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A General and Efficient Copper Catalyst for the Double Carbonylation Reaction

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ABSTRACT

The use of (NHC)CuI complex in combination with a N-heterocyclic carbene precursor as catalyst for the double carbonylation of aryl Iodides and secondary amines solves the problem of using the precious metal Pd and phosphine ligands. The new protocol requires a nonprecious metal catalyst and has greater generality than those previously reported.

The transition metal-catalyzed carbonylation reaction is a widely used transformation that has been applied to the synthesis of complex organic molecules and commodity chemicals.[1] Among the carbonylation reactions, a double carbonylation reaction can produce α-keto amides, esters and acids depending on the nucleophiles employed.[2] These compounds are an important unit in several biologically important natural products or versatile intermediates for synthesis of α-hydroxy acids, α-amino acids and others.[3,4] The traditional protocols for the double carbonylation reaction require the precious metal palladium as the catalyst.[5−8] Air-sensitive phosphine ligands are usually required to promote the selectivity of double carbonylation. The use of phosphine ligands is a major problem associated with the double carbonylation reaction. Developing a novel catalytic system that is not dependent on phosphine ligands or precious metals to efficiently mediate this reaction is required. Since the first stable N-heterocyclic carbene (NHC) isolated by

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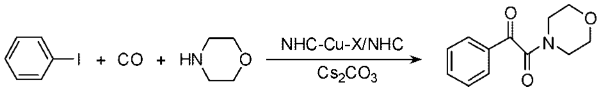
Arduengo et al. in 1991, NHCs have emerged as a class of ligands in metal-mediated reactions due to their strong σ-donor properties compared with phosphine ligands, thereby enhancing the stability of NHC complexes toward heat and moisture.[9] This characteristic property is suitable for maintaining efficient activity in the carbonylation because it is always carried out under rigorous conditions. Various catalytic applications for NHC complexes have been involved recently, including several Pd- or Rh NHC-complex mediated carbonylation reactions,[10−13] but very few nonprecious metal NHC complexes have been reported for carbonylation reactions.[10f,12,13] We developed an excellent process for the synthesis of 2-oxazolidinone with good yields and selectivities catalyzed by a [(NHC)CuI] complex.[13] (NHC)Cu complexes now serve as outstanding catalysts for several homogeneous reactions and sometimes show unique performance.[14−17] As a part of our ongoing interest in the construction of N-containing carbonyl compounds with carbonylation methods,[12,13,18] we report herein a [(NHC)-CuX]-based (X = Cl, Br, I) catalytic system together with imidazolium salts for the double carbonylation of aryl iodides with secondary amines.

Table 1. Double Carbonylation of Iodobenzene and Morpholine under Different Conditions[a]



entry	catalyst[b]	base	solvent	yield[c]
1	A	Cs_2CO_3	1,4-dioxane	0
2	B	Cs_2CO_3	1,4-dioxane	57
3	C	Cs_2CO_3	1,4-dioxane	52
4	D	Cs_2CO_3	1,4-dioxane	2
5	E	Cs_2CO_3	1,4-dioxane	93
6	F	Cs_2CO_3	1,4-dioxane	86
7	G	Cs_2CO_3	1,4-dioxane	89
8	H	Cs_2CO_3	1,4-dioxane	71
9	E	K_2CO_3	1,4-dioxane	60
10	E	K_3PO_4	1,4-dioxane	49 (16[d])
11	E	DABCO	1,4-dioxane	NR
12	E	DBU	1,4-dioxane	46
13	E	Cs_2CO_3	THF	86
14	E	Cs_2CO_3	toluene	81
15	E	Cs_2CO_3	CH_3CN	68
16[e]	E	Cs_2CO_3	1,4-dioxane	41
17[f]	E	Cs_2CO_3	1,4-dioxane	82

[a] Reactions were carried out in 5.0 mL of solvent under 3.0-MPa pressure of CO for 10 h with 1.0 mmol iodobenzene, 4.0 mmol morpholine, 2.0 mmol base, 0.01 mmol IPrCuX with or without 0.02 mmol ligand (for CuI: 0.01 mmol CuI and 0.03 mmol ligand). [b] A: CuI; B: CuI + L^1; C: CuI + L^2; D: IPrCuI; E: IPrCuI + L^1; F: IPrCuI + L^2; G: IPrCuCl + L^1; H: IPrCuBr + L^1. [c] Isolated yield. [d] GC yield of single carbonylation product. [e] 80 °C. [f] 2 MPa of CO.

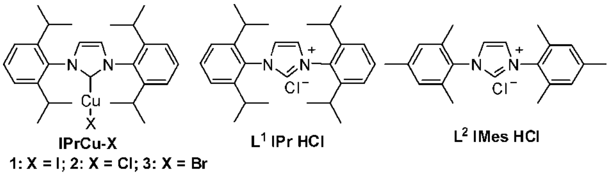


Figure 1. (NHC)Cu-X complexes and carbene precursors used in the study.

Iodobenzene and morpholine were chosen as model substrates in our initial study. Some selected screening results are summarized in Table 1 with the catalyst and corresponding ligand structures depicted in Figure 1. In general, the use of CuI as the sole catalyst showed no catalytic activity. Only 2% yield was observed when IPrCuI [IPr = *N*,*N*′-bis(2,6-diisopropyl-phenyl)imidazol-2-ylidene] was used as the catalyst. IPrCuI and the NHC precursor IPr•HCl (ligand L^1) made an elegant combination in the double carbonylation, affording the double carbonylation product in a 93% yield. The NHC precursor IMes•HCl also exhibited considerable enhancement, which gave an 86% yield of double carbonylation product in combination with IPrCuI complex under identical conditions. The influence of halogen anions on the (NHC)Cu-X (X = Cl, Br, I) complex was further examined in the preparation of 1-morpholino-2-phenyl-ethane-1,2-dione. IPrCuCl and IPrCuBr showed less reactivity than that of IPrCuI, giving the product in 89 and 71% yields, respectively. We also surveyed the effect of various bases and solvents on the copper-catalyzed double carbonylation reaction. The choice

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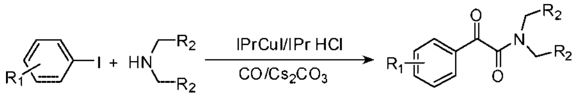
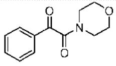
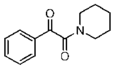
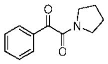
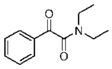
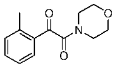
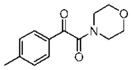
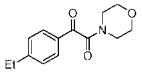
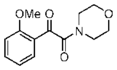
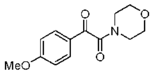
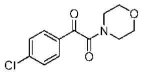
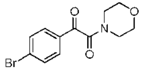
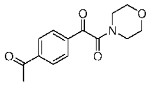
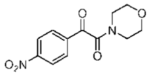
Table 2. Scope of NHC-Cu Catalyzed Double Carbonylation[a]



entry	aryl-I	amine	product	yield[b]
1	Ph **1a**	morpholine **2a**	 **3aa**	92
2	Ph **1a**	piperidine **2b**	 **3ab**	89
3	Ph **1a**	pyrrolidine **2c**	 **3ac**	83
4[c]	Ph **1a**	diethylamine **2d**	 **3ad**	79
5	*o*-Me-C$_6$H$_4$ **1b**	morpholine **2a**	 **3ba**	80
6	*p*-Me-C$_6$H$_4$ **1c**	morpholine **2a**	 **3ca**	91
7	*p*-Et-C$_6$H$_4$ **1d**	morpholine **2a**	 **3da**	76
8[d]	*o*-MeO-C$_6$H$_4$ **1e**	morpholine **2a**	 **3ea**	93
9[d]	*p*-MeO-C$_6$H$_4$ **1f**	morpholine **2a**	 **3fa**	68
10	*p*-Cl-C$_6$H$_4$ **1g**	morpholine **2a**	 **3ga**	93
11	*p*-Br-C$_6$H$_4$ **1h**	morpholine **2a**	 **3ha**	88
12	*p*-MeCO-C$_6$H$_4$ **1i**	morpholine **2a**	 **3ia**	72
13	*p*-NO$_2$-C$_6$H$_4$ **1j**	morpholine **2a**	 **3ja**	89

[a] Reactions were carried out in 5.0 mL of solvent under 3.0-MPa pressure of CO at 100 °C for 10 h with 1.0 mmol aryl iodides, 4.0 mmol amine, 2.0 mmol Cs$_2$CO$_3$, IPrCuI 0.01 mmol, and IPr·HCl 0.02 mmol. [b] Isolated yield. [c] 130 °C for 10 h. [d] IPrCuI 0.02 mmol and IPr·HCl 0.04 mmol was used as catalyst.

of base had a more important role than nature of the catalyst; double carbonylation proceeded best with Cs$_2$CO$_3$ as the base (Table 1, entries 5, 9−12). When K$_3$PO$_4$ was selected as the base, a single carbonylation product was formed in a 16% yield (Table 1, entry 10). Among the solvents tested, 1,4-dioxane was the best choice for the double carbonylation reaction.

The scope of the copper-catalyzed double carbonylation reaction was explored using 1−2 mol % of IPrCuI, 2−4 mol % of IPr·HCl ligand, and Cs$_2$CO$_3$ as the base. The reaction of various aryl iodides and amines are summarized in Table 2. The scope of the amine components was initially investigated. The double carbonylation of iodobenzene with morpholine gave the desired product in high yield, and the reaction with piperidine, pyrrolidine and diethylamine gave the corresponding α-keto amides with slightly reduced yields (Table 2, entries 1−4). Aryl iodides possessing an electron-donating group in the para and ortho positions, such as a methyl and methoxyl group, gave the double carbonyl products in high yields. When 4-methoxy-1-iodobenzene, 2-methy-1-iodobenzene and 4-ethyl-1-iodobenzene were employed in the reaction with morpholine (2a), the desired products were also isolated in reduced yields. Aryl iodides bearing an electron-withdrawing group such as chloro, bromo and nitro were well tolerated (Table 2, entries 10, 11, 13). The reaction of 4-acetyl-1-iodobenzene and morpholine (2a) also afforded the corresponding product in satisfactory yield (Table 2, entry 12).

We were also interested in the possible influence of the additional NHC precursor on the double carbonylation reaction. Based on reported work, a bis-carbene copper complex would be formed if an additional NHC precursor was introduced to the reaction system.[16] The reaction also occurred with [Cu(IPr)$_2$]BF$_4$ as the sole catalyst; 42% yield of double carbonylation product was isolated (Figure 2).[16]

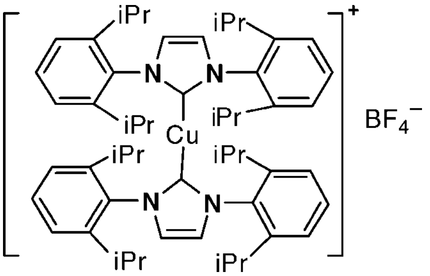


Figure 2. [Cu(IPr)$_2$]BF$_4$ complex.

When the [Cu(IPr)$_2$]BF$_4$ and NaI were employed as catalysts, the double carbonylation reaction proceeded uneventfully with nearly quantitative transformation.[19] The bis-carbene copper complex would therefore be the active species.

In conclusion, we developed a highly efficient NHC-Cu-X based catalyst system for the double carbonylation reaction of aryl iodides and secondary amines. The new protocol requires a nonprecious metal, and has greater generality than those previously reported.

This methodology represents a valuable and environmentally benign alternative to the use of toxic phosphine ligands

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(19) When 1 mol % of [Cu(IPr)$_2$]BF$_4$ was applied to the double carbonylation of iodobenzene with morpholine, 42% isolated yield of 1-morpholino-2-phenylethane-1,2-dione was obtained. Desired double carbonylation product was isolated in 93% yield with the use of 10 mol % of NaI and 1 mol % of [Cu(IPr)$_2$]BF$_4$ as catalyst. (See Supporting Information).

and precious metal palladium catalysts. Further investigations on the reaction mechanism and utilization of other aryl halides as substrates are ongoing.

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Supporting Information Available: Experimental procedures for catalyst synthesis and double carbonylation reaction, spectroscopic data for catalysts and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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