Catalytic Construction and Reconstruction of Guanidines: Ti-Mediated Guanylation of Amines and Transamination of Guanidines

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The catalytic formation and transformation of C−N bonds by group 4 complexes is an active research area.[1−3] We are interested in contributing to this field by developing new catalysts, reactions, and targets. We recently reported that imido complex [{(Me$_2$N)C-(N^{i}Pr)$_2$}$_2$Ti=N(2,6-Me$_2$C$_6$H$_3$)] (**1a**) is a catalyst for alkyne hydroamination and have determined that the imido group of **1a** can undergo a clean exchange with other aromatic amines to afford new imine complexes (e.g. {(Me$_2$N)C(N^{i}Pr)$_2$}$_2$Ti=NC$_6$F$_5$ (**1b**)).[1o,4] These observations provided an impetus for exploring the ability of **1a** and related compounds to function as competent catalyst precursors for other C−N bond transformations.

Substituted guanidines are CN rich targets that represent an essential functionality in many biologically relevant compounds.[5] Typical synthetic routes to guanidines employ the reaction of an amine with an electrophilic guanylating reagent.[6] A variety of such agents have been developed which rely on displacement of a leaving group, Y, from a protected carbodiimide-equivalent, **A**, and often require that the nitrogen substituents be carbamate-protecting groups which activate the reagent to reaction with amine and allow for direct synthesis of protected guanidines. These restrictions frequently limit the products to mono- or *N,N*-disubstituted guanidines. Consequently, new efficient and catalytic methods for assembling the guanidines from a diverse set of amines would be valuable. We report the first examples of transition metal-catalyzed guanylation of amines with carbodiimide using complexes **1a** and **1b** as precatalysts (eq 2). Significantly, these species are also capable of catalyzing the first examples of guanidine transamination (eq 3).
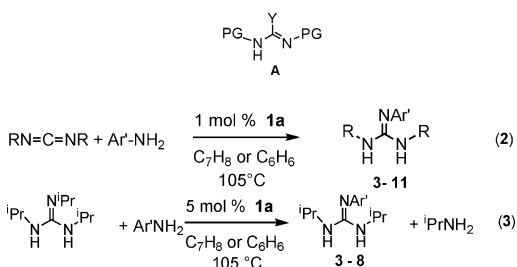
Aliphatic amines will undergo direct guanylation with carbodiimides to yield *N,N′,N″*-trialkylguanidines albeit under rather forcing conditions (e.g. 120−140 °C, **3d**).[7] However, less nucleophilic aromatic amines do not react with diisopropylcarbodiimide to any detectable degree even with prolonged heating at 140 °C. The addition of 1−5mol % of catalyst precursor **1a** led to efficient guanylation of 2,6-dimethylaniline with diisopropylcarbodiimide to yield guanidine **3** (eq 2). This result is generalized to other substituted anilines as summarized in Table 1. The progress of these reactions was monitored by ^{1}H NMR spectroscopy and GC−MS and in all cases was quantitative in less than 18 h. For example, the guanylation of two isomers of MeOC$_6$H$_4$NH$_2$ (entries 4 and 5) was complete in less than 8 h. The resulting guanidines could be

Table 1. Guanylation of Aromatic Amines According to Eq 2

entry	RNCNR	Ar′NH$_2$	product	yield (%)^a
1	R$_1$ = R$_2$ = ^{i}Pr	2,6-Me$_2$C$_6$H$_3$NH$_2$	**3**	81.5^c
2	R$_1$ = R$_2$ = ^{i}Pr	C$_6$F$_5$NH$_2$	**5**	92.3^c
3	R$_1$ = R$_2$ = ^{i}Pr	*p*-MeOC$_6$H$_4$NH$_2$	**6**	82.8^c
4	R$_1$ = R$_2$ = ^{i}Pr	*o*-MeOC$_6$H$_4$NH$_2$	**7**	87.2^b
5	R$_1$ = R$_2$ = ^{i}Pr	*p*-ClC$_6$H$_4$NH$_2$	**8**	96.6^b
6	R$_1$ = R$_2$ = ^{i}Pr	*p*-NCCH$_2$C$_6$H$_4$NH$_2$	**9**	47.6^b
7	R$_1$ = R$_2$ = ^{i}Pr	*p*-C$_6$H$_4$(NH$_2$)$_2$	**10**^{d}	97.2^b
8	R$_1$ = ^{i}Pr; R$_2$ = Cy	2,6-Me$_2$C$_6$H$_3$NH$_2$	**11**	92

^{a} All reactions were carried to 100% conversion. ^{b} Yields determined by integration of ^{1}H NMR relative to internal standard of either 1,3-(MeO)$_2$C$_6$H$_4$ or O(SiMe$_3$)$_2$. ^{c} Isolated yields. ^{d} Product is the biguanidine, (^{i}PrNH)$_2$C=N−(C$_6$H$_4$)−N=C(^{i}PrNH)$_2$.

Scheme 1

$$N\frown N = \{(Me_2N)C(Ni Pr)_2\}$$
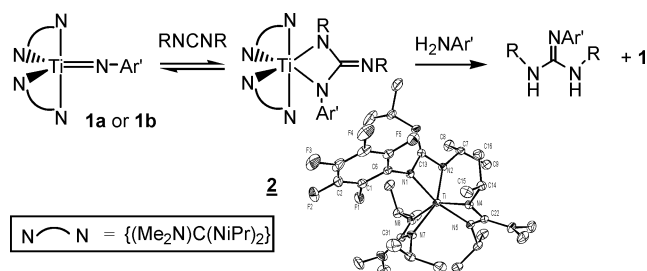
isolated by simple crystallization in good to excellent yield.[8] Complex **1b** is also an effective precatalyst for this transformation and exhibited similar conversion rates to **1a**.

Complex **1b** reacted readily and reversibly with diisopropylcarbodiimide at room temperature to afford the diazametallacycle complex **2**. The molecular structure for complex **2** was confirmed by X-ray crystallographic analysis (Scheme 1). The coordination sphere of this pseudo-octahedral Ti (IV) species consists of two bidentate monoanionic guanidinate ligands, that originated from the starting material, and one bidentate dianionic guanidinate ligand derived from a [2 + 2] addition reaction of ^{i}PrN=C=N^{i}Pr with the Ti arylimido group of **1b**. The bond distances and angles within the dianionic ligand are consistent with the valence bond picture shown for **2** and similar to Cp$_2$Zr((^{t}Bu)NC=N(SiMe$_3$)N(SiMe$_3$)).[2a] For example, the exocyclic C(13)−N(3) distance of 1.268(5) Å suggests a C=N and the two remaining C−N distances (C(13)−N(1) = 1.412(4) Å, C(13)−N(2) = 1.416(4) Å) are consistent with single bonds between two sp^2 centers.

When 1 equiv of 2,6-dimethylaniline is added to an NMR sample of **2**, compounds **1a** and **5** were formed. These observations lead us to propose a catalytic cycle for the guanidine formation using **1a/1b** that is shown in Scheme 1. The cycle begins with [2 + 2] addition of a carbodiimide to the Ti=N moiety.[1e,2a] A proton-transfer reaction between aromatic amine and metal-bound dianionic guanidinate ligand releases guanidine and reforms the Ti imido

Table 2. Transamination of Trialkylguanidine with Aromatic Amines According to Eq 3

entry	Ar'NH$_2$	product	conversion (%)	yield (%)^a	time (h)
1	2,6-Me$_2$C$_6$H$_3$NH$_2$	**3**	100	100	18
2	C$_6$H$_5$NH$_2$	**4**	100	100	18
3	C$_6$F$_5$NH$_2$	**5**	100	100 (70.0)^b	18
4	*p*-MeOC$_6$H$_4$NH$_2$	**6**	100	93	36
5	*o*-MeOC$_6$H$_4$NH$_2$	**7**	54	35^b	66
6	*p*-ClC$_6$H$_4$NH$_2$	**8**	100	100	18

^{a} Yields determined by integration of ^{1}H NMR relative to internal standard of either 1,3-(MeO)$_2$C$_6$H$_4$ or O(SiMe$_3$)$_2$. ^{b} Isolated yield.

group to complete the cycle. Complex **2** is also an effective precatalyst for the guanylations summarized in Table 1. Careful examination of the reaction products from these guanylation reactions by GC–MS did show the formation of 1–5% of [RN-(H)]$_2$CN(Me$_2$C$_6$H$_3$) and [RN(H)]$_2$CN(C$_6$F$_5$) in reactions employing **1a** and **1b**, respectively. These products arise from starting material as it enters the cycle in Scheme 1.

To expand the scope and elucidate the mechanistic details for these transformations, we examined other potential catalyst precursors for eq 2. In particular, the Zr complex {^{i}PrN(H)C(N^{i}Pr)$_2$}$_2$ZrN-(2,6-Me$_2$C$_6$H$_3$) (**11**)^{10} displayed no catalytic activity. The Ti–imido complex Ti(=N^{t}Bu)Cl$_2$py$_2$ (**12**)^9 is a precatalyst for the formation of **3**. However, it has a reaction rate that was approximately half that of **1a**. The tantalum–imido complex (2,6-Me$_2$C$_6$H$_3$)N=TaCl$_3$-(THF)$_2$ (**13**)^{10} led to catalytic formation of **3** but exhibited even poorer activity than **12**.

We suspected that **1a** and **1b** might be capable of facilitating a transamination reaction between guanidine and amine, leading to guanidine reconstruction (eq 3). To our knowledge, this reaction has not yet been reported. Complex **1a** is a competent catalyst for this transformation, and the results for the conversion of *N,N′,N″*-tri(isopropyl)guanidine to aryl(diisopropyl)guanidines **3**–**8** are summarized in Table 2. Reactions were monitored by ^{1}H NMR spectroscopy, which further confirmed that no reaction occurred between the trialkylguanidine and arylamine under these conditions in the absence of precatalyst. In most cases full conversion of the starting material was achieved in less than 18 h and led selectively to the formation of monoarylguanidines even with longer reaction times.

A comparison of reactions 2 and 3 for the formation of **6** and **7** shows that while both employ similar conditions and form the same product there is a clear difference in the rates for these processes. As noted, the guanylation of *o*- and *p*-H$_2$NC$_6$H$_3$(OMe) proceeds to full conversion in less than 8 h. In contrast the conversion to **6** (93% isolated yield) according to eq 3 takes approximately 36 h. Furthermore, the transamination of the ortho isomer proceeded to only 54% conversion in 66 h. The lower rate for guanidine formation via the transamination route compared to that for the amine guanylation pathway is consistent with relative stability of aryldialkylguanidine > trialkylguanidine > arylamine/carbodiimide.

Further elucidating the mechanism of these reactions, expanding the range of substrates, and developing new catalyst precursors are the focus of our ongoing work. We anticipate that this effort will lead to new catalysts with improved activity and application.

Supporting Information Available: Experimental procedures and characterization of new compounds, structural data for complexes **1b**, **2**, and **7 (PDF)**. X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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