

NH₂ was coupled with benzotriazole-1-yl-oxy-tris(pyrrolidinophosphonium)hexafluorophosphate/*N,N*-diisopropylethylamine to the octiphenylene scaffold (55%) and deprotected with trifluoroacetic acid to give **1** (quant.) following previously described protocols without significant changes.^[1] Selected data: H-Leu-Lys(Boc)-Leu-NH₂: [α]_D²⁰ = −29.5 (*c* = 1.00 in MeOH); m.p. 179.5–180.1 °C; elemental analysis calcd for C₂₅H₄₅N₅O₅: C 58.57, H 9.62, N 14.85; found: C 58.47, H 9.65, N 14.71. Leu-Lys(Boc)-Leu-rod (**1**-Boc): ESI-MS (MeOH): *m/z* (%): 1633 (100) [*M*+3Na]³⁺, 2438 (85) [*M*+2Na]²⁺. Leu-Lys-Leu-rod (**1**): CD (EYPC-SUVs, pH 6.4): λ_{max} [nm] ($\Delta\epsilon_{\text{max}}$ [M^{−1}cm^{−1}]) = 333 (+6.4), 307 (−5.1), 252 (−3.7), 237 (+32.6), 215 (−56.0); ESI-MS (MeOH): *m/z* (%): 1008 (100) [*M*+4H]⁴⁺, 1344 (13) [*M*+3H]³⁺. Before use, spectroscopically pure **1** was repurified by RP-HPLC (YMC pack ODS-A, 10 × 250 mm coupled with a Jasco PU-980 pump and a Jasco UV-970 UV/Vis detector, acetonitrile: methanol:trifluoroacetic acid = 49.5:49.5:1, *R*_t = 4.10 min) until constant activity was confirmed (dye efflux).

Fluorescence depth quenching (Figure 2) and dye efflux (Figure 3) were performed as described.^[29] To measure the conductances, a bilayer of EYPC was formed by painting a solution of EYPC (Northern Lipids Inc.) in *n*-decane (33 mg mL^{−1}) containing 0–0.5 mol% of **1** on an orifice (*d* = 150 μm) in a polystyrene cup separating two chambers of a bilayer apparatus (BCH-13, Warner Instrument Corp.). These chambers contained 1 mL saline buffer (5 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES), 2 M NaCl, pH 7.4), a magnetic stirring bar, and a glass KCl (1 M) agar bridge connection to Ag/AgCl electrodes. Oligophenylenes **1** (0.8 mmol in MeOH, 0–30 μL) were added to the stirred *cis* compartment. Formation of EYPC-BLM in the presence of **1**, and addition of **1** to final EYPC-BLM gave comparable results. Currents were recorded at different holding potentials (*trans* at *I* = 0) in a home-made Faraday cage with a bilayer clamp amplifier (BC-525c, Warner Instrument Corp.), low-pass filtered with an 8-pole Bessel filter at 1 kHz (LPF-8, Warner Instrument Corp.), converted (Digipack 1200-2, Axon Instruments), and sampled at 2 kHz by computer. Data were analyzed with pClamp 8.0 software (Axon Instruments).

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A Novel Catalytic System for the Mannich-Type Reaction of Silyl Enolates: Stereoselective Synthesis of β -Aminoketones**

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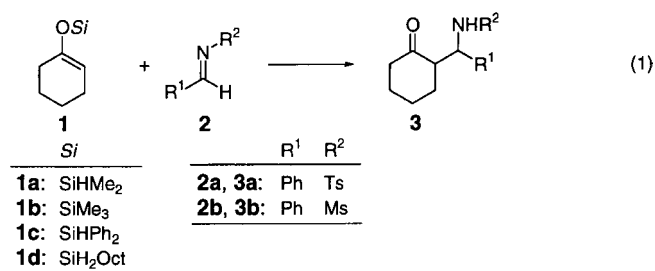
The Lewis acid promoted addition of ester silyl enolates to imines and iminium salts enables the stereoselective construction of β -aminoesters and β -lactams.^[1] However, it is not widely known that the Mannich-type reaction with ketone silyl enolates reveals high stereoselectivity in terms of the relative configuration between the newly formed chiral centers.^[2, 3] Here, we describe that dimethylsilyl (DMS) enolates react with *N*-sulfonylimines in the presence of H₂O and a catalytic amount of a base to afford β -aminoketones with high levels of diastereoselectivity.

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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

Treatment of imine **2a** with DMS enolate **1a**, H₂O, and *i*Pr₂NH (**2a**:**1a**:H₂O:amine = 1:1.2:0.6:0.024) in DMF at room temperature for 1 h gave **3a** (*anti:syn* = 94:6) in 95 % yield [Eq. (1)].^[4] The yield dropped to 9–16 % without H₂O and/or



*i*Pr₂NH. Other amines and aqueous NaOH also worked as efficient catalysts for this process (base, yield, *anti:syn*: pyridine, 82 %, 93:7; Et₃N, 91 %, 83:17; 2M NaOH (aq), 91 %, 68:32). The H₂O-*i*Pr₂NH-mediated reaction proceeded even at –78 °C to achieve higher *anti* selectivity (d.r. = 99:1). Trimethylsilyl enolate **1b** was insensitive to **2a** even in the presence of H₂O/*i*Pr₂NH. In contrast, diphenylsilyl and octylsilyl enolates, **1c** and **1d**, smoothly added to **2a** at room temperature (enolate, yield, *anti:syn*: **1c**, 98 %, 95:5; **1d**, 91 %, 91:9). *N*-Mesylimine **2b** (mesyl = methanesulfonyl) as well underwent the base-catalyzed Mannich-type reaction with **1a** to give **3b** in 92 % yield (*anti:syn* = 88:12); however, other imines (R¹ = Ph, R² = Ph, Bn, NHTs, OH, SPh, and SPh) gave no adduct. The high reactivity of *N*-sulfonylimines to **1a** arises from their high electrophilicity as a result of the presence of the sulfonyl group.

The use of aromatic and α,β -unsaturated imines led to high yield and selectivity (Table 1), while aliphatic imines **2i, j** (R¹ = *c*Hex, *t*Bu, R² = Ts) did not react with **1a** at all. Acyclic

Table 1. Base-catalyzed reaction of **1a** with imines **2**.

Entry	Imine R ¹ (R ² = Ts)	T [°C]	t [h]	β -Aminoketone 3 Yield [%]	<i>anti:syn</i> ^[a]
1	2a Ph	–78	18	3a 91	99:1
2	2c <i>p</i> -MeC ₆ H ₄	–50	9	3c 88	99:1
3	2d <i>p</i> -MeOC ₆ H ₄	–50	18	3d 95	99:1
4	2e <i>p</i> -NCC ₆ H ₄	–50	18	3e 90	95:5
5	2f <i>p</i> -O ₂ NC ₆ H ₄	–50	18	3f 90	97:3
6	2g 2-furyl	–78	24	3g 88	98:2
7	2h (<i>E</i>)-PhCH=CH	–78	9	3h 82	96:4

[a] Determined by HPLC analysis.

silyl enolates **4a–e** and ketene silyl thioacetal **4f** also underwent reaction with **2a** (Table 2). In all cases, *anti*-selectivity was observed irrespective of the geometry of the enolates. The low yield in entry 2 (Table 2) appeared to be a result of the low reactivity of **4b**, which has no substituent at the position of electrophilic attack,^[5] as well as it undergoing hydrolysis. Indeed, the use of D₂O instead of H₂O to reduce the rate of hydrolysis raised the yield to 58 %.

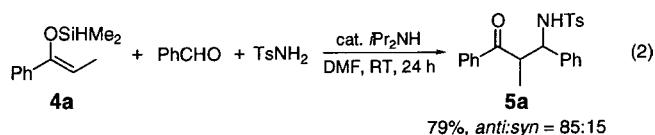
A competitive reaction of **1a** with **2a** versus PhCHO (**1a**:**2a**:PhCHO = 1.2:1:1) proved that **1a** activated by H₂O and *i*Pr₂NH has high reactivity to **2a** (**3a**, 96 %; aldol adduct,

Table 2. Base-catalyzed reaction of enolates **4** with **2a**.

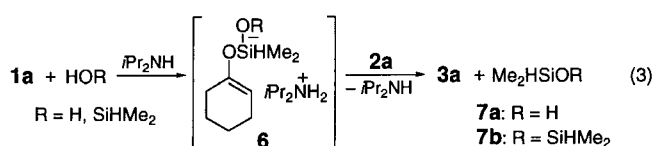
Entry	Silyl enolate 4 R ³ R ⁴ E:Z	T [°C]	t [h]	β -Aminoketone 5 Yield [%]	<i>anti:syn</i> ^[a]
1	4a Ph Me <2:98	–78	24	5a	98 99:1
2	4b Ph H –	–78	67	5b	27 –
3	4c Et Me 67:33	–78	24	5c	79 92:8
4	4c Et Me 20:80	–78	24	5c	97 90:10
5 ^[b]	4d <i>i</i> Pr Me 44:56	–50	24	5d	84 90:10
6 ^[b]	4e <i>t</i> Bu Me <2:98	–50	48	5e	88 93:7
7 ^[b]	4f <i>t</i> BuS Me 8:92	–78	18	5f	98 95:5

[a] Determined by HPLC or ¹H NMR (entries 5 and 7) analysis. [b] Increased amounts of reagents were used: **2a**:**4**:H₂O:*i*Pr₂NH = 1:2:1:0.04.

<1 %).^[6] From this observation, it occurred to us that a three-component coupling reaction among aldehydes, TsNH₂, and DMS enolates could be realized with only a catalytic amount of *i*Pr₂NH since the condensation between aldehydes and TsNH₂ into imines yields H₂O.^[7] As expected, the *i*Pr₂NH-catalyzed reaction of PhCHO, TsNH₂, and **4a** (PhCHO:TsNH₂:**4a**:amine = 1:1:2:0.02) gave β -aminoketone **5a** in good yield with no aldol adduct [Eq. (2)].



The H₂O-*i*Pr₂NH-catalyzed reaction of **1a** with **2a** in [D₇]DMF followed by ¹H NMR analysis revealed that **3a** and (Me₂HSi)₂O (**7b**) were formed in an approximately 2:1 molar ratio before aqueous work up. This observation suggests the possibility of the following catalytic cycle [Eq. (3)]: 1) **1a** reacts with H₂O and *i*Pr₂NH to form



ammonium silicate **6** as an intermediate, 2) the addition of **6** to **2a** provides **3a** along with *i*Pr₂NH and silanol **7a**, and 3) **7a** also works as an activator of **1a** to form disiloxane **7b**. The intermediate arising from **1a** might be a naked enolate bearing a diisopropylammonium ion as a counterion. However, the low reactivity to aldehydes and the change in diastereoselectivity with **1a**, **1c**, and **1d** support the presence of **6** rather than a naked enolate.^[8] The observed difference in reactivity between **1a** and **1b** is attributable to the ease of oxygen coordination in the formation of **6**.^[4] The origin for the *anti*-selective addition of DMS enolates is unclear, but it can be rationalized by an antiperiplanar transition-state model disposing tosyl and R⁴ groups on the opposite sides, which seems to be energetically favorable in view of nonbonding

interaction and dipole–dipole repulsion between C=O and C=N bonds.^[9]

In conclusion, we have found a unique catalytic system in which DMS enolates activated by *i*Pr₂NH and H₂O exhibit high reactivity to *N*-tosylimines. To the best of our knowledge, the base-catalyzed Mannich-type reaction of metal enolates is unprecedented. The present reaction provides an efficient method for the stereoselective synthesis of β -aminocarbonyl compounds, which are versatile building blocks for the synthesis of numerous, biologically significant compounds.

Experimental Section

Typical procedure (entry 1 in Table 1): **1a** (94 mg, 0.60 mmol) and *i*Pr₂NH (1.6 μ L, 12 μ mol) were added to a solution of **2a** (130 mg, 0.50 mmol) and H₂O (5.4 mL, 0.30 mmol) in DMF (1.0 mL) at -78°C . After 18 h, the resultant mixture was quenched with 2 M aqueous HCl (10 mL), then neutralized with saturated aqueous NaHCO₃. The aqueous phase was extracted with ethyl acetate and the combined organic phases dried over Na₂SO₄ before being evaporated. Purification of the residue by column chromatography on silica gel (hexane:ethyl acetate, 4:1) afforded **3a** (166 mg, 91 %). Further details can be found in the Supporting Information.

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An Unprecedented Hexapotassium-Hexamagnesium 24-Membered Macrocyclic Amide: A Polymetallic Cationic Host to Six Monodeprotonated Arene Anions**

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In memory of Ron Snaith[†]

We are currently developing a new concept in macrocyclic host–guest chemistry of amide-supported heterodimetallic cationic rings which formally act as hosts to anionic guests.^[1–3] This idea emerged from our investigations into the effects of mixing an alkali-metal amide with a magnesium bis(amide). While some of the reaction mixtures studied follow a straightforward path leading to simple heterodimetallic compositions,^[4, 5] others take an unexpected turn to behave as powerful oxygen scavengers or as regioselective dideprotonating agents to yield two distinct categories of macrocyclic complex. One type of complex is the eight-membered [(MNMgN)₂]²⁺ (M = Li, Na, K) ring systems with oxo O^{2–} or peroxo (O₂)^{2–} cores;^[1] this first category has the generalized structure **I** (shown with the oxo core). We refer to this type as “inverse crown ether” complexes, on account of their inverse relationship to conventional crown ether complexes. The single potassium^[2] example **1** is strictly a poly(inverse crown ether) complex since its (KNMgN)₂ ring is not discrete (unlike the (LiNMgN)₂ or (NaNMgN)₂ analogues), but is linked into chains through intermolecular K $\cdots$ CH₃(SiMe₂) agostic interactions.^[6] The second category have the generalized structure **II**, which are twelve-membered [(NaNMgNNaN)₂]²⁺ ring systems with dianionic [C₆H₃(CH₃)₂]^{2–} or (C₆H₄)^{2–} cores derived from toluene or benzene, respectively.^[2] We reveal herein the latest and most remarkable category of macrocyclic complexes yet discovered in this special family of heterodimetallic compounds. Expecting structures akin to that of **II** on replacing sodium by a larger alkali metal, our synthesis and crystallographic characterization of the new potassium 2,2,6,6-tetramethylpiperidide (tmp) complexes **2** and **3** have, in contrast, uncovered an unprecedented twenty-four membered [(KNMgN)₆]⁶⁺ ring system, which acts as a polymetallic host to six *singly* deprotonated arene anions.

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[†] Ron Snaith was a close personal friend of R.E.M.; this dedication is in recognition of his inspired teaching and his many outstanding contributions to s-block chemistry.