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Cobalt-Catalyzed Intermolecular Oxidative Isocyanide Insertion with Two Amines: An Approach to Guanidines

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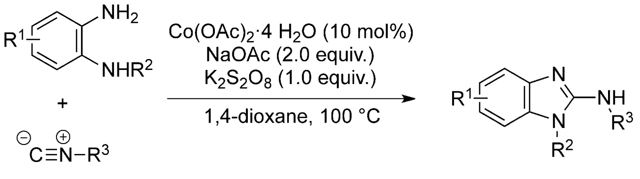
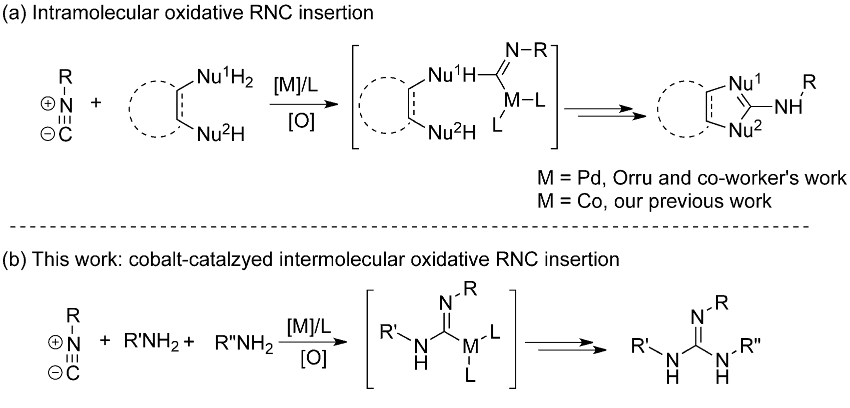
Abstract: A novel and efficient cobalt-catalyzed oxidative isocyanide insertion with amines *via* two C–N bond formation reactions under ultrasound irradiation conditions has been developed. This protocol provides a simple, clean and general way to synthesize guanidines or their corresponding hydrochlorides from simple starting materials under ultrasonic conditions. This chemistry could also be applied to an efficient synthesis of optically active guanidines without loss of enantioselectivity.

Keywords: cobalt; guanidines; isocyanides; oxidative insertion

Isocyanide multicomponent reactions (IMCRs) have attracted considerable attention for the atom- and step-economic efficient construction of organic molecules. Two of the most famous IMCRs are the Passerini reaction[1] and the Ugi reaction,[2] which play an important role in modern isocyanide chemistry. Most of these IMCRs such as Passerini-type and Ugi-type reactions follow the same mechanism: the isocyanide reacts with an electrophile to give the nitrilium ion intermediate followed by nucleophilic addition.[3] The somophilic isocyanide insertion reactions have also been well studied and expanded the synthetic applications of IMCRs *via* a radical insertion mechanism.[4,5] Recently, IMCRs catalyzed by transition metals, especially palladium, have become increasingly popular.[6] More recently, Orru's group and our group reported the palladium-catalyzed[7] and cobalt-catalyzed[8] synthesis of 2-aminobenzimidazoles from isocyanides with 2-aminoanilines *via* intramolecular trapping of the insertion coupling intermediates, respectively (Scheme 1, a and Scheme 2). Based on these factors, we hypothesized that the open-chain trisubstitued

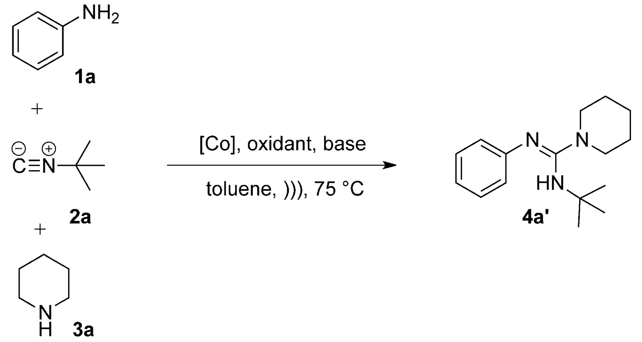


Scheme 2. Cobalt-catalyzed synthesis of 2-aminobenzimidazoles from isocyanide with amines.



Scheme 1. Typical IMCRs and our design.

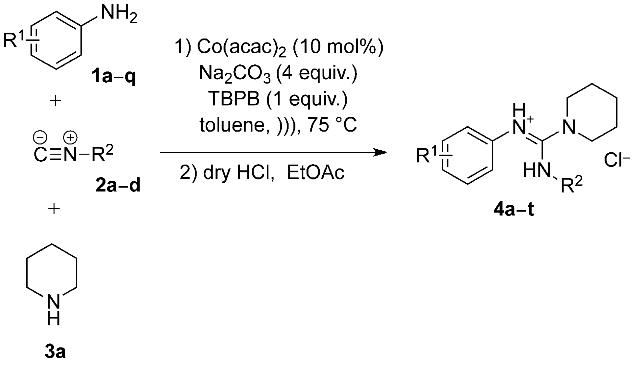
Table 1. Cobalt-catalyzed insertion reactions of aniline **1a** with *tert*-butyl isocyanide **2a** and piperidine **3a**.[a]

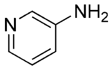


Entry	Co^{II}-catalyst (10 mol%)	Oxidant (1 equiv.)	Base (2 equiv.)	Yield [%][b]
1[c]	$Co(OAc)_2{\cdot}4H_2O$	TBHP[g]	–	2
2	$Co(OAc)_2{\cdot}4H_2O$	TBHP	–	6
3	$CoSO_4{\cdot}7H_2O$	TBHP	–	trace
4	$CoCl_2{\cdot}6H_2O$	TBHP	–	7
5	$Co(NO_3)_2{\cdot}6H_2O$	TBHP	–	trace
6	$Co(acac)_2$	TBHP	–	25
7	$Co(acac)_2$	TBPB[h]	–	30
8	$Co(acac)_2$	DTPB[i]	–	15
9	$Co(acac)_2$	CHP[j]	–	25
10	$Co(acac)_2$	H_2O_2	–	24
11	$Co(acac)_2$	$K_2S_2O_8$	–	trace
12	$Co(acac)_2$	BQ[k]	–	0
13	$Co(acac)_2$	TBPB	LiOAc	25
14	$Co(acac)_2$	TBPB	NaOAc	36
15	$Co(acac)_2$	TBPB	KOAc	31
16	$Co(acac)_2$	TBPB	CsOAc	21
17	$Co(acac)_2$	TBPB	Na_2CO_3	40
18	$Co(acac)_2$	TBPB	K_2CO_3	37
19	$Co(acac)_2$	TBPB	NaOPiv	15
20	$Co(acac)_2$	TBPB	$NaHCO_3$	36
21	$Co(acac)_2$	TBPB	NaOH	30
22	$Co(acac)_2$	TBPB	NEt_3	26
23	$Co(acac)_2$	TBPB	DABCO[l]	23
24[d]	$Co(acac)_2$	TBPB	Na_2CO_3	43
25[e]	$Co(acac)_2$	TBPB	Na_2CO_3	59
26[f]	$Co(acac)_2$	TBPB	Na_2CO_3	87

[a] *Reaction Conditions:* aniline **1a** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.6 mmol), piperidine **3a** (2 equiv.), $Co(acac)_2$ (10 mol%), base (2 equiv.), oxidant (1 equiv.), in 1,4-dioxane (3 mL), 75 °C, under ultrasound irradiation 1 h.
[b] Xields were determined by GC analysis with biphenyl as the internal standard.
[c] The reaction mixture was heated at 110 °C in a silicone oil bath for 20 h.
[d] 4 equiv. of base were used.
[e] The reaction was carried out in toluene.
[f] Reaction time: 5 h.
[g] TBHP = *tert*-butyl hydroperoxide.
[h] TBPB = *tert*-butyl benzoperoxoate.
[i] DTBP = di-*tert*-butyl peroxide.
[j] CHP = cumyl hydroperoxide.
[k] BQ = benzoquinone.
[l] DABCO = 1,4-diazabicyclo[2.2.2]octane.

Table 2. Cobalt-catalyzed insertion reactions of isocyanides **2a–c** with amines **1a–q** and piperidine **3a**.[a]



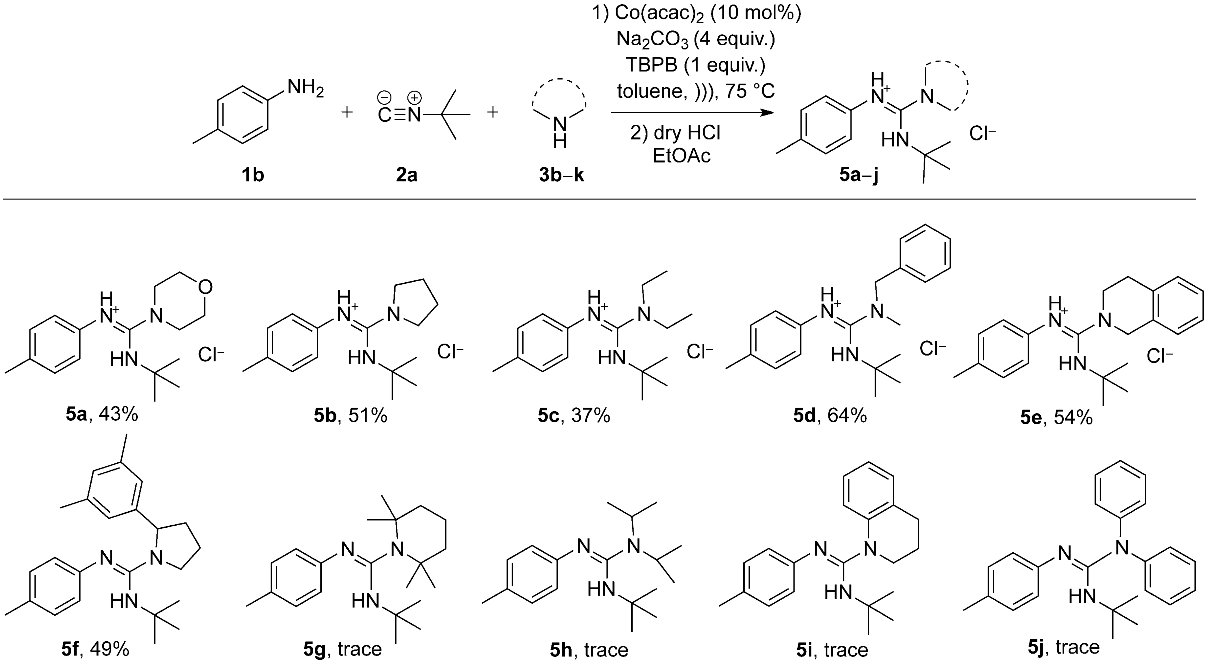
Entry	1		2		4	Yield [%][b]
1	**1a**	$R^1 = H$	**2a**	$R^2 = t$-Bu	**4a**	81
2	**1b**	$R^1 = 4$-Me	**2a**	$R^2 = t$-Bu	**4b**	77
3	**1c**	$R^1 = 3$-Me	**2a**	$R^2 = t$-Bu	**4c**	63
4	**1d**	$R^1 = 2$-Me	**2a**	$R^2 = t$-Bu	**4d**	75
5	**1e**	$R^1 = 2$-Me, 4-Me	**2a**	$R^2 = t$-Bu	**4e**	74
6	**1f**	$R^1 = 4$-t-Bu	**2a**	$R^2 = t$-Bu	**4f**	51
7	**1g**	$R^1 = 4$-OMe	**2a**	$R^2 = t$-Bu	**4g**	66
8	**1h**	$R^1 = 4$-OEt	**2a**	$R^2 = t$-Bu	**4h**	71
9	**1i**	$R^1 = 4$-OBn	**2a**	$R^2 = t$-Bu	**4i**	61
10	**1j**	$R^1 = 3$,4-methylenedioxy	**2a**	$R^2 = t$-Bu	**4j**	80
11	**1k**	$R^1 = 4$-NO_2	**2a**	$R^2 = t$-Bu	**4k**	21
12	**1l**	$R^1 = 4$-CN	**2a**	$R^2 = t$-Bu	**4l**	39
13	**1m**	$R^1 = 4$-Cl	**2a**	$R^2 = t$-Bu	**4m**	73
14	**1n**	$R^1 = 4$-Br	**2a**	$R^2 = t$-Bu	**4n**	75
15	**1o**		**2a**	$R^2 = t$-Bu	**4o**	46
16[c]	**1b**	$R^1 = 4$-Me	**2b**	$R^2 = Cy$	**4p**	71
17[c]	**1b**	$R^1 = 4$-Me	**2c**	$R^2 = n$-Bu	**4q**	49
18	**1p**	cyclohexylamine	**2a**	$R^2 = t$-Bu	**4r**	trace
19	**1q**	butylamine	**2a**	$R^2 = t$-Bu	**4s**	trace
20	**1b**	$R^1 = 4$-Me	**2d**	$R^2 = 2$,6-$CH_3C_6H_4$	**4t**	messy

[a] *Reaction conditions:* amines **1a–q** (0.5 mmol), isocyanides **2a–d** (0.6 mmol), piperidine **3a** (1 mmol), $Co(acac)_2$ (10 mol%), Na_2CO_3 (4 equiv.), TBPB (1 equiv.), in toluene (3 mL), 75 °C, under ultrasound irradiation 5 h.
[b] Isolated yield.
[c] The guanidine was isolated directly instead of its salt.

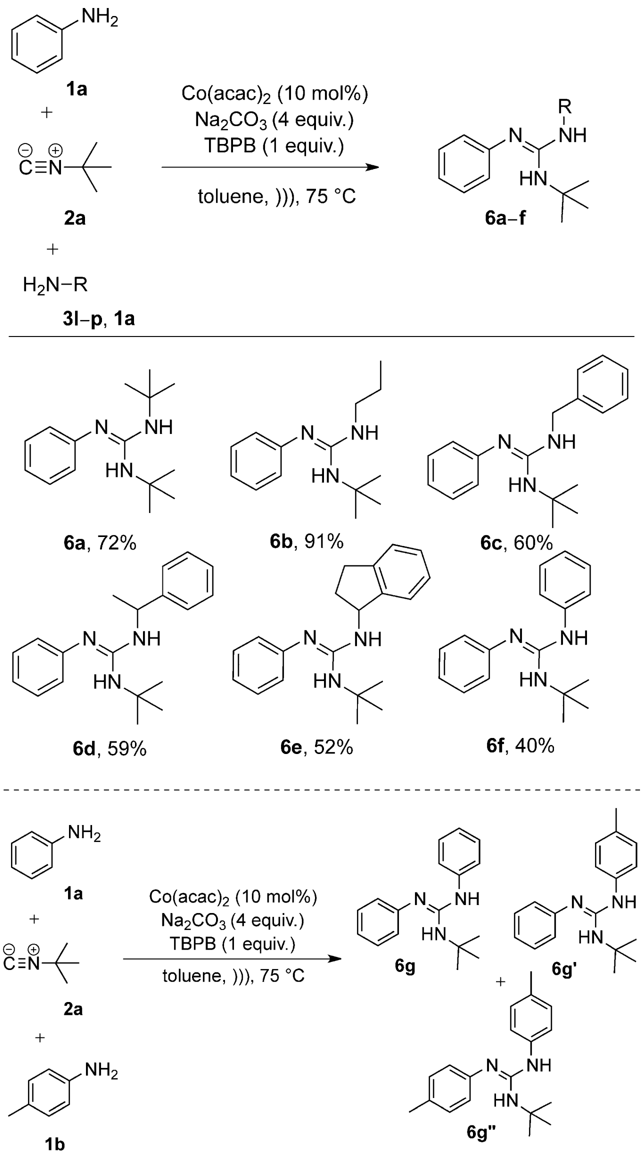
guanidines could be formed by an intermolecular metal-catalzyed isocyanide insertion with two nucleophiles such as two amines *via* intermolecular trapping of the insertion coupling intermediates (Scheme 1, b). Guanidines are ubiquitous structural features found in amino acids, natural products, and pharmaceuticals.[9] They also serve as valuable reagents, intermediates and organocatalysts in organic synthesis.[10] To the best of our knowledge, transition metal-catalyzed reactions to construct open-chain guanidines are rare.[11] Herein, we report a new simple and chemoselective cobalt-catalyzed synthesis of open-chain guanidines employing aromatic amines, aliphatic amines and isocyanides as substrates.

Disappointingly, preliminary attempts towards isocyanide insertion with two amines under Orru's palladium-catalyzed conditions[7] were unsuccessful. Therefore, we studied the reaction of aniline **1a**, *tert*-butyl isocyanide **2a**, and piperidine **3a** (2 equiv.) under the identical reaction conditions as previous reported for the construction of aminobenzimidazoles.[8] Fortunately, when TBHP was used as the oxidant instead of $K_2S_2O_8$, the guanidine product **4a′** was formed in 2% GC yield under conventional heating conditions at 100 °C for 20 h (Table 1, entry 1). To our delight, **4a′** could be formed in 6% GC yield under ultrasonic irradiation condition at 75 °C for 1 hour (Table 1, entry 2). Cobalt salt screening indicated that $Co(acac)_2$ was a suitable catalyst for this reaction (Table 1, entries 2–6). Subsequently, other oxidants were screened for this reaction. TBPB showed the best activity and the yield of **4a′** was increased to 30% GC yield (Table 1, entry 7). Then, the effects of various bases were investigated. The results indicated that the base was critical to the success of reaction (Table 1, entries 13–23). Only 26% and 23% GC yields of **4a′** were obtained when the organic bases NEt_3 and DABCO were used, respectively (Table 1, entries 22 and 23). The best result was obtained when Na_2CO_3 was utilized as the base, affording **4a′** in 40% GC yield (Table 1, entry 17). Other bases were not very good for this transformation. When the amount of Na_2CO_3 was increased to 4 equiv., the GC yield of **4a′** was increased to 40% (Table 1, entry 24). Next, we focused on the effects of solvents and the reaction time. It was found that the optimal reaction conditions comprise $Co(acac)_2$ (10 mol%), Na_2CO_3 (4 equiv.), TBPB (1 equiv.) in toluene under ultrasound irradiation at 75 °C and **4a′** could be formed in 87% GC yield (Table 1, entry 26). In order to facilitate isolation of the guanidine product, its corresponding hydrochloride **4a** was obtained using dry HCl in ethyl acetate.

With the optimized conditions in hand, the scope of this reaction was investigated and the results are summarized in Table 2. We first evaluated a range of aromatic amines and were able to introduce a variety of electron-donating substituents under the optimized conditions. The substituted anilines (**1b–j**) reacted well with *tert*-butyl isocyanide **2a** and piperidine **3a** (Table 2, entries 2–10), affording the desired hydrochloride products **4b–j** in moderate to excellent yields (51–80%). However, with anilines bearing electron-withdrawing groups (NO_2 and CN), the yields of desired products dropped to 21% and 39% (Table 2, entries 11 and 12). In addition, good yields were obtained when 4-chloroaniline and 4-bromoaniline were used, and the desired products were achieved in 73% and 75% yields, respectively (Table 2, entries 13 and 14). The position of the substituents on the phenyl ring of the anilines affected the reaction yield only



Scheme 3. Cobalt-catalyzed insertion reactions of *tert*-butyl isocyanide **2a** with *para*-toluidine **1b** and other secondary amines **3b–k**. *Reaction conditions: para*-toluidine **1b** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.6 mmol), secondary amines **3b–k** (1 mmol), $Co(acac)_2$ (10 mol%), Na_2CO_3 (4 equiv.), TBPB (1 equiv.), toluene (3 mL), 75 °C, under ultrasound irradiation 5 h. Isolated yields are given.

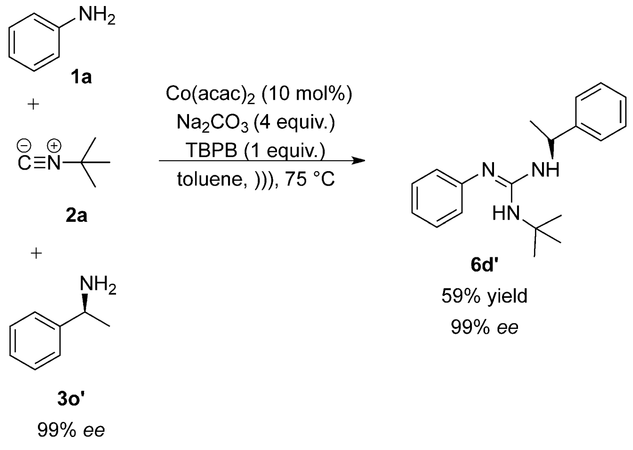


Scheme 4. Cobalt-catalyzed insertion reactions of *tert*-butyl isocyanide **2a** with aniline **1a** and other primary amines **3l–p**. *Reaction conditions:* aniline **1a** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.6 mmol), primary amines **3l–p** (1 mmol), Co(acac)$_2$ (10 mol%), Na$_2$CO$_3$ (4 equiv.), TBPB (1 equiv.), toluene (3 mL), 75 °C, under ultrasound irradiation 5 h. Isolated yields are given.

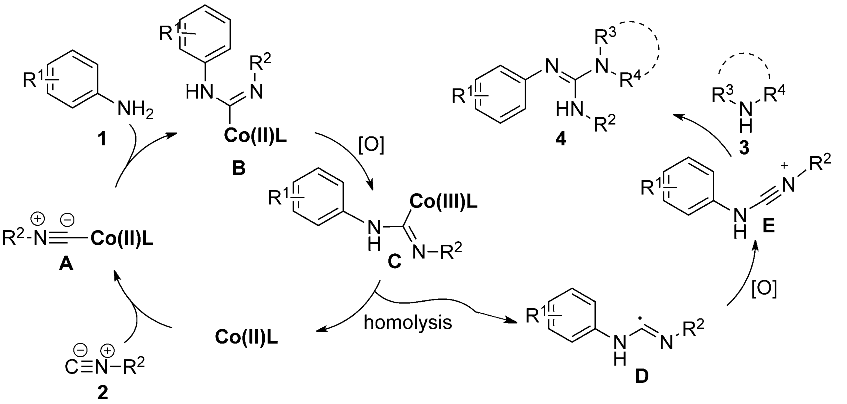
slightly. Good yields were obtained when *meta*-toluidine **1c**, *ortho*-toluidine **1d**, and 2,4-dimethylaniline **1e** were used as starting materials (entries 3, 4, 5). Moreover, a heterocyclic aromatic amine (pyridin-3-amine **1o**) could offer the desired product **4o** in 46% yield (Table 2, entry 15). Then, several structurally varied isocyanides were also explored. When the isocyanides **2b** and **2c** were applied to the reaction, the reactions also proceeded smoothly, which led to the guanidines **4p** and **4q** in 71% and 49% yields, respectively (Table 2, entries 16 and 17). Unfortunately, when aliphatic amines were subjected to the reaction, only traces of the desired products were detected (Table 2, entries 18 and 19). We tried to subject 2-isocyano-1,3-dimethylbenzene **2d** to the reaction with **1b** under identical conditions. However, the reaction was messy (Table 2, entry 20).

To further explore the scope of the reaction, various secondary amines were employed to react with *para*-toluidine **1b** and *tert*-butyl isocyanide **2a** under the optimized conditions (Scheme 3). When morpholine **3b**, pyrrolidine **3c**, diethylamine **3d**, *N*-methyl-1-phenylmethanamine **3e**, and 1,2,3,4-tetrahydroisoquinoline **3f** were subjected to the reactions, the desired guanidine salts **5a–e** were obtained in moderate yields (37–64%). The reactions of substituted pyrrolidines such as **3g** could also proceed well to give the desired guanidine **5f** in 49% yield. However, sterically hindered secondary amines, for example, 2,2,6,6-tetramethylpiperidine **3h** and diisopropylamine **3i**, proved to be ineffective reagents for this kind of transformation. Some other secondary amines, such as 1,2,3,4-tetrahydroquinoline **3j** and diphenylamine **3k** also could not offer the desired products.

Then, we explored the reactions of primary amines instead of secondary amines under the optimized conditions and the results are summarized in Scheme 4. A series of primary amines including butylamine **3l**, propylamine **3m**, phenylmethanamine **3n**, 1-phenylethanamine **3o**, and 2,3-dihydro-*1H*-inden-1-amine **3p** were well tolerated under the optimal reaction conditions, and the desired guanidine products were obtained in moderate to excellent yields (52–91%, Scheme 4). When we only added aniline **1a** (1 mmol) with *tert*-butyl isocyanide under the optimized condition, we could obtain the guanidine product **6f** in 40% yield. But when a mixture of aniline **1a** and *para*-toluidine **1b** was applied to the reaction with *tert*-butyl isocyanide **2a** three guanidines **6g**, **6g′**, **6g″** could be detected (Scheme 4).



Scheme 5. Cobalt-catalyzed synthesis of a chiral guanidine from **1a** with **2a** and **3o′**.



Scheme 6. The proposed mechanism.

To expand the application of our method, we have tried the reaction of **1a** with **2a** and **3o′** under identical conditions. To our delight, the desired product was furnished without loss of enantioselectivity (Scheme 5).

Based on the literature reports[8,12–15] and the above results, a plausible mechanism is proposed in Scheme 6. First, the Co(II) salt may react with isocyanide **2** to give Co(II) complex **A**. Aromatic amine **1** then reacts with the Co(II) complex **A** to give a more stable Co(II) carbene complex **B** than an aliphatic amine does, even piperidine is more nucleophilic than aniline. Co(II) complex **B** can be easily oxidized and results in cobalt(III) complex **C**. Complex **C** undergoes hemolysis to afford the active imidoyl radical **D** and the catalyst Co(II) salt to complete the catalytic cycle. Then, nitrilium intermediate **E** is formed by the oxidation of **D**. Finally, **E** is trapped by amine **3** and isomerization, affording the corresponding guanidines **4**.

In conclusion, a novel and efficient cobalt-catalyzed oxidative isocyanide insertion with amines *via* two C–N bond formation reactions has been developed. This protocol provides a simple, clean and general way to create guanidines or their corresponding hydrochlorides from simple starting materials under ultrasonic conditions. Further studies to understand the cobalt-catalyzed insertion reaction mechanism and to extend this protocol to synthetic applications such as the synthesis of optically pure guanidines for organocatalysis are ongoing in our laboratory.

Experimental Section

General Procedure

To a mixture of aniline (0.5 mmol), isocyanide (0.6 mmol), secondary or primary amine (1 mmol), Co(acac)$_2$ (10 mol%), Na_2CO_3 (4 equiv., 2 mmol), and TBPB (0.5 mmol, 100 μL), were added 3 mL in toluene (3 mL). The system was irradiated by ultrasound for an appropriate time at 75 °C for 5 h (checked by TLC, if it does not show cleanly, immerse it in $KMnO_4$ developer), then cooled to room temperature. When the reaction used a secondary amine, the mixture was poured into ice/water (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (30 mL), and dried over Na_2SO_4. Then the solvent was evaporated under the reduced pressure. The residue was dissolved in dry ethyl acetate, then exposed to dry hydrogen chloride gas for 0.5–1 hour and the resulting solid was filtered off. Alternatively, the mixture was evaporated under the reduced pressure directly. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as eluents to afford the pure product. When the reaction used a primary amine, the mixture was evaporated under reduced pressure directly. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as eluents to afford the pure product.

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Cobalt-Catalyzed Intermolecular Oxidative Isocyanide Insertion with Two Amines: An Approach to Guanidines

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