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COMMUNICATIONS

Published on Web 06/11/2010

Carboxylation of C−H Bonds Using *N*-Heterocyclic Carbene Gold(I) Complexes

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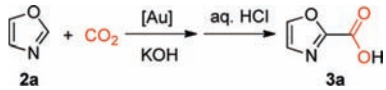
Carbon dioxide (CO_2) is considered an abundant and renewable C1 source; thus transition-metal mediated activation of this thermodynamically and kinetically stable molecule has received much attention over the past decade.[1] In this context, C−C bond formation reactions simply involving CO_2 and a unique metal center with allyl halides, alkenes, alkynes, and allenes have been achieved, although with limited functional group compatibility.[2−5] Recently, Hou and co-workers reported the catalytic carboxylation of organoboronic esters[6] using *N*-heterocyclic carbene (NHC) copper complexes as a route to functionalized carboxylic acid derivatives.[7] One fundamental drawback of this coupling reaction is the required use of a stoichiometric amount of an expensive organometallic reagent, which requires prior preparation or is generated *in situ*.

We and others have recently reported that gold(I) complexes bearing strong donor ligands can perform the activation of C−H bonds of electron-deficient arenes.[8,9] The strongly basic [(IPr)AuOH] (**1**) (IPr = 1,3-bis(diisopropyl)phenylimidazol-2-ylidene) species which has a $pK_{a_{DMSO}}$ of 30.3(2) as determined by potentiometric titrimetry (see Supporting Information (SI)) is of particular interest as it effects bond activation by a simple protonolysis mechanism which could possibly be extrapolated to a methodology for C−H bond functionalization. Furthermore, these protonolysis reactions occur under remarkably mild conditions with H_2O formed as the waste product.

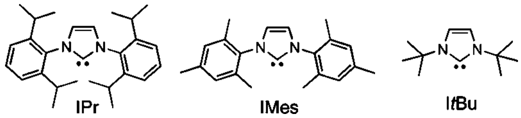
We hypothesized that [(IPr)AuOH] (**1**) could act as an effective catalyst for the carboxylation of aromatic C−H bonds featuring protons with a $pK_{a_{DMSO}}$ below 30.3,[10] furnishing important structural motifs found in numerous biologically active compounds and natural products.[11] We initially examined the reaction of oxazole (**2a**) ($pK_{a_{DMSO}}$= 27.1)[10] with CO_2 using isolated [(NHC)AuOH] complexes. In the presence of 3 mol % **1** and 1.05 mmol of KOH in THF at 45 °C, treatment of **2a** (1 mmol) with CO_2 (1.5 bar) and subsequent acid hydrolysis afforded oxazole 2-carboxylic acid (**3a**) in a quantitative yield (Table 1, entry 1). Under otherwise identical conditions, carboxylation took place neither in the absence of either [(IPr)AuOH] or KOH nor in the presence of only free NHC ligand. Screening revealed that catalyst loading could be reduced to 1.5 mol %, with higher turnover frequencies at lower temperatures, an observation that correlates with the increased solubility of CO_2 (Table 1, entries 2−4). The [(IPr)Au] species generated *in situ* from [(IPr)AuCl] and KOH also demonstrated activity for the carboxylation of **2a**,[12] but profiles of CO_2 consumption versus time clearly show the existence of a significant induction period at lower temperatures (Table 1, entries 5 and 6). Interestingly, the presence of alternative NHC ligands[13] led to lower yields of **3a** (Table 1, entries 7 and 8). We suspected that the efficacy of this catalyst system was grounded in the solution stability of the active species. We felt that this resilience could be best showcased in catalyst recycling experiments. Aqueous extraction of the catalyst solution at 45 °C allowed recovery of potassium oxazole 2-carboxylate and efficient recycling of [(IPr)AuOH] in the organic phase. A single aliquot of the catalyst solution could be recycled six times with 98% activity retention per cycle, giving a cumulative turnover number of 78.1 mol per mol of catalyst (see SI).

Table 1. Carboxylation of Oxazole with NHC-Gold(I) Catalysts[a]



Entry	[Au]	Loading (mol %)	*T* (°C)	TOF[b] (h^{-1})	Yield[c] (%)
1	[(IPr)AuOH] (**1**)	3.0	45	14.1	94
2	**1**	1.5	45	13.8	93
3	**1**	1.5	20	16.5	96
4	**1**	1.5	8	16.9	94
5	[(IPr)AuCl]	3.0	45	8.7	88
6	[(IPr)AuCl]	3.0	25	0.4	86
7	[(IMes)AuCl]	3.0	45	n.d.	76
8	[(*It*Bu)AuCl]	3.0	45	n.d.	68

[a] Conditions: 1 mmol of **2a**, 1.05 mmol of KOH, pCO_2 = 1.5 bar, 5 mL of THF, *t* = 12 h. [b] Turnover frequency determined after 2 h, defined as mol of acid per mol of Au per hour. [c] Yield of isolated product.



To ascertain a scope for this methodology, a number of other aromatic heterocycles were subjected to carboxylation catalysis under optimized catalytic conditions. Gratifyingly, gold(I) mediated C−H activation showed high regioselectivity for the most acidic C−H bond. The oxazoles were converted cleanly to the corresponding C2 carboxylic acids (Table 2, entries **3a**−**3c**). Carboxylation of the related thiazoles afforded comparable selectivities; parent thiazole gave a 2.3/1 mixture of C2/C5 regioisomers, attributed to the presence of similarly acidic protons in these positions (Table 2, entries **3d**−**3f**). The azoles and pyrimidine were not activated by [(IPr)AuOH] as all C−H bonds have a $pK_{a_{DMSO}}$ exceeding 30.3; however the more basic [(*It*Bu)AuOH] (*It*Bu=1,3-di-*tert*-butylimidazol-2-ylidene) species (pK_a = 32.4(2); see SI) could catalyze their carboxylation (Table 2, entries **3g**−**3i**). It is interesting to note that **2a**, **2b**, **2d**, **2e**, and **2g** react selectively at the C4 position when traditional acylation methodologies are employed.[14] Substrates containing three or four heteroatoms were also converted to their corresponding carboxylic acids with high regioselectivity (Table 2, entries **3j**−**3l**).

Synthetic methodology often necessitates the conversion of carboxylic acid to ester, which encouraged us to explore the possibility for their direct formation using the present methodology. Following this carboxylation protocol, the potassium carboxylate salts of **3a**−**3c** and **3e**−**3f** were quenched with iodomethane to

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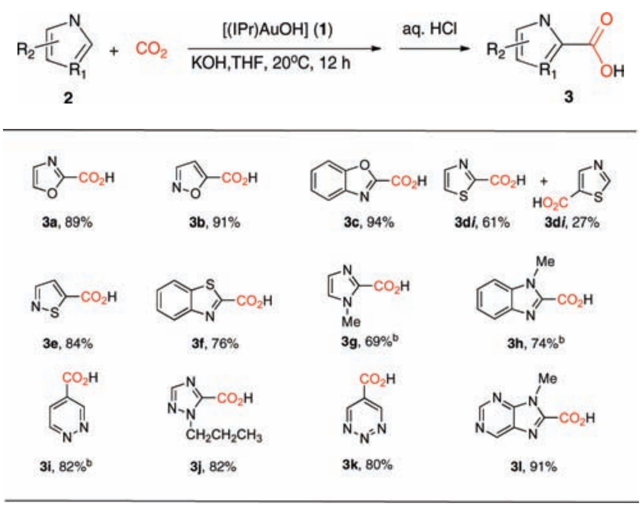
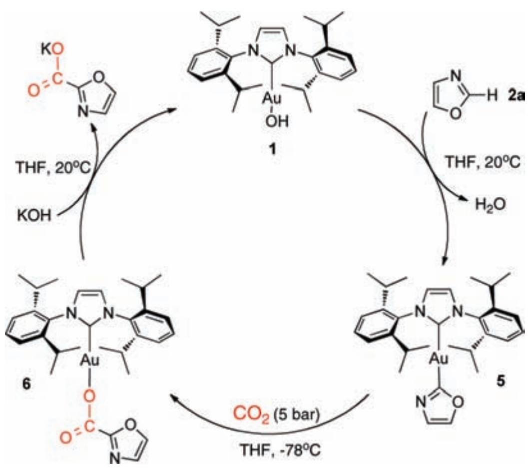
Table 2. Carboxylation of Aromatic Heterocycles with [(IPr)AuOH]



[a] Yields are isolated and average of two runs. [b] Reaction performed using [(I*t*Bu)AuOH].

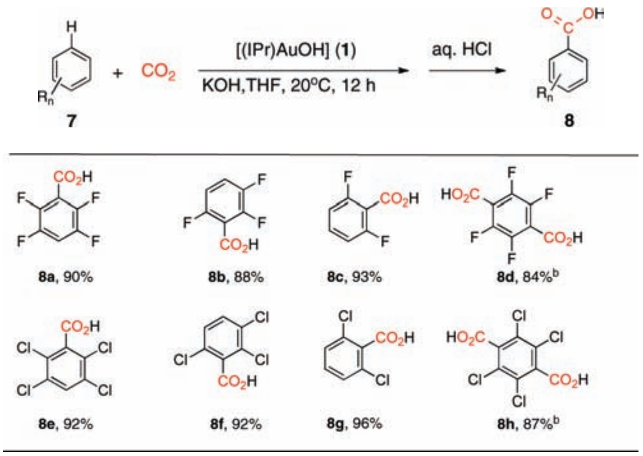
afford the corresponding methyl esters **4a**−**4c** and **4e**−**4f** in good isolated yields (>80%). The mechanism postulated for copper(I) catalyzed carboxylation of organoboronic esters was validated for the current methodology by stoichiometric reactions (Scheme 1).[7,15] Thus, protonolysis of [(IPr)AuOH] by 1 equiv of **2a** gave the gold(I) oxazole species **5**, isolated in 93% yield. A solution of **5** was saturated with CO$_2$ at −100 °C; nucleophilic addition of the oxazole ligand to the electron-deficient carbon atom of CO$_2$ thus afforded carboxylate complex **6**, isolated in 86% yield. [(IPr)AuOH] was regenerated upon metathesis of **6** with 1 equiv of KOH, with precipitation of potassium oxazole-2-carboxylate. Isolated species **5** and **6** demonstrated high activity for the carboxylation of **2a**, both affording **3a** in 88% yield.

Scheme 1. Intermediates Involved in the Carboxylation of **2a**



As activated heterocyclic C−H bonds showed a propensity for activation/functionalization, the previously examined activated arenes[8] and congeners were subjected to similar carboxylation catalysis. To our delight, the transformations examined cleanly converted to the corresponding carboxylic acid (Table 3).

Table 3. Carboxylation of arenes with [(IPr)AuOH][a]



[a] Yields are isolated and average of two runs. [b] Reaction performed using 2 equivalents of KOH.

In summary, we have shown that NHC gold(I) hydroxide complexes can catalyze the carboxylation of carbo- and heterocycles with high regioselectivity at the most acidic C−H bond position. The selective carboxylation can be rationalized in terms of simple acid/base theory. The proposed catalytic intermediates have been isolated, characterized, and shown to be active in the carboxylation reaction. Further work is underway to integrate this methodology into tandem sequences and to test the limits of this seemingly very straightforward Coinage Metal C−H bond functionalization reaction.

Acknowledgment. Financial support for this work was provided by the EPSRC and the ERC (FUNCAT).

Supporting Information Available: Detailed experimental procedures and characterization data; pK_a and titrimetry data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA103429Q