$Zn(OTf)_2$-catalyzed addition of amines to carbodiimides: efficient synthesis of guanidines and unpredicted formation of Zn–N amido species†

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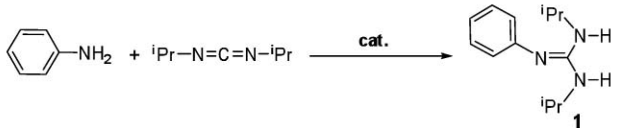
$Zn(OTf)_2$ acts as an excellent catalyst precursor for addition of various amine N–H bonds to carbodiimides under an atmosphere of air, offering a convenient synthesis of substituted guanidines with high functional-group tolerance. A Zn–N amido species is shown to act as the active species.

Introduction

The search for readily available and cheap catalyst system for more convenient and efficient chemical transformations is of great interest and importance for academic and industrial research. The general strategy is to explore the untouched elements with the expectation superior to the known catalysts. Recently, catalytic addition reaction of amine N–H bonds to carbodiimides (catalytic guanylation reaction of amines or hydroamination of carbodiimides) has received much current interest[1,2] because it provides a highly efficient and straightforward preparation of multi-substituted guanidines serving as building blocks for many biologically relevant compounds.[3] The titanium imido complexes were reported first in 2003 by Richeson and coworkers to effect the catalytic addition of only primary aromatic amines to carbodiimides because the catalytic process required the regeneration of a "Ti=N" double bond moiety.[4] In 2006, a rare earth metal–nitrogen single bond species generated *in situ* from a half-sandwich rare earth metal alkyl complex and amines was reported by Hou and coworkers to achieve the catalytic addition of both primary and secondary amines to carbodiimides through the nucleophilic addition mechanism of a metal–nitrogen single bond to a carbodiimide.[2h,i] Montilla and coworkers reported that the vanadium imido chloride $Cl_3V{=}N(C_6H_3{}^iPr_2\text{-}2,6)$ could also serve as a catalyst precursor for this addition, whose mechanism was confirmed *via* the pathway of carbodiimide insertion into a V–N amido bond combining the experimental and DFT calculation methods.[5] Other catalyst systems bearing M–N (M = Li, Ti, Ca, Al, and lanthanides) amido moiety had been found to have high catalytic activity.[2] These reported catalyst systems were generally sensitive to air and moisture and reactions were carried out under the inert atmosphere. In contrast, the use of late transition metal catalyst as well as the catalyst system open to air has not been reported previously. We report here readily available $Zn(OTf)_2$ acts as an excellent catalyst precursor for the addition of amine N–H bonds to carbodiimides under a closed air atmosphere yielding efficiently substituted guanidines with high functional-group tolerance. The mechanistic studies show an unpredicted Zn–N amido species is produced by release of a guanidinium triflate, but acts as active intermediate in this process.

Table 1 $Zn(OTf)_2$-catalyzed addition of aniline to $^iPrN{=}C{=}N^iPr$[a]



1

Entry	**cat.** (mol%)	Solvent	T/°C	Time/h	Yield[b](%)
1	—	C_6D_5Cl	140	24	**1** (0)
2	$AlCl_3$ (5)	C_6D_6	80	3	**1** (59)
3	$FeCl_3$ (5)	C_6D_6	80	3	**1** (0)
4	$ZnCl_2$ (5)	C_6D_6	80	3	**1** (0)
5	$CuCl_2$ (5)	C_6D_6	80	3	**1** (20)
6	$PdCl_2$ (5)	C_6D_6	80	10	**1** (>95)
7	$Pd(PPh_3)_4$ (5)	C_6D_6	80	24	**1** (60)
8	$Pd(OAc)_2$ (5)	C_6D_6	80	2	**1** (95)
9	$Sc(OTf)_3$ (5)	C_6D_6	80	3	**1** (25)
10	$La(OTf)_3$ (5)	C_6D_6	80	3	**1** (30)
11	$Zn(OTf)_2$ (5)	C_6D_6	80	3	**1** (quant.)
12	$Zn(OTf)_2$ (3)	C_6D_6	80	5	**1** (quant.)
13	$Zn(OTf)_2$ (3)	THF-d_8	80	6	**1** (quant.)
14	$Zn(OTf)_2$ (3)	Toluene-d_8	80	6	**1** (quant.)

[a] Conditions: aniline, 0.52 mmol; *N*,*N*′-diisopropylcarbodiimide, 0.50 mmol. [b] Yields were determined by ^1H NMR.

Results and discussion

Catalytic addition of primary aromatic amines to carbodiimides

The neat aniline could not react with *N*,*N*′-diisopropylcarbodiimide $^iPrN{=}C{=}N^iPr$ at room temperature or higher temperatures (Table 1, entry 1). Gratifyingly, addition of 5 mol% of $AlCl_3$ at 80 °C led to rapid addition of aniline to $^iPrN{=}C{=}N^iPr$ to give the *N*,*N*′,*N*″-trisubstituted guanidine **1** in 59% yield (entry 2). This result encouraged us to screen various metal salts (entries 3–14). Finally, $Zn(OTf)_2$ was discovered the best choice for the reaction, but the polarity of solvents did not show a significant influence on the catalytic activity (entries 11–14).

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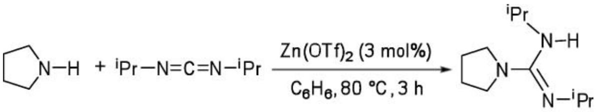
† Electronic supplementary information (ESI) available: Experimental details, X-ray data for **20** and **22**, and scanned NMR spectra of all new products. CCDC reference numbers 741355 + 741356. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b923249b

A broad range of substituted aniline could be used for this catalytic addition reaction, which was not affected by either electron-withdrawing or -donating substituents or their positions at the phenyl ring with high functional-group tolerance (Table 2, entries 1–16). The aromatic C–X (X = F, Cl, Br, or I) bonds (entries 4–7), nitro NO_2 (entry 12), and terminal alkyne unit (entry 9) can survive the reaction conditions. It is noted that the reaction of 4-acetylaniline and ethyl 4-aminobenzoate with ^{i}PrN=C=N^{i}Pr gave the corresponding products **15** and **16** in benzene at 80 °C, respectively (entries 14 and 15). This result is in striking contrast with what was observed previously for the reported catalysts such as a rare earth metal-alkyl or amido complexes[1a,2h,i] and $AlMe_3$,[2a] which failed to produce the corresponding guanidines because of their sensitivity to carbonyl group and ester group. In addition, when a diamine was used to react with 2 eq. of ^{i}PrN=C=N^{i}Pr, the corresponding biguanidine **17** was produced in high yield (entry 16). Heteroatom-containing amines such as amino-substituted pyridine and thiazole were also applicable (entries 17 and 18).

Secondary amine, such as pyrrolidine in the presence of 3 mol% of $Zn(OTf)_2$, could be added to ^{i}PrN=C=N^{i}Pr at 80 °C for 3 h, to give the corresponding *N*,*N′*,*N″*,*N″*-tetrasubstituted guanidines **19a** in 94% yield (eqn (1)).



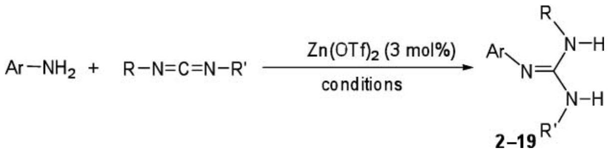
19a, 94% (1)

Mechanistic studies

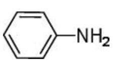
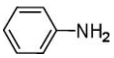
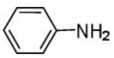
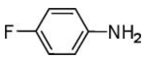
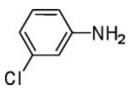
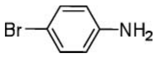
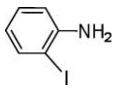
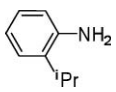
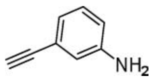
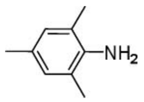
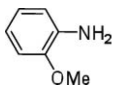
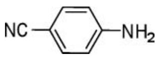
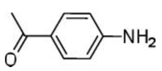
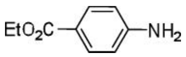
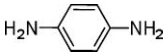
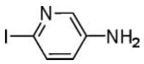
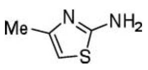
a) Reaction of 2- isopropylaniline, $Zn(OTf)_2$ and carbodiimide

The reaction of $Zn(OTf)_2$ with an excess amount of 2- isopropylaniline at elevated temperatures was attempted to obtain the active species in this catalytic process. Interestingly, the amine-coordinated zinc complex **20** was isolated quantitatively from a THF solution and confirmed by an X-ray diffraction analysis (Fig. 1).‡ There is a crystallographic inversion centre in **20**. Complex **20** adopts a dimeric structure, in which the two Zn atoms are bridged by two triflate units through the oxygen atoms. Unexpectedly, a guanidinium triflate **22** was isolated from the reaction of **20** with ^{i}PrN=C=N^{i}Pr at room temperature. The structure of **22** was unambiguously characterized by NMR spectroscopy and an X-ray diffraction analysis (Fig. 2).‡ Further, we isolated the Zn–N amido species **21** from the residue after the guanidinium triflate **22** was isolated (Scheme 1). Although a single crystal of **21** suitable for X-ray crystallographic analysis was not obtained, its ^{1}H and ^{13}C NMR spectra was rather informative for the elucidation of the structure. The formation

Table 2 Catalytic addition of various amines to carbodiimides[a]



2–19

Entry	Ar–NH$_2$	R, R′	Conditions	Product (yield/%)[b]
1		Cy	C_6H_6, 80 °C, 5 h	**2**, 96
2		^{t}Bu	C_6H_6, 80 °C, 8 h	**3**, 96
3		CH_2Ph,Ph	C_6H_6, 80 °C, 5 h	**4**, 91
4		^{i}Pr	C_6H_6, 80 °C, 3 h	**5**, 97
5		^{i}Pr	C_6H_6, 80 °C, 3 h	**6**, 97
6		^{i}Pr	C_6H_6, 80 °C, 3 h	**7**, 97
7		^{i}Pr	C_6H_6, 80 °C, 3 h	**8**, 95
8		^{i}Pr	C_6H_6, 80 °C, 3 h	**9**, 96
9		^{i}Pr	C_6H_6, 80 °C, 4 h	**10**, 94
10		^{i}Pr	C_6H_6, 80 °C, 3 h	**11**, 97
11		^{i}Pr	C_6H_6, 80 °C, 3 h	**12**, 95[c]
12		^{i}Pr	CH_2Cl_2, reflux, 3 h	**13**, 85[c]
13		^{i}Pr	C_6H_6, 80 °C, 3 h	**14**, 92[c]
14		^{i}Pr	C_6H_6, 80 °C, 3 h	**15**, 95[c]
15		^{i}Pr	C_6H_6, 80 °C, 3 h	**16**, 95[c]
16		^{i}Pr	CH_2Cl_2, reflux, 3 h	**17**, 94[d]
17		^{i}Pr	C_6H_6, 80 °C, 5 h	**18**, 95
18		^{i}Pr	THF, reflux, 5 h	**19**, 93

[a] Conditions: amines, 2.06 mmol; carbodiimides, 2.00 mmol; $Zn(OTf)_2$, 0.06 mmol; benzene, 5 mL. [b] Isolated yield. [c] $Zn(OTf)_2$, 5 mol%. [d] The biguanidine was isolated when a carbodiimide (4.00 mmol) was used.

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‡ Crystal data for **20**: $C_{48}H_{68}F_{12}N_4O_{14}S_4Zn_2$, M_w = 1412.04 g mol^{-1}, T = 173(2) K, Tetragonal, space group I4(1)/a, a = 35.199(5), b = 35.199(5), c = 11.268(2) Å, β = 90°, V = 13960(4) Å^3, Z = 8, ρ_c = 1.344 Mg m^{-3}, μ = 0.894 mm^{-1}, reflections collected: 62839, independent reflections: 6130 (R_{int} = 0.0623), Final R indices [$I > 2\sigma I$]: R_1 = 0.0644, wR_2 = 0.1956, R indices (all data): R_1 = 0.0681, wR_2 = 0.1999. **22**: $C_{17}H_{28}F_3N_3O_3S$, M_w = 411.48 gmol^{-1}, T = 173(2) K, Orthorhombic, space group Pna2(1)/a, a = 16.419(3), b = 12.458(3), c = 10.520(2) Å, β = 90°, V = 2151.8(7) Å^3, Z = 4, ρ_c = 1.270 Mg m^{-3}, μ = 0.196 mm^{-1}, reflections collected: 16883, independent reflections: 4604 (R_{int} = 0.0369), Final R indices [$I > 2\sigma I$]: R_1 = 0.0441, wR_2 = 0.0945, R indices (all data): R_1 = 0.0482, wR_2 = 0.0977.

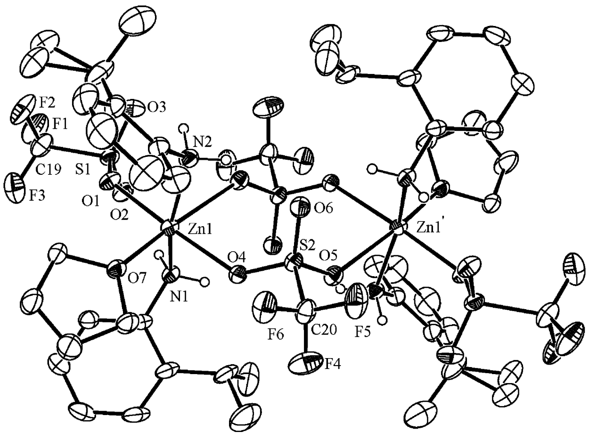


Fig. 1 ORTEP drawing of **20** with 30% thermal ellipsoids. Hydrogen atoms except those on the nitrogen atoms are omitted for clarity. Selected bond length (Å): Zn(1)–N(1) 2.090(3), Zn(1)–N(2) 2.106(3), Zn(1)–O(1) 2.115(3), Zn(1)–O(4) 2.194(3), Zn(1)–O(7) 2.036(3), S(2)–O(4) 1.455(3), S(2)–O(5) 1.442(3), S(2)–O(6) 1.441(3). ' = -x, -y + 1, -z + 2.

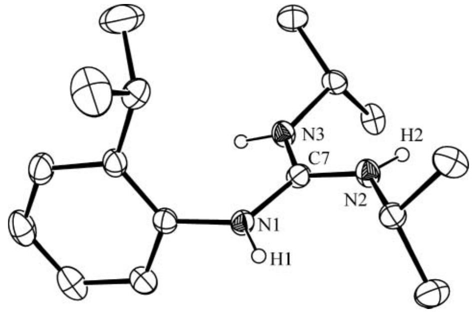
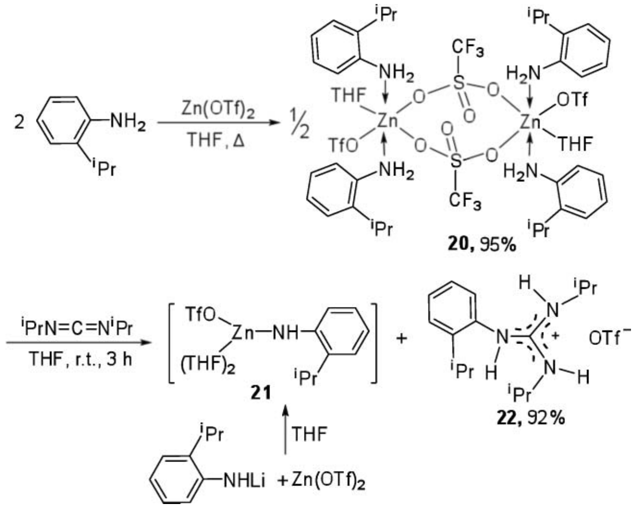
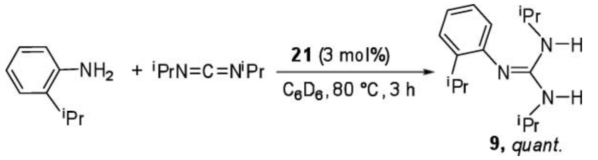


Fig. 2 ORTEP drawing of **22** with 30% thermal ellipsoids. Triflate and hydrogen atoms except those on the nitrogen atoms are omitted for clarity. Selected bond length (Å) and angles (°): N(1)–C(7) 1.357(3), N(2)–C(7) 1.332(3), N(3)–C(7) 1.325(3), N(1)–C(7)–N(2) 119.94(19), N(1)–C(7)–N(3) 118.93(19), N(2)–C(7)–N(3) 121.11(19).



Scheme 1 Formation of the Zn–N amido species **21** and guanidinium triflate **22**.

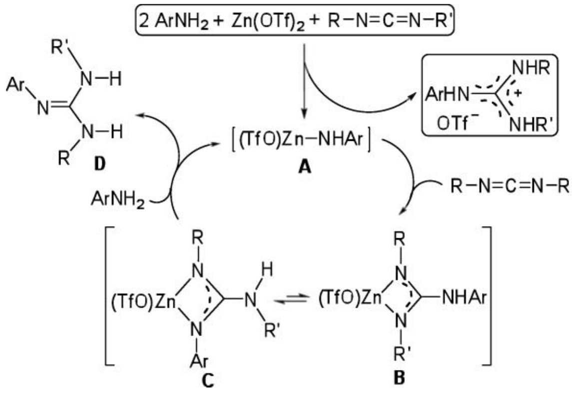
of **21** could be easily confirmed by the 1 : 1 reaction of Zn(OTf)$_2$ with isopropylbenzenamido lithium which was *in situ* generated from the corresponding amine and *n*-BuLi. **21** could also serve as an excellent catalyst active species for the addition of 2-isopropylaniline to ^{i}PrN=C=N^{i}Pr to yield the guanidine **9** in almost quantitative yield (eqn (2)).



(2)

b) Possible mechanism

Based on the above observations, a possible catalytic cycle for the addition reaction of primary aromatic amines to carbodiimides is proposed in Scheme 2.[6] The reaction among primary amine, Zn(OTf)$_2$ and carbodiimide should yield straightforwardly an amido species such as **A** by release of a guanidinium triflate. Nucleophilic addition of the amido species **A** to a carbodiimide would afford the guanidinate species **B** or **C**.[7,8] Protonolysis of **B** or **C** by another molecule of primary amine would regenerate the amido **A** and release the more stable, final guanidine **D**.



Scheme 2 A possible mechanism of catalytic addition of amines to carbodiimides.

Conclusions

We have demonstrated that Zn(OTf)$_2$, under an atmosphere of air, serves as an excellent catalyst precursor for the addition of various primary and secondary amine N–H bonds to carbodiimides yielding substituted guanidines. This work has the following features: i) the use of cheap and readily available catalyst; ii) operational simplicity carried out for the first time under an atmosphere of air; iii) high functional-group tolerance, especially for carbonyl and ester group surviving the present conditions which are sensitive to previous catalyst systems. iv) an unpredicted Zn–N amido species, which is produced by release of a guanidinium triflate, acts as the active species in this catalytic process.

Experimental

General

Unless otherwise noted, all starting materials and solvents were commercially available and were used without further purification. C_6D_6, Toluene-d_8, DMSO-d_6 and THF-d_8 (all 99+ atom% D) were obtained from Acros for NMR reactions. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL-AL400 spectrometer (FT, 400 MHz for ^{1}H; 100 MHz for ^{13}C) or a JEOL JNM-AL300 spectrometer (FT, 300 MHz for ^{1}H; 75 MHz for ^{13}C) at room temperature.

Typical procedures for the catalytic reaction of primary aromatic amines to carbodiimides

i) NMR tube reaction. Under an atmosphere of air, a J. Young valve NMR tube was charged with Zn(OTf)$_2$ (6 mg, 0.015 mmol), C_6D_6 (0.5 mL), aniline (48 mg, 0.52 mmol), *N*,*N′*-diisopropylcarbodiimide (63 mg, 0.50 mmol). The tube was sealed and then heated at 80 °C. Formation of **1** was easily monitored by ^{1}H NMR spectroscopy. The reaction was quantitative and finished within 5 h.

ii) Preparative scale reaction. Under an atmosphere of air, a solution of aniline (192 mg, 2.06 mmol) in benzene (5 mL) was added to Zn(OTf)$_2$ (22 mg, 0.06 mmol) in a Schlenk tube. *N*,*N′*-Diisopropylcarbodiimide (252 mg, 2.00 mmol) was then added to the above reaction mixture. The Schlenk tube was sealed, and the reaction was carried out at 80 °C for 5 h. After the solvent was removed under reduced pressure, the residue was extracted with ether and filtered to give a clean solution. After removing the solvent under vacuum, the residue was recrystallized in ether to provide a colorless solid **1**.

14. Colorless solid, yield 92%. ^{1}H NMR (300 MHz, C_6D_6): δ 0.87 (d, J = 6.3 Hz, 12H, CH_3), 3.50–3.61 (m, 4H, CH and NH), 6.79–7.17 (m, 4H, C_6H_4). ^{13}C NMR (75 MHz, C_6D_6): δ 23.0, 43.3, 103.4, 120.2, 123.8, 133.5, 150.0, 156.1. IR (neat): v (C=O) = 1574 cm^{-1}; HRMS calcd. for $C_{15}H_{24}N_3O$: 262.1914, found 262.1909.

15. Colorless solid, yield 95%, m. p. 115.4~115.9 °C. ^{1}H NMR (300 MHz, C_6D_6): δ 1.01 (d, J = 6.3 Hz, 12H, CH_3), 2.20 (s, 3H, CH_3), 3.79–3.83 (m, 2H, CH), 4.26 (br, 2H, NH), 7.06–7.89 (m, 4H, C_6H_4). ^{13}C NMR (75 MHz, C_6D_6): δ 23.1, 26.0, 43.4, 122.9, 129.9, 130.6, 151.0, 157.4, 196.3. IR (neat): v (C=O) = 1582 cm^{-1}; HRMS calcd. for $C_{16}H_{26}N_3O_2$: 292.2019, found 292.2016.

Isolation and reaction of the zinc complex 20

To a solution of 2-isopropylaniline (608 mg, 4.5 mmol) in THF (1 mL) was added Zn(OTf)$_2$ (727 mg, 2.0 mmol) in a Schlenk tube. The reaction mixture was stirred at 100 °C for 3 h. After cooling to room temperature, the reaction mixture was filtered and the solid product was washed with hexane until the filtrate became colorless. The filtrate was recrystallized in THF/Hexane to provide a colorless zinc complex **20**. Then *N*,*N′*-Diisopropylcarbodiimide (252 mg, 2.0 mmol) was added to a solution of complex **20** (706 mg, 1.0 mmol) in THF (5 mL). The reaction was carried out at room temperature for 3 h. After the solvent was removed under reduced pressure, the residue was recrystallized in THF/Hexane to provide a colorless solid **22**.

20. Single crystals suitable for X-ray analysis were grown in THF/Hexane at room temperature for 12 h. Colorless solid, yield 95%. ^{1}H NMR (300 MHz, THF-d_8): δ 1.20 (d, J = 6.9 Hz, 24H, CH_3), 1.72–1.18 (br m, 8H, CH_2), 2.90–3.04 (m, 4H, CH), 3.61–3.65 (br m, 8H, CH_2), 4.45 (br, 8H, NH), 6.62–7.04 (m, 16H, C_6H_4). ^{13}C NMR (75 MHz, THF-d_8): δ 22.8, 28.1, 26.4, 68.4, 117.0, 119.2, 123.4, 125.8, 127.1, 133.5, 145.0.

22. Single crystals suitable for X-ray analysis were grown in THF/Hexane at room temperature for 12 h. Colorless solid, yield 92%. ^{1}H NMR (300 MHz, THF-d_8): δ 1.19–1.24 (m, 18H, CH_3), 3.08–3.22 (m, 1H, CH), 3.92–4.02 (m, 2H, CH), 6.68 (br, 2H, NH), 7.18–7.43 (m, 4H, C_6H_4), 8.53 (br, 1H, NH). ^{13}C NMR (75 MHz, THF-d_8): δ 22.6, 23.7, 28.7, 45.9, 127.9, 128.2, 128.4, 129.5, 134.3, 146.4, 154.8.

Isolation of Zn–N amido species 21 from the reaction of the zinc complex 20 with *N*,*N′*-diisopropylcarbodiimide

N,*N′*-Diisopropylcarbodiimide (252 mg, 2.0 mmol) was added to a solution of complex **20** (706 mg, 1.0 mmol) in THF (5 mL). The reaction was carried out at room temperature for 3 h. After the solvent was removed under reduced pressure, the residue was recrystallized in THF/Hexane to provide a colorless solid **22** after filtering. Zn–N amido species **21** was obtained from the filtrate.

Preparation of the Zn–N amido species 21 by the 1 : 1 reaction of Zn(OTf)$_2$ with isopropylbenzenamido lithium

To a solution of 2-isopropylaniline (135 mg, 1.0 mmol) in THF was added *n*-BuLi (0.63 mL, 1.0 mmol) at −78 °C. After the mixture was stirred for 1 h at the same temperature, Zn(OTf)$_2$ (364 mg, 1.0 mmol) was added and stirring was continued at −78 °C for 1 h. Then the reaction mixture was allowed to warm to room temperature for 1 h. After the solvent was removed under reduced pressure, the residue was washed with hexane. The residue was recrystallized in ether to provide a colorless solid **21**.

21. Colorless solid, yield 90%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (d, J = 6.9 Hz, 6H, CH_3), 1.72–1.76 (br m, 8H, CH_2), 2.86–2.99 (m, 1H, CH), 3.56–3.60 (br m, 8H, CH_2), 4.71 (br, 1H, NH), 6.48–7.34 (m, 4H, C_6H_4). ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.6, 25.4, 26.7, 67.4, 115.3, 116.9, 119.0, 123.3, 125.2, 126.4, 131.7.

X-Ray crystallographic studies for 20 and 22

Crystals for X-ray analyses of **20** and **22** were obtained as described in the preparations. Data collections were performed at −100 °C on a Rigaku SATURN 724+ CCD diffractometer, using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The determination of crystal class and unit cell parameters was carried out by the CrystalClear (Rigaku Inc., 2008) program package. The raw frame data were processed using the CrystalClear (Rigaku Inc., 2008) to yield the reflection data file. The structure was solved by use of SHELXTL program.[9] Refinement was performed on F^2 anisotropically for all the non-hydrogen atoms by the full-matrix least-squares method. The hydrogen atoms were placed at the calculated positions and were included in the structure calculation without further refinement of the parameters. Crystal data, data collection and processing parameters for **20** and **22** were given only in Supporting Information.†

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