ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 3021–3024

www.rsc.org/chemcomm

HIGHLIGHT

Direct C–H carboxylation with complexes of the coinage metals

Ine I. F. Boogaerts and Steven P. Nolan*

DOI: 10.1039/c0cc03890c

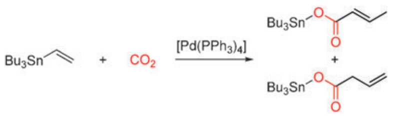
Advances into the functionalisation of C-H bonds by coinage metal complexes that make use of carbon dioxide are described.

Carbon dioxide (CO_2) is appealing as an economical non-toxic chemical reagent and a renewable C_1 source.[1] From a synthetic perspective, the most interesting reaction of CO_2 effects construction of a new bond between the carbon atom and a second carbon fragment.[2] The high thermodynamic stability and low reactivity of CO_2 usually necessitates the use of highly nucleophilic organometallics,[1b] typically metal enolates, Grignards and organolithiums.[3] The reactivity of these reagents severely limits functional group tolerance in the reaction. Furthermore, they tend to react with their carbonated analogues generating mixtures of ketones and tertiary alcohols unless a large excess of CO_2 is present.[4] Transition metals offer a comparatively mild alternative for the activation of CO_2,[1f,5] however an efficient methodology for its incorporation into organic molecules has until recently remained elusive.

Current methods for metal-catalysed C–C bond formation with CO_2[6] relate primarily to the carboxylation of less nucleophilic organometallic reagents, such as allylstannanes (Pd),[7] organoboronic esters (Rh)[8] and organozincs (Ni, Pd)[9] (eqn (1)–(3)). Activated substrates such as organohalides and those with extensive π systems likewise undergo metal-assisted C–C bond formation with CO_2 in the presence of a strong reducing agent, typically $AlEt_3$ or $ZnEt_2$. Rovis *et al.* have applied nickel complexes to incorporate CO_2 into alkenes (eqn (4));[10] analogous transformations of alkynes[11] and allenes[12] have also been reported (eqn (5) and (6)). In pioneering asymmetric transformations, a chiral nickel catalyst was used for the carboxylation of bis-dienes (eqn (7)).[13] Organopalladium intermediates derived from polyhalogenated arenes were also found capable of fixing CO_2.[14]

Most of these approaches are unfortunately of limited scope and applicability. In many instances the substrate must be independently functionalised with a reactive handle, often *via* the Grignard or organolithium precursor, which offers little advantage over using these compounds themselves. Additionally, the organotin, boron and zinc compounds are resistant to carboxylation unless elevated temperatures and pressures are employed.[15] In contrast, the coupling of organocopper reagents with CO_2 is known to proceed at ambient temperature and 1 atm; this is the first example of coinage metal-catalysed carboxylation (eqn (8)).[16] It is worth noting that the arylcuprates were synthesised from activated copper and the corresponding aryl iodides, thus avoiding the constraints of using Grignard or organolithium reagents and allowing wider functional group tolerance.[17]

Copper complexes of *N*-heterocyclic carbenes (NHCs) have recently been reported as expedient catalysts for transforming numerous carbonyl substrates[18] and for the addition of organoboranes to electrophiles.[19] In this context, Hou *et al.* have described the carboxylation of organoboronic esters with NHC–Cu(I) species as a route to functionalised carboxylic acids (eqn (9)).[20] Electron-donating and electron-withdrawing moieties, reactive functionalities and sterically imposing groups on arylboronic esters were all tolerated, as were heteroaromatic and alkenyl derivatives. A detailed mechanism for this reaction was postulated on the basis of DFT calculations.[21]



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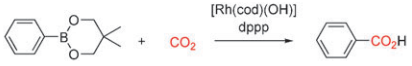

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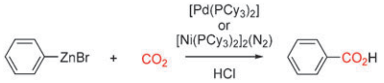

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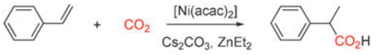

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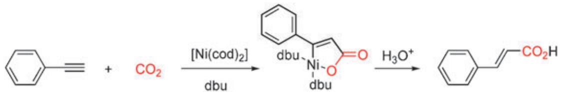

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EaStCHEM School of Chemistry, University of St. Andrews, St Andrews KY16 9ST, UK.
E-mail: snolan@st-andrews.ac.uk;
Fax: +44 (0)1334 463 808;
Tel: +44 (0)1334 463 763

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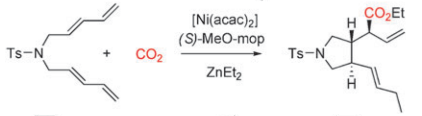

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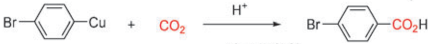

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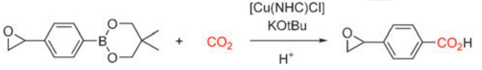

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The carboxylation does not proceed in the absence of a metal precursor,[20,22] however it must be noted that reaction of non-ligated NHCs with CO_2 is well-known.[23] CO_2 adducts of NHCs have attracted attention as NHC-transfer agents[24] and in the synthesis of amidates,[25a] phosphenium adducts[25b] and ionic liquids.[25c] NHCs have also been successfully applied as organocatalysts,[26] particularly in the hydrosilylation of CO_2,[27a] the reduction of CO_2 to carbon monoxide[27b] and CO_2 coupling with epoxides.[23b]

Catalyst systems comprised of simple Cu(I) salts and nitrogen-donor ligands were also shown to be active for these transformations; interestingly, Cu(II) complexes are ineffective.[22]

Despite the wider functional group compatibility, these approaches remain limited by the stoichiometric consumption of an organometallic reagent. To directly couple a C–H bond in an organic substrate with CO_2 is most efficient in terms of atom economy,[1b,28] best exemplified in the Kolbe–Schmitt synthesis of salicylic acid,[29] but has remained a challenge.

Gold(I)-catalysed C–H carboxylation

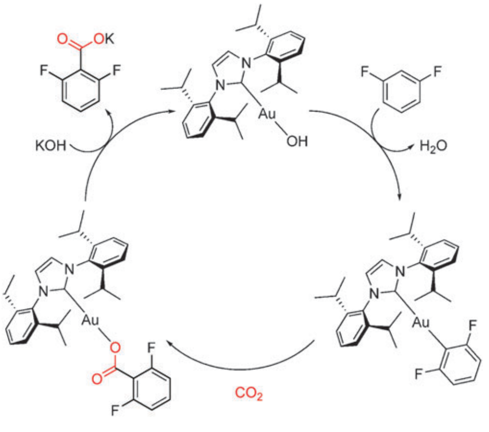
Homogeneous gold catalysis has over the last decade generated numerous methodologies for C–C bond formation,[30] many employing Au(I) or Au(III) complexes as powerful π-acids for the activation of unsaturated hydrocarbons *via* a σ-bond metathesis pathway.[31] Despite possible π-coordination to arenes, Au(I)-mediated activation of aromatic C–H bonds was for a long time unachievable.[32] The first examples were reported recently by Larrosa *et al.*, using Au(I) complexes bearing strong σ-donor ligands and electron-deficient arenes.[33] The authors suggested a concerted metalation–deprotonation mechanism involving the complex [Au(P*t*Bu$_3$)(OPiv)] (Piv = pivaloyl), in which the pivaloate ligand behaves as a Brønsted base *via* a six-membered transition state,[34] but could not preclude an oxidative addition mechanism involving a transient Au(III) hydride species.[35]

We have reported upon C–H activation in aromatic substrates using the strongly basic complex [Au(IPr)(OH)] (IPr = 1,3-bis(diisopropyl)phenylimidazol-2-ylidene).[36] In the protonolytic mechanism frequently identified with transition metal hydroxide species,[37] [Au(IPr)(OH)] behaves as a Brønsted base towards suitably acidic C–H bonds ($\mathrm{p}K_{\mathrm{aDMSO}} < 30.3$) and the organogold intermediates generated were found to be capable of nucleophilic attack on CO_2.[38] Activation could be extended to less acidic C–H bonds ($\mathrm{p}K_{\mathrm{aDMSO}} < 32.4$) by increasing the σ-donor capacity of the NHC ligand. Various arenes and heteroaromatics were thus carboxylated in good to excellent yield (69–96%) and with high regioselectivity for the most acidic C–H bond position. Regioisomeric mixtures were only recovered where the substrate contains comparably acidic protons ($\mathrm{p}K_{\mathrm{aDMSO}} \pm 0.2$).

Mechanistic aspects were construed from stoichiometric reactions, and a catalytic cycle was proposed (Scheme 1). Protonolysis of [Au(IPr)(OH)] by an aromatic substrate would give the corresponding organogold complex [Au(IPr)Ar]. Nucleophilic addition of the coordinated substrate to the electron-deficient carbon atom on CO_2 should afford the carboxylate species [Au(IPr)(OC(O)Ar)]. We accomplished higher turnover frequencies at lower temperatures which correlates with the increased solubility of CO_2, suggesting that its insertion into the gold–carbon bond is the rate-limiting step in the catalytic pathway. Metathesis of [Au(IPr)(OC(O)Ar)] with KOH would regenerate the active precursor with the release of KOOCAr. Aqueous extraction of the catalyst solution allows recovery of the carboxylate salt and efficient recycling of [Au(IPr)(OH)] in the organic phase. A single aliquot of the catalyst solution was successively recycled six times with high retention of activity, giving a cumulative turnover number of 78.1 mol per mol of catalyst (Fig. 1). The potassium carboxylate can be either hydrolysed to the acid or treated with an organohalide to give the ester.

Copper(I)-catalysed C–H carboxylation

Following our discovery of a Au(I)-mediated process, Hou *et al.* identified the [Cu(IPr)(O*t*Bu)] complex as an economic and alternative catalyst for direct carboxylation of the acidic C–H bond in aromatic heterocycles with CO_2.[39] Stoichiometric reactions implicated



Scheme 1 Mechanism for the carboxylation of fluorobenzenes with [Au(IPr)(OH)] (stoichiometric reactions).

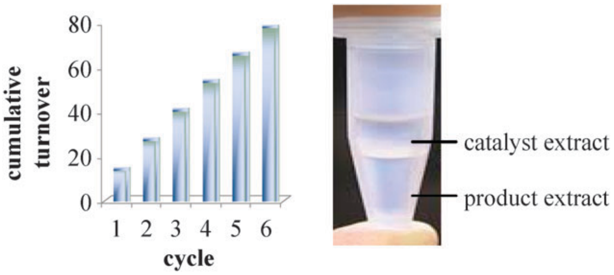


Fig. 1 Recycling experiments with [Au(IPr)(OH)].

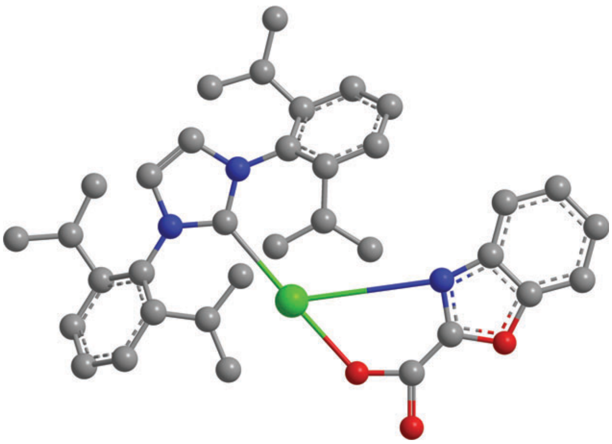


Fig. 2 3-D structure of [Cu(IPr)(oxazolyl-carboxylate)].

the aforementioned catalytic cycle, and an X-ray crystallographic diffraction study established that chelation of the heterocyclic-carboxylate ligand imparts extra stability to the carboxylate species [Cu(IPr)(OC(O)Ar)] (Fig. 2). In twelve examples, substituted benzoxazoles underwent quantitative conversion (50–89%) with high functionality tolerance (Me, Ph, Br, CF_3, NO_2, OMe, CO_2R, CN). However, only trace conversion was observed for substrates containing less acidic C–H bonds.

Employing a related complex, similar observations were rationalised in terms of a Brønsted–Lowry framework. We have systematically shown that [Cu(IPr)(OH)] can only effect the activation, and thence carboxylation, of bonds more acidic than itself ($pK_{a\text{DMSO}}$ = 27.4).[40] The catalyst is considerably less costly than its gold analogue, but against this must be set its lower basicity. This both narrows the substrate scope and necessitates elevated temperatures to promote quantitative carboxylation. Furthermore, high sensitivity to oxygen traces renders its handling and recyclability more difficult than the stable gold congener.

Looking forward

Transition metal-mediated C–C bond formation between CO_2 and carbon nucleophiles often requires meticulous synthetic planning and modification of the substrate with an appropriate reactive handle. Very recently Hu *et al.* reported direct carboxylation of the acidic C–H bond in aromatic heterocycles with CO_2 using only Cs_2CO_3 as the base.[41] Previous reports by Daugulis *et al.* on copper-catalysed sp^2 C–H arylation have shown that deprotonation of a C–H bond can be accomplished by strong inorganic bases.[42] Thus, comparatively acidic bonds ($pK_a < 27$) can be deprotonated with K_3PO_4 but for less acidic ones (pK_a 27–35) a lithium alkoxide base is required. As expected, only mild bases effect good regioselectivity and functional group tolerance.

Comparatively, the NHC complexes of Au(I) and Cu(I) have shown high specific activity for direct carboxylation of the ubiquitous C–H bond. Such an approach to CO_2 fixation is highly attractive in the syntheses of chemical commodities and complex natural products. The methodologies are limited by the necessity for a C–H bond in the substrate that is more acidic than the catalyst, and we are currently trying to extend scope boundaries by ligand modification on the transition metal hydroxide complexes. The NHCs continue to surprise and we have no doubt the C–H bond functionalisation area can benefit from such electron-rich and stabilising yet reactive metal species.

The EPSRC and the ERC (Advanced Investigator Award to SPN) are gratefully acknowledged for support of this work. SPN is a Royal Society-Worlfson Research Merit Award holder.

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