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Cobalt(II)-Catalyzed Isocyanide Insertion Reaction with Amines under Ultrasonic Conditions: A Divergent Synthesis of Ureas, Thioureas and Azaheterocycles

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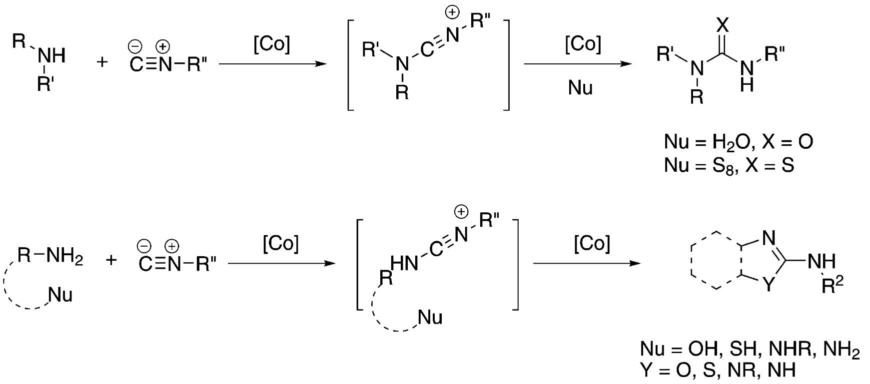
Abstract: Cobalt(II) acetylacetonate-catalyzed isocyanide insertion reactions with amines utilizing *tert*-butyl hydroperoxide (TBHP) as an oxidant under ultrasound conditions have been developed, which lead to the synthesis of ureas, thioureas, as well as 2-aminobenzimidazoles, 2-aminobenzothiazoles, and 2-aminobenzoxazoles under the general reaction conditions in up to 96% yields, respectively. The intermediate amino methylidyneaminiums, initiated by cobalt(II) acetylacetonate-catalyzed reactions of isocyanides with amines, could be easily trapped by different nucleophiles such as water, sulfur, and intramolecular nucleophilic functional groups. This method provides a simple, general and practical protocol for the divergent synthesis of ureas, thioureas and azaheterocycles.

Keywords: cobalt(II) catalyst; isocyanides; thioureas; ultrasound; ureas

Introduction

N,*N*′-Disubstituted urea derivatives have attracted a great deal of attention due to their applications in agrochemicals, dyes, antioxidants and HIV inhibitors.[1–3] In addition, they are also used as organocatalysts and precursors for organic synthesis.[4] *N*,*N*′-Disubstituted thioureas are structurally similar to ureas, but show significantly different properties. They are also widely applied in organic chemistry, medicinal chemistry, as well as materials chemistry.[5] 2-Aminobenzoxazoles, 2-aminobenzothiazoles, and 2-aminobenzimidazoles are essential components in numerous potent biologically active compounds and natural products.[6] Typically, ureas and thioureas are prepared from isocyanates or isothiocyanates, which are generated with the requirement of difficult-to-access precursors and/or hazardous agents such as phosgene and azides. Recently, transition metal-catalyzed cross-coupling reactions allowed for the synthesis of ureas.[7] Guan's group reported a palladium-catalyzed coupling reaction of aromatic amines with CO for the synthesis of symmetrical ureas.[8] Buchwald provided an efficient protocol for construction of unsymmetrical ureas *via* palladium-catalyzed cross-coupling reactions of aryl chlorides and triflates with sodium cyanate.[9] Although many approaches toward thioureas as well as 2-aminobenzoxazoles, 2-aminobenzothiazoles, and 2-aminobenzimidazoles have also been well studied, general and versatile methodologies to prepare ureas, thioureas and azaheterocycles using readily accessible starting materials under mild conditions are still desirable.

Reactions involving isocyanides have received considerable attention, of which the major focus is on the well-known Ugi reactions.[10,11] Recently, palladium-catalyzed isocyanide insertion (similar to carbon monoxide insertion) reactions have become increasingly popular.[12] In addition, since Kharasch's[13] pioneering works on the homocoupling reactions of Grignard reagents, cobalt catalysts, which are widely available, not expensive, and have low toxicity, have received particular attention.[14–17] As a continuation of our work on the insertion of isocyanides into active N−H bonds under ultrasound irradiation,[18] herein, we hoped to apply this insertion strategy to construct of ureas, thioureas, 2-aminobenzoxazoles, 2-aminobenzothiazoles, and 2-aminobenzimidazoles[19] by trapping



Scheme 1. The direct strategy for synthesis *via* isocyanide insertion.

the insertion coupling intermediates of isocyanides with amines.

Our current study has focused on the cobalt(II) acetate-catalyzed isocyanide insertion to amine-based bisnucleophiles directed towards the formation of 2-aminobenzoxazoles, 2-aminobenzothiazoles, and 2-aminobenzimidazoles.[19] This article is a full account of the Co(II)-catalyzed isocyanide insertion reaction with amines under ultrasound conditions as a general strategy to the synthesis of ureas, thioureas and aza-heterocycles (Scheme 1), where we disclose (i) the Co(II)-catalyzed synthesis of ureas from isocyanides with amines in the presence of water; (ii) the Co(II)-catalyzed synthesis of thioureas from isocyanides with amines in the presence of sublimed sulfur; (iii) the Co(II)-catalyzed synthesis of 2-aminobenzoxazoles from isocyanides with 2-aminophenols; (iv) the Co(II)-catalyzed synthesis of 2-aminobenzimidazoles and 2-aminobenzimidazoles from isocyanides with 2-aminoanilines and 2-aminobenzenethiol.

Results and Discussion

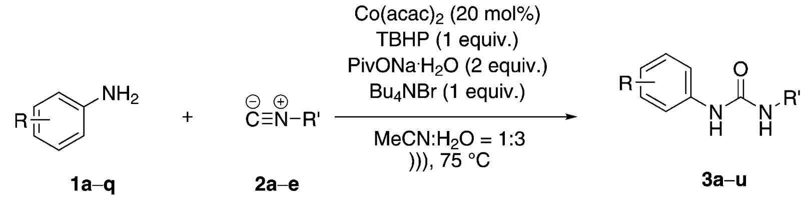
Our initial studies focused on developing a more efficient catalytic system by investigating isocyanide insertion reactions and we used the reaction of aniline **1a** and *tert*-butyl isocyanide **2a** as a model system. After optimization of the reaction conditions (see the Supporting Information and Table 1 for details), it was found that the optimal reaction conditions consist of Co(acac)$_2$(20 mol%), PivONa·H_2O (2 equiv.), TBHP (1 equiv.) and Bu_4NBr (1 equiv.) in the solvent MeCN: $H_2O = 1{:}3$ under ultrasound irradiation at 75 °C (HPLC yield 86%). However, when we used the same conditions under the regular heating, even if the reaction was prolonged to let it work better, the result was unsatisfactory (for details see the Supporting Information), and the system was messy. This result indicated that ultrasound irradiation could make the reaction run more efficiently.

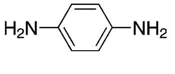
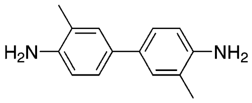
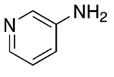
With the optimized conditions in hand, the scope of this reaction was investigated and the results are summarized in Table 1. Wide ranges of anilines and isocyanides were employed as substrates. The substituted anilines (**1b–n**) reacted well with *tert*-butyl or cyclohexyl isocyanide **2a** or **2b** (Table 1, entries 2–20), giving the desired products **3b–r** in moderate to excellent yields. It is noteworthy that anilines bearing electron-donating groups (Me, OMe, OBn, OH, NH_2) could offer the desired products in good yields. However, when anilines bearing electron-withdrawing groups (NO_2 or COMe) were used, no desired product was observed (Table 1, entries 21and 22). Furthermore, relatively bulky substrates such as **1d**, **1e**, **1f** and **1j** also efficiently underwent the transformation, generating the desired products **3d**, **3e**, **3f**, and **3j** in 64%, 48%, 75% and 62% yields, respectively (Table 1, entries 4, 5, 6, and 10). Then, several structurally varied isocyanides were also investigated. When other aliphatic and aromatic isocyanides (**2b–e**) were employed, the reactions also proceeded smoothly in moderate yields (52%–93%) (Table 1, entries 15–18). However, the reaction of pyridin-3-amine **3q** could not furnish the desired product (Table 1, entry 23).

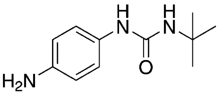
To evaluate the general performance of our method, we further explored the reactions of other amines. The results are listed in Table 2. Aliphatic primary amines such as tryptamine **4a**, 1-phenylethanamine **4b**, and amino acid methyl esters **4c**, **4d**, **4e** were investigated with *tert*-butyl isocyanide **2a** under the optimal conditions, which afforded the corresponding products **4aa–ea** in up to 96% yields (Table 2). In addition, secondary amines **5a–d** could also provide moderate to excellent yields except for diphenylamine **5e**.

Interestingly, the reaction of the *tert*-butyl isocyanide **2a** with enantiopure amine (*S*)-**4b** or (*R*)-**4b** produced enantiopure carboxamides (*S*)-(+)-**4ba** and (*R*)-(−)-**4ba**, respectively, in good yields with retention of the chiral configuration (Scheme 2). These re-

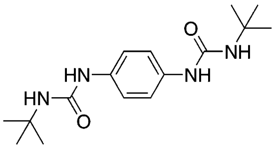
Table 1. Cobalt-catalyzed insertion reactions of isocyanides **2a–e** with substituted anilines **1a–n**.[a]



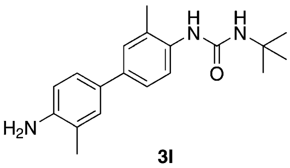
Entry	1		2		Yield of Product [%][b]	
1	**1a**	R = H	**2a**	R′ = *t*-Bu	**3a**	85
2	**1b**	R = 4-Me	**2a**		**3b**	96
3	**1c**	R = 3-Me	**2a**		**3c**	88
4	**1d**	R = 2-Me	**2a**		**3d**	64
5	**1e**	R = 2-Et	**2a**		**3e**	48
6	**1f**	R = 2-Me, 4-Me	**2a**		**3f**	75
7	**1g**	R = 4-OMe	**2a**		**3g**	96
8	**1h**	R = 4-OBn	**2a**		**3h**	73
9	**1i**	R = 4-OH	**2a**		**3i**	76
10	**1j**	R = 4-OH, 2-Me	**2a**		**3j**	62
11	**1k**	 1k	**2a**		**3k**	34
12	**1k**		**2a**		**3k’**	43
13	**1l**	 1l	**2a**		**3l**	39
14	**1l**		**2a**		**3l’**	9
15	**1b**		**2b**	R′ = Cy	**3m**	89
16	**1b**		**2c**	R′ = *n*-Bu	**3n**	63
17	**1b**		**2d**	R′ = 2,6-$Me_2C_6H_3$	**3o**	52
18	**1b**		**2e**	R′ = Bn	**3p**	93
19	**1m**	R = 4-Cl	**2b**		**3q**	46
20	**1n**	R = 4-Br	**2b**		**3r**	41
21	**1o**	R = 4-NO_2	**2a**		**3s**	trace
22	**1p**	R = 4-COMe	**2a**		**3t**	trace
23	**1q**	 1q	**2a**		**3u**	trace



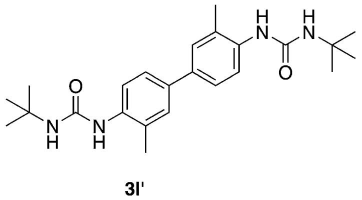
3k



3k'



3l



3l'

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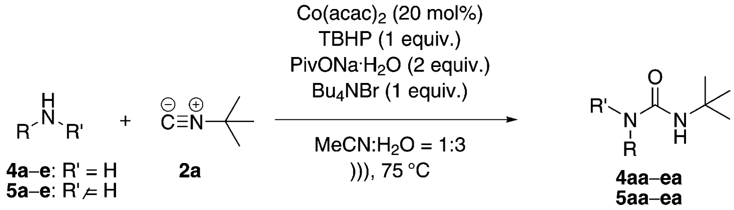
[a] *Reaction conditions:* anilines **1a–q** (0.5 mmol), isocyanides **2a–e** (0.6 mmol), $Co(acac)_2$ (20 mol%), PivONa·H_2O (2 equiv.), TBHP (1 equiv.), Bn_4NBr (1 equiv.), solvent (3 mL), 75 °C, under ultrasound irradiation for 1 h.

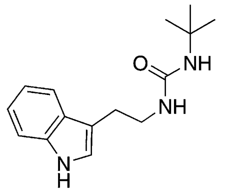
[b] Isolated yield.

sults show that the cobalt-catalyzed isocyanide insertion reactions are also applicable for the preparation of chiral ureas from chiral substrates.

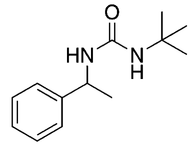
As it is well-known, sulfur is a good nucleophile the same as water. So, we reasoned that thioureas could be formed by a similar strategy. Then, we further explored the Co(II)-catalyzed isocyanide insertion with amines in the presence of sublimed sulfur instead of water (Table 3). As expected, thiourea **6a** could be obtained by the model reaction of aniline **1a**, *tert*-butyl isocyanide **2a** and sulfur under the ultrasound conditions. Fortunately, after the further optimization of reaction conditions (see the Supporting Information and Table 2 for details), it was found that the best reaction conditions comprise $Co(acac)_2$ (20 mol%), Na_2CO_3 (2 equiv.), and TBHP (1 equiv.) in the 1,4-dioxane under ultrasound irradiation at

Table 2. Cobalt-catalyzed isocyanide insertion reactions with other amines **4** and **5**.[a,b]

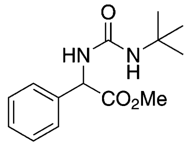




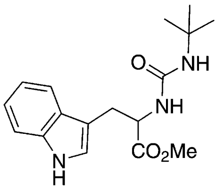
4aa, 96%



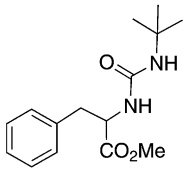
4ba, 96%



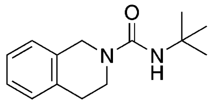
4ca, 79%



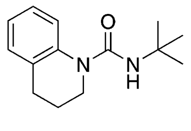
4da, 86%



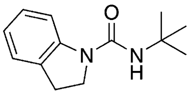
4ea, 81%



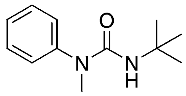
5aa, 95%



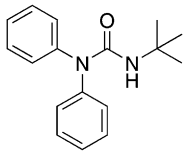
5ba, 54%



5ca, 96%



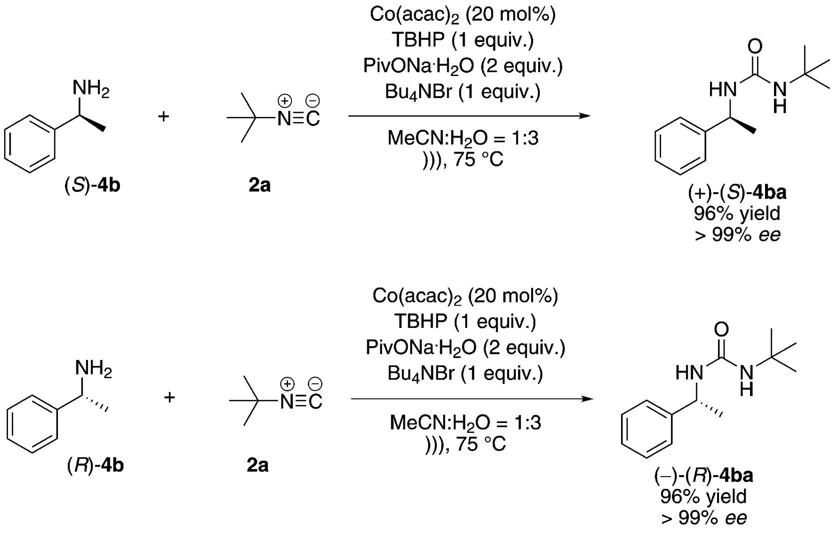
5da,51%



5ea, 0%

[a] *Reaction conditions:* amine **4** or **5** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.6 mmol), Co(acac)$_2$ (20 mol%), PivONa·H$_2$O (2 equiv.), TBHP (1 equiv.), Bn$_4$NBr (1 equiv.), solvent (3 mL), 75 °C, under ultrasound irradiation fo 1 h.

[b] Isolated yield.

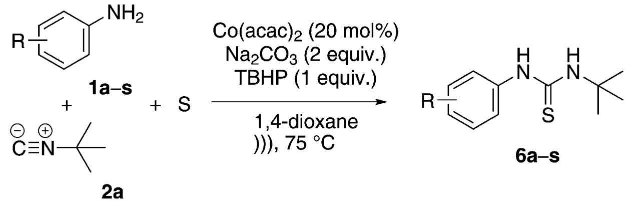


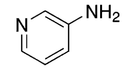
Scheme 2. Cobalt-catalyzed synthesis of chiral amides.

75 °C. It could produce 1-*tert*-butyl-3-phenylthiourea **6a** in 53% isolated yield (61% LC yield).

With these promising conditions in hand, we investigated the scope of this reaction. As shown in Table 3, different anilines **1a–s** were applied to the reaction under the optimal conditions. It was found that the functional group on the phenyl ring had a great effect on this isocyanide insertion reaction. The reactions of *tert*-butyl isocyanide **2a** and sulfur with substituted aromatic amines bearing electron-donating

Table 3. Cobalt-catalyzed insertion reactions of *tert*-butyl isocyanides **2a** with substituted anilines **1a–s**.[a]



Entry	Ar-NH$_2$		Yield [%]	
1	**1a**	R = H	**6a**	53
2	**1b**	R = 4-Me	**6b**	45
3	**1c**	R = 3-Me	**6c**	40
4	**1d**	R = 2-Me	**6d**	36
5	**1e**	R = 2-Et	**6e**	46
6	**1r**	R = 4-Et	**6r**	45
7	**1f**	R = 2-Me, 4-Me	**6f**	31
8	**1g**	R = 4-OMe	**6g**	44
9	**1s**	R = 4-OEt	**6s**	42
10	**1m**	R = 4-Cl	**6m**	37
11	**1o**	R = 4-NO2	**6o**	trace
12	**1p**	R = 4-COMe	**6p**	trace
13	**1q**		**6q**	trace

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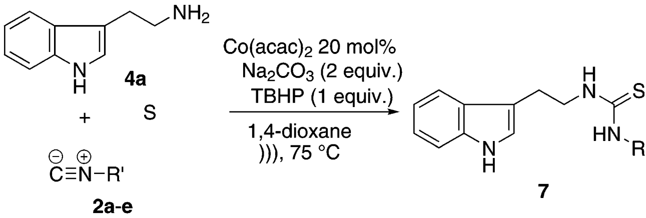
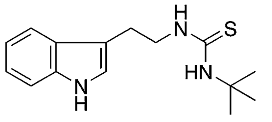
[a] *Reaction conditions:* anilines **1a–s** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.6 mmol), and sublimed sulfur (2 equiv.) Co(acac)$_2$ (20 mol%), Na$_2$CO$_3$ (2 equiv.), TBHP (1 equiv.), 1,4-dioxane (3 mL), 75 °C, under ultrasound irradiation for 1 h.

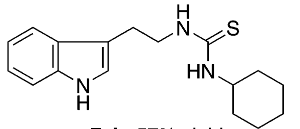
[b] Isolated yield.

Table 4. Cobalt-catalyzed insertion reactions of isocyanides **2a–e** with tryptamine **4a**.[a,b]

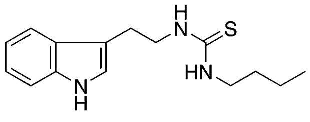




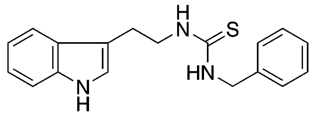
7aa, 67% yield



7ab, 57% yield



7ac, 53% yield



7ae, 65% yield

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[a] *Reaction conditions:* tryptamine **4a** (0.5 mmol), isocyanides **2a–e** (0.6 mmol), Co(acac)$_2$ (20 mol%), Na$_2$CO$_3$ (2 equiv.), TBHP (1 equiv.), 1,4-dioxane (3 mL), 75 °C, under ultrasound irradiation for 1 h.

[b] Isolated yield.

groups such as methyl, ethyl, methoxy, ethoxy could also furnish the desired products in 36%–53% yields (Table 3, entries 1–9). Unfortunately, when substituted aromatic amines such as **1o** and **1p** with electron-withdrawing groups or pyridin-3-amine **6q** were subjected to the reaction under the identical codntions, no desired product was observed (Table 3, entries 11–13). Relatively bulky substrates such as **1d**, **1e**, and **1f** also efficiently underwent the transformation, affording the desired products **6d**, **6e**, and **6f** in 36%, 46%, and 31% yields, respectively (Table 2, entries 4, 5, and 7).

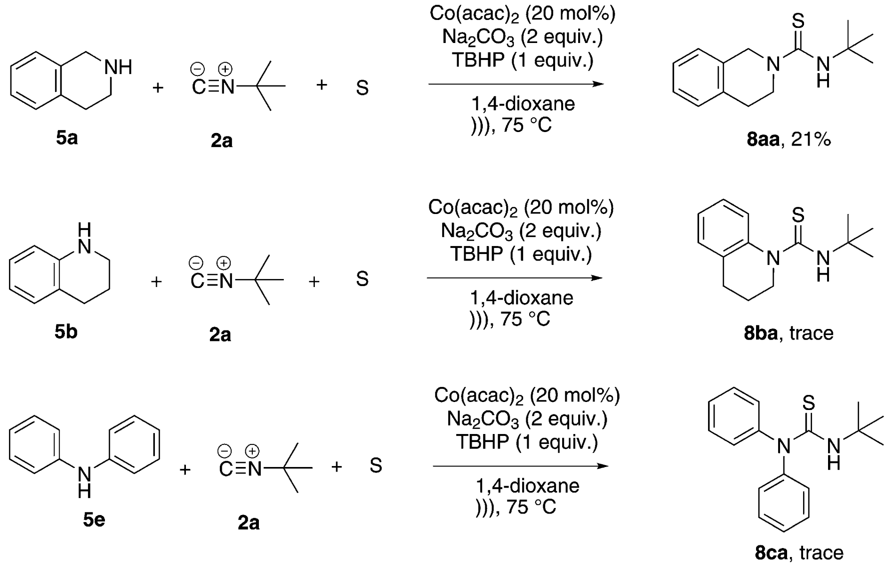
Subsequently, we explored the reactions of the aliphatic amine tryptamine **4a** and different isocyanides with sulfur. To our delight, the desired thiourea product **7aa** could be obtained in 67% yield (Table 4). We further investigated the scope of isocyanides and the generality of the method. When isocyanides **2b–e** were applied to the reaction, the thioureas **7ab–ae** could also be obtained in 53%–65% yields.

Then, we studied the effects of secondary amines on the reaction. The reaction of 1,2,3,4-tetrahydroisoquinoline **5a** could also lead to the desired thiourea **8aa** in 21% yield. When 1,2,3,4-tetrahydroquinoline **5b** was subjected to the reaction, no thiourea product was formed. The reaction of diphenylamine **5e** could not afford the desired product **5ea** (Scheme 3).

Recently, we reported a protocol using the cobalt-catalyzed oxidative isocyanide insertion to amine-based bis-nucleophiles to synthetize substituted 2-aminobenzimidazoles, 2-aminobenzothiazoles, and 2-aminobenzoxazoles.[19] However, that method needed longer times at high temperature. It would be more efficient if the cobalt-catalyzed oxidative isocyanide insertion to amine-based bis-nucleophiles could be achieved under ultrasonic conditions.

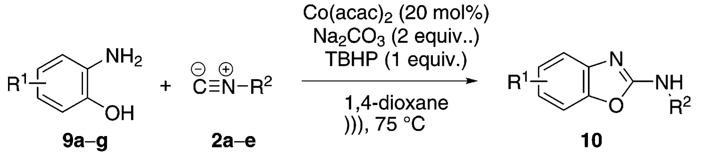
Fortunately, the reaction of **9a** and **2a** under the above-optimized conditions [Co(acac)$_2$ (20 mol%), Na$_2$CO$_3$ (2 equiv.), and TBHP (1 equiv.) in the 1,4-dioxane under ultrasound irradiation at 75 °C for 1 h] could proceed well to give the desired product **10a** in 77% yield. Subsequently, 2-aminophenols **9a–g** and isocyanides **2a–e** were investigated for this reaction and the results are summarized in Table 5. It was found that the substituted 2-aminophenols **9a–g** performed well with *tert*-butyl isocyanide **2a** (Table 5, entries 1–7), affording the desired products 2-aminobenzoxazoles **10a–g** in moderate to good yields (54%–84%). When isocyanides **2b–e** were subjected to the reactions with **9a**, **10h–k** could also be realized in 25%–56% yields (Table 5, entries 8–11).

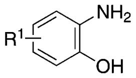
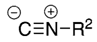
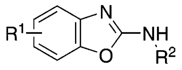
In addition, our protocol could also be applied to the synthesis of 2-aminobenzothiazoles and 2-aminobenzimidazoles from isocyanides. As shown in



Scheme 3. Cobalt-catalyzed insertion reactions of *tert*-butyl isocyanides **2a** with secondary amines **5a**, **5b** and **5e**.

Table 5. Co(II)-catalyzed insertion reactions of isocyanides **2a–e** with substituted 2-aminophenols **9a–g**.[a]



Entry	9 		2 		Product 	Yield [%][b]
1	**9a**	$R^1=H$	$R^2=t\text{-Bu}$	**2a**	**10a**	77
2	**9b**	$R^1=5\text{-NO}_2$	$R^2=t\text{-Bu}$	**2a**	**10b**	74
3	**9c**	$R^1=4\text{-NO}_2$	$R^2=t\text{-Bu}$	**2a**	**10c**	54
4	**9d**	$R^1=3\text{-NO}_2$	$R^2=t\text{-Bu}$	**2a**	**10d**	77
5	**9e**	$R^1=4\text{-Cl}$	$R^2=t\text{-Bu}$	**2a**	**10e**	84
6	**9f**	$R^1=5\text{-CH}_3$	$R^2=t\text{-Bu}$	**2a**	**10f**	61
7	**9g**	$R^1=4\text{-OCH}_3$	$R^2=t\text{-Bu}$	**2a**	**10g**	81
8	**9a**	$R^1=H$	$R^2=\text{Cy}$	**2b**	**10h**	56
9	**9a**	$R^1=H$	$R^2=n\text{-Bu}$	**2c**	**10i**	50
10	**9a**	$R^1=H$	$R^2=2,6\text{-Me}_2\text{C6H}_3$	**2d**	**10j**	31
11	**9a**	$R^1=H$	$R^2=\text{Bn}$	**2e**	**10k**	25

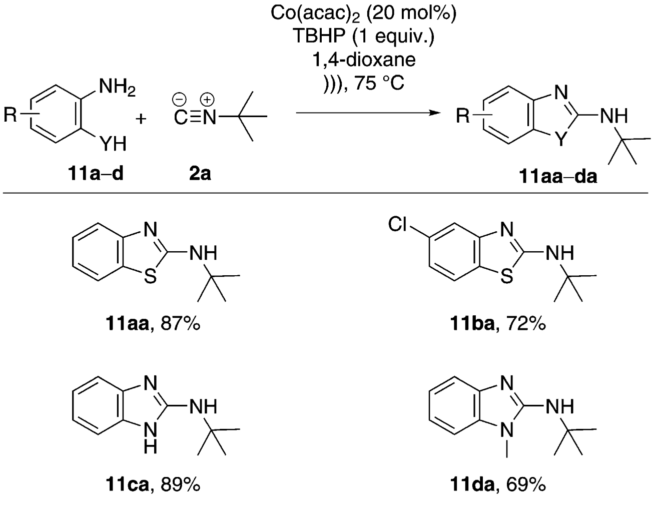
[a] *Reaction conditions:* 2-aminophenols **9a–g** (0.5 mmol), isocyanides **2a–e** (0.6 mmol), $Co(acac)_2$ (20 mol%), Na_2CO_3 (2 equiv.). TBHP (1 equiv.), 1,4-dioxane (3 mL), 75 °C, under ultrasound irradiation for 1 h.

[b] Isolated yield.

Table 6, the reactions of some other bis-nucleophiles **11a–d** with *tert*-butyl isocyanide **2a** under the optimal conditions. proceeded smoothly to furnish the desired products in 69%–89% yields.

Based on the above results and the chemistry of isonitriles, a plausible mechanism was proposed as shown in Scheme 4. $Co(acac)_2$ could easy react with isonitrile to give the cobalt(II)-isonitrile complex **A**, followed by coordination with another isonitrile to furnish cobalt(II)-isonitrile complex **B**. After addition of amine to the cobalt(II)-isonitrile complex **B** under basic conditions, cobalt(II)-isonitrile carbene complex **C** is formed followed by oxidation by the *tert*-butoxide radical originating from the decomposition of TBHP[20] to give cobalt(III) carbene complex **D**. The radical intermediate **E** is formed from compelx **D** with the regeneration of complex **A**. Then, the amino methylidyne aminium intermediate **F** is formed *via* an

Table 6. Cobalt-catalyzed insertion reactions of isocyanide **2a** with bisnucleophiles **11a–d**.[a,b]



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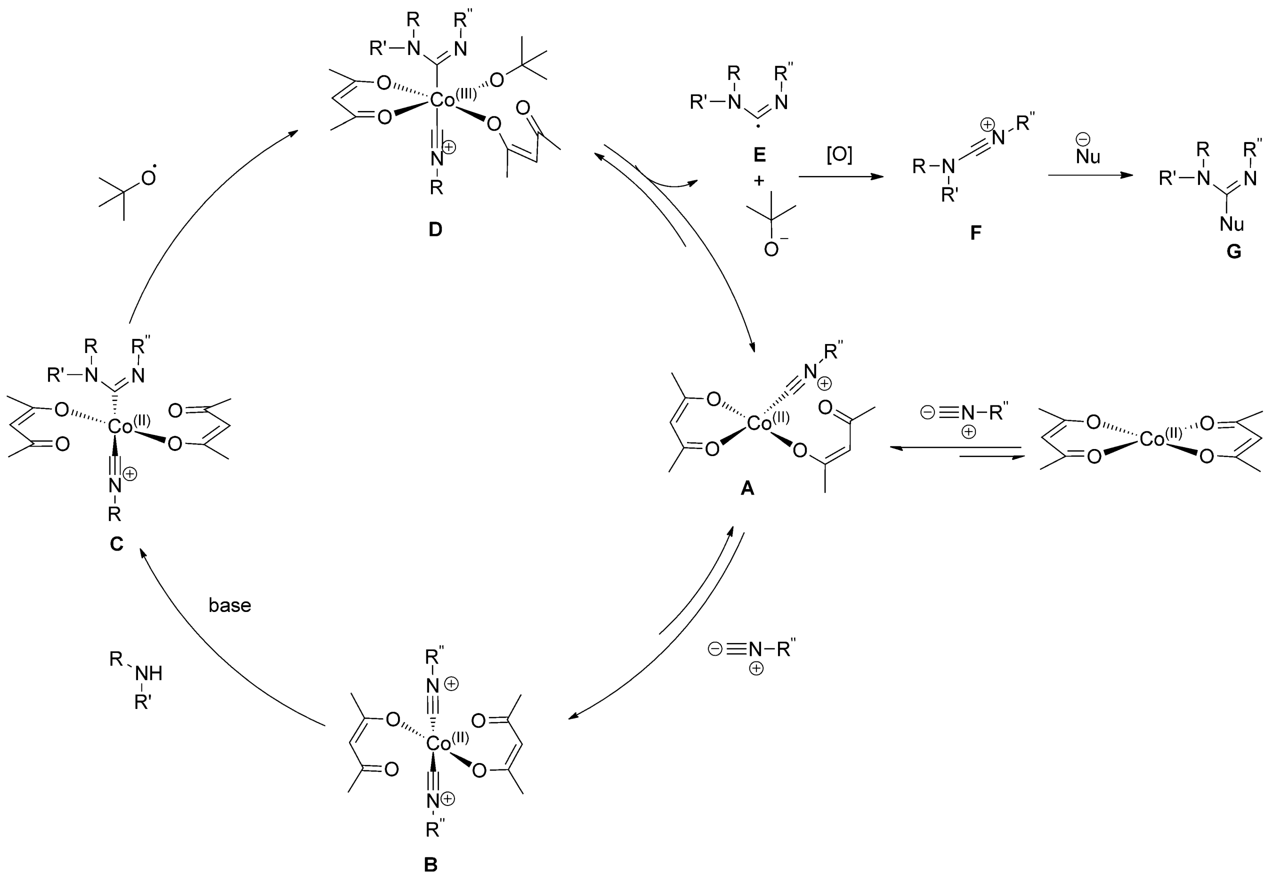
[a] *Reaction conditions:* **11a–d** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.6 mmol), Co(acac)$_2$ (20 mol%), Na_2CO_3 (2 equiv.), TBHP (1 equiv.), 1,4-dioxane (3 mL), 75 °C, under ultrasound irradiation for 1 h.

[b] Isolated yield.

SET process and subsequently attacked by nucleophiles to give intermediate **G**, followed by isomerization to give the target molecules.[21]

Conclusions

In conclusion, the cobalt(II) acetylacetonate-catalyzed isocyanide insertion to form amino methylidyneaminiums utilizing various readily available isocyanides with amines under ultrasound conditions has been developed. Amino methylidyneaminiums were successfully applied as an important and general intermediate to be trapped by water, sulfur or intramolecular nucleophilic functional groups to construct the corresponding ureas, thioureas as well as to prepare of 2-aminobenzimidazoles, 2-aminobenzothiazoles, and 2-aminobenzoxazoles. This method not only expands the scope of cobalt-catalyzed cross-coupling reactions, but also provides a novel, extensive, efficient and diverse approach leading to valuable products. Further studies to understand the cobalt-catalyzed insertion reaction mechanism and to extend this strategy to other synthetic applications are ongoing in our laboratory.



Scheme 4. Proposed mechanism.

Experimental Section

Typical Experimental Procedure (Urea 3a)

To a mixture of aniline **1a** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.6 mmol), Co(acac)$_2$ (20 mol%), PivONa·H$_2$O (2 equiv., 1 mmol), TBHP (70%, 0.5 mmol, 72 μL), and Bu$_4$NBr (0.5 mmol) were added 3 mL of mixed solvent acetonitrile: H$_2$O = 1:3. The system was irradiated by ultrasound for an appropriate time at 75 °C (for 1 h; checked by TLC, if it does not show clearly, please immerse it into KMnO$_4$ developer). Then the reaction mixture was cooled to room temperature, and poured into ice/water (20 mL). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic layers were washed with brine (30 mL), and dried over Na$_2$SO$_4$. Then the solvent was evaporated under the reduced pressure. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as eluents to afford pure product.

Typical Experimental Procedure (Thiourea 6a)

To a mixture of aniline **1a** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.6 mmol), sublimed sulfur (2 equiv., 1 mmol), Co(acac)$_2$ (20 mol%), Na$_2$CO$_3$ (2 equiv., 1 mmol), and TBHP (70%, 0.5 mmol, 72 μL), were added 3 mL 1,4-dioxane. The system was irradiated by ultrasound for an appropriate time at 75 °C (for 1 h; checked by TLC). Then the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as eluents to afford pure product.

Typical Experimental Procedure (2-Aminobenzoxazole 10a)

To a mixture of 2-aminophenol **9a** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.6 mmol), Co(acac)$_2$ (20 mol%), Na$_2$CO$_3$ (2 equiv., 1 mmol), and TBHP (70%, 0.5 mmol, 72 μL), were added 3 mL 1,4-dioxane. The system was irradiated by ultrasound for an appropriate time at 75 °C (for 1 h; checked by TLC). Then the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as eluents to afford pure product.

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