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# Guanidines: from classical approaches to efficient catalytic syntheses



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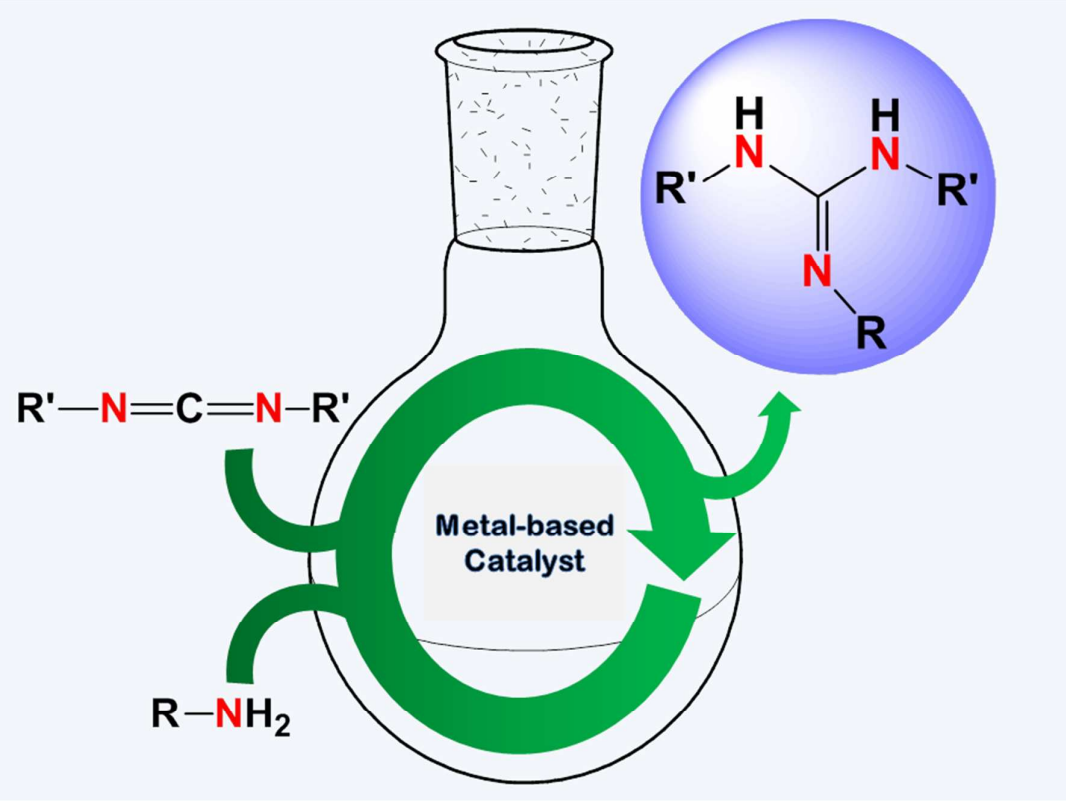
GRAPHICAL ABSTRACT




This review focuses on the metal-mediated catalytic addition of amines to carbodiimides as an atom-economical alternative to the classical synthesis of guanidines.

# Guanidines: from classical approaches to efficient catalytic syntheses

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Fernando Carrillo-Hermosilla was born in Madrid, Spain, in 1967. He studied Chemistry at the University of Alcalá and obtained his Ph.D. from the University of Castilla-La Mancha in 1993. After a post-doctoral fellowship at the Institut de Recherches sur la Catalyse-CNRS-Lyon with Professor Jean-Marie Basset (1994–1995), he returned to Castilla-La Mancha where is now a Lecturer in Inorganic Chemistry at the Faculty of Chemical Sciences and Technologies. His research is focused on the coordination and organometallic chemistry of early transition metals and the development of new catalytic processes for the efficient synthesis of organic compounds with carbon-heteroatom bonds.

Carlos Alonso-Moreno was born in Alcázar de San Juan, Spain, in 1978. He received his Ph.D. from the University of Castilla-La Mancha in 2004 and was then a post-doctoral fellow at the School of Chemical Sciences and Pharmacy in Norwich, UK (2005–2006) and at the University of Rey Juan Carlos in Madrid, Spain (2007–2008). He was appointed to a Lectureship in Inorganic Chemistry at the School of Pharmacy of the University of Castilla-La Mancha in 2009, where his research has mainly involved the design and development of new organometallic entities as efficient catalysts for the guanylation of amines and Ring-Opening Polymerization of lactides.

Antonio F. Antiñolo was born in Cartagena, Spain, in 1956. He obtained his B.Sc. in 1978 from the University of Murcia and his Ph.D. in 1982 from the University of Alcalá de Henares. After a post-doctoral appointment with Professor M. F. Lappert at the University of Sussex in The United Kingdom (1983–1984), he took up a lectureship at the University of Alcalá de Henares in 1985. In 1990 he moved to Ciudad Real and for more than 10 years he has worked at the University of Castilla-La Mancha in collaboration with Professor A. Otero. He became a Full Professor in 1999 at the same University. His current research interests are focused on the synthesis and characterization of metallocene and non-metallocene derivatives of early transition metals as possible stereoselective or stereospecific catalysts in organic synthesis and the activation of small molecules and C-heteroatom bonds.

Antonio Otero was born in Minglanilla (Cuenca), Spain. He obtained his graduate degree in 1973 from the University of Murcia and his PhD in Sciences in 1976 under the supervision of Professor Pascual Royo. From 1978-1979, he worked as a postdoctoral fellow at the University of Oxford with Professor Malcolm Green. From 1979 to 1989 he was a Lecturer at the University of Alcalá, Spain. In December 1989, he was appointed Full Professor in Inorganic Chemistry at the University of Castilla-La Mancha, Spain. His current research interest includes organometallic chemistry of early transition, rare-earth and main group metals, and homogeneous catalytic ring opening polymerization (ROP) processes of polar monomers.


## Abstract

From organosuperbases capable of base-catalyzing organic reactions, through versatile 'ligand-sets' for use in coordination chemistry, to fundamental entities in medicinal chemistry, guanidines are amongst the most interesting, attractive, valuable, and versatile organic molecules. Since the discovery of these compounds, synthetic chemists have developed new methodologies that are mainly based on multi-step and stoichiometric reactions. Despite the fact that these methodologies are still being used by the interested scientific and industrial communities, drawbacks such as the poor availability of precursors, low yields, and use and production of undesirable substances highlight the need for safe, simple and efficient syntheses of these entities. This review focuses on the metal-mediated catalytic addition of amines to carbodiimides as an atom-economical alternative to the classical synthesis.


## Introduction

One hundred and fifty-two years after the first synthesis from guanine,[1] guanidines are still considered to be amongst the most attractive structures for organic chemists in the search for relatively simple and versatile molecules with interesting biochemical properties. $R_1$–N=C($NR_2R_3$)($NR_4R_5$) is the general formula for this family of compounds, which share a Y-shaped $CN_3$ functional group that is claimed to be responsible for the stability of its cationic (guanidinium) and anionic (guanidinate) derivatives (Figure 1).[2]

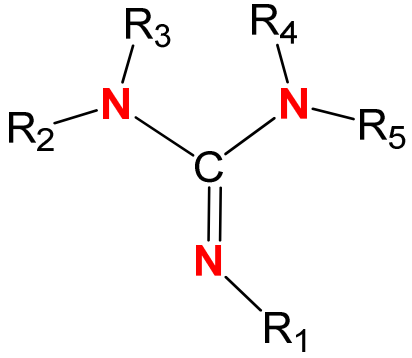



**Figure 1.** General formula for substituted guanidines.

'Guanidine is categorized as an organosuperbase with amine basicity due to the resonance stabilization of its conjugated acids' is the recurrent way in which Ishikawa describes the particular strongly basic property of this system (Figure 2).[3] In fact, guanidines are stronger bases than other nitrogen compounds such as pyridines, amines, diamines and amidines and some biguanidine derivatives are even more basic than the classical 'Proton Sponge'.[4] Thus, guanidines have been widely explored in numerous base-catalyzed organic reactions and some guanidines have proven to be advantageous when compared with other types of organic bases.[5] A variety of chiral guanidines can be easily obtained by the introduction of chirality on the guanidinyl nitrogens and such compounds have been used as asymmetric catalysts for different reactions.[6]

'Guanidines are considered as fundamental entities in medicinal chemistry which is not surprising taking into account their occurrence in the nucleobases' is a statement from a review focused on transition metal-catalyzed *N*-arylation of guanidines by Maes and Rauws[7] to highlight the significance of guanidines in the field of medicinal chemistry. The guanidine moiety is an essential substructure in many molecules of biological importance, such as arginine, creatine phosphates, and purines.[8] In addition, a variety of natural products directly isolated from terrestrial, marine and freshwater microorganisms, marine and terrestrial invertebrates, marine sponges, and higher plants with prominent pharmacological and biological activities are also based on these entities.[9]

Several decades ago guanidine-containing drugs were shown to have pharmaceutical properties and, over the years, these have been subjected to intensive preclinical and clinical evaluation.[10] In fact, some of these guanidine derivatives are actually top selling pharmaceuticals. Some representative examples of drugs that contain guanidine fragments are listed below. *Rosuvastatin* is one of the best selling drugs in the United States and it is used to treat high cholesterol and prevent cardiovascular disease.[11] *Guanabenz* is used clinically as an antihypertensive.[12] *Imanitib* is a tyrosine kinase inhibitor that is used as an anticancer drug.[13] *Cimetidine* was the first blockbuster

drug used to treat peptic ulcers.[3] *Zanamivir* was the first neuraminidase inhibitor to be commercially developed.[14]

The great importance of guanidines has promoted the synthesis of promising new lead structures with a guanidine core, which are suitable for the development of potential derivatives in other areas of interest such as crystal engineering, supramolecular chemistry, and as ionic liquids.[15] One noteworthy example is *Lugduname*, which is part of a family of extremely potent sweeteners that contain acetic acid functional groups attached to guanidine. This compound is one of the most potent sweetening agents reported to date.[16] *Akacid* is a guanidine-based polymer that acts as a potent biocide and disinfectant agent.[17] Nitroguanidine derivatives are used as explosive propellants and insecticides and they have a comparable effect to nicotine.[15] Finally, the use of some guanidine derivatives as catalysts for the transesterification of vegetable oils is worth highlighting.[18]

Taking into account the aforementioned properties and applications of this class of compounds, several reviews have been published in this field. For example, Ishikawa reviewed the synthetic utility of this family of compounds in organic chemistry,[3] whereas Coles[19] focused his attention on the practical applications of bicyclic guanidine derivatives as organocatalysts. Moreover, Taylor *et al.*[20] described the nucleophilic nature of guanidines as organocatalysts and Tan and Fu[21] discussed thoughtfully the mechanistic aspects of guanidine-catalyzed reactions.

In 2006 Coles stated that 'Guanidine framework constitutes a versatile ligand-set for use in coordination chemistry' to summarize the relevant role of this family of compounds in coordination chemistry.[22] The physical properties of guanidines make them useful *N*-based donor ligands in coordination chemistry.[23] In fact, a plethora of substituted guanidines and negatively charged guanidinates is already known to act as ligands.[24] Particular emphasis has been placed on the development of rare-earth metal complexes bearing guanidinate ligands.[25] Some members of this class of complexes have been synthesized for use as efficient catalysts in homogeneous catalysis, such as the polymerization of nonpolar and polar monomers, the hydroamination of alkynes, and the hydrosilylation of alkenes.[26] Zinc guanidinate complexes were found to behave well for the polymerization of lactide,[27] whereas chiral guanidine derivatives of zinc and molybdenum were tested in Henry reactions.[28] In a recent study, some of us described the first examples of ruthenium complexes containing asymmetrical monoanionic guanidinate ligands as catalysts for the redox isomerization of allylic alcohols.[29] In recent studies concerning the coordination chemistry of this type of ligands our group have reported, among other things, that the properties associated with

guanidinate ligands could have a pronounced effect on the chemistry of the resultant complexes.[30]

In this review, first we will cover several aspects concerning the well-established syntheses of guanidines through synthetic methodologies based mainly on stoichiometric reactions that involve the use of 'guanylating agents'. Particular emphasis is placed on the catalytic metal-mediated processes to prepare guanidines by the atom-economical hydroamination of carbodiimines by taking a journey through the different families of metal complexes that have been involved in the development of this field in the ten years since the pioneering work of Richeson in 2003.[31]

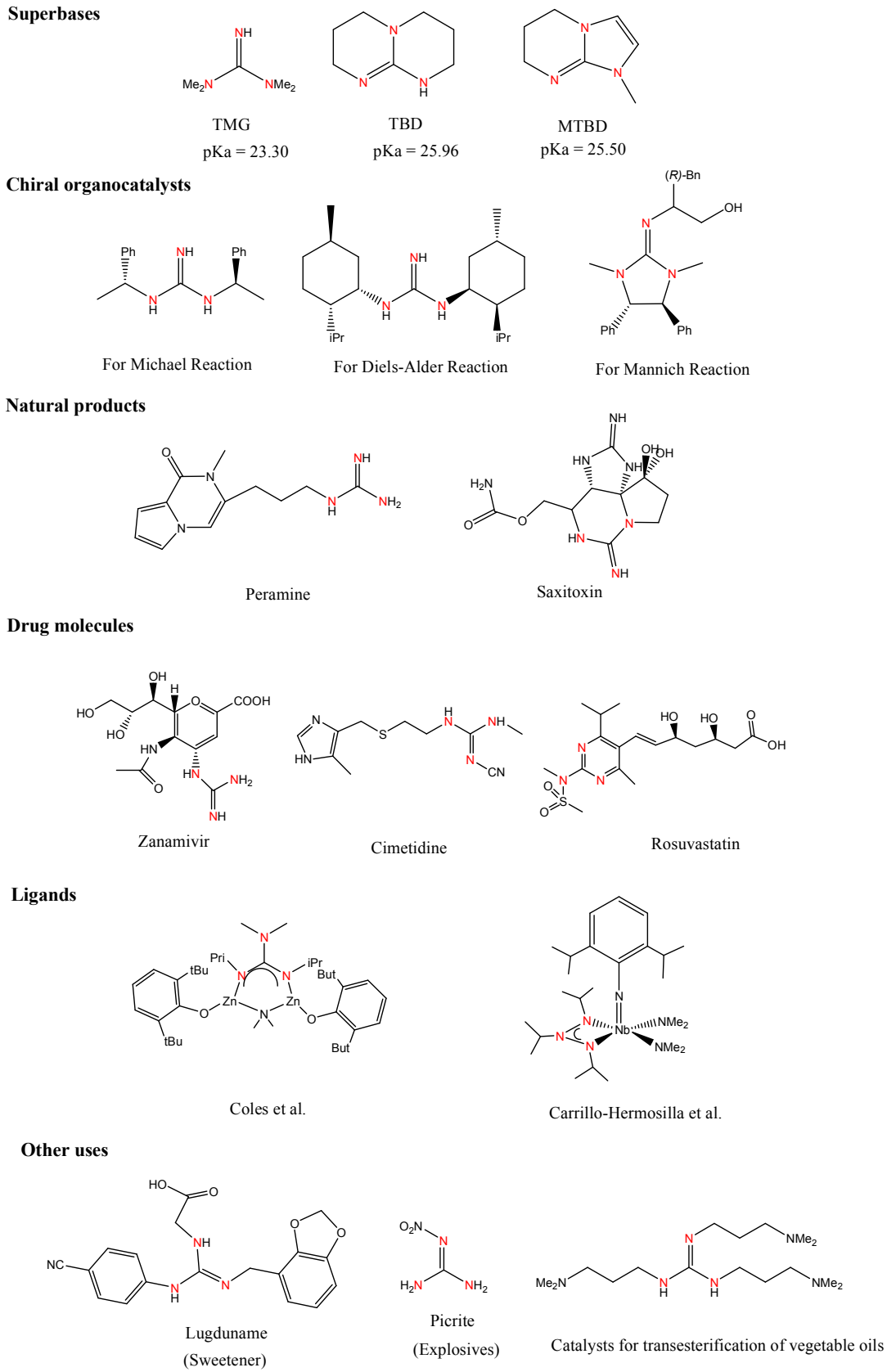



**Figure 2.** Examples of guanidines as fragments within superbases, chiral organocatalysts, natural products, drug molecules, ligands, sweeteners, explosives and catalysts for the transesterification of vegetable oils.

## Classical guanidine synthesis

There are two routes known for the synthesis of guanidines. The first one is considered as the 'classical guanidine synthesis' and uses reagents named as 'guanylating agents' by Katritzky *et al.*[32] An overview published in 2005 covers this synthetic methodology, which is mainly based on stoichiometric reactions. Nowadays, this is the most commonly used methodology to synthesize a wide range of guanidines and derived drugs of great importance, such as *Zanamivir*[14] and *Famotidine*.[33]

The guanidine core can be built up by chemical transformation from thioureas, isothioureas, amidine sulfonic acids, cyanamides, carbodiimides, triflyl guanidines, and carboximidamide derivatives as the most significant reagents (Figure 3).[32] The most commonly used reagents include derivatives of pyrazole-1-carboximidamide, *S*-alkylisothioureas, and protected thiourea derivatives. All of these reagents require the introduction of a protecting group, of which Boc is the most common, to avoid synthetic difficulties associated with the reactivity and purification of the final product.

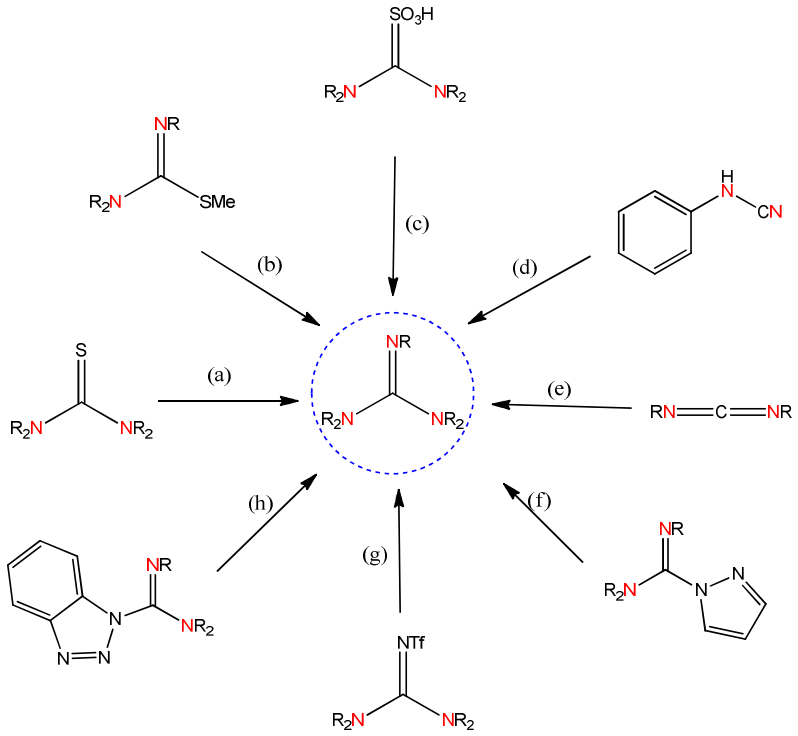



**Figure 3.** Classical guanidine synthesis. Guanidine core structure obtained by chemical transformation from: (a) Thioureas, (b) Isothioureas (c) Amidine sulfonic acids, (d) Cyanamides, (e) Carbodiimides, (f) Pyrazole carboximidamides, (g) Triflyl guanidines, (h) Benzotriazoles.

The most straightforward route for the synthesis of di-, tri, and tetra-substituted guanidines involves the reaction of amines with electrophilic thiourea derivatives as guanylation reagents. A competitive decomposition of the carbodiimide intermediate[34] makes optimization of the reaction conditions a prerequisite. Thioureas containing electron-withdrawing protecting groups, which can be removed by standard methods, in conjunction with an activating agent, typically Mukaiyama's[35] or other peptide coupling reagents,[36] minimize this problem and are successfully converted into *N*-substituted guanidines by different amines.[37] *N*- and *N,N'*-Substituted guanidines can be obtained by the reaction of di-Boc thioureas with primary and secondary amines in the presence of a thiophilic metal salt [typically Hg(II) or Cu(II)] and a tertiary amine, which accelerate the desulfurization.[38]

Thiourea-derived sulfonic acids are also reported to be guanylating agents.[39] Improvements in yields, better oxidation reactions, and one-pot procedures are already important goals in optimizing the protocol for guanidine preparation by this methodology.

Carbodiimides are thought to be an intermediate in the synthesis of guanidines from thioureas. Although the isolation and characterization of these species as intermediates have not been achieved because of the speed of the reaction, some carbodiimides have been converted into guanidines by reaction with aromatic amines in the presence of a slight excess of TBAF.[40] The limited scope of the reaction with aromatic carbodiimides and electron rich amines makes this methodology less attractive.

In general terms, the synthesis of guanidines from thioureas works well and it is the methodology of choice in late stage syntheses. Although widely used, the synthesis is not direct, it requires the separate preparation of each precursor, and it involves the use of undesirable toxic reagents such as mercury salts. These drawbacks undeniably limit the use of this approach on a large scale.

Isothioureas have been well developed as guanylating reagents due to their easy preparation and commercial availability. In particular, 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-isothiourea is by far the most commonly used reagent to install the guanidine unit and it has been used to afford a significant number of guanidine derivatives in good yields in the presence of mercuric chloride after a simple work-up.[32]

Pyrazole carboximidamide transfer reagents[41] have been developed to avoid the use of toxic metals. The greatest achievement of this precursor concerns its use as a guanylating agent to convert several amino acids into guanidine acids.[42] However, this classical method suffers from poor yields along with the requirement of multiple synthetic steps with costly reagents, since the presence of protecting groups and an electron-withdrawing group in the pyrazole ring are required to allow milder reaction conditions.

Sequential displacement of benzotriazole or imidazole moieties in carboximidamide derivatives by amines provides easy access to tetra-substituted guanidines.[43] The products are obtained in moderate to high yields under mild conditions but this approach requires not only a final purification protocol but also the use of cyanogen bromide in the synthetic procedure. Due to the acute toxicity of cyanogen bromide, which causes a variety of nonspecific symptoms, the synthesis of biguanidine derivatives by means of cyanamide precursors is unappealing for most organic synthesis groups.

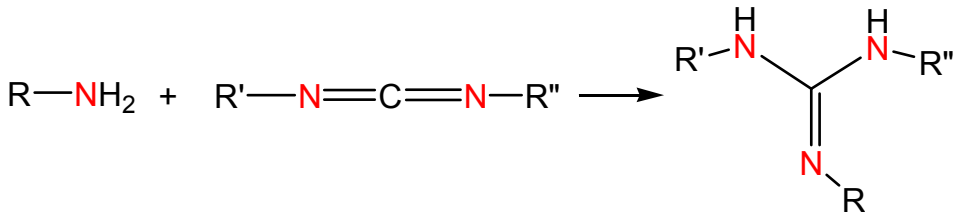
Conversion of di-Boc-triflylguanidine or di-CBz-triflylguanidine by treatment with primary and secondary amines to give different guanidines was reported in 1998 by Goodman *et al.*[36] Since then, triflylguanidine reagents have been become popular because of their ability to guanylate weakly nucleophilic amines. However, the use of these reagents is limited by the availability of the starting guanidines.

To finish this overview of the classical guanidine synthesis, it is worth mentioning that a library of synthetic guanidine derivatives has been extensively explored by functionalization of pre-existing guanidines, especially those involving cycloguanylation.[44] Moreover, the use of immobilized reagents in some procedures has helped the sustainable development of the classical synthetic methodology in guanidine chemistry.[45]

The aim of this review is to focus on the use of organometallic and coordination compounds to promote the second route reported for the synthesis of guanidines, which is based on catalytic processes. As mentioned previously, the majority of the effort in this field has been directed towards the synthesis of guanidines by classical methods, the functionalization of pre-existing guanidines, and also the applications of these compounds as ligands, organosuperbases or asymmetric catalysts. In contrast, the use of metallic complexes to extend the synthetic methodology of these compounds is a very recent and ever-growing field.

## Catalytic access to substituted guanidines

The direct guanylation of amines with symmetrical and unsymmetrical carbodiimides seems to be the most efficient and atom-economical way to obtain *N*-substituted guanidines (Scheme 1).




**Scheme 1.** Addition of amines or hydroamination of carbodiimides.

Aliphatic amines undergo this direct reaction under harsh conditions and give moderate yields.[46] However, aromatic amines, which are less nucleophilic, do not react even on prolonged heating. Thus, catalytic procedures for the assembly of guanidines from the diverse library of amines and carbodiimides started to appear in the literature. The first catalytic construction and reconstruction of guanidines from aromatic amines was reported by Richeson *et al*. in 2003.[31] Imido titanium(IV) complexes (1-5 mol%) (Table 1, Figure 4) bearing guanidinate ligands are the precursors of the catalytic intermediate after [2+2] addition of a carbodiimide to the Ti=N moiety. Proton transfer from the aromatic amine to the dianionic guanidinate ligand formed in the cycloaddition yields guanidine and reforms the imide complex to complete the cycle (Scheme 2). Good yields were obtained for diverse substituted anilines, but this reactivity was not translated to analogous Zr- or Ta-imido complexes.

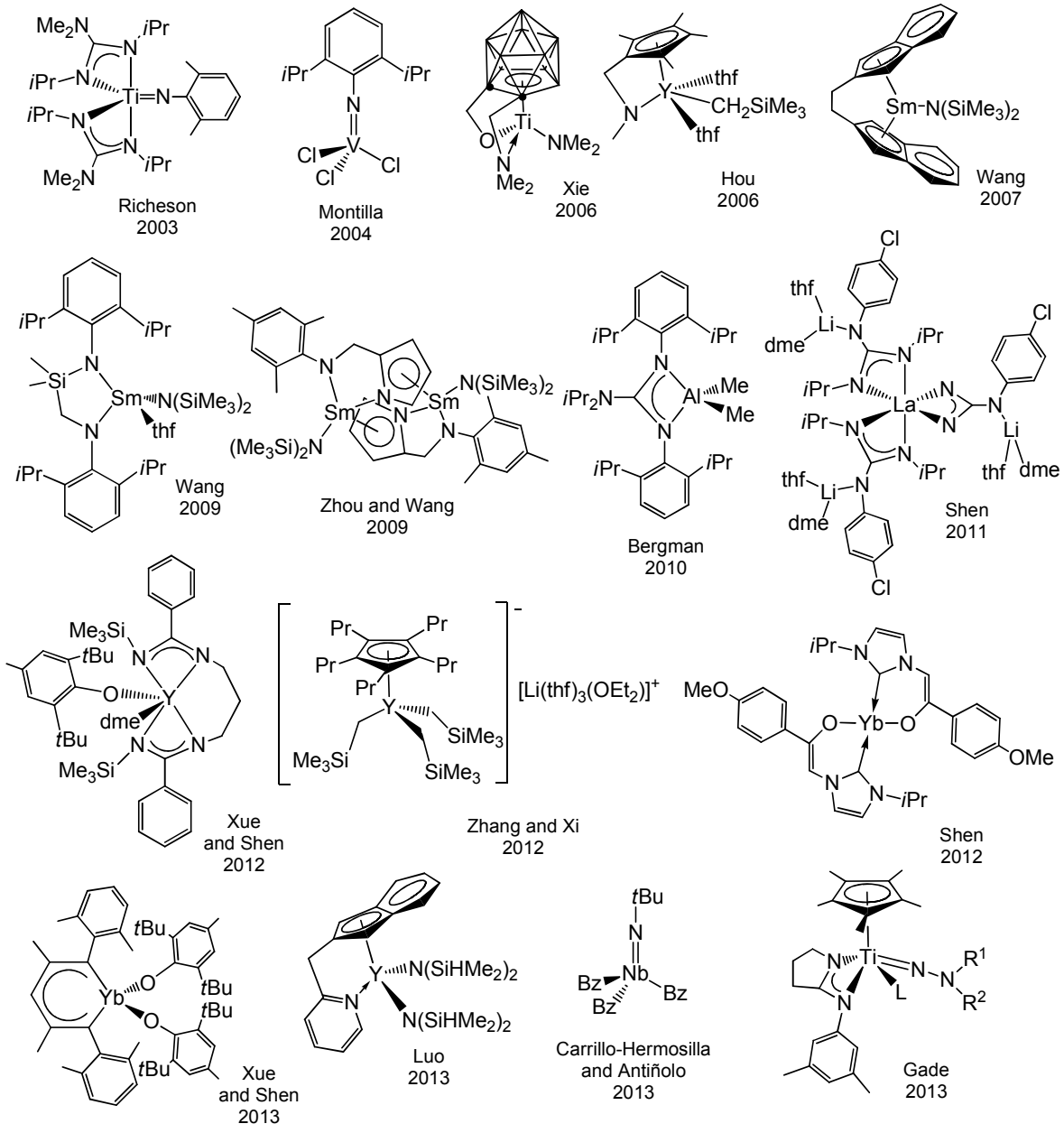
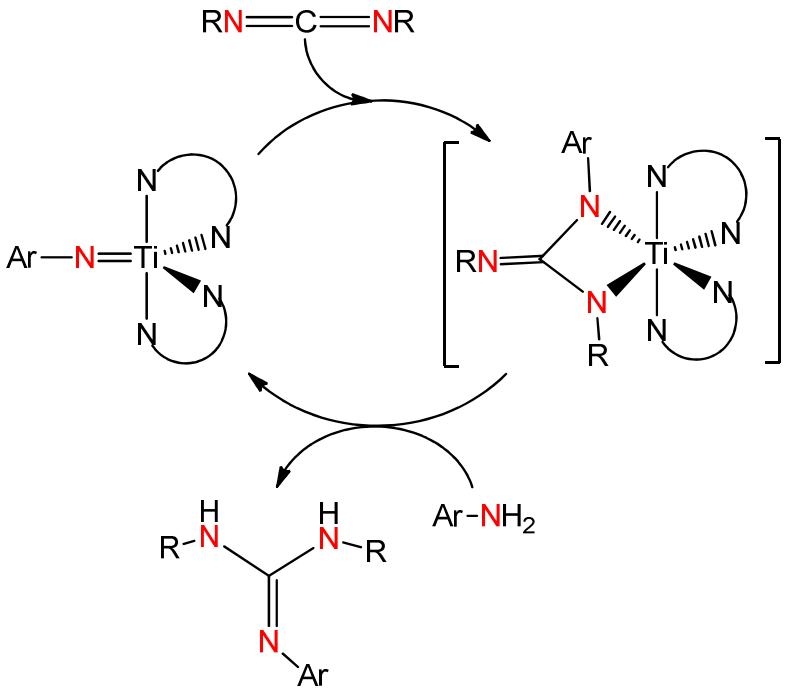



**Figure 4.** Non-exhaustive selection of complex catalysts.

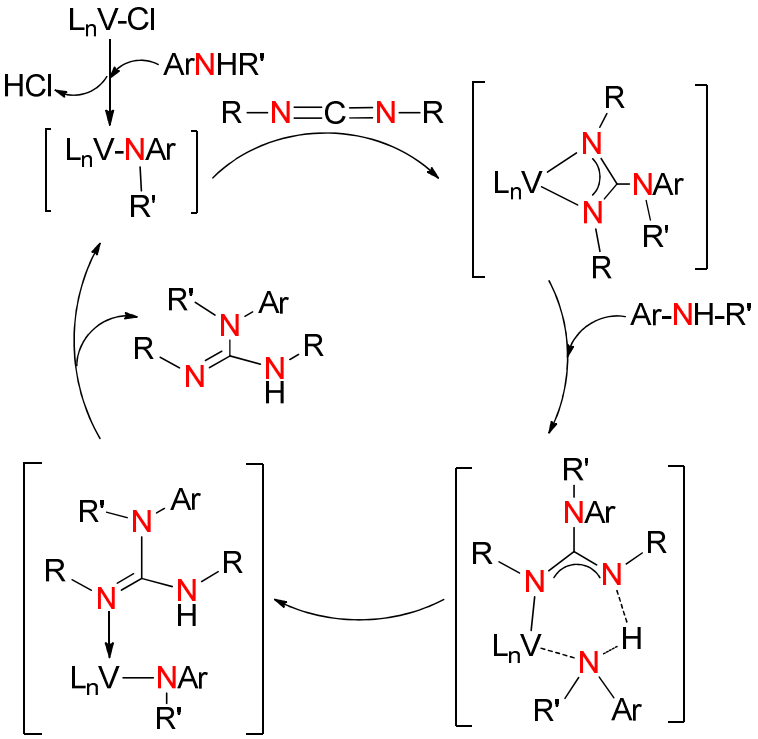



**Scheme 2.** Catalytic guanylation by [2+2] addition.

The [2+2] addition mechanism was initially postulated for imidovanadium complexes, *i.e.* [V(=NR)$X_3$] (2 mol%), in the first report on the group 5 metal-catalyzed guanylation of aromatic amines.[47] However, in subsequent works[48] a more favourable mechanism was demonstrated that involves insertion of the carbodiimide into an amido-vanadium bond, generated by the amonolysis of a chloro-metal bond. The amonolysis results in the formation of the key guanidinate intermediate. Reaction of this intermediate with an additional molecule of amine liberates the guanidine product and regenerates the amido catalyst (Scheme 3). This mechanism allows the guanylation of secondary amines. In the [2+2] addition mechanism the regeneration of the imido catalyst requires primary amines as substrates. Recently[30d] our group have found that an alkyl-imidoniobium complex, [Nb(=N*t*Bu)$Bz_3$] (2 mol%),[49] acts as an efficient guanylation catalyst under milder conditions in comparison to those required for imidovanandium complexes.

**Table 1.** Transition metal based catalysts.

| Catalysts | Ref. |
|---|---|
| [{($Me_2N$)C(N*i*Pr)$_2$}$_2$Ti{N(2,6-$Me_2C_6H_3$)}], **1**; [{($Me_2N$)C(N*i*Pr)$_2$}$_2$Ti{N($C_6F_5$)}], **2** | 31 |
| [V(N-2,6-*i*$Pr_2C_6H_3$)$Cl_3$], **3**; [VO(acac)$_2$], **4** | 47, 48a |
| [$VOCl_3$], **5**; [$VOCl_{3-x}(OR)_x$] (x = 1, R = Me, **6**, Et, **7**, Pr, **8**; x = 2, R = Me, **9**, Et, **10**, Pr, **11**); [V{N(2,6-i$Pr_2C_6H_3$)}$Cl_{3-x}(OR)_x$] (x = 1, R = Me, **12**, Et, **13**, Pr, **14**; x = 2, R = Me, **15**, Et, **16**, Pr, **17**) | 48b |
| [$NbBz_3$(N*t*Bu)], **18** | 30d |
| [{($OCH_2$)($Me_2NCH_2$)$C_2B_9H_9$}Ti($NMe_2$)], **19** | 51, 82, 83 |
| [($C_5Me_5$)($NC_4H_3$){N(3,5-$Me_2C_6H_3$)}Ti(NNR$^1$R$^2$)(L)] ($R^1$ = $R^2$ = Ph, L = *t*$BuNH_2$, **20**; $R^1$ = $R^2$ = Ph, no L, **21**; $R^1$ = Me, $R^2$ = Ph, L = py, **22**; $R^1$ = $R^2$ = Me, L = DMAP, **23**; $R^1$ = $R^2$ = 4-$BrC_6H_5$, L = *t*$BuNH_2$, **24**; $R^1$ = Ph, $R^2$ = 4-$MeC_6H_5$, L = *t*$BuNH_2$, **25**; $R^1$ = Ph, $R^2$ = 4-$FC_6H_5$, L = *t*$BuNH_2$, **26**; $R^1$ = Ph, $R^2$ = 4-$OMeC_6H_5$, L = *t*$BuNH_2$, **27**; $R^1$,R2 = fluorene, L = py, **28** | 74 |
| [$CuCl_2$], **29**; [$PdCl_2$], **30**; [Pd($PPh_3$)$_4$], **31**; [Pd($OAc$)$_2$], **32** | 75 |
| [Fe($OAc$)$_2$], **33**; [Fe($OTf$)$_2$], **34**; [($C_5Me_5$)($CH_2$)(CHPh)($C_3H_2$NNMe)Fe(CO)I], **35**; [$FeCl_2$], **36**; [$FeCl_3$], **37**, [$Fe_3(CO)_{12}$], **38** | 80 |
| [$PdCl_2$($NCCH_3$)$_2$], **39** | 81 |
| Silica-supported palladium nanoparticles, **40** | 84 |




**Scheme 3.** Catalytic guanylation *via* an amido intermediate.

These compounds were not the first to be used to catalyze the addition of secondary amines to carbodiimides. In fact, the half-sandwich alkyl complex $[\{Me_2Si(C_5Me_4)(NPh)\}Y(CH_2SiMe_3)(thf)_2]$, which was prepared by Hou *et al.*, offered the first atom-economical route to tetrasubstituted guanidines from less reactive aliphatic secondary amines.[50] On the basis of the proposed formation of an amido intermediate, the scope of substrates that can be guanylated was fully expanded by Xie *et al.* in a pioneering work on the use of a half-sandwich amidotitanacarborane complex, $[\{\sigma:\eta^1:\eta^5\text{-}(OCH_2)(Me_2NCH_2)C_2B_9H_9\}Ti(NMe_2)]$, which tolerates many functional groups.[51] The use of such a complex (3-5 mol%), as well as substituted aromatic amines, allowed heterocyclic, aliphatic, and secondary acyclic and cyclic amines to be transformed into the corresponding guanidines. Although simple aromatic derivatives were obtained at room temperature in high yields, it was necessary to heat the reaction mixture at 110 ºC in toluene for several hours for less reactive substrates.

The aforementioned yttrium half-sandwich complex, which bears a silylene-linked cyclopentadienyl-amido ligand, can also serve as a catalyst precursor (1-3 mol%) for the catalytic guanylation of various N–H bonds, leading to a series of guanidine compounds with a wide range of functional groups, including C≡N, C≡CH or aromatic C–X bonds (X = halogen).[52] Chemoselectivity towards the primary amino group can also be achieved in the presence of a secondary N–H bond. The information provided by mechanistic studies have demonstrated that a guanidinate fragment, often considered as spectator or supporting ligand, can participate in the reaction in a catalytic fashion, as described in Scheme 3.

**Table 2.** Lanthanide based catalysts.

| Catalysts | Ref. |
|---|---|
| [{$Me_2Si(C_5Me_4)(NR)$}Ln($CH_2SiMe_3$)$(thf)_n$] (Ln = Y, R = Ph, n =2, **41**; Ln = Y, R = 2,4,6-$Me_3C_6H_3$, n = 1, **42**; Ln = Y, R = *t*Bu, n = 1, **43**; Ln = Yb, R = Ph, n = 2, **44**; Ln = Lu, R = Ph, n = 2, **45**) | 50, 52 |
| [$(CH_2)_2(C_9H_6)_2$Ln{$N(SiMe_3)_2$}] ( Ln = Y, **46**; Sm, **47**; Yb, **48**) | 53 |
| [{$C_9H_6CMe_2CH_2C_5H_4N$-α}Ln{$N(SiHMe_2)_2$}$_2$] (Ln = Sc, **49**; Y, **50**; La, **51**; Sm, **52**; Nd, **53**; Er, **54**; Lu, **55**) | 54 |
| [$(C_5Pr_4Ph)$Ln($CH_2SiMe_3$)$_3$][Li$(thf)_n(OEt_2)_{4-n}$] (Ln = Y, n =3, **56**; Ho, n = 4, **57**; Er, n = 3, **58**; Tm, n = 3, **59**; Lu, n = 3, **60**) | 55 |
| [{$(Me_3Si)_2N$}$_3$Ln(μ-Cl)Li$(thf)_3$] (Ln = La, **61**; Sm, **62**; Eu, **63**; Y, **64**; Yb, **65**); [Ln{$N(SiMe_3)_2$}$_3$] (Ln = Y, **66**, Yb, **67**) | 56, 65 |
| [{$(CH_2SiMe_2)$[(2,6-*i*$Pr_2C_6H_3$)N]$_2$}Ln{$N(SiMe_3)$}(thf)] (Ln = Yb, **68**; Y, **69**; Dy, **70**; Sm, **71**; Nd, **72**) | 57 |
| [{(2,4,6-$Me_3C_6H_3$)$NCH_2C_4H_3N$}Ln{$N(SiMe_3)_2$}]$_2$ (Ln = Y, **73**; Nd, **74**; Sm, **75**; Dy, **76**; Er, **77**) | 58 |
| [Li(thf)(dme)]$_3$Ln[(*i*PrN)$_2$C($NC_6H_4$-*p*-R)]$_3$ (R = Cl, Ln = Nd. **78**, Y, **79**, La, **80**; R = H, Ln = Nd, **81**) | 59 |
| [{4-$OMeC_6H_4COCH(C_3H_2NNiPr)$}$_2$Ln{$N(SiMe_3)_2$}] (Ln = Y, **82**; Nd, **83**; Sm, **84**; Yb, **85**) | 61 |
| [Ln$(OAr)_3(thf)_2$] (Ar = 2,6-*t*$Bu_2$-4-$MeC_6H_2$, Ln = Y, **86**, Nd, **87**, Sm, **88**, Yb, **89**; Ar = 2,6-*i*$Pr_2C_6H_3$, Ln = Y, **90**; Ar = 2,6-$Me_2C_6H_3$, Ln = Y, **91**) | 62 |
| [{$(CH_2)_3$[NCPhN$(SiMe_3)$]$_2$}Ln(OAr)(dme)] (Ar = 2,6-$Me_2C_6H_3$, Ln = Y, **92**; 2,6-*i*$Pr_2C_6H_3$, Ln = Y, **93**; 2,6-*t*$Bu_2$-4-$MeC_6H_2$, Ln = Y, **94**; Nd, **95**; Sm, **96**; Yb, **97**) | 63 |
| [{N(2,6-$Me_2C_6H_3$)CMe}$_2$CH]YbCl(thf){O(2,6-*t*$Bu_2$-4-$MeC_6H_2$)}] **98**; [{N(2,6-$Me_2C_6H_3$)CMe}$_2$CH]Yb{O(2,6-*t*$Bu_2$-4-$MeC_6H_2$)}$_2$], **99**; [{N(2,6-$Me_2C_6H_3$)CMe}$_2$CH]Yb(thf){O(2,6-*i*$Pr_2MeC_6H_3$)}$_2$]. **100**; [{N(2,6-$Me_2C_6H_3$)CMe}$_2$CH]Yb(thf){O(2,6-$Me_2MeC_6H_3$)}$_2$], **101** | 64 |
| [$LnL_2(thf)_x$] (L = $N(SiMe_3)_2$, x = 3, Ln = Sm, **102**, Eu, **103**; Yb, **104**; L = $MeC_5H_4$, x = 2, Ln = Sm, **105**; L = 2,6-*t*$Bu_2$-4-$MeC_6H_2$, x = 2, Ln = Sm, **106**) | 65 |
| $SmI_2$, **107** | 65, 66 |
| [Ln$(OTf)_3$] (Ln = Yb, **108**; La, **109**; Nd, **110**; Sm, **111**; Eu, **112**; Er, **113**, Sc, **114**) | 67, 75 |

Since then, the high reactivity of rare earth metal complexes towards this catalytic process has been widely explored (Table 2). Yttrium, samarium and ytterbium(III) *ansa*-bisindenyl amido complexes (2 mol%) proved to be very versatile towards the addition of both N–H and C–H bonds to carbodiimides to give the corresponding guanidines and interesting propiolamidine analogues.[53] Similarly, pyridyl-functionalized monoindenyl bis(amide) complexes, among which yttrium species (0.5 mol%) showed the highest activity, catalyze the nucleophilic addition of primary aromatic amines to carbodiimides.[54] In both cases, the presence of bulky substituents, such as isopropyl, in the aromatic moiety has a steric influence on the active centre and this affects the reaction conditions. The bulky substituted 1-phenyl-2,3,4,5-tetrapropylcyclopentadienyl ligand ($Cp^{4PrPh}$)

allowed the isolation of active anionic trialkyl rare-earth metal complexes, $[Cp^{4PrPh}Ln(CH_2SiMe_3)_3][Li(thf)_n(OEt_2)_{4-n}]$ (Ln = Y, Er, Lu, Ho, Tm; n = 3–4). In addition to aromatic or secondary cyclic amines, the yttrium derivative (1 mol%) was the first catalyst to be effective for the guanylation of secondary aromatic amines of general formula ArRNH (R = alkyl or aryl).[55] Simple and readily available cyclopentadienyl-free lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ and $Ln[N(SiMe_3)_2]_3$ (Ln = La, Sm, Eu, Y, Yb) are efficient catalysts that require a low catalyst loading (1 mol%) and are compatible with a wide range of solvents and amines,[56] including bulky aromatic and aliphatic secondary amines. These catalysts provide high product yields at milder temperatures than the indenyl derivatives mentioned above. Supporting ligands other than the cyclopentadienyl ones have been shown to stabilize rare earth metal complexes that are active in this catalytic reaction. Diamido-supported complexes $[\{(CH_2SiMe_2)[(2,6\text{-}i\text{-}Pr_2C_6H_3)N]_2\}Ln\{N(SiMe_3)_2\}(thf)]$ (Ln = Sm, Yb, Y, Dy, Nd) (3 mol%) exhibited high catalytic activity in the guanylation of aromatic and heterocyclic amines.[57] The samarium complex can even catalyze the reaction of 4-nitroaniline with carbodiimides. This would suggest that these compounds are more active than the indenyl lanthanocene amides, which are not active for the 4-nitroaniline substrate. Pyrrolyl ligands can be used as an alternative to cyclopentadienyl as they can bind in a $\eta^5$ fashion. Pyrrolyl dinuclear amidocomplexes $[\{(\mu\text{-}\eta^5\text{:}\eta^1)\text{:}\eta^1\text{-}2\text{-}[(2,4,6\text{-}Me_3C_6H_2)NCH_2]C_4H_3N\}Ln\{N(SiMe_3)_2\}]_2$ (Ln = Y, Nd, Sm, Dy, Er) (2 mol%) displayed high catalytic activities for the guanylation of aryl amines that bear either electron-donating groups or strong electron-withdrawing groups such as $–NO_2$.[58] Shen *et al.* proposed a series of cyclopentadienyl-free lanthanide complexes as active precursors for catalytic guanylation. Heterobimetallic dianionic guanidinate lanthanide and lithium complexes $[\{Li(thf)(DME)\}_3Ln\{\mu\text{-}\eta^2\text{:}\eta^1(i\text{PrN})_2C(NC_6H_4\text{-}p\text{-}R)\}_3]$ (R = H, Cl, Ln = Nd, Y, La, Nd) were active in the catalytic formation of guanidines from aromatic and aliphatic primary amines or secondary amines, at room temperature, with a low catalyst loading (0.5 mol %).[59] Useful biguanidines[60] were also obtained in quantitative yield under these conditions by a double catalytic addition of aromatic diamines to carbodiimides. It should be noted that this reaction proceeds under solvent-free conditions. Ubiquitous *N*-heterocyclic carbenes are also suitable to stabilize amido lanthanide precatalysts $[L_2Ln\{N(SiMe_3)_2\}]$ (L = 4-OMe-$C_6H_4C_2O$(CNCHCHN-*i*Pr), Ln = Y, Nd, Sm, Yb) (0.5 mol%) and these are also active under solvent-free conditions.[61]

In comparison with the lanthanide alkyl and amide complexes used in the previously described studies, lanthanide aryloxides are simpler to obtain and they are less sensitive to air. For example, Shen's group investigated the reactivity of Ln-aryloxide species in the guanylation reaction (0.5-1

mol% of catalyst loading). The use of bulky aryloxide ligand [2,6-*t*Bu$_2$-4-MeC$_6$H$_2$O] led to Y and Yb compounds that were capable of coordinating carbodiimide and activating it towards the intramolecular nucleophilic attack of a coordinated amine. This process is mediated by an active Ln–OAr group (Figure 5).

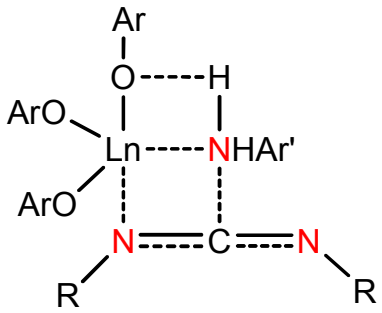
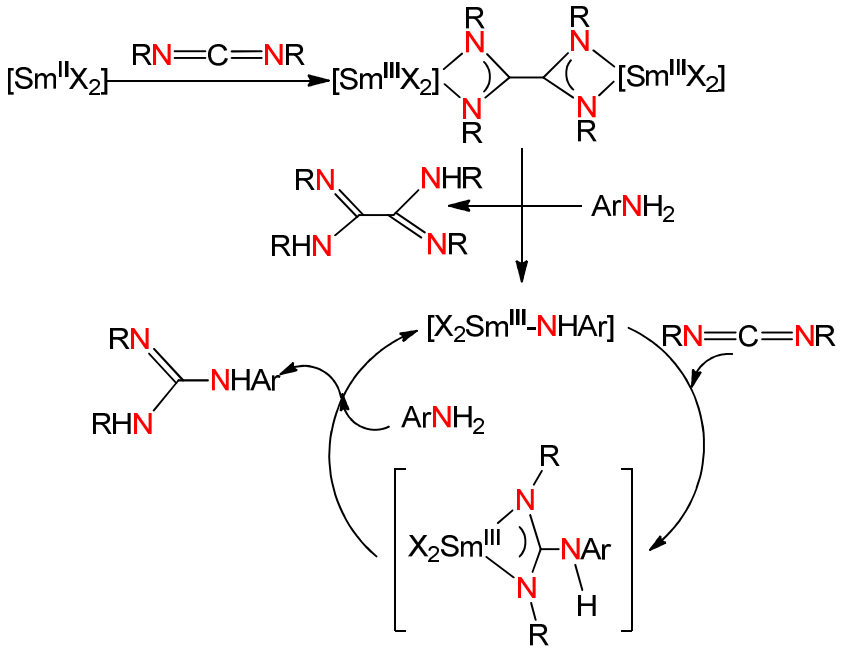



**Figure 5.** Transition state proposed in the OAr-assisted amine addition to carbodiimide.

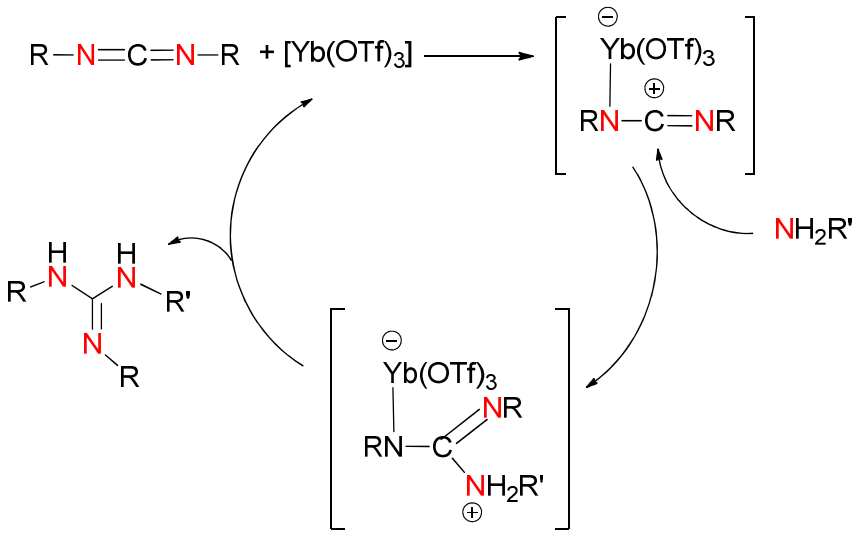
The resulting guanidinate complex reacts with another amine molecule to afford the corresponding amide intermediate and the process then follows a mechanism similar to that depicted in Scheme 3.[62] The influence of ancillary ligands on the reactivity of these aryloxide species was investigated. Bridged bis(amidinate)[63] or β-diketinimato[64] ligands altered the mechanism, with the Ln–OAr bond becoming more reactive to the protonation reaction with the amine. In this approach it is proposed that the first step involves the formation of an amido compound prior to the reaction with the carbodiimide according to the well-established mechanism. These complexes (0.5 mol%) catalyze the addition of aromatic and secondary cyclic amines under solvent-free and mild conditions with low catalyst loading.

Among the different families of lanthanide compounds, divalent ones are efficient single-electron reducing agents. The metallocene [Sm($\eta^5$-MeC$_5$H$_4$)$_2$(thf)$_2$] and amide complexes [Ln{N(SiMe$_3$)$_2$}$_2$(thf)$_2$] (Ln = Sm, Eu, Yb), aryloxide, [Sm(OAr)(thf)$_2$] (Ar = [2,6-*t*Bu-4-MeC$_6$H$_2$]),[65] or the simple compound SmI$_2$[65,66] enable the reductive coupling of carbodiimides to produce the corresponding bimetallic bisamidinate samarium(III) complexes. These bisamidinate intermediates undergo protonolysis by primary and secondary amines to generate the necessary amide intermediate in the guanylation process with low catalyst loadings (0.5-3 mol%), under solvent-free conditions (Scheme 4).



**Scheme 4.** Proposed mechanism for the addition of amines to carbodiimides based on $Sm^{II}$ precatalysts.

Despite the fact that most of the efficient catalysts described above are very complex compounds, one can see a trend towards simplicity that could encourage the use of this methodology to obtain interesting and useful guanidines. For instance, ytterbium triflate (0.5-2 mol%) has been reported to be effective for the catalytic addition of aromatic, aliphatic and heterocyclic secondary amines to carbodiimides under solvent-free conditions.[67] This 'water-tolerant, reusable and environmentally friendly catalyst' possibly acts by a different mechanism: ytterbium triflate would react as a Lewis acid catalyst and activate a coordinated carbodiimide towards the nucleophilic addition of an amine. Intramolecular proton transfer would then generate the guanidine product (Scheme 5).



**Scheme 5.** Proposed mechanism for the addition of amines to carbodiimides based on Lewis acid catalysts.

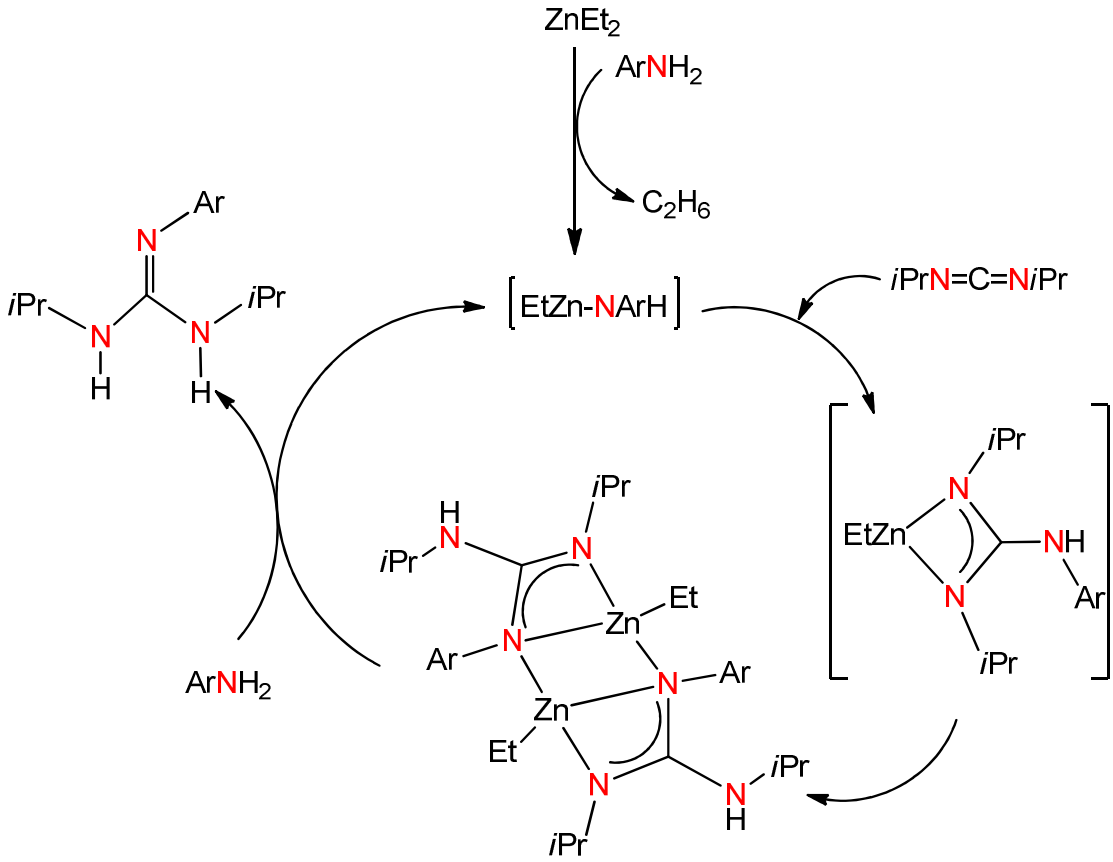
**Table 3.** Main-group metal based catalysts.

| Catalysts | Ref. |
|---|---|
| [$LiN(SiMe_3)_2$], **115** | 68 |
| [$AlClMe_2$], **116** | 69 |
| [$AlCl_3$], **117** | 69, 70, 71, 75 |
| [$AlMe_3$], **118**; [$AlEt_3$], **119**; [$AlClEt_2$], **120** | 71 |
| [$Al(NMe_2)_3]_2$, **121**; [$(2,6\text{-}i\text{Pr}_2C_6H_3)_2NC(N i\text{Pr}_2)AlMe_2$], **122** | 69, 73 |
| [$Zn(OTf)_2$], **123** | 75 |
| [$ZnEt_2$], **124**; [$Mg n\text{Bu}_2$], **125**; [$n$BuLi], **126** | 76, 29, 30a, 30e |
| [$MgBz_2(thf)_2$], **127** | 77 |
| [$M\{N(SiMe_3)_2\}_2(thf)_2$] (M = Ca, **128**; Sr, **129**; Ba, **130**) | 78 |
| Zn-Al hydrotalcite, **131** | 85 |
| [ZnO] nanoparticles, **132** | 86 |

Some simple and readily available main group metal compounds constitute another remarkable group of precatalysts for the amine guanylation reaction (Table 3). Richeson *et al.* proposed lithium hexamethyldisilazide, [$LiN(SiMe_3)_2$] (2 mol%), as a catalyst precursor for the guanylation of aromatic amines (and the addition of carbodiimides to terminal alkynes) with carbodiimides. Excellent yields were achieved with a variety of substituted anilines at room temperature with the addition of TMEDA to activate the catalyst.[68] Reaction with *p*-benzylaminoaniline afforded chemoselectively the anilide-substituted guanidine. Non-aromatic amines such as 2,3-dimethylindole and acetamide were converted to the corresponding guanidines in moderate yields. Taking this work as a starting point, DFT calculations demonstrated that amidoaluminium complexes could provide catalysts with excellent performance that is comparable to that of the lithium systems for this process.[69] In fact, simple aluminium precursors, e.g. [$AlCl_3$],[70] [$Al(NMe_2)_3$] and especially [$AlClMe_2$] (5 mol%), were found to be active for the guanylation of anilines, including heterocyclic and disubstituted substrates. Other commercial alkylaluminiums such as [$AlEt_3$], [$AlEt_2Cl$] or [$AlMe_3$] (2 mol%) can also serve as catalyst precursors for the catalytic addition of amines, including both aromatic and heterocyclic derivatives, to carbodiimides.[71] Potential reactive groups such as halogen or terminal alkynes remain unaltered after the reaction, thus demonstrating the selectivity of these catalysts. The isolation of an aluminium guanidinate that was active in the catalytic guanylation supports the mechanism proposed in Scheme 3. The commercial amido compound [$Al(NMe_2)_3]_2$ (1 mol%) allows access to interesting aminoguanidine species[72] on using 1,1-disubstituted hydrazines as substrates.[73] Very recently, titanium

hydrazinediido complexes have also been proposed as catalysts for the hydrohydrazination of carbodiimides to obtain aminoguanidines, a process that follows a similar mechanism to that proposed by Richeson (see Scheme 2).[74]

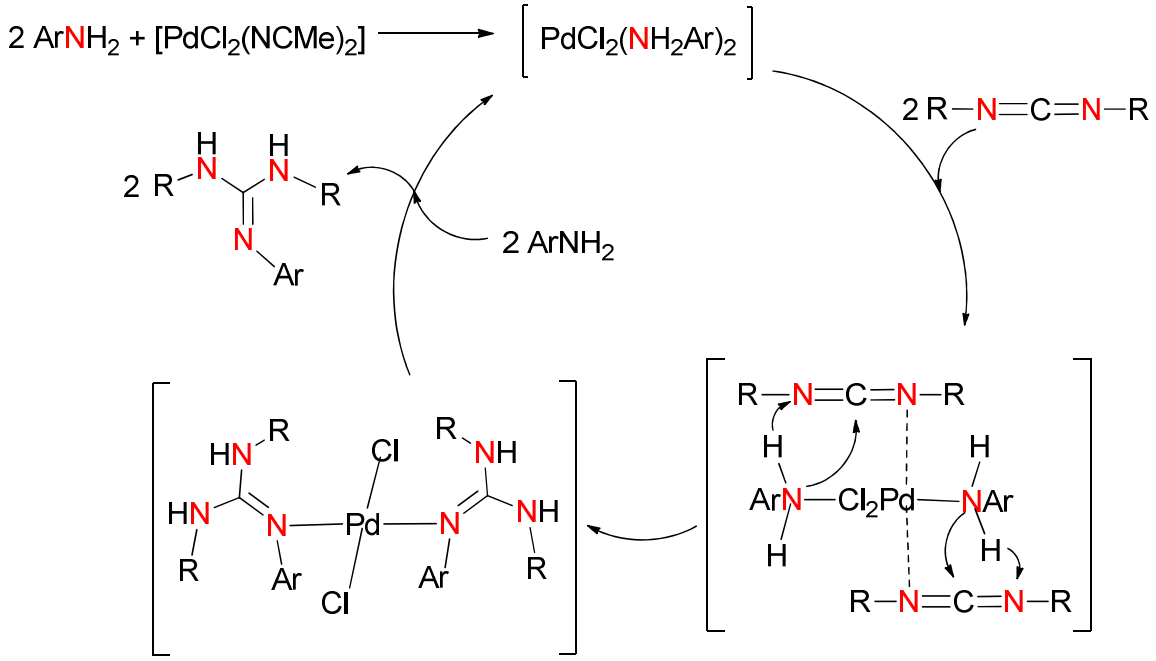
Zhang and Xi introduced zinc triflate (3 mol%) as a cheap and excellent catalyst for the addition of aromatic primary amines and secondary cyclic amines without the need for an inert atmosphere.[75] The reaction could proceed with an amido intermediate as the active species after the formation of a guanidinium triflate. A Lewis acid mechanism similar to that proposed for ytterbium triflate was not ruled out. At the same time, we reported the use of cheap and commercially available $ZnEt_2$ (as a solution in hexane, 1.5 mol% of catalyst loading) as a very effective catalyst for the guanylation reaction[76] of primary and secondary aromatic amines, including aromatic diamines[30a], aliphatic[30e], heterocyclic and secondary cyclic amines under milder conditions. A zinc guanidinate was isolated and structurally characterized and it proved to be a good catalyst in the same reaction (Scheme 6). This work demonstrated that the mechanism proceeds through this kind of guanidinate intermediate, which is formed by insertion of a carbodiimide molecule into the Zn–N bond of an amido complex that, in turn, is formed by reaction between $ZnEt_2$ and the amine substrate.




**Scheme 6.** Proposed mechanism for the catalytic addition of amines to carbodiimides, based In $ZnEt_2$.

In the same work, other commercial solutions of compounds such as Mg*n*Bu$_2$ or *n*BuLi were also investigated and these gave very active catalysts for the guanylation of aromatic amines. Unfortunately, these compounds proved to be less efficient than ZnEt$_2$ towards heterocyclic and secondary cyclic amines. Recently,[77] we found that the crystalline compound [MgBz$_2$(thf)$_2$] (1.5 mol%) catalyzes the guanylation of aromatic amines at room temperature, whereas Mg*n*Bu$_2$ requires gentle warming of the reaction mixture to give similar results. Low cost and easily synthesized heavier alkaline earth complexes have been used for the hydroamination and hydrophosphination of carbodiimides.[78,79] Amido compounds [M{N(SiMe$_3$)$_2$}$_2$(thf)$_2$] (M = Ca, Sr, Ba) (2 mol%) were reported as catalyst precursors for the guanylation of aromatic amines and these worked well at room temperature and in short reaction times. Unfortunately, attempts to extend the scope of this approach to aliphatic primary amines were unsuccessful.

Finally, although most of the examples discussed above correspond to lanthanide or main group metal complexes, transition metals also provide simple compounds that have been reported as catalysts for the guanylation of amines. For instance, we reported that the commercial compound [VOCl$_3$] (2 mol%) acts as a precursor of an active catalyst for a wide range of amines.[48b] On the other hand, iron compounds represent the sustainable alternative to traditional catalysts based on more toxic heavy metals. For example, iron(II) acetate (2-5 mol%) was found to be a versatile catalyst for the addition of a variety of amines to carbodiimides in air and with solvents that did not require pretreatment. The only drawback of this method was the high temperature required.[80] Even electron-rich late transition metals such as palladium provide simple compounds that are capable of catalyzing the guanylation of amines. In this way, the known precursor [PdCl$_2$(NCMe)$_2$] (4 mol%) was reported to be a moderately efficient catalyst for the addition of substituted anilines to carbodiimides. The proposed mechanism starts with amine coordination to give a bisamino complex. After coordination, the carbodiimide undergoes attack by the adjacent amine to give a bisguanidino intermediate, which liberates the guanidine product by exchange with new amine molecules and regeneration of the bisamino species (Scheme 7).[81]




**Scheme 7.** Proposed mechanism for the addition of anilines to carbodiimides based on palladium complexes.

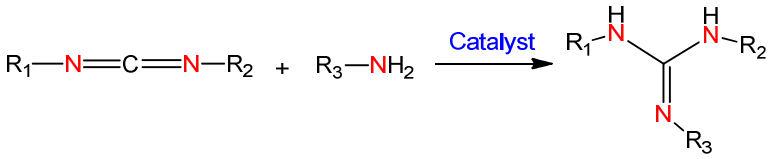
## Conclusions and Outlook

The guanidine group is a key feature in many biological and pharmaceutically relevant compounds. In addition, guanidines as ligands can exhibit a variety of coordination modes with a wide range of metal centres throughout the Periodic Table. Despite the fact that recent progress has been made in classical guanidine synthesis, a completely satisfactory and wide-ranging guanylation reaction has not been developed to date. Drawbacks include the poor availability of the amine precursors, incompatibility of known guanylating reagents with solid-phase synthesis, low yields for a comprehensive array of substrates, the use and production of undesirable substances and the use of expensive starting materials. As a consequence, there is a need for safe and efficient synthetic routes to these entities considering the broad scope of their applications. Over last ten years, several studies have been published on the catalytic guanylation of amines with carbodiimides to give biguanidines, amino-, aliphatic-, aromatic-, heterocyclic, secondary cyclic-, and cyclic-guanidines (see Scheme 8-14) using metal complexes as catalysts. Reactive lanthanide and electropositive main group metal compounds have been the most widely used systems to accomplish this reaction for a variety of amines, including aromatic, aliphatic and heterocyclic species. The mechanism of this catalytic process proceeds primarily through the formation of an amido intermediate followed by

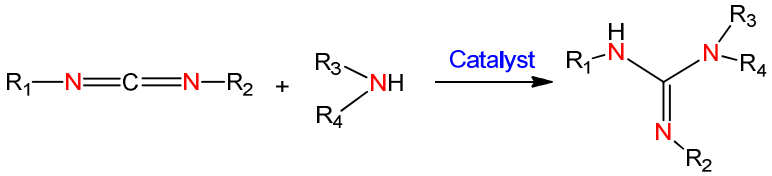
the insertion of a carbodiimide molecule to give guanidinate compounds. Further amonolysis results in the formation of the guanidine product.

The results reviewed here show a trend towards the search for catalysts with applications on a wide range of substrates, with the ultimate goal of obtaining targeted guanidines with specific applications or complementary properties. Alternatives to the direct guanylation, such as the transamination starting from the large number of available guanidines, are possible by using the amido titanacarborane complex described above.[82] This catalyst is also capable of catalyzing the one-step synthesis of interesting mono- and bicyclic guanidines, including chiral examples, from di- and triamines.[83] Another attractive option is the use of heterogeneous catalysts. Corma *et al.* reported the use of supported palladium nanoparticles for the tandem C–C coupling and guanylation reactions of iodoanilines to give styrylguanidines as monomers for the preparation of polymeric agents.[84] Zn-Al modified hydrotalcite clay is a ready available heterogeneous catalyst to form substituted guanidines in moderate yields but with the advantage of recovering and reuse.[85] Furthermore, there is increasing interest in developing simple and efficient catalysts that can be widely used by synthetic chemists. Commercial nanocrystalline zinc oxide has recently been reported as a reusable guanylation catalyst under atmospheric conditions.[86]

In conclusion, a great deal of work has been carried out in this area but numerous issues still need to be addressed in the development of new homogeneous and heterogeneous catalysts for the guanylation of amines. Further studies are needed to optimize the activity of the catalysts and to extend the scope of this reaction to a wider range of substrates, including those with interesting functional groups.

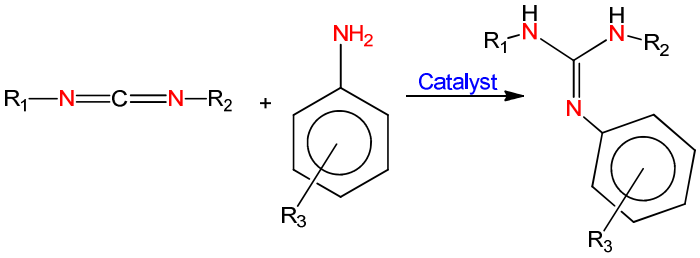



| Substituents | Catalysts |
|---|---|
| $R_1$, $R_2$ = *i*Pr; $R_3$ = $(CH_2)_3CH_3$ | **80, 102, 108, 117, 124** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = $(CH_2)_7CH_3$ | **19** |
| $R_1$, $R_2$, $R_3$ = *i*Pr | **124** |
| $R_1$, $R_2$, $R_3$ = Cy | **131, 132** |




| Substituents | Catalysts |
|---|---|
| $R_1$, $R_2$ = *i*Pr; $R_3$, $R_4$ = $CH_2CH_3$ | **19, 41, 46, 65** |
| $R_1$, $R_2$ = *i*Pr; $R_3$, $R_4$ = $(CH_2)_2CH_3$ | **19** |
| $R_1$, $R_2$ = *i*Pr; $R_3$, $R_4$ = $CH_2CH(CH_3)_2$ | **19** |
| $R_1$, $R_2$ = *i*Pr; $R_3$, $R_4$ = $CH_2CH{=}CH_2$ | **41** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = Me; $R_4$ = $CH_2CH(CH_3)_2$ | **41** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = Me; $R_4$ = $CH_2C_6H_5$ | **80, 102, 108** |
| $R_1$, $R_2$ = Cy; $R_3$, $R_4$ = $CH_2CH_3$ | **46, 65, 132** |
| $R_1$, $R_2$ = Cy; $R_3$, $R_4$ = $(CH_2)_3CH_3$ | **132** |

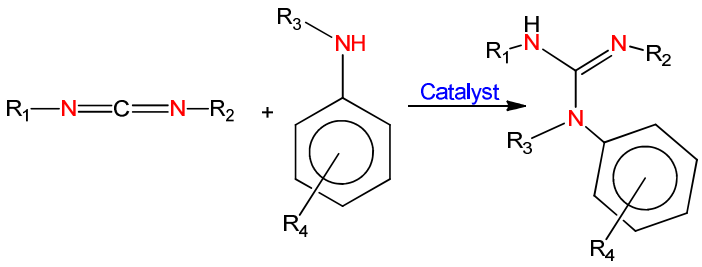
**Scheme 8.** Catalytic synthesis of guanidines from aliphatic amines.




| Substituents | Catalysts | Substituents | Catalysts |
|---|---|---|---|
| $R_1$, $R_2$ = *i*Pr; $R_3$ = H | **5, 18, 19, 29-32, 41-60, 65, 71, 75, 78-120, 122-126, 128, 131, 132** | $R_1$, $R_2$ = Cy; $R_3$ = 4-*i*Pr | **47, 65, 71** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-Me | **47, 50, 65, 71, 85, 86, 94, 99, 102, 107, 108, 117, 121, 122, 128, 131, 132** | $R_1$, $R_2$ = Cy; $R_3$ = 4-F | **33, 80, 85, 94, 102, 107, 108, 117, 122** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 3-Me | **33** | $R_1$, $R_2$ = Cy; $R_3$ = 2-F | **128** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2-Me | **47, 50, 65, 80, 86, 94, 99, 102, 107, 108, 117** | $R_1$, $R_2$ = Cy; $R_3$ = 4-Br | **33, 47, 65, 71, 107, 116, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2-*i*Pr | **118, 123** | $R_1$, $R_2$ = Cy; $R_3$ = 4-Cl | **33, 47, 50, 65, 71, 107** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-*i*Pr | **47, 65, 71, 118** | $R_1$, $R_2$ = Cy; $R_3$ = 2-Cl | **80, 86, 94, 99, 102, 107, 108, 117** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-*t*Bu | **5, 18, 41, 56, 124-127** | $R_1$, $R_2$ = Cy; $R_3$ = 4-I | **33** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-F | **18, 33, 56, 62, 80, 85, 86, 94, 99, 102-104, 107, 108, 117, 118, 122, 123** | $R_1$, $R_2$ = Cy; $R_3$ = 2-I | **33, 131, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2-F | **41, 128-130** | $R_1$, $R_2$ = Cy; $R_3$ = 4-OMe | **33-38, 47, 50, 67, 65, 71, 75, 85, 107, 108, 115, 117, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-Br | **5, 18, 19, 41, 47, 65, 71, 85, 94, 102, 116, 118, 123-127** | $R_1$, $R_2$ = Cy; $R_3$ = 2-OMe | **33, 80, 85, 86, 94, 99, 102, 108, 117, 128** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2-Br | **56, 115** | $R_1$, $R_2$ = Cy; $R_3$ = 4-$NO_2$ | **33, 65-67, 71, 75, 131, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-Cl | **1, 2, 18, 33, 41, 47, 50, 65, 71, 80, 85, 86, 94, 99, 102, 107, 108, 117** | $R_1$, $R_2$ = Cy; $R_3$ = 3-$NO_2$ | **47** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 3-Cl | **41, 56, 118, 123** | $R_1$, $R_2$ = Cy; $R_3$ = 2-$NO_2$ | **33, 65** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2-Cl | **3, 56, 80, 86, 94, 99, 102, 107, 108, 115, 117** | $R_1$, $R_2$ = Cy; $R_3$ = 4-CN | **33, 41, 131, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-I | **33, 40, 41** | $R_1$, $R_2$ = Cy; $R_3$ = 4-(COMe) | **33** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 3-I | **40** | $R_1$, $R_2$ = Cy; $R_3$ = 3-(COMe) | **131, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2-I | **41, 56, 118, 123, 132** | $R_1$, $R_2$ = Cy; $R_3$ = 4-(COPh) | **132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 3-(C≡CH) | **118, 123** | $R_1$, $R_2$ = Cy; $R_3$ = 4-(COOMe) | **33, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-OMe | **1, 2, 18, 19, 33, 39, 47, 50, 65, 71, 75, 85, 94, 99, 102, 107, 108, 115, 117, 124, 127** | $R_1$, $R_2$ = Cy; $R_3$ = 4-(COOEt) | **132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2-OMe | **1, 2, 33, 41, 56, 80, 85, 86, 94, 99, 102, 108, 115, 123, 128** | $R_1$, $R_2$ = Cy; $R_3$ = 4-($CONH_2$) | **132** |

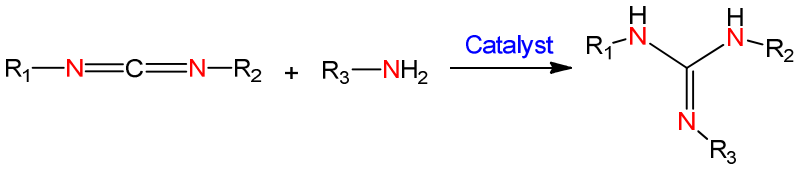
| | |
|---|---|
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-$NO_2$ | **19, 33, 50, 65, 71, 75, 80, 85, 86, 102, 117, 118, 123, 131** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 3-$NO_2$ | **19** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2-$NO_2$ | **33, 65, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-CN | **33, 56, 123** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-($CH_2CN$) | **1, 2, 115** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-(C≡CH) | **41** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2-(C≡CH) | **117** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-($COCH_3$) | **123** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-($CO_2CH_2CH_3$) | **123** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2,6-$Me_2$ | **1, 2, 50, 56, 115, 118** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2,6-*i*$Pr_2$ | **47, 50, 65, 71, 80, 85, 94, 99, 102, 107, 108, 117, 124** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2,6-$F_2$ | **56** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2,6-$Cl_2$ | **19** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2F,4I | **39, 40** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2,4-$(MeO)_2$ | **47, 65** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2,4,6-$Me_3$ | **3, 4, 5-18, 33, 107, 118, 123-126** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-I, 2,5-$Me_2$ | **40** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 3,4-(-$OCH_2O$-) | **39** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2,3,4,5,6-$F_5$ | **1, 2, 115** |
| $R_1$, $R_2$ = *i*Pr; $C_6H_5R_3$ = 1-$C_{10}H_7$ | **19, 47, 65, 80, 85, 86, 94, 99, 102, 107, 108, 117, 118, 128** |
| $R_1$, $R_2$ = *i*Pr; $C_6H_5R_3$ = 2-$C_{10}H_7$ | **19, 75** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 3-($CH=CH_2$) | **40** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-($CH=CH_2$) | **40** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2-F,4-($CH=CH_2$) | **40** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 2,5-$Me_2$, 4-($CH=CH_2$) | **40** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-$CH_2NH_2$ | **115, 116** |
| $R_1$, $R_2$ = Cy; $R_3$ = 2-($C_6H_5$) | **41** |
| $R_1$, $R_2$ = Cy; $R_3$ = 2,6-$Me_2$ | **1, 2** |
| $R_1$, $R_2$ = Cy; $R_3$ = 3,4-$Me_2$ | **132** |
| $R_1$, $R_2$ = Cy; $R_3$ = 2,6-i$Pr_2$ | **47, 50, 65, 71, 107, 128** |
| $R_1$, $R_2$ = Cy; $R_3$ = 2,4-$(OMe)_2$ | **47, 65** |
| $R_1$, $R_2$ = Cy; $R_3$ = 2,4,6-$Me_3$ | **3, 33, 124-126** |
| $R_1$, $R_2$ = Cy; $R_3$ = 4-$CH_2NH_2$ | **116** |
| $R_1$, $R_2$ = Cy; $C_6H_5R_3$ = 1-$C_{10}H_7$ | **47, 65** |
| $R_1$, $R_2$ = Cy; $C_6H_5R_3$ = 2-$C_{10}H_7$ | **75** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 1,2,3,4-tetrahydroisoquinolin-5-yl | **41** |
| $R_1$ = Cy; $R_2$ = *i*Pr; $R_3$ = 2,6-$Me_2$ | **1, 2** |
| $R_1$ = Cy; $R_2$ = Ph; $R_3$ = H | **118** |
| $R_1$, $R_2$ = *t*Bu; $R_3$ = H | **56, 65, 118, 123** |
| $R_1$, $R_2$ = *t*Bu; $R_3$ = 4-Cl | **65** |
| $R_1$, $R_2$ = *t*Bu; $R_3$ = 4-Me | **65, 132** |
| $R_1$, $R_2$ = *t*Bu; $R_3$ = 2-F | **128** |
| $R_1$ = *t*Bu; $R_2$ = Et; $R_3$ = H | **56, 118** |
| $R_1$ = *t*Bu; $R_2$ = Et; $R_3$ = 4-Me | **132** |
| $R_1$ = *t*Bu; $R_2$ = Et; $R_3$ = 2-F | **128** |
| $R_1$ = *t*Bu; $R_2$ = Et; $R_3$ = 2,4,6-$Me_3$ | **124-126** |
| $R_1$ = *t*Bu; $R_2$ = Et; $C_6H_5R_3$ = 1-$C_{10}H_7$ | **41, 85** |
| $R_1$ = *t*Bu; $R_2$ = Ph; $R_3$ = H | **115** |
| $R_1$ = *t*Bu, $R_2$ = Ph; $R_3$ = 4-OMe | **115** |
| $R_1$, $R_2$ = Ph; $R_3$ = 2-Br | **115** |
| $R_1$ = Ph; $R_2$= $CH_2Ph$; $R_3$ = H | **123** |
| $R_1$, $R_2$ = Tolyl; $R_3$ = 4-$NO_2$ | **132** |

| | | | |
|---|---|---|---|
| $R_1$, $R_2$ = Cy; $R_3$ = H | **19, 33, 50, 56, 61-65, 67-77, 80, 86, 94, 99, 102, 107, 108, 116-118, 122, 123, 128, 131, 132** | $R_1$, $R_2$ = Tolyl; $R_3$ = 4-Me | **65** |
| $R_1$, $R_2$ = Cy; $R_3$ = 2-Me | **33, 47, 50, 65, 80, 94, 102, 107, 108** | $R_1$, $R_2$ = Tolyl; $R_3$ = 3,4-$Me_2$ | **132** |
| $R_1$, $R_2$ = Cy; $R_3$ = 3-Me | **33** | | |
| $R_1$, $R_2$ = Cy; $R_3$ = 4-Me | **33, 47, 50, 65, 71, 85, 107, 122, 128, 131, 132** | | |



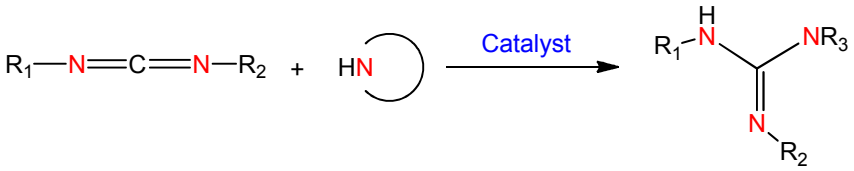

| Substituents | Catalysts |
|---|---|
| $R_1$, $R_2$ = *i*Pr; $R_3$ = $CH_3$; $R_4$ = H | **5, 33, 56, 124 -126** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = $CH_3$; $R_4$ = 4-Me | **3, 56** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = $C_6H_5$; $R_4$ = H | **33, 56, 116** |
| $R_1$, $R_2$ = Cy; $R_3$ = $CH_3$; $R_4$ = H | **33, 132** |
| $R_1$, $R_2$ = Cy; $R_3$ = $C_6H_5$; $R_4$ = H | **56, 116, 132** |
| $R_1$, $R_2$ = Cy; $R_3$ = $CH_3$; $R_4$ = 4-Me | **3** |

**Scheme 9.** Catalytic synthesis of guanidines from aromatic amines.



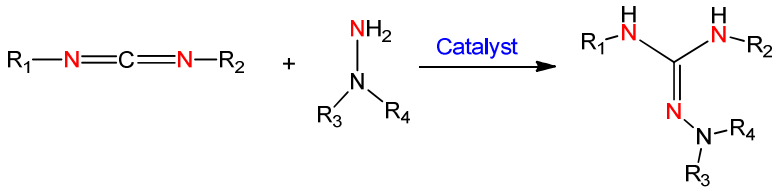

| Substituents | Catalysts | Substituents | Catalysts |
|---|---|---|---|
| $R_1$, $R_2$ = *i*Pr; $R_3$ = pyrazin-2-yl | **71, 75** | $R_1$, $R_2$ = *i*Pr; $R_3$ = 6-chlorobenzo[d]thiazol-2-yl | **41** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = pyridin-3-yl | **18, 124-126** | $R_1$, $R_2$ = Cy; $R_3$ = pyridin-2-yl | **33, 50, 71, 75, 116** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = pyridin-2-yl | **33, 41, 50, 71, 75, 116-118** | $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-Me-pyridin-2-yl | **71** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 6-Me-pyridin-2-yl | **71** | $R_1$, $R_2$ = Cy; $R_3$ = pyridin-3-yl | **131, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 5-Me-pyridin-2-yl | **132** | $R_1$, $R_2$ = Cy; $R_3$ = 6-Me- pyridin-2-yl | **71** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 3-Me-pyridin-2-yl | **19** | $R_1$, $R_2$ = Cy; $R_3$ = 5-Me-pyridin-3-yl | **132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 6-iodopyridin-3-yl | **123** | $R_1$, $R_2$ = Cy; $R_3$ = pyrimidin-2-yl | **33, 50** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 3,5-$Me_2$-pyridin-2-yl | **124** | $R_1$, $R_2$ = Cy; $R_3$ = 4-Me-pyrimidin-2-yl | **71** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = pyrimidin-2-yl | **33, 50** | $R_1$, $R_2$ = Cy; $R_3$ = pyrazin-2-yl | **71, 75** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-Me- pyrimidin-2-yl | **71** | $R_1$, $R_2$ = Cy; $R_3$ = 5-Cl-pyridin-2-yl | **33** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 5-methylisoxazol-3-yl | **41, 118** | $R_1$, $R_2$ = Cy; $R_3$ = 5-methylisoxazol-3-yl | **41** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 3-methyl-1-phenyl-1H-pyrazol-5-yl | **41, 118** | $R_1$ = *t*Bu; $R_2$ = Et; $R_3$ = 5-methylisoxazol-3-yl | **41, 118** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-methylthiazol-2-yl | **41, 56, 118, 123** | $R_1$ = *t*Bu; $R_2$ = Et; $R_3$ = 3-methyl-1-phenyl-1H-pyrazol-5-yl | **41** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 1-methyl-1H-benzo[d]imidazol-2-yl | **41** | | |

**Scheme 10.** Catalytic synthesis of guanidines from heterocyclic amines.



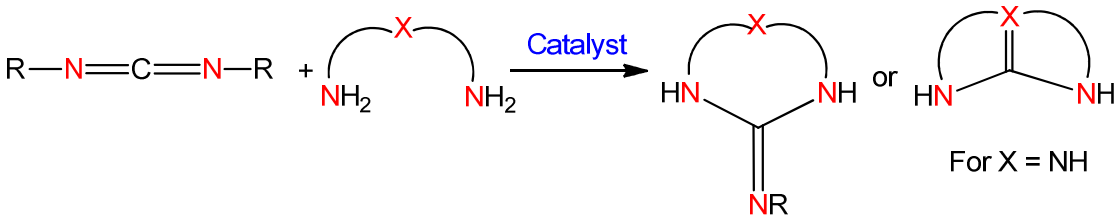

| Substituents | Catalysts | Substituents | Catalysts |
|---|---|---|---|
| $R_1$, $R_2$ = *i*Pr; $R_3$ = piperidin-1-yl | **5, 18, 19, 33, 46, 56, 65, 80, 85, 94, 99, 102, 108, 117, 124-126, 132** | $R_1$, $R_2$ = *i*Pr; $R_3$ = (R)-(2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl | **41** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = morpholino | **5, 18, 33, 46, 56, 65, 80, 85, 94, 102, 108, 117, 132, 124-126** | $R_1$, $R_2$ = Cy; $R_3$ = 1H-pyrrol-1-yl | **19** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-methylpiperazin-1-yl | **102, 108** | $R_1$, $R_2$ = Cy; $R_3$ = pyrrolidin-1-yl | **46, 65, 80, 85, 102, 108, 117, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = pyrrolidin-1-yl | **19, 46, 56, 65, 80, 85, 94, 99, 102, 108, 117, 132** | $R_1$, $R_2$ = Cy; $R_3$ = piperidin-1-yl | **33, 46, 65, 80, 85, 102, 108, 117, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 1H-pyrrol-1-yl | **19** | $R_1$, $R_2$ = Cy; $R_3$ = morpholino | **33, 46, 65, 80, 85, 102, 108, 117, 132** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 1H-benzo[d][1,2,3]triazol-1-yl | **19** | $R_1$, $R_2$ = Cy; $R_3$ = 4-methylpiperazin-1-yl | **102, 108** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 1H-indol-1-yl | **19** | $R_1$, $R_2$ = Cy; $R_3$ = 4-(pyrrolidin-1-yl)piperidin-1-yl | **41** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 3-methyl-1H-indol-1-yl | **19** | $R_1$, $R_2$ = Cy; $R_3$ = 3,4-dihydroisoquinolin-2(1H)-yl | **41** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = indolin-1-yl | **19** | | |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = indolin-2-yl | **41** | | |

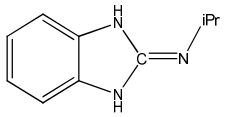
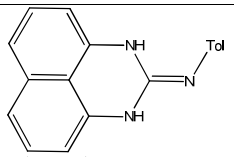
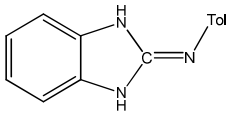
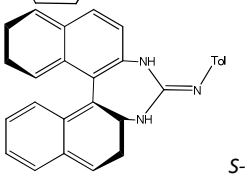
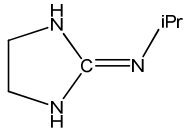
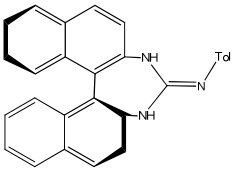
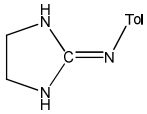
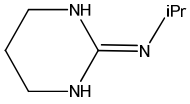
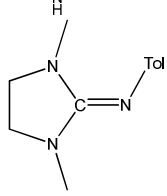
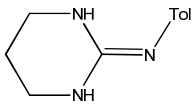
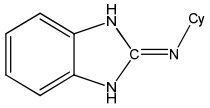
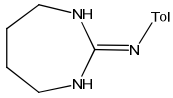
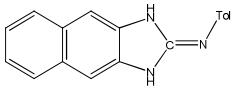
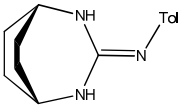
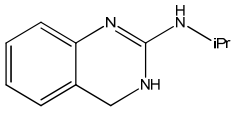
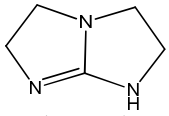
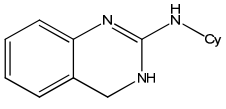
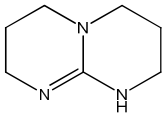
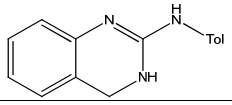
**Scheme 11.** Catalytic synthesis of guanidines from secondary cyclic amines.



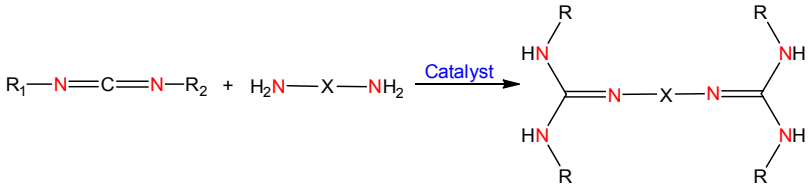

| Substituents | Catalysts |
|---|---|
| $R_1$, $R_2$ = *i*Pr; $R_3$, $R_4$ = Me | **20-28, 121** |
| $R_1$, $R_2$ = *i*Pr; $R_3$-$R_4$ = piperidin-1-yl | **121** |
| $R_1$, $R_2$ = *i*Pr; $R_3$, $R_4$ = Ph | **20-28, 121** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = Me; $R_4$ = Ph | **20-28** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-Me$C_6H_5$; $R_4$ = Ph | **20-28** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-OMe$C_6H_5$; $R_4$ = Ph | **20-28** |
| $R_1$, $R_2$ = *i*Pr; $R_3$ = 4-F$C_6H_5$; $R_4$ = Ph | **20-28** |
| $R_1$, $R_2$ = *i*Pr; $R_3$, $R_4$= 4-Br$C_6H_5$ | **20-28** |
| $R_1$, $R_2$ = *i*Pr; $R_3$-$R_4$= 9*H*-fluoren-9-ylidene | **20-28** |
| $R_1$, $R_2$ = Cy; $R_3$, $R_4$ = Me | **121, 20-28** |
| $R_1$, $R_2$ = Cy; $R_3$-$R_4$ = piperidin-1-yl | **121** |
| $R_1$, $R_2$ = Cy; $R_3$, $R_4$ = Ph | **20-28** |
| $R_1$, $R_2$ = Cy; $R_3$ = Me; $R_4$ = Ph | **20-28** |
| $R_1$, $R_2$ = Cy; $R_3$ = 4-Me$C_6H_5$; $R_4$ = Ph | **20-28** |
| $R_1$, $R_2$ = Cy; $R_3$, $R_4$ = 4-Br$C_6H_5$ | **20-28** |
| $R_1$, $R_2$ = Cy; $R_3$-$R_4$= 9*H*-fluoren-9-ylidene | **20-28** |
| $R_1$ = Et; $R_2$ = *t*Bu; $R_3$, $R_4$ = Ph | **20-28** |
| $R_1$ = Et; $R_2$ = *t*Bu; $R_3$ = Me; $R_4$ = Ph | **20-28** |
| $R_1$ = Et; $R_2$ = *t*Bu; $R_3$, $R_4$ = 4-Br$C_6H_5$ | **20-28** |
| $R_1$ = Et; $R_2$ = *t*Bu; $R_3$, $R_4$ = 9*H*-fluoren-9-ylidene | **20-28** |
| $R_1$, $R_2$ = Tol; $R_3$, $R_4$ = Ph | **20-28** |
| $R_1$, $R_2$ = Tol; $R_3$ = Me; $R_4$ = Ph | **20-28** |
| $R_1$, $R_2$ = Tol; $R_3$, $R_4$ = 9*H*-fluoren-9-ylidene | **20-28** |
| $R_1$, $R_2$ = 2,6-*i*Pr$_2$$C_6H_3$; $R_3$, $R_4$ = Me | **121** |
| $R_1$, $R_2$ = 2,6-*i*Pr$_2$$C_6H_3$; $R_3$-$R_4$ = piperidin-1-yl | **121** |
| $R_1$ = Et; $R_2$ = $(CH_2)_3N(CH_3)_2$; $R_3$ = Me; $R_4$ = Ph | **20-28** |
| $R_1$ = Et; $R_2$ = $(CH_2)_3N(CH_3)_2$; $R_3$, $R_4$ = 9*H*-fluoren-9-ylidene | **20-28** |

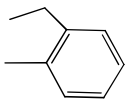
**Scheme 12.** Catalytic synthesis of amino guanidines.

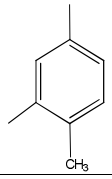



| Product | Catalysts | Product | Catalysts |
|---|---|---|---|
|  | **19** |  | **19** |
|  | **19** |  *S-* | **19** |
|  | **19** |  *rac-* | **19** |
|  | **19** |  | **19** |
|  | **19** |  | **19** |
|  | **19** |  | **19** |
|  | **19** |  | **19** |
|  | **19** |  | **19** |
|  | **19** |  | **19** |
|  | **19** | | |

**Scheme 13.** Catalytic synthesis of cyclic and bicyclic guanidines.




| Substituents | Catalysts | Substituents | Catalysts |
|---|---|---|---|
| $R_1$, $R_2$ = *i*Pr; X = $(CH_2)_2$ | **80** | $R_1$, $R_2$ = *i*Pr; X = | **41** |
| $R_1$, $R_2$ = *i*Pr; X = $(CH_2)_3$ | **80** | $R_1$, $R_2$ = *i*Pr; X = | **41, 80** |
| $R_1$, $R_2$ = *i*Pr; X = $(CH_2)_4$ | **80** | $R_1$, $R_2$ = *i*Pr; X = | **80** |
| $R_1$, $R_2$ = *i*Pr; X = $(CH_2)_6$ | **80** | $R_1$, $R_2$ = *i*Pr; X = | **80** |
| $R_1$, $R_2$ = Cy; X = $(CH_2)_2$ | **80** | $R_1$, $R_2$ = *i*Pr; X = | **41** |
| $R_1$, $R_2$ = *i*Pr; X= | **1, 2, 18, 19, 47, 65, 80, 85, 116, 123, 124** | $R_1$, $R_2$ = Cy; X = | **80** |
| $R_1$, $R_2$ = *i*Pr; X= | **116** | $R_1$, $R_2$ = Cy; X = | **116** |
| $R_1$, $R_2$ = *i*Pr; X=  | **80** | $R_1$, $R_2$ = Cy; X = | **47, 65, 80, 116** |
| $R_1$, $R_2$ = *i*Pr; X= | **41, 80, 85** | $R_1$, $R_2$ = Cy; X = | **80** |
| $R_1$, $R_2$ = *i*Pr; X = | **80** | $R_1$, $R_2$ = Cy; X = | **80** |

| | | | |
|---|---|---|---|
| $R_1$, $R_2$ = *i*Pr; X = |  | **80** | |

**Scheme 14.** Catalytic synthesis of biguanidines.

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