed an overall magnetization of 139.6 emu g^{-1}, which is in good agreement with the expected values, namely, a little lower than the saturation magnetization of nonfunctionalized C/Co (lower content of organics or carbon; 158 emu g^{-1}).[36] It is notable that the saturation magnetization of this material is still much higher than even the strongest conventional magnetite−silica nanoparticles (30−50 emu g^{-1}).[37]

The high saturation magnetization is of relevance because it permits rapid and easy separation.[38] To confirm the chemical stability and robustness of C/Co@DMAN (**7**), we recorded transmission electron microscopy (TEM) images of nanocarrier system **7** before and after reaction runs. Particles remained spherical and uniformly sized, in the diameter range of 20 to 60 nm (Figure S2). The reactivity of the herein proposed magnetic base C/Co@DMAN (**7**) was compared to reactions using similar catalysts from the literature. Another reference material, polystyrene-based resin-supported DMAN (**S2**), was synthesized (Scheme S2), fully characterized (Figure S3 and Table S2), and used for comparison.

Reliable recycling and separation of a reagent requires a robust confirmation of covalent attachment. Therefore, we used several test reactions (Scheme S1) to prove the covalent nature of DMAN's attachment to the nanomagnets. As a first control experiment, C/Co@hexamethyleneisocyanate (**5**), which bears one free, active isocyanate moiety, was reacted with pure (not aminated) DMAN. The lack of a free amine group in DMAN does not allow covalent attachment. Using the same synthesis and purification/washing procedure as for the herein proposed reagents, product analysis (Table S1) revealed the absence of both nitrogen incorporation and physisorption effects. As a separate control experiment, C/Co@hexamethylene-isocyanate (**5**) was first quenched with water, leading to a primary amine (i.e., the linker was deliberately rendered nonfunctional). Nonfunctional **5** was then exposed to functionalized, amine-bearing DMAN derivative **6**; product analysis after applying the same purification/washing procedure as in the preparation of the functional magnetic base again confirmed the absence of reactivity (Table S1). These two experiments show that both the linker and the amination of the DMAN are necessary for the covalent binding of a DMAN moiety to the nanomagnet.

Scheme 1. Synthesis of Immobilized Magnetic Superbase 7[a]



[a]C/Co (**1**) was coupled to 4-aminobenzylamine (**2**) via diazonium chemistry to yield C/Co@amine (**3**), which was further reacted with hexamethylendiisocyanate (**4**), resulting in C/Co@hexamethyleneisocyanate (**5**), bearing an active isocyanate moiety. C/Co@hexamethyleneisocyanate (**5**) was coupled with 4-amino-1,8-bis(dimethylamino) naphthalene (**6**) to yield C/Co@DMAN (**7**).

The experiments further show the absence of base physisorption, a potential experimental error in such reagent-anchoring studies.

Knoevenagel and Claisen−Schmidt Condensation. The literature states that DMAN indeed has catalytic activity in Knoevenagel condensation.[39] After identity confirmation, the catalytic activity of C/Co@DMAN (**7**) for the Knoevenagel

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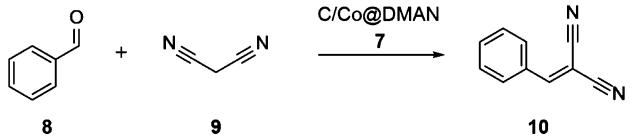
Table 1. Knoevenagel Condensation of Benzaldehyde and Malononitrile under Different Reactions Conditions



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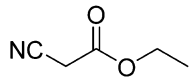
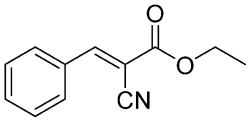
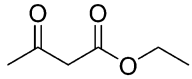
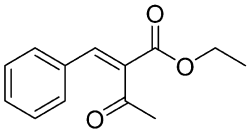
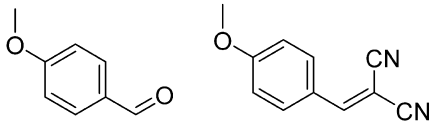
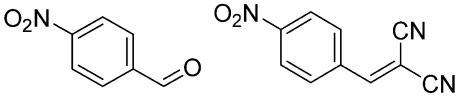
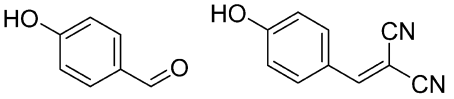
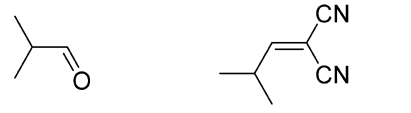
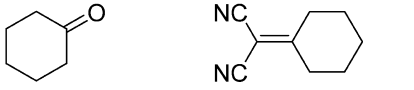
entry	catalyst	catalytic amount	solvent	time (h)	conversion (%)[a]	isolated yield (%)[b]	purity (%)
1	**7**	2 mmol %	toluene	7.5	63	61	99
2	**7**	2 mmol %	H_2O	7.5	99 (2)[c]	97	94
3	**7**	2 mmol %	MeOH	7	93 (85)	89	95
4	**7**	2 mmol %	MeOH[d]	4.5	98 (95)	91	96
5	**7**	0.2 mmol %	MeOH[d]	6	92 (90)	91	92
6	DMAN[e]	2 mmol %	MeOH	6	99	63[f]	96
7	**S2**	2 mmol %	toluene	6	99	97	98
8			MeOH	5.5	30	*g*	
9	C/Co	100 mg	MeOH	7.5	90	77	86
10	$CoCl_2$	5 mg	MeOH	6	33	*g*	

[a]Conversion was determined by HPLC with the reference product as the standard (benzaldehyde/malononitrile = 1:1). [b]Isolated yield after recrystallization. [c]Numbers in parentheses represent the percent conversion without washing the particles once with 3 mL of toluene. [d]Reaction carried out using an ultrasound bath. [e]Experiment was carried out using 2 mmol % of the free base. [f]Isolated yield after column chromatography (DCM/MeOH = 20:1). [g]No direct product isolation possible without column chromatography.

Table 2. Knoevenagel Condensation with Various Substrates Catalyzed by C/Co@DMAN (7)

entry[a]	basic substrate	aldehyde / ketone	product	temperature (°C)	conversion (%)[b]	isolated yield (%)
1		**8**		40	96[c]	95 [99][d]
2		"		40	7	-[e]
3		**9**		40	99	96 [91][d]
4		"		40	83	73[f] [96][d]
5		"		40	8	-[e]
6		"		RT	81	-[e]
7		"		40	37	-[e]

[a]Reaction conditions: catalyst loading, 2 mmol %; basic substrate, 0.4 mmol; aldehyde or ketone, 0.4 mmol; MeOH, 5 mL; 16 h. [b]GC conversion. [c]After three consecutive cycles, conversion was still 95%. [d]Purity detected by NMR is given in brackets []. [e]No direct product isolation was possible without column chromatography. [f]Isolated yield after recrystallization (DCM/hexane).

reaction of benzaldehyde (**8**) with malononitrile (**9**) was evaluated in different solvents at room temperature (Table 1, entries 1−3). If toluene was used as a solvent, then only 61% yield could be obtained. However, in water, quantitative conversion was achieved after 7.5 h. Still, the catalyst had to be washed once with toluene to release the product from the carbene surface. Therefore, methanol was tested as a solvent with promising results (Table 1, entries 3−5). The use of ultrasound during catalysis is known to ensure good reagent dispersion and consistently leads to excellent yields at shorter contact times. Indeed, when the reaction was conducted in an ultrasonication bath, a higher yield (91%) was obtained in a

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shorter time span (Table 1, entry 4). If the catalyst loading was decreased 10-fold, then similar yields were detected but a longer reaction time was necessary (Table 1, entry 5). Alternatively, running the same reaction using free DMAN where product workup and purification were not considered, quantitative conversion was obtained after 6 h (Table 1, entry 6). However, column chromatography had to be used to separate the catalyst residues from the product, which resulted in a significant drop in isolated yield. Magnetic base C/Co@DMAN (7) was separated within seconds, and recrystallization of the crude product (leading to the pure product) was achieved within minutes. Using polystyrene-immobilized proton sponge **S2** gave good yields as well, but filtration of the polymer was tedious and not very solvent-efficient. It is remarkable that even in the absence of any catalysts for the chosen reaction a low conversion (30%) was detected after 5.5 h (Table 1, entry 8). More surprisingly, the chosen reaction showed enhanced conversion (90%) in the presence of nonmodified (i.e., naked carbon surface) nanoparticles (Table 1, entry 9). To study further this unexpected finding, we included additional experiments. One probable hypothesis is based on leached cobalt ions functioning as a source of activity (hypothesis 1). Also plausible is that the carbon surface itself acts as an active catalyst (hypothesis 2). To exclude the first hypothesis, the reaction was carried out with a deliberate addition of cobalt(II) chloride ($CoCl_2$; Table 1, entry 10), the species that is supposedly leaching from the particles.[40] The addition of cobalt salts did not significantly affect the conversion (Table 1, entry 10; conversion = 33%); therefore, we do not assign significant activity of ionic cobalt in this kind of reaction. With regard to the second hypothesis, however, it is known that carbon-based surfaces (e.g., graphene, carbon nanotubes (CNT), carbon nanorods (CNR), etc.) indeed have been reported to support catalytic reactions (so-called carbocatalysis).[41,42] Thus, our finding is in line with similar carbon-surface activity and is subject to further extended studies by our group.

In the next part of the investigation, we tested different substrates (Table 2, entries 1−7). Ethyl cyanoacetate (Table 2, entry 1) reacted smoothly with benzaldehyde, and the product (ethyl α-cyanocinnamate) was detected in high yield and purity (96 and 99%, respectively) after 16 h at 40 °C; even after three consecutive cycles, the conversion was similarly high (95%). The less acidic and thus more demanding substrate ethyl acetoacetate (Table 2, entry 2) was not very active, and only low yields could be obtained. Also, different aldehydes and ketones were reacted with malononitrile. 4-Methoxy benzaldehyde performed very well (Table 2, entry 2), whereas the electron-poor nitro substrate was slightly less active (Table 2, entry 3). Surprisingly, 4-methoxy benzaldehyde reacted quickly, whereas 4-hydroxy benzaldehyde showed a slow conversion rate (Table 2, entry 6). An explanation may be the formation of hydrogen bonds with the solvent; one can imagine a shell of solvent molecules shielding the substrate from the catalyst. Nonaromatic substrates such as isobutyraldehyde and cyclohexanone were tested as well (Table 2, entries 6 and 7), and isobutyraldehyde performed better because of steric reasons (i.e., hindrance of nucleophilic attack on ketones).

Kinetic plots (Figures 1 and 2) confirmed the different reaction rates of C/Co@DMAN (7) when different solvents and mixing conditions (stirring vs sonication) were used. As expected, the reaction rate increased when the superbase was mixed more thoroughly with the reactants (i.e., a higher degree

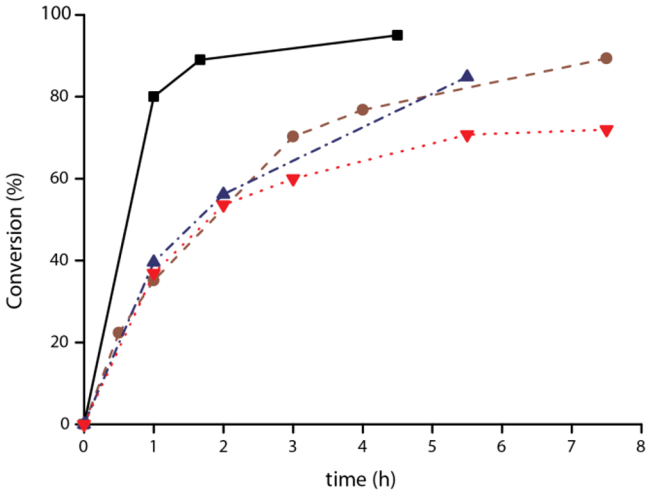

Figure 1. Kinetic plots for the Knoevenagel condensation of benzaldehyde (1.5 equiv) with malononitrile (1 equiv). All reactions used 2.5 mmol % 7 unless otherwise specified. Solvents and conditions for each reaction include ■, methanol and ultrasonication; ●, toluene and stirring; ▲, methanol and stirring; and ▼, C/Co instead of 7, methanol and stirring.

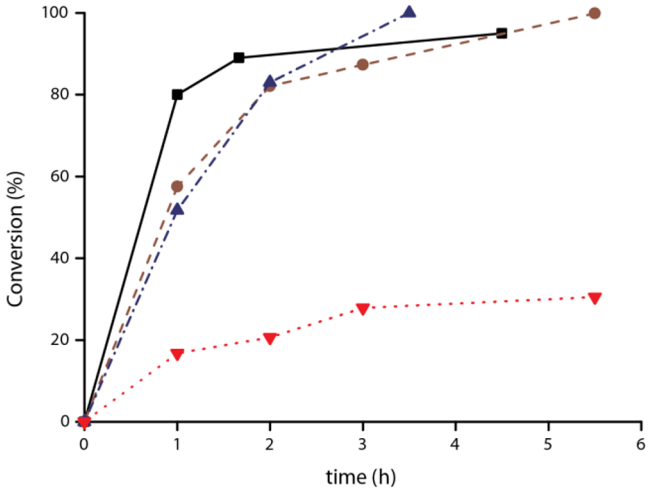

Figure 2. Kinetic plots for reactions with different catalysts (2.5 mmol %) under optimal conditions for each: ■, 7 in methanol, using ultrasonication (taken from Figure 1); ●, free DMAN in methanol; ▲, polymer-bound DMAN (**S2**) in toluene; ▼, without catalyst in methanol.

of mixing). To put the performance of C/Co@DMAN (7) in an appropriate context and to provide a fair comparison, we measured reaction kinetics for free DMAN (no mass-transfer limitation expected) and polystyrene-bound superbase **S2** (under optimal conditions in toluene) (Figure 2). C/Co@DMAN (7) initially catalyzes the chosen reaction at least as well as free DMAN, which leads to comparable or even slightly higher efficiency after 1 h of reaction time. The conversions converge with time, leading to high final conversion for all catalysts. The immobilized magnetic base C/Co@DMAN (7) can therefore be considered tp be directly competitive with existing or alternative catalytic systems. The minor changes in activity (i.e., rapid first part) may be a result of the altered electronic structure (note that DMAN was derivatized at position 4 to anchor the nanoparticle).

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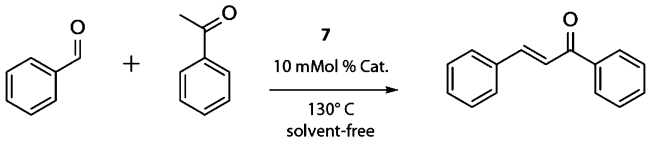
To determine the relevance of and to illustrate a broad applicability of magnetic organic bases such as C/Co@DMAN (7), another type of condensation reaction (Claisen–Schmidt) between acetophenone and benzaldehyde was tested (Table 3).

Table 3. Claisen–Schmidt Condensation of Acetophenone and Benzaldehyde



11 12 13

entry	catalyst	run	conversion (%)[a]	isolated yield (%)[b]	time (h)	Co (ppm)[c]
1	7	1	66	62 [97.6]	16	19
2	7	2	78	*d*	20	16
3	7	3	71	*d*	18	5
4	7	4	68	*d*	18	44
5	7	5	76	75 [98.6]	20	64
6	DMAN	1	<1	*e*	20	
7	Co/C	1	58	*e*	21	42
8		1	<1	*e*	21	
9	**S2**	1	<1	*e*	20	

[a]Conversion was determined by HPLC using the reference product as the standard. [b]Isolated yield after solvent evaporation; purity as detected by NMR is given in brackets [ ]. [c]ICP-OES detection limit for Co = 0.2 ppb. [d]No product isolation has been carried out. [e]No direct product isolation was possible without column chromatography.

This well-known reaction yields *trans*-chalcone, an important precursor for flavonoids that are widely used in medicine as anti-inflammatory,[43] antiviral,[44] and anticancer agents.[45] Immobilized magnetic base C/Co@DMAN (7) catalyzed the reaction with a yield of up to 75% and high levels of purity. Additionally, the same catalyst was reused in five iterative runs with similar yields. The harsh temperature (130 °C) leads to the conclusion that C/Co@DMAN (7) indeed remains stable using covalent-linker systems (Table 3, entries 1–5). Surprisingly, free DMAN does not catalyze the above condensation reaction (Table 3, entry 6; yield = 1%). This behavior is explainable considering the pK_a values. Because acetophenone has a higher pK_a value (pK_a = 25)[46] than does DMAN (pK_a = 12.1),[2] it can be concluded that the basicity of DMAN is not the key factor governing this catalysis. Furthermore, this result is in line with earlier work in the literature. Corma et al. experimentally investigated a similar case and reported that heterogeneous base catalysts work considerably better than free bases.[47]

Comparison to Known Solid-Supported Catalytic Base Reagents. In the recent literature, a number of excellent examples describe immobilized base catalysts.[1,2,6,13,47,48] Magnetic supports have been realized using modified magnetite and cobalt ferrite with good yields (Table 4, entries 6–7). In comparison to metal-based C/Co@DMAN (7), the oxidic supports exhibit a much lower saturation magnetization (133 emu/g for C/Co@DMAN (7), ca. 70 emu/g for magnetite[49]). This is a direct result of the inherently lower level of magnetization of most oxides. This value is important because it correlates directly with separation efficiency/speed and has recently enabled magnetic metal nanoparticles to purify water on a ton per hour scale.[50] In a typical laboratory setting, the improved magnetization facilitates workup, as demonstrated

Table 4. Comparison to Different Solid Support Base Reagents

entry	catalyst/base	saturation magnetization (emu g^{-1})	reaction	solvent	desired product	loading (mmol %)	time (h)	conversion (%)	conversion after three cycles (%)
1	7	139	Knoevenagel condensation	benzaldehyde	α-ethyl-2-cyanocinnamate	2	16	96	95
2	PS-MCM-41-DMAN[1]		Knoevenagel condensation	EtOH	α-ethyl-2-cyanocinnamate	0.5	7	99	85
3	DMAN/SiO_2-0.5[2]		Knoevenagel condensation	EtOH	α-ethyl-2-cyanocinnamate	1	6	90	85
4	TMGN/SiO_2-0.5[2]		Knoevenagel condensation	EtOH	α-ethyl-2-cyanocinnamate	1	6	100	97
5	7	139	Knoevenagel condensation	MeOH	benzylidene malononitrile	2	4.5	98	96
6	$CoFe_2O_4$@Si–N1-propylethane-1,2-diamine[3]	30[5]	Knoevenagel condensation	benzene	benzylidene malononitrile	2.5	0.33	100	100
7	Fe_2O_3@HAP@SiImidazoliumsalt[6]	55[12]	Knoevenagel condensation	H_2O	benzylidene malononitrile		1	98	97
8	7	139	Claisen–Schmidt condensation	acetophenone	*trans*-chalcone	10	20	78	71
9	DMAN/SiO_2-0.5[2]		Claisen–Schmidt condensation	acetophenone	*trans*-chalcone	1	24	95	
10	TMGN/SiO_2-0.5[2]		Claisen–Schmidt condensation	acetophenone	*trans*-chalcone	1	14	98	
11	Fe_3O_4-DABCO[13]	<60	Morita–Baylis–Hillman	MeOH	2-(hydroxy(4-nitrophenyl)methyl)acrylonitrile	20	5	88	88

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using commercially available silica−iron oxide particles and the herein described metal reagent (Figure 3). The high level of

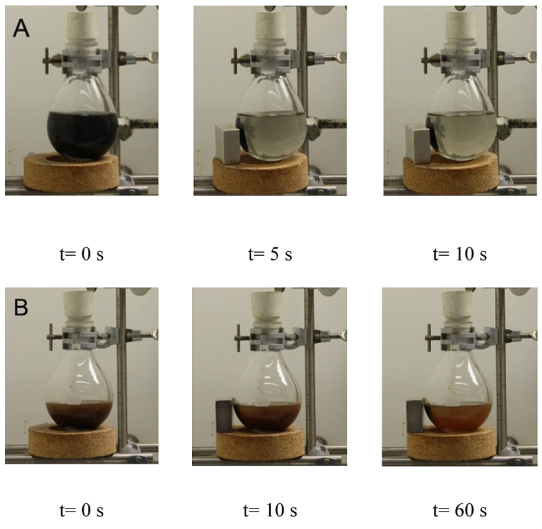

Figure 3. Recovery of organic base bound to magnetic nanoparticles using a low-cost external magnet. Model system in H_2O; same particle concentration as used in all experiments (0.7 mg mL^{-1}). A, metal-based reagents derived from Co/C; B, silica-coated Fe_3O_4. Note the different times above and below.

magnetization of the carbon-coated cobalt allows clean, quantitative separation of the organic base within seconds. Established nonmagnetic immobilized catalyst supports are frequently based on zeolites and silica beads. The active site/moiety is predominantly attached by a siloxane-type linker.[51,52] These catalytic systems usually show excellent performance and reusability (Table 4, entries 2−4, 9−10). In the case of harsh reaction conditions (e.g., strong base), the weakest of these otherwise well-performing materials are the siloxane-type moieties. It is well known that extremely acidic or basic environments (i.e., pH <4 or >9) hydrolyze silane linkers. In contrast, the herein presented dialkyl urea moiety exhibits a high stability over a broad range of pH.

To confirm this statement experimentally, we directly compared siloxane linkers to the herein used C/Co@DMAN (7) in a number of representative acidic and basic environments. After 24 h at room temperature and pH 4, more than 20% of the siloxane linkers were cleaved, but less than 5% of the urea-type linkers were cleaved (Figure 4). At pH 9.5, the dialkyl urea linkers afforded lower stability (about 10% cleaved), but it is notable that under the same conditions >75% of the siloxane linkers were cleaved. Furthermore, the stability of these linkers was tested at elevated temperatures in different solvents (toluene and water). The dialkyl urea linkers performance under these conditions was superior to that of their silane-based pendants (Figure 4). The intrinsic stability of these particles in acidic or basic media has already been investigated[19] and has also been proven to be superior to that of silica-coated magnetite.

■ CONCLUSIONS

We have described the preparation of a covalently bound, chemically stable, magnetic nanoparticle-immobilized organic superbase and its extensive characterization using quantitative elemental microanalysis, infrared spectroscopy, vibrating sample magnetometry, and transmission electron microscopy.

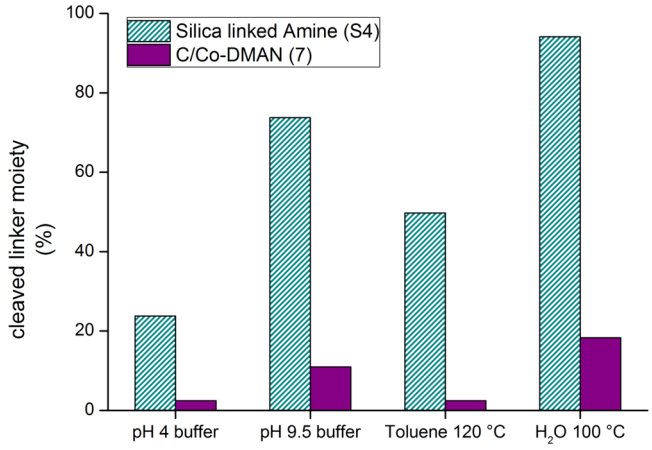

Figure 4. Immobilization linker stability tests under harsh reaction conditions overnight. The amount of cleaved linker was determined by analyzing the nitrogen content of the materials before and after exposure using quantitative elemental microanalysis. pH 4 buffer, 0.1 M potassium hydrogen phthalate with HCl; pH 9.5 buffer, 0.1 M carbonate-bicarbonate.

A number of control reactions were conducted to prove that the reagent was indeed chemically linked to the nanoparticles, and these confirmed the importance of linker type and reliability under relevant, harsh reaction conditions. We further demonstrated the experimental advantages of magnetic bases in a number of Knoevenagel condensations, reporting quantitative conversion and rapid product isolation in minutes. The demanding Claisen−Schmidt condensation afforded conversions of around 70% at 130 °C. The base catalyst was separated from the reaction mixtures in less than 1 min and could be recycled through at least five iterative runs. A quantitative comparison between siloxane linkers used in many immobilization studies and the herein described carbon shell-based chemistry revealed the important role of linker stability when designing reliable reagents for rough, everyday laboratory use.

■ EXPERIMENTAL SECTION

General Experimental Details. Carbon-coated cobalt nanoparticles[20] were suspended by the use of an ultrasonic bath and subjected to various reactions. After a reaction or a pretreatment step, nanoparticles were recovered from the reaction mixture with the aid of a conventional magnet (neodymium-based magnet, side length = 12 mm). Silica-coated magnetite nanoparticles (350 nm) were purchased from a chemical supplier. Commercially available reagents were used as received. All air-sensitive reactions were carried out under an argon atmosphere. The nanoparticles were analyzed by FT-IR spectroscopy (5% in KBr) and elemental microanalysis. HPLC measurements were performed (particle size, 5 μm; column size, 2.1 × 150 mm^2) to determine the conversion of the catalytic reactions. GC−MS measurements were performed (capillary, 30 m × 250 × 0.5 μm^2) with split injection (250 °C; ratio = 50:1; injection volume, 1 μL) and a temperature program (80 °C for 2 min; increase at 20 °C min^{-1} until 250 °C). The cobalt concentration present in solution was measured by inductively coupled plasma−atomic emission spectroscopy (ICP-OES).

Synthesis of C/Co@amine (3). Carbon-coated cobalt nanoparticles (**1**) were purchased from a chemical supplier. The particles were functionalized according to reported procedures (i.e., 3 g of **1** was suspended in 20 mL of H_2O, and 4-aminobenzylamine (**2**) (0.7 mL, 5.3 mmol) were added). Then sodium nitrite (0.8 g, 11.5 mmol) was added to the slurry. The vessel was put in the sonication bath, and 2 mL of concentrated HCl was slowly added dropwise. Upon completion of the reaction (30 min), the nanoparticles were recovered

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from the reaction mixture with a magnet and washed with toluene (2 × 10 mL), EtOH (1 × 10 mL), and acetone (2 × 10 mL) and dried for 24 h at 50 °C in vacuo. FT-IR: 1603, 1503, 1015, 831 cm^{-1}.

Synthesis of C/Co@hexamethyleneisocyanate (5). C/Co@amine (**3**, 2 g) was degassed three times in a Schlenk flask. Fifty milliliters of dry DMF, hexamethylendiisocyanate (HDMI) (6 mL, 37 mmol, 97 equiv, 98%), and triethylamine (NEt_3, 0.01 mL, 99%) were added under an argon atmosphere. Then the solution was dispersed in a sonication bath for 5 min. The dispersion was heated to 70 °C and stirred for 6 h. Upon completion of the reaction, the nanobeads were recovered from the reaction mixture with a magnet and washed with anhydrous DMF (2×). FT-IR: 2927, 2857, 1689, 1553, 1018 cm^{-1}.

Synthesis of C/Co@DMAN (7). Freshly synthesized C/Co@hexamethyleneisocyanate (**5**, 2 g) was used directly in a 250 mL Schlenk flask under an argon atmosphere. Forty milliliters of dry DMF and triethylamine (NEt_3, 0.01 mL, 99%) were added. The solution was dispersed in a sonication bath for 5 min. 4-Amino-1,8-bis-(dimethylamino)naphthalene (DMAN-NH_2 (**6**), 1 g, 4.3 mmol) was degassed three times in a Schlenk flask, dissolved in 10 mL of anhydrous DMF, and added dropwise to the C/Co-HMDI solution. The dispersion was heated to 35 °C and stirred overnight (16 h). Upon completion of the reaction, the nanoparticles were recovered from the reaction mixture with a magnet, washed with DMF (2 × 10 mL), EtOH (1 × 10 mL), acetone (2 × 10 mL), and dried for 24 h at 50 °C in vacuo. FT-IR: 2931, 2857, 2783, 1676, 1532, 1249 cm^{-1}.

Synthesis of Polystyrene-Supported DMAN (S2). Chloromethyl polystyrene (1 g, 2% DVB, 100−200 mesh, 0.9−1.5 mmol/g,) was used in a 50 mL Schlenk flask. Twenty milliliters of anhydrous DMF and triethylamine (NEt_3, 0.01 mL, 99%) were added under an argon atmosphere. DMAN-NH_2 (**6**) (0.6 g, 2.58 mmol) was degassed three times in a Schlenk flask, dissolved in 5 mL of anhydrous DMF, and added dropwise to the polystyrene slurry. The dispersion was heated to 40 °C and stirred overnight (20 h). Upon completion of the reaction, the functionalized polymer was filtered and intensively washed with acetone, 0.1 M NaOH, H_2O, EtOH, and acetone and dried for 24 h at 50 °C in vacuo. FT-IR: 3030, 2927, 2775, 1944, 1874, 1726, 1602 cm^{-1}.

Synthesis of Silica-Amine (S4). Silica gel 230−400 mesh (1 g) was placed in a 50 mL Schlenk flask and degassed three times. Twenty milliliters of anhydrous toluene was added, and the slurry was heated to 60 °C. *N*1-(2-Aminoethyl)-*N*2-(3-(trimethoxysilyl)propyl)ethane-1,2-diamine (0.3 mL, 11.6 mmol) was added dropwise to the solution, which then was stirred for 24 h. The resulting solid was filtered with 50 mL of toluene, 100 mL of DCM, and 20 mL of Et_2O and dried for 24 h at 50 °C in vacuo. FT-IR: 3289, 2940, 2828, 1863, 1474, 1109 cm^{-1}.

General Procedure for Knoevenagel Condensation Reactions. A mixture of solvent (5 mL) and C/Co@DMAN (**7**, 0.1 g, 0.01 mmol) was sonicated in an ultrasonication bath for 5 min in a Schlenk flask and then stirred at room temperature. Benzaldehyde (0.5 mmol) and malononitrile (0.5 mmol) were added, and the progress of the reaction was monitored by HPLC (MS to ensure product identity, UV at 280 nm for quantification) or GC-FID using a commercially available product as a reference.

*Benzylidenemalononitrile (**10**).* Isolated product was obtained by recrystallization in hot EtOH and hexane, followed by filtration. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 7.86−7.82 (m, 2H), 7.71 (s, 1H), 7.57−7.43 (m, 3H).

α-Cyanocinnamic Acid Ethyl Ester. Pure isolated product was obtained by evaporation at 40 °C. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 8.19 (s, 1H), 7.9 (m, 2H), 7.47−7.43 (m, 3H), 4.37−4.27 (q, 2H), 1.37−1.30 (t, 3H).

2-(4-Methoxybenzylidene)malononitrile. Pure isolated product was obtained by evaporation at 40 °C. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 7.86−7.75 (m, 2H), 7.58 (s, 1H), 6.96−6.92 (m, 2H), 3.84 (s, 3H).

2-(4-Nitrobenzylidene)malononitrile. Isolated product was obtained by evaporation of the solvent, followed by recrystallization in DCM/hexane. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 8.73 (s, 1H), 8.45−8.42 (m, 2H), 6.96−6.92 (m, 2H).

General Procedure for Claisen−Schmidt Condensations. A solvent-free mixture of acetophenone (2 mL) and C/Co@DMAN (**7**, 0.1 g, 0.01 mmol) was sonicated in an ultrasonication bath for 5 min and then stirred at 130 °C under a nitrogen atmosphere. Benzaldehyde (0.1 mmol) was added, and the progress of the reaction was monitored by HPLC (MS to ensure product identity, UV at 280 nm for quantification) using a commercially available product as a reference.

*1,3-Diphenyl-2-propen-1-one (**13**).* Isolated product was obtained by evaporation in high vacuum at 65 °C. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 7.93−7.97 (m, 2H), 7.18−7.71 (m, 10H).

General Washing/Drying Procedure for Catalyst Recovery. Used catalyst was washed by sonication (5 min) with the reaction solvent of the catalytic reaction and acetone (2×) and dried for 4 h at 50 °C in vacuo.

General Procedure for Linker Stability Tests. A sample (30 mg) was placed in a 10 mL round-bottomed flask, and solvent (10 mL) was added. The solution was dispersed via ultrasonication bath and then shaken overnight. The solid sample was washed by either sonication (magnetic samples) or filtration (silica samples) with EtOH, H_2O, and acetone and dried for 4 h at 50 °C in vacuo.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data, elemental analysis data, IR spectra, TEM and SEM micrographs of the magnetic and polymeric compounds, scheme depicting the test reactions carried out to verify covalent linkage, and linker stability tests with a duration of 1 week. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): W.J.S. and R.N.G. declare financial interests, because they are shareholders of TurboBeads LLC, a company active in magnetic nanoparticles.

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