ORGANOMETALLICS
Article

Organometallics **2010,** *29,* 2789–2795 2789
DOI: 10.1021/om1003122

Simple, Versatile, and Efficient Catalysts for Guanylation of Amines

Carlos Alonso-Moreno,*[,†] Fernando Carrillo-Hermosilla,[†] Andrés Garcés,[‡] Antonio Otero,*[,†] Isabel López-Solera,[†] Ana M. Rodríguez,[†] and Antonio Antiñolo[†]

[†]*Departamento de Química Inorgánica, Orgánica y Bioquímica, Facultad de Ciencias Químicas, Universidad de Castilla−La Mancha, Campus Universitario de Ciudad Real, 13071-Ciudad Real, Spain, and* [‡]*Departamento de Química Inorgánica y Analítica, Universidad Rey Juan Carlos, 28933-Móstoles, Spain*

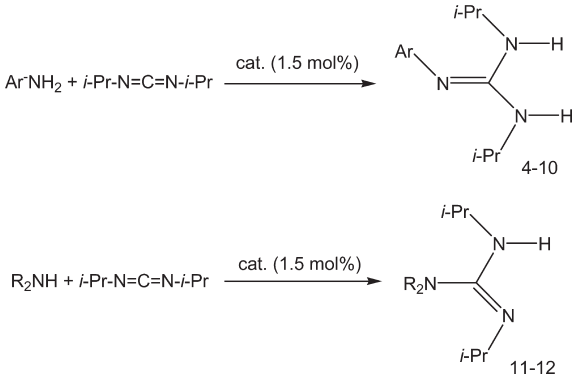
Received April 19, 2010

Commercially available products such as $ZnEt_2$ (**1**), $MgBu_2$ (**2**), and *n*-BuLi (**3**) can act as excellent catalytic precursors for the catalytic addition of amines to carbodiimides. Aromatic primary amines bearing different substituents, secondary amines, and heterocyclic amines can undergo this reaction. The synthesis and structural characterization of the zinc guanidinate complex $[Zn(Et)\{(4\text{-}t\text{-}BuC_6H_4)\text{-}N{=}C(N\text{-}i\text{-}Pr)(NH\text{-}i\text{-}Pr)\}]_2$ (**15**) and the synthesis and characterization of the lithium guanidinate complex $[Li\{(2,4,6\text{-}Me_3C_6H_4)N{=}C(N\text{-}i\text{-}Pr)(NH\text{-}i\text{-}Pr)\}(THF)]$ (**16**), both of which act as catalysts in the guanylation reaction, allowed us to propose a mechanism involving the formation of amido intermediates. These amido compounds subsequently react with the carbodiimide in an insertion process.

Introduction

The C−N bond formation reactions are of considerable interest in both synthetic organic and industrial chemistry due to the importance of amines and their derivatives in almost all areas of chemistry. In particular, guanidine derivatives are very useful pharmacophores in medicinal chemistry due to their capacity to interact with functional groups present in enzymes or receptors through hydrogen bonds and electrostatic interactions.[1] As a result, guanidine derivatives have also been widely used as ancillary ligands for the stabilization of different metal complexes. The unique properties of metal complexes containing these versatile guanidinate ligands have led to the active study of these systems and their applications.[2] The synthesis of guanidines has been intensively investigated by a variety of methods.[3] Primary aliphatic amines can undergo direct addition to carbodiimides under rather forcing conditions.[4] However, aromatic amines or secondary amines do not react with carbodiimides under the same (or even harsher) conditions. Among the direct methods for the synthesis of guanidines, the catalytic hydroamination of carbodiimides is the most relevant, as it has an atom-economy of 100% and is a waste-free process.[5] In 2003, Richeson et al. reported the first example of the transition metal-catalyzed guanylation of aromatic amines with carbodiimides.[6] Titanium complexes undergo this kind of reaction, but these complexes are not able to promote the reaction with secondary aromatic amines because the process requires the regeneration of an M=N imido moiety. The guanylation of aromatic amines catalyzed by lithium bis(trimethylsilyl)-amide has been reported.[7] The guanylation of both aromatic and secondary amines was catalyzed, for the first time, by using half-sandwich lanthanide.[8a] Titanacarboranyl amido or vanadium imido complexes can catalyze the guanylation

Scheme 1. Catalyzed Guanylation Reactions



*To whom correspondence should be addressed. Phone: +34-26-295-326. Fax: +34-26-295-318. E-mail: Antonio.Otero@uclm.es; Carlos.AMoreno@uclm.es.

(1) (a) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep.* **2008**, *25*, 919. (b) Durant, G. J. *Chem. Soc. Rev.* **1985**, *14*, 375. (c) *The Pharmacological Basis of Therapeutics*, 7th ed.; Gilman, A., Gododman, L. S., Rall, T. W., Murad, T., Eds.; Pergamon Press: New York, 1990; p 899.

(2) Coles, M. P. *Dalton Trans.* **2006**, 985.

(3) See for example: (a) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133. (b) Wu, Y.-Q.; Hamilton, S. K.; Wilkinson, D. E.; Hamilton, G. S. *J. Org. Chem.* **2002**, *67*, 7553. (c) Ghosh, A. K.; Hol, W. G. J.; Fan, E. *J. Org. Chem.* **2001**, *66*, 2161. (d) Tamaki, M.; Han, G.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1038.

(4) Thomas, E. W.; Nishizawa, E. E.; Zimmermann, D. C.; Williams, D. J. *J. Med. Chem.* **1989**, *32*, 228.

(5) (a) Zhang, W.-X.; Hou, Z. *Org. Biomol. Chem.* **2008**, *6*, 1720. (b) Schow, S. In *Encyclopedia of Reagents for Organic Synthesis*; Paquete, L. A., Ed.; Wiley: Sussex, U.K., 1995; pp 1408−1410.

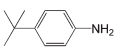
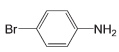
(6) Ong, T.-G.; Yap, G. P. A.; Richeson, D. S. *J. Am. Chem. Soc.* **2003**, *125*, 8100.

(7) Ong, T.-G.; O'Brien, J. S.; Korobkov, I.; Richeson, D. S. *Organometallics* **2006**, *25*, 4728.

(8) (a) Zhang, W.-X.; Nishiura, M.; Hou, Z. *Synlett* **2006**, *8*, 1213. (b) Zhang, W.-X.; Nishiura, M.; Hou, Z. *Chem.—Eur. J.* **2007**, *13*, 4037. (c) Zhou, S.; Wang, S.; Yang, G.; Li, Q.; Zhang, L.; Yao, Z.; Zhou, Z.; Song, H. *Organometallics* **2007**, *26*, 3755. (d) Li, Q.; Wang, S; Zhou, S.; Yang, G.; Zhu, X.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 6763. (e) Wu, Y.; Wang, S.; Zhang, L.; Yang, G.; Zhu, X.; Liu, C.; Yin, C.; Rong, J. *Inorg. Chim. Acta* **2009**, 2814.

Published on Web 05/27/2010

Table 1. Catalytic Addition of Amines to *N,N′*-Diisopropylcarbodiimide with $ZnEt_2$[a]

Entry	Catalyst	Amine	T(°C)	Solvent	Time (h)	Product (conv. %)[b]
1	-		50	Toluene	16	**4**, 0
2	-		120	Toluene	16	**4**, 0
3	$ZnEt_2$		50	Toluene	0.5	**4**, >99
4	$ZnEt_2$		rt	Toluene	16	**4**, >99
5	$ZnEt_2$		50	THF	0.5	**4**, >99
6	$ZnEt_2$		50	Toluene	0.5	**5**, >99
7	$ZnEt_2$		50	Toluene	0.5	**6**, >99
8	$ZnEt_2$		50	Toluene	0.5	**7**, >99
9	$ZnEt_2$		50	Toluene	0.5	**8**, 87
10	$ZnEt_2$		50	Toluene	0.5	**9**, 68
11	$ZnEt_2$		50	Toluene	0.5	**10**, 64
12	$ZnEt_2$		50	Toluene	0.5	**11**, 41
13	$ZnEt_2$		50	Toluene	0.5	**12**, >99

[a] Conditions: amine (1 mmol); *N,N′*-diisopropylcarbodiimide (1 mmol); 1.5 mol % catalyst. [b] Determined by ^{1}H NMR.

of aromatic and secondary amines.[9] Similarly, other lanthanide amido complexes,[8] commercial alkyl aluminums,[10a] and heavier group 2 amides have shown high levels of catalytic activity.[11] Nevertheless, the construction of the CN-rich functionalized guanidines plays an essential role in their biological activity, and the design of efficient catalysts capable of promoting addition of amines to inactivated carbodiimides still remains to be developed. In the context of the information outlined above, we present here a new approach to C−N bond formation[12] that involves the use of commercially available products such as $ZnEt_2$, $MgBu_2$, and *n*-BuLi, as cheap, simple, versatile, and efficient catalysts for guanylation reactions.

Results and Discussion

In the development of catalytic systems for the ring-opening polymerization of cyclic esters[13] the synthesis of the organometallic entities often required the use of commercial compounds (such as $ZnEt_2$, $MgBu_2$, and *n*-BuLi) as starting materials. It was envisaged that these commercially available products could be used as catalyst precursors for guanylation reactions.

The catalytic activity of $ZnEt_2$ (**1**), $MgBu_2$ (**2**), and *n*-BuLi (**3**) in the guanylation of primary, secondary, and heterocyclic aromatic amines was investigated (Scheme 1, Tables 1−3). The conversion values were determined by ^{1}H NMR spectroscopy. The use of *N,N′*-diisopropylcarbodiimide at 50 or 120 °C with 2,4,6-trimethylaniline in deuterated toluene did not lead to a reaction (Table 1, entries 1 and 2). In contrast, the addition of a small amount (1.5 mol %) of the readily available $ZnEt_2$ (**1**) under mild conditions (50 °C) led to rapid addition of 2,4,6-trimethylaniline to *N,N′*-diisopropylcarbodiimide to give more than 99% conversion to the *N,N′,N″*-trisubstituted guanidine in 30 min (Table 1, entry 3). The polarity of the solvents did not seem to have a significant influence

(9) (a) Shen, H.; Chan, H. S.; Xie, Z. *Organometallics* **2006**, *25*, 5515. (b) Montilla, F.; Pastor, A.; Galindo, A. *J. Organomet. Chem.* **2004**, *689*, 993.

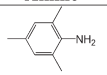
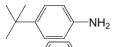
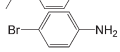
(10) (a) Zhang, W.-X.; Li, D.; Wang, Z.; Xi, Z. *Organometallics* **2009**, *28*, 882. (b) In the course of the preparation of this article, new results about the use of a commercial zinc compound, $Zn(OTf)_2$, as an effective catalyst for guanylation reactions were reported: Li, D.; Guang, J.; Zhang, W.-X.; Wang, Y.; Xi, Z. *Org. Biomol. Chem.* **2010**, DOI: 10.1039/b923249b.

(11) Lachs, J. R.; Barret, A. G. M.; Crimmin, M. R.; Kociock-Kohn, G.; Hill, M. S.; Mahon, M. F.; Procopiou, P. A. *Eur. J. Inorg. Chem.* **2008**, 4173.

(12) Alonso-Moreno, C.; Carrillo-Hermosilla, F.; Romero-Fernández, J.; Rodríguez, A. M.; Otero, A.; Antiñolo, A. *Adv. Synth. Catal.* **2009**, *351*, 881.

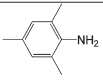
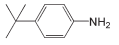
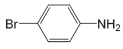
(13) (a) Otero, A.; Fernandez-Baeza, J.; Lara-Sanchez, A.; Alonso-Moreno, C.; Marquez-Segovia, M. I.; Sanchez-Barba Merlo, L. F.; Rodriguez, A. M. *Angew. Chem.* **2009**, *48*, 2176. (b) Otero, A.; Fernandez-Baeza, J.; Antiñolo, A.; Lara-Sanchez, A.; Tejeda, J.; Martinez-Caballero, E.; Marquez-Segovia, I.; Lopez-Solera, I.; Sanchez-Barba Merlo, L. F.; Alonso-Moreno, C. *Inorg. Chem.* **2008**, *47*, 4996. (c) Otero, A.; Fernandez-Baeza, J.; Lara-Sanchez, A.; Martinez-Caballero, E.; Tejeda, J.; Sanchez-Barba Merlo, L. F.; Antiñolo, A.; Alonso-Moreno, C.; Lopez-Solera, I. *Organometallics* **2008**, *27*, 976. (d) Alonso-Moreno, C.; Garces Osado, A.; Sanchez-Barba Merlo, L. F.; Fernandez-Baeza, J.; Otero, A.; Lara-Sanchez, A.; Antiñolo, A.; Broomfield, L.; Lopez-Solera, I. *Organometallics* **2008**, *27*, 1310. (e) Sánchez-Barba, L. F.; Garcés, A.; Fajardo, M.; Alonso-Moreno, C.; Otero, A.; Fernández-Baeza, J.; Antiñolo, A.; Tejeda, J.; Lara-Sánchez, A.; López-Solera, I. *Organometallics* **2007**, *26*, 6403.

Table 2. Catalytic Addition of Amines to *N*,*N*′-Diisopropylcarbodiimide with $MgBu_2$[a]

Entry	Catalyst	Amine	T(°C)	Solvent	Time (h)	Product (conv. %)[b]
1	$MgBu_2$		50	Toluene	0.5	**4**, >99
2	$MgBu_2$		50	Toluene	0.5	**5**, >99
3	$MgBu_2$		50	Toluene	0.5	**6**, >99
4	$MgBu_2$		50	Toluene	0.5	**7**, >99
5	$MgBu_2$		50	Toluene	0.5	**8**, 88
6	$MgBu_2$		50	Toluene	0.5	**9**, 62
7	$MgBu_2$		50	Toluene	5	**10**, traces
8	$MgBu_2$		50	Toluene	0.5	**11**, 21
9	$MgBu_2$		50	Toluene	0.5	**12**, 29

[a] Conditions: amine (1 mmol); *N*,*N*′-diisopropylcarbodiimide (1 mmol); 1.5 mol % catalyst. [b] Determined by ^{1}H NMR.

Table 3. Catalytic Addition of Amines to *N*,*N*′-Diisopropylcarbodiimide with *n*-BuLi[a]

Entry	Catalyst	Amine	T(°C)	Solvent	Time (h)	Product (conv.%)[b]
1	*n*-BuLi		rt	Toluene	0.5	**4**, >99
2	*n*-BuLi		rt	Toluene	0.5	**5**, >99
3	*n*-BuLi		rt	Toluene	0.6	**6**, 83
4	*n*-BuLi		rt	Toluene	0.5	**7**, >99
5	*n*-BuLi		rt	Toluene	0.5	**8**, >99
6	*n*-BuLi		50	Toluene	0.5	**9**, 20
7	*n*-BuLi		50	Toluene	0.5	**10**, traces
8	*n*-BuLi		50	Toluene	5	**11**, 71
9	*n*-BuLi		25	Toluene	2.6	**12**, 32

[a] Conditions: amine (1 mmol); *N*,*N*′-diisopropylcarbodiimide (1 mmol); 1.5 mol % catalyst. [b] Determined by ^{1}H NMR.

on the catalytic activity in the reaction, but the temperature is crucial for the reaction to proceed efficiently (Table 1, entries 3−5). Encouraged by the performance of $ZnEt_2$ in the guanylation of *N*,*N*′-diisopropylcarbodiimide with 2,4,6-trimethylaniline, we decided to expand the scope of the substrates to include examples with different substitution patterns in the aniline (Table 1, entries 6−8). Electron-donating and electron-withdrawing susbtituents on the aniline ring were well tolerated in this process. The conversion levels in this reaction were found to be very high in all cases, and complete conversion was achieved in 30 min. The versatility of $ZnEt_2$ in the guanylation reactions under mild conditions was supported by the fact that the precatalyst was able to add secondary aromatic and cyclic amines to inactivated carbodiimide in 30 min (Table 1, entries 9, 12, and 13; secondary cyclic amines do no react in the absence of catalyst, after 20 h at 50 °C) and that the reaction also occurs with heterocyclic amines (Table 1, entries 10 and 11) in moderate to high yields.

The direct synthesis of all guanidines mentioned above by reaction of the amines with carbodiimides catalyzed by $ZnEt_2$ was also achieved on a Schlenk-tube scale, with the guanidine products isolated as white solids or colorless oily products (**8**) in high yields. The new guanidines were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis. In the case of the previously described 1-(4-bromophenyl)-2,3-diisopropylguanidine (**7**),[8b] the molecular structure

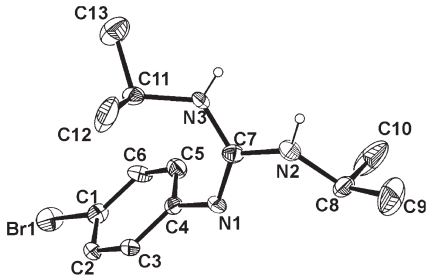


Figure 1. ORTEP drawing of 1-(4-bromophenyl)-2,3-diisopropylguanidine, **7**. Hydrogen atoms, except those on the nitrogen atoms, are omitted for clarity. Selected bond lengths [Å] and angles [deg]: N(1)−C(7) 1.287(8), N(2)−C(7) 1.374(9), N(3)−C(7) 1.357(9), N(1)−C(7)−N(2) 118.5(7), N(2)−C(7)−N(3) 113.2(6), N(1)−C(7)−N(3) 128.3(7).

was established by X-ray diffraction (Figure 1). The crystal data are summarized in the Experimental Section.

Commercially available $MgBu_2$ (**2**) also behaves as a simple, versatile, and efficient catalyst for the guanylation reaction under mild conditions, as evidenced by the reaction of different amines with *N*,*N*′-diisopropylcarbodiimide (Table 2). It can be seen from the results in Table 2 that $MgBu_2$ behaves in a similar way to $ZnEt_2$ as a catalytic precursor for the guanylation reaction. In fact, $MgBu_2$ can catalyze the reaction of aniline as well as primary aromatic amines bearing electron-donating or electron-withdrawing substituents in 30 min and with high efficiency (Table 2, entries 1−4). It is noteworthy that this species was also able to convert a secondary aromatic amine to the corresponding guanidine in high yield (Table 2, entry 5). However, examination of the catalytic activity in reactions with heterocyclic and secondary cyclic amines showed $MgBu_2$ to be a less efficient catalyst than $ZnEt_2$ (Table 2, entries 6−9). In the case of 4,6-dimethylpyridin-2-amine, $MgBu_2$ afforded only a trace of the corresponding guanidine product. Comparison of the catalytic precursors $ZnEt_2$ and $MgBu_2$ with other commercially available compounds such as alkyl aluminums or the zinc triflate used by Zhang et al.[10] shows that $ZnEt_2$ and $MgBu_2$ have very similar catalytic activities under milder conditions than the aluminum alkyl compounds at room temperature. This activity includes guanylation reactions with secondary aromatic amines, which demonstrates the high versatility of this approach. Furthermore, these compounds were similar to or more effective than $Zn(OTf)_2$. Finally, the lower toxicity and less hazardous nature of these species in comparison with alkyl aluminums lead us to propose them as more convenient catalytic precursors. In 2006, Richeson et al. described $LiN(SiMe_3)_2$ as an effective precatalyst for guanylation reactions with very high conversion yields.[7] In that communication it was suggested that other organolithium and lithium amides should present similar rates of conversion based on an initiation step in which the formation of lithium amide was expected. However, representative results for this hypothesis were not presented. In the context of this work we became interested in exploring *n*-BuLi as a catalytic precursor (Table 3). The addition reaction between 2,4,6-trimethylaniline and *N*,*N*′-diisopropylcarbodiimide catalyzed by commercially available *n*-BuLi was achieved at room temperature in less than 30 min (Table 3, entry 1). Although *n*-BuLi was highly efficient as a catalyst for the guanylation reaction of primary (Table 3, entries 1−4) and secondary (Table 3, entry 5) aromatic amines, the conversion of heterocyclic and cyclic secondary amines

Scheme 2. Catalytic Addition of 2,4,6-Trimethylaniline to Different Carbodiimides

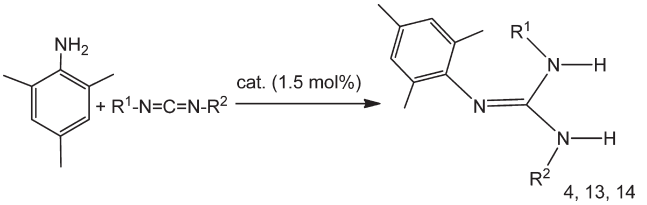


Table 4. Catalytic Addition of 2,4,6-Trimethylaniline to Different Carbodiimides[a]

entry	R^1, R^2	catalyst	product (conv %)[b]
1	*i*-Pr, *i*-Pr	$ZnEt_2$	**4**, >99
2	*i*-Pr, *i*-Pr	$MgBu_2$	**4**, >99
3	*i*-Pr, *i*-Pr	*n*-BuLi	**4**, >99
4	Et, *t*-Bu	$ZnEt_2$	**13**, >99
5	Et, *t*-Bu	$MgBu_2$	**13**, >99
6	Et, *t*-Bu	*n*-BuLi	**13**, >99
7	Cy, Cy	$ZnEt_2$	**14**, 75
8	Cy, Cy	$MgBu_2$	**14**, 52
9	Cy, Cy	*n*-BuLi	**14**, 75

[a] Conditions: 2,4,6-trimethylaniline (1 mmol); carbodiimide (1 mmol); 1.5 mol % catalyst; temperature 50 °C for **1** and **2**, 25 °C for **3**; toluene. [b] Determined by ^{1}H NMR at 30 min.

varied from low to moderate yields (Table 3, entries 6−9). As for precatalysts **1** and **2**, the presence of a *p*-bromo substituent (Table 3, entry 4) was well tolerated. Primary reactivity of this organolithium compound toward acidic amine protons could explain this behavior. Similar results were obtained with reactive lithium amide[7] or $AlMe_3$.[10a]

In order to extend the scope of the reaction to other carbodiimides, we explored the use of *N*,*N*′-*tert*-butylethylcarbodiimide and *N*,*N*′-cyclohexylcarbodiimide (Scheme 2, Table 4) for the guanylation reaction with $ZnEt_2$, $MgBu_2$, and *n*-BuLi as catalysts. In the case of *N*,*N*′-*tert*-butylethylcarbodiimide the catalytic processes showed similar conversions to the diisopropyl system (Table 4, entries 1−6), but the use of the bulkier *N*,*N*′-cyclohexylcarbodiimide gave lower conversions, probably due to steric hindrance (Table 4, entries 7−9).

Of the commercially available products tested as catalysts in the guanylation reaction, $ZnEt_2$ was chosen for kinetic investigation, as it is cheap, harmless, and versatile and the simplest catalyst used. In order to obtain quantitative kinetic data, the reactions of *N*,*N*′-diisopropylcarbodiimide with an equal number of equivalents of 2,4,6-trimethylaniline in the presence of $ZnEt_2$ as catalyst were carried out. The reaction rates of the guanylation reaction were monitored over time by ^{1}H NMR spectroscopy. The kinetics were studied with different catalyst precursor concentrations: [Zn] = 1.5 mol %, 5 mol %, and 8 mol %, at 50 °C, using toluene as solvent. The semilogarithmic plot of $\ln([A]_0/[A]_t)$ versus reaction time is shown in Figure 2, where $[A]_0$ is the initial amine concentration and $[A]_t$ is the amine concentration after a given reaction time. In all cases the linearity of the plot shows that the propagation was first order with respect to amine when the reaction was carried out at 50 °C in toluene. An induction period was not observed. The absence of an induction period indicates that the catalyst was reactive from the beginning of the process and that rearrangement of initiator aggregates was not necessary to form the active species. The linearity of the plot also illustrates that termination processes did not occur during the reaction. The fastest reaction was observed

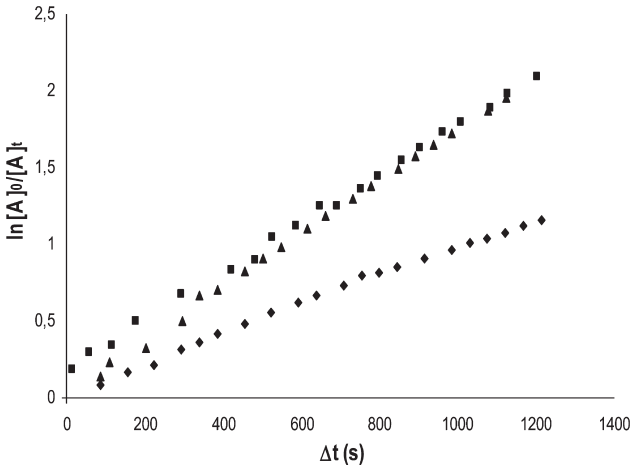


Figure 2. First-order kinetic plots for the guanylation reaction of *N,N′*-diisopropylcarbodiimide and 2,4,6-trimethylaniline with $ZnEt_2$ as catalyst in toluene at 50 °C: (a) ■ [$ZnEt_2$] = 1.5 mol %, $k_{app} = 1.6 \times 10^{-3}\ s^{-1}$ (linear fit, $R = 0.999$), (b) ● [$ZnEt_2$] = 5 mol %, $k_{app} = 1.7 \times 10^{-3}\ s^{-1}$ (linear fit, $R = 0.999$), (c) ▲ [$ZnEt_2$] = 8 mol %, $k_{app} = 0.9 \times 10^{-3}\ s^{-1}$ (linear fit, $R = 0.998$).

for [Zn] = 1.5 mol %, with a pseudo-first-order rate constant of $1.6 \times 10^{-3}\ s^{-1}$. A very similar k_{app} was observed with [Zn] = 5 mol %. However, an increase in the charge of catalyst to 8 mol % gave a $k_{app} = 0.9 \times 10^{-3}\ s^{-1}$, which is much lower than for [Zn] = 1.5 mol % under the same conditions. This finding supports the formation of less reactive aggregates in solution.

The influence of temperature on the guanylation reaction using $ZnEt_2$ was also investigated (Figure 3). It can be seen from Figure 3 that the reaction rate increased with temperature, with a calculated activation energy (E_a) of 59.5 kJ mol^{-1}.

A possible mechanism for the guanylation reaction catalyzed by $ZnEt_2$ is proposed in Figure 4. A straightforward acid−base reaction to yield the alkyl-amido species is postulated as the first step. Participation of both ethyl groups in this process cannot be ruled out. In a second step, nucleophilic addition of the amido species to the carbodiimide would afford the guanidinate species, which would act as the true catalyst. Protonolysis by another molecule of amine could give the final product.

Two approaches were used in an effort to find evidence for the intermediates in the proposed mechanism for the guanylation reactions. First, the addition of a hexane solution of $ZnEt_2$ to a toluene solution of {2-(4-(*tert*-butyl)phenyl)-1,3-diisopropylguanidine}, previously obtained by catalytic means, allowed us, after crystallization, to obtain white crystals of compound **15** appropriate for X-ray diffraction. The molecular structure is shown in Figure 5 along with the numbering system used in the crystallographic study. The crystal data are summarized in the Experimental Section.

Complex **15** crystallized as a dimeric compound, [Zn(Et)-{(4-*t*-BuC_6H_4)N═C(N-*i*-Pr)(NH-*i*-Pr)}]$_2$, with a $\mu,\eta^2{:}\eta^1$-coordination mode of the guanidinate ligand, resulting in a planar Zn_2N_2 ring metallacycle. Both the ethyl and guanidinate groups show a relative *anti* arrangement around the planar ring. This situation is in contrast with a similar compound described by Coles and Hitchcock,[14] where the ligands adopt a *syn* distribution. The metal atoms show a distorted

(14) Coles, M. P.; Hitchcock, P. B. *Eur. J. Inorg. Chem.* **2004**, 2662.

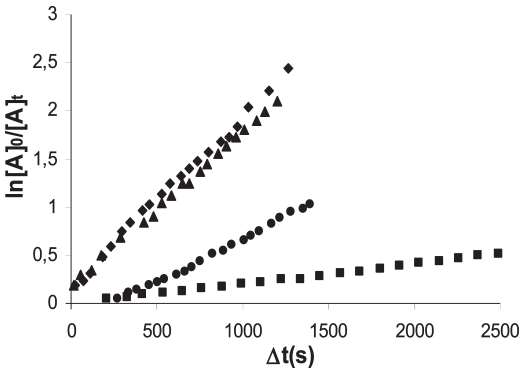


Figure 3. First-order kinetic plots for the guanylation reaction of *N,N′*-diisopropylcarbodiimide and 2,4,6-trimethylaniline in toluene with [$ZnEt_2$] = 1.5 mol %: (a) ■ at 30 °C, $k_{app} = 0.2 \times 10^{-3}\ s^{-1}$ (linear fit, $R = 0.9987$); (b) ● at 40 °C, $k_{app} = 0.9 \times 10^{-3}\ s^{-1}$ (linear fit, $R = 0.998$); (c) ▲ at 50 °C, $k_{app} = 1.6 \times 10^{-3}\ s^{-1}$ (linear fit, $R = 0.999$); (d) ♦ at 60 °C, $k_{app} = 1.8 \times 10^{-3}\ s^{-1}$ (linear fit, $R = 0.998$).

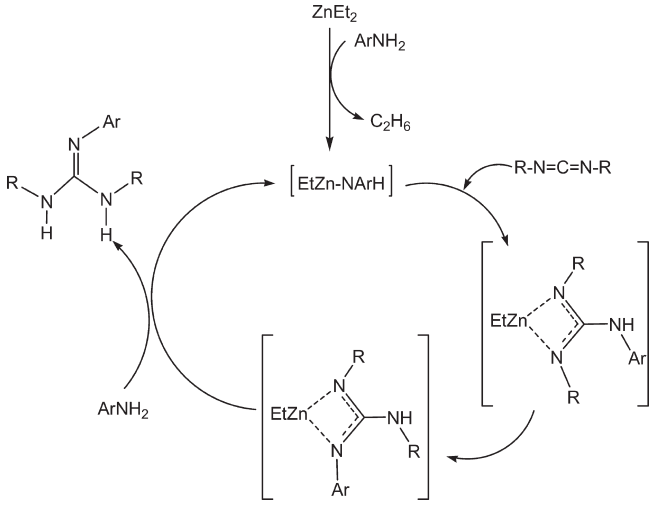


Figure 4. Proposed mechanism for the guanylation reaction catalyzed by $ZnEt_2$.

tetrahedral geometry [angles in the range 62.3(4)−127.6(4)°]. Similarly, the bridging nitrogen atoms show an analogous disposition [angles in the range 81.8(9)−123.5(7)°]. It is worth noting that the metal−nitrogen distance between the ligand of one [Zn(Et){(4-*t*-BuC_6H_4)N═C(N-*i*-Pr)(NH-*i*-Pr)}] unit and the metal of the another [Zn−N1A = 2.04(1) Å] is shorter than that within the chelating guanidinate itself [Zn−N1 = 2.34(1) Å]. This finding suggests a strong interaction between the two monomeric units in the solid state. Charge delocalization around the guanidinate atoms is postulated on the basis of the C−N distances [1.30(1), 1.37(1), and 1.38(1) Å for N(2)−C6, N(1)−C6, and N(3)−C6, respectively], which are intermediate between the value expected for C−N single and C═N double bonds.

Furthermore, the equimolar reaction of *n*-BuLi, 2,4,6-trimethylaniline, and *N,N′*-diisopropylcarbodiimide in hexanes/THF at room temperature quantitatively gave the lithium guanidinate complex [Li{C(NH-2,4,6-$Me_3C_6H_4$)(N-*i*-Pr)$_2$}-(THF)] (**16**) as a white solid in high yield. Unfortunately, crystals suitable for X-ray diffraction were not obtained. Similar reactions with magnesium compound **2** gave rise to unstable products that could not be isolated. Compounds **15**

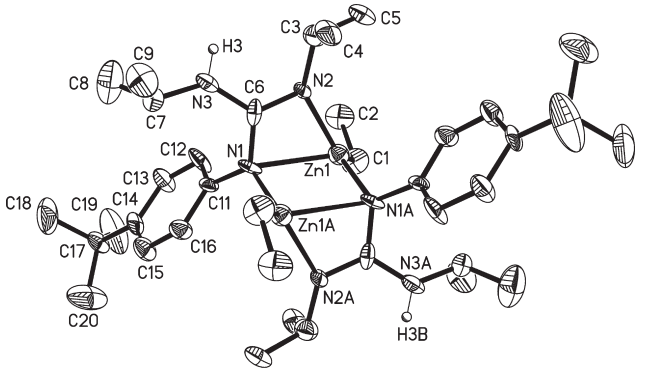


Figure 5. ORTEP drawing of [Zn(Et){(4-*t*-BuC_6H_4)N=C(N-*i*-Pr)(NH-*i*-Pr)}]$_2$, **15**. Hydrogen atoms, except those on the nitrogen atoms, are omitted for clarity. Selected bond lengths [Å] and angles [deg]: Zn(1)−C(1) 1.96(1), Zn(1)−N(1) 2.34(1), Zn(1)−N(2) 2.04(1), Zn(1)-N(1A) 2.04(1), N(1)−C6 1.37(1), N(2)−C6 1.30(1), N(3)−C6 1.38(1), C(1)−Zn(1)−N(1) 121.2(4), C(1)−Zn(1)−(N2) 127.6(4), N(1)−Zn(1)−N(2) 62.3(4), N(1)−Zn(1)−N(1A) 93.9(4).

and **16** were tested as catalysts in the guanylation reaction of 2,4,6-trimethylaniline. Both compounds show the same activity as the precursor compounds **1** and **3**, and this provides plausible evidence that these or similar species play a role in the mechanism proposed for the guanylation reaction.

Conclusions

In conclusion, we report the use of the commercially available compounds $ZnEt_2$, $MgBu_2$, and *n*-BuLi as cheap, simple, versatile, and efficient catalysts for the guanylation reaction of carbodiimides with a wide range of primary aromatic amines, secondary aromatic amines, and heterocyclic amines. The isolation and reactivity of zinc and lithium guanidinate intermediates **15** and **16** confirms that the guanylation reaction proceeds through nucleophilic addition of an amido species to a carbodiimide, followed by amine protonolysis of the resultant guanidinate species. Further studies are underway aimed at examining thoroughly the use of other commercially available zinc alkyls, Grignard reagents, and lithium compounds, the effect of changes in the substituents on the carbodiimide framework and the catalytic addition of terminal alkynes to carbodiimides, and to extend the scope of the reaction to other primary aromatic amines, secondary amines, and heterocyclic amines.

Experimental Section

General Procedures. All reactions were performed using standard Schlenk and glovebox techniques under an atmosphere of dry nitrogen. Solvents were distilled from appropriate drying agents and degassed before use. Microanalyses were carried out with a Perkin-Elmer 2400 CHN analyzer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity FT-300 spectrometer and are referenced to the residual deuterated solvent. The g-HSQC spectra were recorded on a Varian Inova FT-500 spectrometer using standard VARIAN-FT software. $ZnEt_2$, $MgBu_2$, *n*-BuLi, amines, and carbodiimides were purchased from Aldrich. Liquid amines were distilled from CaH_2.

General Procedure for Guanylation Reactions at NMR Tube Scale. Catalytic reactions were performed on a small scale in an NMR tube fitted with a concentric Teflon valve. Reactions were performed in the NMR spectrometer with 1 mmol of amine, 1 mmol of carbodiimide, and 1.5 mol % of catalyst in the appropriate deuterated solvent under nitrogen. Conversion of the starting material to product was determined by integration of the product resonances relative to the substrate peaks in the ^{1}H NMR spectrum.

Preparative Scale Synthesis of the Guanidines. In a glovebox, a solution of amine (6.00 mmol) in toluene (20 mL) was added to a solution of $ZnEt_2$ in hexanes (0.09 mmol) in a Schlenk tube. The carbodiimide (6.00 mmol) was then added to the above reaction mixture. The Schlenk tube was taken outside the glovebox, and the reaction was carried out at 50 °C for 2 h. The solvent was removed under reduced pressure, and the residue was extracted with diethyl ether and filtered to give a clear solution. The solvent was removed under vacuum, and the residue was recrystallized from ether to provide the solid guanidine products or distilled under vacuum in the case of liquid guanidine **8**. Guanidines **4**,[9b] **5**,[7] **7**,[8b] **11**,[9a] **12**,[8c] and **14**[9b] were previously described in the literature.

Characterization of {2-(4-(*tert*-Butyl)phenyl)-1,3-diisopropylguanidine}, 6. Yield: 1.57 g, 95%. Anal. Calcd for $C_{17}H_{29}N_3$: C, 74.13; H, 10.61; N, 15.26. Found: C, 74.28; H, 10.34; N, 15.31. ^{1}H NMR (toluene-d_8, 297 K): δ 7.27, 6.99 (2d, 2H each, $^3J_{H-H}$ = 8.5 Hz, N-C_6H_4-$C(CH_3)_3$), 3.67 (m, 2H, N-C$H(CH_3)_2$), 3.61 (bs, 2H, N*H*), 1.26 (s, 9H, N-C_6H_4−$C(CH_3)_3$), 0.91 (d, 12H, $^3J_{H-H}$ = 6.4 Hz, N-CH(CH_3)$_2$). ^{13}C{^{1}H} NMR (toluene-d_8, 297 K): δ 149.5 (*C*=N), 143.4, 137.4, 126.3, 123.2 (N-C_6H_4-$C(CH_3)_3$), 43.3 (N-*C*H$(CH_3)_2$), 34.2 (N-C_6H_4-*C*$(CH_3)_3$), 31.7 (N-C_6H_4-$C(CH_3)_3$), 23.2 (N-CH(CH_3)$_2$).

Characterization of {2,3-Diisopropyl-1-methyl-1-phenylguanidine} 8. Yield: 1.10 g, 79%. Anal. Calcd for $C_{14}H_{23}N_3$: C, 72.06; H, 9.93; N, 18.01. Found: C, 72.40; H, 10.01; N, 18.50. ^{1}H NMR (toluene-d_8, 297 K): δ 7.19, 6.73 (m, 5H, N-C_6H_5), 3.54 (m, 2H, N-C$H(CH_3)_2$), 3.02 (s, 3H, N-CH_3), 1.02 (m, 12H, N-CH-(CH_3)$_2$). ^{13}C{^{1}H} NMR (toluene-d_8, 297 K): δ 149.7 (*C*=N), 146.8, 129.4, 118.4, 113.8 (N-C_6H_5), 45.4 (N-*C*H$(CH_3)_2$), 37.4 (N-*C*H_3), 24.3 (N-CH(*C*H_3)$_2$).

Characterization of {1,3-Diisopropyl-2-(pyridin-3-yl)guanidine}, 9. Yield: 0.79 g, 60%. Anal. Calcd for $C_{12}H_{20}N_4$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.29; H, 9.44; N, 25.21. ^{1}H NMR (toluene-d_8, 297 K): δ 8.09, 7.95, 7.08, 7.07 (4 m, 1H each, N-C_5NH_4), 4.76 (bs, 2H, N*H*), 3.86 (m, 2H, N-C$H(CH_3)_2$), 1.10 (d, 12H, $^3J_{H-H}$ = 6.6 Hz, N-CH(CH_3)$_2$). ^{13}C{^{1}H} NMR (toluene-d_8, 297 K): δ 151.5 (*C*=N), 148.1, 145.3, 140.8, 129.2, 126.5 (N-C_5NH_4), 31.8 (N-*C*H$(CH_3)_2$), 22.8 (N-CH(*C*H_3)$_2$).

Characterization of {2-(4,6-Dimethylpyridin-2-yl)-1,3-diisopropylguanidine}, 10. Yield: 0.83 g, 59%. Anal. Calcd for $C_{14}H_{24}N_4$: C, 67.70; H, 9.74; N, 22.56. Found: C, 67.55; H, 9.94; N, 22.44. ^{1}H NMR (toluene-d_8, 297 K): δ 6.47, 6.34 (2 m, 1H each, N-C_5NH_2-Me_2), 4.65 (bs, 2H, N*H*), 4.12 (m, 2H, N-C$H(CH_3)_2$), 2.35, 2.20 (2s, 3H each, N-$C_5NH_2Me_2$), 1.26 (d, 12H, $^3J_{H-H}$ = 6.6 Hz, N-CH(CH_3)$_2$). ^{13}C{^{1}H} NMR (toluene-d_8, 297 K): δ 147.4 (*C*=N), 164.5, 154.7, 154.3, 120.7, 118.2 (N-$C_5NH_2Me_2$), 49.4, 42.9 (N-$C_5NH_2Me_2$), 32.5 (N-*C*H$(CH_3)_2$), 23.8 (N-CH(*C*H_3)$_2$).

Characterization of {1-(*tert*-Butyl)-3-ethyl-2-mesitylguanidine}, 13. Yield: 1.44 g, 92%. Anal. Calcd for $C_{16}H_{27}N$: C, 73.51; H, 10.41; N, 16.07. Found: C, 73.85; H, 10.19; N, 15.99. ^{1}H NMR (toluene-d_8, 297 K): δ 6.91 (s, 2H, N-$C_6H_2Me_3$), 3.30 (bs, 2H, N*H*), 2.61 (bs, 2H, N-CH_2CH_3), 2.31 (s, 3H, N-$C_6H_2Me_2$-(*p*-*Me*)), 2.26 (s, 6H, N-C_6H_2Me(*o*-*Me*)$_2$), 1.50 (bs, 9H, N-C-(CH_3)$_2$), 0.82 (bs, 3H, N-CH_2CH_3). ^{13}C{^{1}H} NMR (toluene-d_8, 297 K): δ 145.2 (*C*=N), 137.3, 129.9, 129.7, 128.9 (N-C_6H_2-Me_3), 50.5 (N-CH_2CH_3), 37.1 (N-*C*$(CH_3)_2$), 31.9 (N-C(*C*H_3)$_2$), 20.9, 18.5 (N-$C_6H_2Me_3$), 15.5 (N-CH_2CH_3).

Synthesis and Characterization of [Zn(Et){(4-*t*-BuC_6H_4)N=C(N-*i*-Pr)(NH-*i*-Pr)}]$_2$, 15. In the glovebox, a solution of $ZnEt_2$ (3.00 mmol, 3 mL of a 1 M solution in hexanes) was added dropwise to a solution of 2-(4-(*tert*-butyl)phenyl)-1,3-diisopropylguanidine (3.00 mmol, 1.10 g) in toluene (30 mL), and the mixture was stirred for 2 h. The mixture was concentrated and stored at −25 °C to give compound **15** as white crystals. Yield: 0.72 g, 65%. Anal. Calcd for $C_{38}H_{68}N_6Zn_2$: C, 61.70; H, 9.27; N,

Table 5. Crystal Data and Structure Refinement for 7 and 15

	7	15
empirical formula	$C_{13}H_{20}BrN_3$	$C_{38}H_{66}N_6Zn_2$
fw	298.23	737.71
temperature, K	290(2)	230(2)
wavelength, Å	0.71073	0.71073
cryst syst	monoclinic	monoclinic
space group	$P2_1/n$	$P2_1/c$
a, Å	8.721(1)	12.392(4)
b, Å	25.988(4)	9.546(3)
c, Å	13.289(2)	17.778(5)
β,°	91.499(4)	96.214(7)
volume, Å^3	3010.9(7)	2090.7(11)
Z	8	2
density (calcd), g/cm^3	1.316	1.172
absorp coeff, mm^{-1}	2.716	1.178
F(000)	1232	792
cryst size, mm^3	0.20 × 0.15 × 0.12	0.22 × 0.19 × 0.12
index ranges	$-10 \le h \le 10$, $-30 \le k \le 30$, $-15 \le l \le 15$	$-10 \le h \le 9$, $-7 \le k \le 7$, $-14 \le l \le 14$
reflns collected	13 829	5060
indep reflns	5105 [R(int) = 0.0941]	1172 [R(int) = 0.0997]
data/restraints/params	5105/0/331	1172/0/219
goodness-of-fit on F^2	0.848	1.000
final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0658$, $wR_2 = 0.1336$	$R_1 = 0.0448$, $wR_2 = 0.1063$
R indices (all data)	$R_1 = 0.2012$, $wR_2 = 0.1732$	$R_1 = 0.0666$, $wR_2 = 0.1195$
largest diff peak and hole, e Å^{-3}	1.038 and −0.533	0.372 and −0.256

11.36. Found: C, 61.88; H, 9.34; N, 11.31. ^{1}H NMR (C_6D_6, 297 K): δ 7.33 (m, 8H, N-C_6H_4-*t*-Bu), 3.67 (bs, 4H, N-C*H*$(CH_3)_2$), 3.61 (bs, 2H, N*H*), 1.74 (t, 6H, $^3J_{H-H}$ = 8.1 Hz, $ZnCH_2CH_3$), 1.31 (s, 18H, N-C_6H_4-C$(CH_3)_3$), 1.16 (bs, 24H, N-CH$(CH_3)_2$), 0.78 (bs, 4H, $ZnCH_2CH_3$). ^{13}C NMR (C_6D_6, 297 K): δ 159.1, (*C*=N), 145.5, 138.5, 121.6, 119.5 (N-C_6H_4-*t*-Bu), 43.2 (N-*C*H$(CH_3)_2$), 41.4 (N-C_6H_4-*C*$(CH_3)_3$), 30.5 ($ZnCH_2CH_3$), 28.1 (N-C_6H_4-C$(CH_3)_3$), 20.5, 19.6 (N-CH$(CH_3)_2$), 10.25 ($ZnCH_2CH_3$).

Synthesis and Characterization of [Li{(2,4,6-Me$_3$C$_6$H$_4$)N=C(N-*i*-Pr)(NH-*i*-Pr)}(THF)], 16. In the glovebox, a solution of 2,4,6-trimethylaniline (6.40 mmol, 0.96 mL) in a mixture of THF/hexane (9:1) (30 mL) was added to a solution of *n*-BuLi (6.40 mmol, 4 mL of a 1.6 M solution in hexanes) in a Schlenk tube. *N*,*N*′-Diisopropylcarbodiimide (6.40 mmol, 1 mL) was added to the above reaction mixture. The mixture was concentrated and stored at −25 °C to give compound **16** as white crystals. Yield: 1.84 g, 85%. Anal. Calcd for $C_{20}H_{34}LiN_3O$: C, 70.77; H, 10.10; N, 12.38. Found: C, 71.01; H, 10.21; N, 12.44. ^{1}H NMR (THF-d_8, 297 K): δ 6.68 (s, 2H, N-$C_6H_2Me_3$), 3.78 (bs, 2H, C*H*$(CH_3)_2$), 3.58 (bs, 4H, THF), 2.12 (s, 3H, N-$C_6H_2Me_2$(*p*-*Me*)), 1.97 (s, 6H, N-C_6H_2(*o*-*Me*)$_2$Me), 1.63 (bs, 4H, THF), 1.05 (bs, 12H, CH(C*H*$_3$)$_2$). ^{13}C NMR (THF-d_8, 297 K): δ 148.5, (*C*=N), 146.0, 130.4, 129.7, 129.1 ($C_6H_2Me_3$), 68.2 (THF), 43.8 (*C*H$(CH_3)_2$), 26.4 (THF), 23.7 (CH(*C*H$_3$)$_2$), 20.9 (N-C_6H_2(*p*-*Me*)Me$_2$), 18.6 (N-C_6H_2(*o*-*Me*)$_2$Me).

General Procedures for the Kinetics Experiments. Carbodiimide (1 mmol) was added to a solution of catalyst and amine (1 mmol) in deuterated toluene in a J-Young tube at room temperature. The reaction rate was measured by monitoring the disappearance of amine and formation of guanidine by ^{1}H NMR spectroscopy.

X-ray Crystallographic Structure Determination. Crystals of compound **15** were of poor quality. We have attempted to repeat the crystallization many times, and we have mounted several crystals, but we were unable to obtain better data. However, considering the importance of the structure, it was solved despite the aforementioned problems. Single crystals of **7** and **15** were mounted on a glass fiber and transferred to a Bruker X8 APEX II CCD-based diffractometer equipped with a graphite-monochromated Mo Kα radiation source (λ = 0.71073 Å). Data were integrated using SAINT,[15] and absorption correction was performed with the program SADABS.[16] The software package SHELXTL version 6.12[17] was used for space group determination, structure solution, and refinement by full-matrix least-squares methods based on F^2. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed using a "riding model" (except H3 in complex **15**, which was located in the difference map) and included in the refinement at calculated positions. Crystallographic data are presented in Table 5.

Acknowledgment. We gratefully acknowledge financial support from the Ministerio de Ciencia e Innovación, Spain (Grant Nos. Consolider-Ingenio 2010 ORFEOCS-D2007-00006, CTQ2008-00318/BQU, CTQ2009-09214) and the Junta de Comunidades de Castilla-La Mancha, Spain (Grant No. PCI08-0010).

Supporting Information Available: Full crystallographic data for **7** and **15** are available free of charge via the Internet at http://pubs.acs.org.

(15) *SAINT+ v7.12a*, Area-Detector Integration Program; Bruker-Nonius AXS: Madison, WI, 2004.

(16) Sheldrick, G. M. *SADABS* version 2004/1, A Program for Empirical Absorption Correction; University of Göttingen: Göttingen, Germany, 2004.

(17) *SHELXTL-NT* version 6.12, Structure Determination Package; Bruker-Nonius AXS: Madison, WI, 2001.