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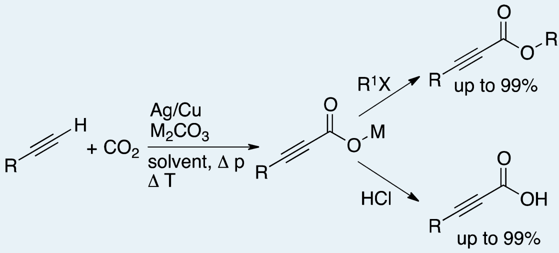
Catalytic C−H Carboxylation of Terminal Alkynes with Carbon Dioxide

Filipe Manjolinho, Matthias Arndt, Käthe Gooßen, and Lukas J. Gooßen*

Department of Chemistry, University of Kaiserslautern, Erwin-Schrödinger-Strasse 54, 67663 Kaiserslautern, Germany

ABSTRACT: Within the past years, several catalyst systems have been discovered that promote the carboxylation of terminal alkynes with formation of propiolic acids. This reaction concept is particularly topical in that it involves the functionalization of a C−H bond and the incorporation of CO_2 into an organic molecule without need for strong bases or aggressive organometallic reagents. The present article reviews the development of this new reaction type and critically compares the reaction and catalyst concepts disclosed in the literature.



KEYWORDS: *carbon dioxide, carboxylation, catalysis, propiolic acids, alkynes*

INTRODUCTION

Carbon dioxide is the most abundant source of carbon on earth. The total amount of CO_2 in the atmosphere and the oceans is estimated to represent 10^{14} tons of carbon.[1,2] Its atmospheric concentration has risen to 390 ppm in the past decades and is expected, because of the release of 29 billion tons of this greenhouse gas per year by combustion of fossil fuels, to keep rising.[3] For this reason, CO_2 constitutes a highly attractive C_1-building block for organic synthesis.[4−8]

Living nature has evolved around the ubiquity of carbon dioxide, using CO_2 fixation for the growth of green plants, which form the basis of the food chain. 170 billion tons of biomass are produced via photosynthesis, that is, the reduction of carbon dioxide by water with sunlight as the energy source.[9,10] In contrast, only few industrial-scale chemical processes have been developed that use carbon dioxide as a carbon source.[11] The main reason for this is that CO_2 is low in energy, highly symmetrical, and, thus, chemically inert and difficult to activate for bond formation. In noncatalytic processes, the intrinsic inactivity of CO_2 can be overcome only by highly reactive reaction partners, such as Grignard or organolithium reagents.[12−14] In these transformations, however, the benefit of using CO_2 is more than offset by the requirement of using such energy-rich substrates. For example, it is usually preferable to obtain carboxylic acids by carbonylating readily available aryl chlorides with carbon monoxide,[15] rather than carboxylating expensive organometallic reagents with CO_2.[16]

A prime focus of contemporary research therefore lies on developing catalytic reactions in which simple organic molecules react with CO_2 with formation of valuable synthetic intermediates. Pioneering contributions to this rapidly emerging area include the copolymerization of CO_2 and epoxides to yield polycarbonates first reported by Inoue, the telomerization of butadiene with CO_2 discovered by Musco, and the codimerization of isoprene with CO_2 originally disclosed by Hoberg.[17−20] Examples of more recent advances are the hydrogenation of CO_2 to formic acid catalyzed, for example, by iridium(III) or ruthenium(II) complexes, the carboxylation of ethylene and methyl iodide with formation of acrylates, the carboxylation of alkynes to acrylic acids mediated by nickel, the addition of CO_2 to epoxides to afford cyclic carbonates, and the reaction of CO_2 with methanol to give dimethyl carbonate.[21−29] These and related processes have been reviewed by Rieger, Mori, Shi, and Beller.[1,30−32]

Only recently, a further reaction mode has emerged, namely, the insertion of CO_2 into C−H bonds. In the presence of coinage metal catalysts and mild bases, arenes, heteroarenes, and terminal alkynes have been found to react with CO_2 to the corresponding carboxylic acids.[33−35] Nolan and Ackermann have reviewed the opportunities of this strategy for the synthesis of aromatic and heteroaromatic carboxylates.[36,37] This perspective article centers on a related, similarly important transformation, namely the C−H carboxylation of terminal alkynes with CO_2 to give propiolic acids.

PROPIOLIC ACIDS AS INTERMEDIATES IN ORGANIC SYNTHESIS

Propiolic acids are valuable intermediates for the chemical and pharmaceutical industry for which new synthetic entries are constantly sought. Synthetic end-products include advanced materials obtainable, for example, via stereospecific polymerization (Scheme 1, entry A).[38] Various bioactive molecules contain propiolic acid derivatives as key synthons. Spiroindolones[39] (Scheme 1, entry B) with antimalarial properties[40] can be synthesized from propiolic acid amides via an insertion/coupling/isomerization/Diels−Alder sequence. Spirobenzofuranones (Scheme 1, entry C) with antifungal properties, antiproliferative effects in cancer cells, and activity against

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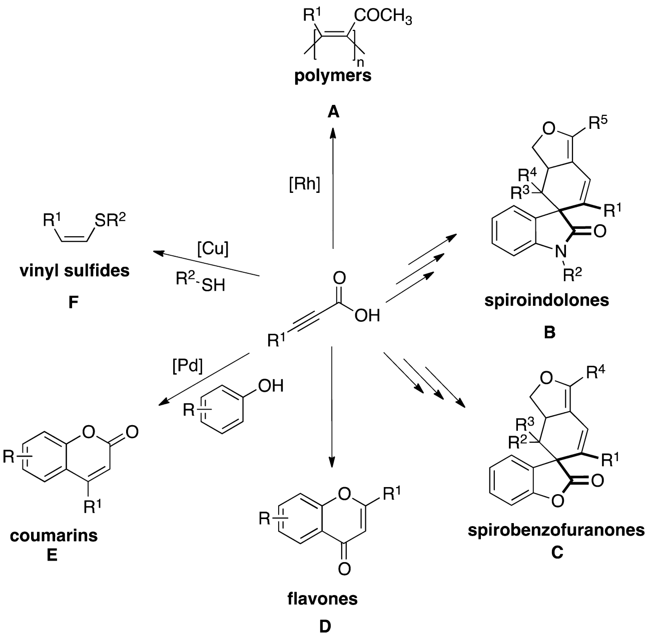
Scheme 1. Use of Propiolic Acids as Synthons in Organic Synthesis



hepatitis C replication[41−46] are obtained by a similar process from propiolic esters.[15] Flavones[47] (Scheme 1, entry D) with antiviral activity[48] are accessible via the addition of propiolic acids to arynes. Propiolic esters can also be converted into coumarins[49] (Scheme 1, entry E), which act as cholesterol-lowering agents and often possess antithrombotic activity, in a sequence that involves a C−H functionalization of phenols.[50,51] Vinyl sulfides are found in many natural products and pharmaceuticals and can be accessed via stereoselective reactions of propiolic acids with thiols (Scheme 1, entry F).[52] Decarboxylative Sonogashira reactions of propiolic acid allow the selective synthesis of unsymmetrical diaryl alkynes, alkynyl arenes, or propiolic acid esters in one step under mild reaction conditions.[53]

Traditional syntheses of propiolic acids include the oxidation of propargylic alcohols[54] or aldehyde derivatives,[55,56] the insertion of CO_2 into alkynyl−metal species[57,58] obtained by deprotonation of alkynes with strong bases such as alkali metal hydrides or organometallic reagents.[59−62]

In comparison to these established routes, the metal-catalyzed insertion of CO_2 into the C−H bond of terminal alkynes would clearly be advantageous. Unfortunately, a comparison of calculated standard enthalpies of formation of starting materials and products revealed that this reaction should be thermodynamically unfavorable (ΔG^θ = 19.1 kcal mol^{-1}). However, if the reaction is carried out in the presence of a mild base so that a carboxylate salt is formed, the overall reaction is predicted to be energetically feasible (ΔG^θ = −10.1 kcal mol^{-1}).[63]

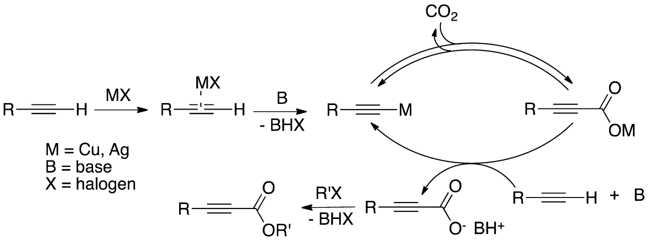
Since CO_2 capture is associated with a decrease in entropy, high reaction temperatures are undesirable as they would shift the equilibrium toward the starting materials. The reverse reaction, the decarboxylation of propiolic acids, is known to proceed rapidly already at 60 °C in the presence of a copper catalyst,[64,65] whereas substantially higher temperatures are required to extrude CO_2 from aromatic carboxylic acids.[66−70] These experimental findings also show that the energy barrier for the (de)insertion of the CO_2 in the presence of a copper catalyst is remarkably low for alkynyl substrates.

On the basis of these considerations, several strategies have been devised to reach high yields in carboxylation reactions. In all cases, the reactions are performed in the presence of mild bases so that propiolate salts rather than propiolic acids are obtained. A way to render the carboxylation irreversible is to convert the intermediate metal propiolates in situ into the corresponding esters by alkylation with alkyl halides. Conceivable strategies to shift the carboxylation/decarboxylation equilibrium toward the carboxylated products without esterification are to increase the CO_2 pressure, to perform the reaction at low temperature using highly active catalysts, and to remove the carboxylate salts from the reaction solution by precipitation.

SYNTHESES OF PROPIOLIC ACID ESTERS VIA CU(I)- AND AG(I)-CATALYZED CARBOXYLATION OF TERMINAL ALKYNES

In 1974, Saegusa et al. reported that phenylacetylene can be carboxylated with CO_2 gas at atmospheric pressure in the presence of stoichiometric amounts of Cu(I) or Ag(I) salts.[71] A shift of the carboxylation/decarboxylation equilibrium toward the desired products was achieved by converting the intermediately formed Cu(I)- or Ag(I)-propiolate complexes into the corresponding propiolic esters by alkylation with methyl iodide (Scheme 2).

Scheme 2. Mechanism of the Cu(I)- and Ag(I)-Mediated Carboxylation of Terminal Alkynes



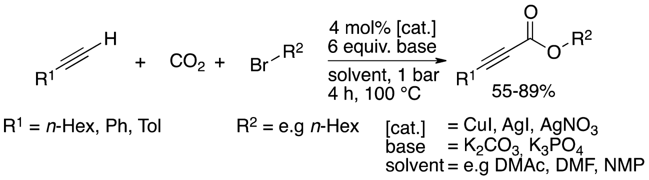
M = Cu, Ag
B = base
X = halogen

In the absence of an alkylating agent, the Cu(I)-phenylpropiolate complexes extrude CO_2 already at 35 °C with formation of copper phenylacetylides. The addition of phosphine ligands was found to shift this equilibrium reaction back to the Cu(I)-phenylpropiolate complexes.[72] This effect was shown to be proportional to the σ-donor strength of the phosphine ligands and their amount. This observation became the basis for the development of effective catalyst systems.

The first example of a catalytic carboxylation of terminal alkynes with C−H functionalization was reported 20 years later by Inoue et al.[73] They found that in the presence of copper or silver salts, CO_2 inserts into the C(sp)−H bond already at ambient pressure and in the presence of bases with pK_a values substantially below that of the C−H bond. The Cu- or Ag-propiolates formed intermediately were once again removed from the equilibrium by in situ alkylation with 1-bromohexane (Scheme 3). This way, various hexyl alkynyl esters with aliphatic and aromatic substituents were synthesized in moderate to good yields.

The proposed catalytic cycle, which is based on the stoichiometric investigations by Saegusa,[31] is initiated by η^2-coordination to the Cu(I)- or Ag(I)-catalyst to the C−C triple bond of the alkyne.[74,75] The bases employed in this reaction are

Scheme 3. Synthesis of Hexyl Alkynyl Esters by Carboxylation of Terminal Alkynes



not sufficiently strong to deprotonate the alkyne, a step that would lead to the direct formation of acetylide anions. However, η^2-coordination of the alkyne to a metal center acidifies the terminal C−H bond, so that metal−acetylides can form already in the presence of carbonate bases. The exact structures of the metal-alkyne species involved in the catalytic cycle are unknown. In stoichiometric reactions, copper and silver complexes with acetylide ligands usually form cluster compounds in which the acetylide bridges the metal centers.[76,77] This demonstrates that both η^1-and η^2-coordination of terminal alkynes is possible.[78,79] Insertion of CO_2 into the metal−carbon bond leads to the reversible formation of a metal propiolate, which is continuously removed from the equilibrium by irreversible esterification with an alkyl halide, regenerating the metal halide catalyst (Scheme 2).

Lu et al. recently disclosed a new version of this catalytic transformation, in which 10 mol % of the *N*-heterocyclic carbene complex 1,3-di-*iso*-propyl-4,5-dimethylimidazol-2-ylidene copper(I) chloride ((IPr)CuCl) are used as the catalyst. In the presence of allyl-, benzyl-, or similarly reactive organochlorides as the alkylating agents and K_2CO_3 as the base, various propiolic esters were obtained in good to excellent yields, albeit at an elevated CO_2 pressure of 15 bar (Scheme 4).[80]

In 2012, Kondo et al. reported that similar products can be accessed at ambient CO_2 pressure and room temperature using a catalyst system generated in situ from 8 mol % CuI and 8 mol % PEt_3 in the presence of 3 equiv of Cs_2CO_3 as the base and alkyl bromides or iodides as alkylating agents (Scheme 4).[81] For electron-deficient aryl-substituted alkynes, 2,2′-bipyridine was employed as ligand, and the reaction temperature was increased to 50 °C. The yields are somewhat lower than those reported by Lu, but this may be a result of the lower CO_2 pressure rather than of a lower catalyst activity. The system was also shown to allow the synthesis of phenylpropiolic acid without in situ esterification.

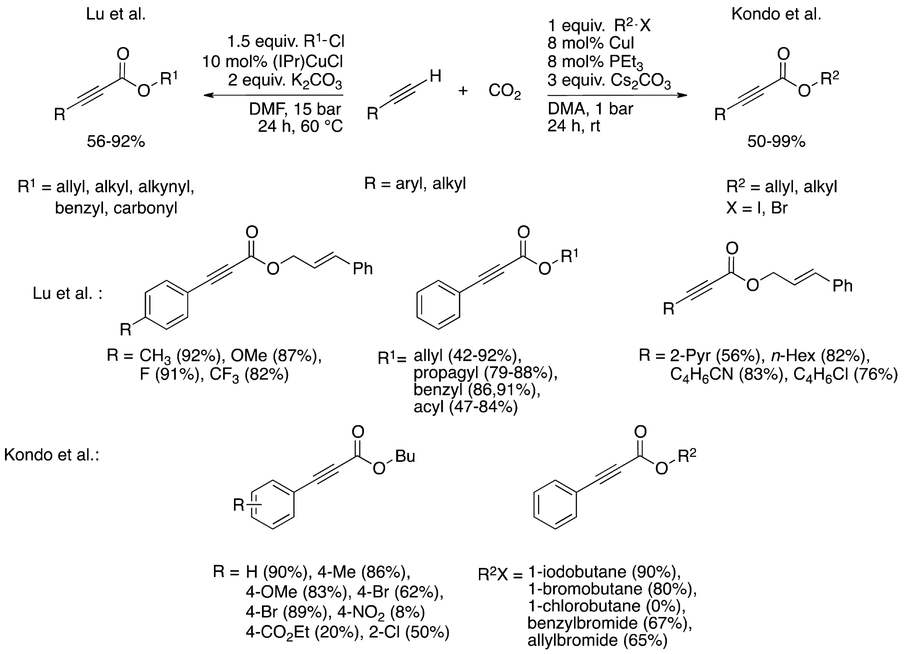
SYNTHESES OF PROPIOLIC ACIDS VIA COPPER-CATALYZED CARBOXYLATION OF TERMINAL ALKYNES

The rapid progress achieved in the field of decarboxylative couplings set the stage for the development of a new generation of carboxylation catalysts. Following the principle of microscopic reversibility, a metal complex that displays high activity in the protodecarboxylation of carboxylic acids should be effective also in the carboxylation of C−H bonds. It was thus reasonable to assume that with copper(I) phenanthroline systems, which are known for their high activity in catalytic decarboxylations,[69,70] the reaction temperatures of a carboxylation should be lowered to an extent that would allow shifting the equilibrium toward the carboxylated products.

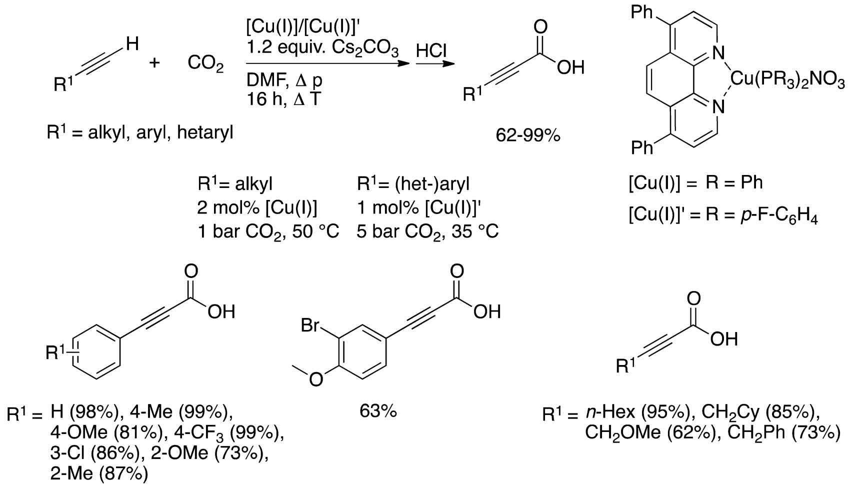
In 2010, we indeed found that in the presence of 2 mol % of (1,10-phenanthroline)-bis-(triphenylphosphine)copper(I) nitrate ([Cu(I)]) and cesium carbonate in dimethylformamide (DMF) at 50 °C, 1-octyne can be carboxylated under atmospheric CO_2 pressure.[82] These mild reaction conditions serve to shift the equilibrium toward the carboxylation product to an extent that 1-α-nonynoic acid was isolated in high yield following acidic workup. This was the first example of an alkyne carboxylation that requires neither high CO_2 pressures nor strong bases or esterification to drive the equilibrium toward the carboxylated products (Scheme 5).

To achieve high yields also for the carboxylation of aryl alkynes, the CO_2 pressure had to be increased to 5 bar, and the temperature lowered to 35 °C. For these substrates, (1,10-

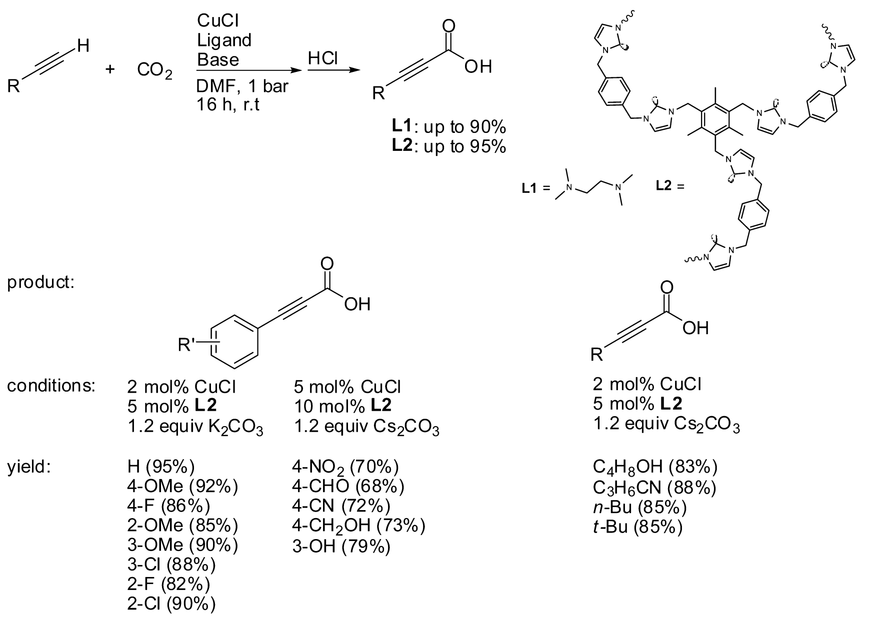
Scheme 4. Improved Protocols for the Carboxylation of Terminal Alkynes



Scheme 5. Synthesis of Propiolic Acids via Carboxylation of Terminal Alkynes



Scheme 6. Cu-catalyzed Carboxylation of Terminal Alkynes under Ambient Conditions



phenanthroline)-bis-[tris(4-fluorophenyl)phosphine]copper(I) nitrate ([Cu(I)]') was found to have superior catalytic activity. Comparative studies revealed that Cs_2CO_3 is a more efficient base than potassium or sodium salts. The presence of polar solvents such as DMF strongly enhanced the yields.

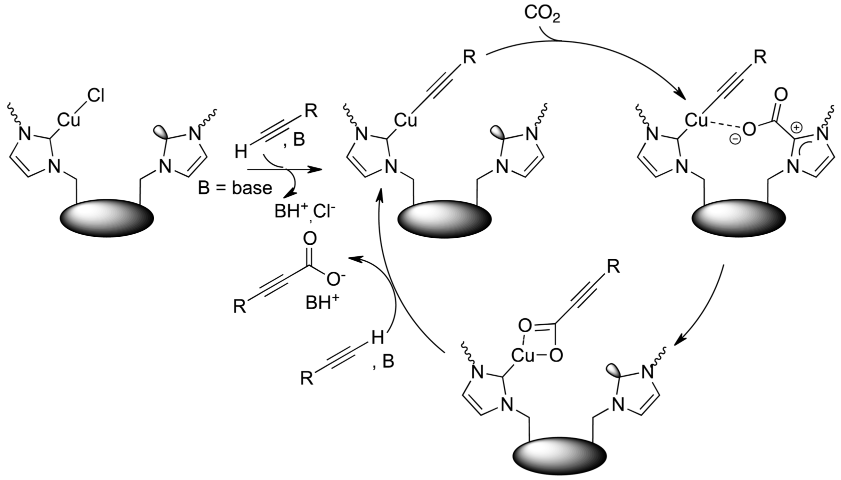
Using the two complementary protocols, a broad range of aryl- and alkyl-substituted propiolic acids were synthesized in good yields. The mild reaction conditions are compatible with many functional groups including ethers, halogens, trifluoromethyl, and alkynyl groups. While alkynes with moderately electron-deficient aryl substituents, for example, 4-(trifluoromethyl)phenylacetylene and 2-ethynylpyridine were smoothly converted, the scope did not extend to aryl alkynes with strongly electron-withdrawing groups such as (4-nitrophenyl)-acetylene. The catalysts were found to also promote the carboxylation of heteroarenes with a similar efficiency as the gold- and copper-NHC catalysts described by Nolan et al.[12]

Only a few weeks later, Zhang et al. disclosed an alternative system for the carboxylation of terminal alkynes.[83] They found that a catalyst system formed in situ from 2 mol % CuCl and 1.5 mol % *N,N,N′,N′*-tetramethylethylene-1,2-diamine (TMEDA, Scheme 6, **L1**) promotes the carboxylation of aryl alkynes at ambient conditions (room temperature, atmospheric CO_2 pressure) in DMF. While for some particularly active substrates, high yields were achieved with inexpensive K_2CO_3, the use of Cs_2CO_3 was required for alkyl-substituted alkynes. Electron-deficient aryl alkynes could not be converted using either system.

To overcome this limitation, Zhang et al. tested various other ligands and found that the addition of poly-*N*-heterocyclic carbenes as ligands (Scheme 6, **L2**) substantially improved the activity of the copper catalyst. Thus, in the presence of 5 mol % CuCl, 10 mol % of the poly-NHC ligand **L2** and Cs_2CO_3, even (4-nitrophenyl)acetylene and similarly electron-deficient derivatives were carboxylated at room temperature and ambient CO_2 pressure. This is remarkable, as the corresponding propiolic acids are particularly unstable.

The authors propose a dual function for the NHC centers, that is, as ligands for the copper and as organocatalysts that activate CO_2. The reason for the high activity of poly-NHC

Scheme 7. Catalytic Cycle for the Poly-NHC-Cu-Catalyzed Carboxylation of Terminal Alkynes



compounds in comparison to monodentate ligands is explained by the mechanism outlined in Scheme 7.

In the first step, an NHC-copper catalyst activates the terminal alkyne so that an alkynyl copper complex forms already in the presence of a mild carbonate base. A free carbene in close proximity to the copper center then reacts with CO_2 to an NHC-carboxylate. The CO_2 is then transferred from the NHC to the copper center, where it inserts into the copper–carbon bond with formation of a copper propiolate. The propiolate salt product is finally liberated by salt metathesis with another alkyne molecule. Although not explicitly depicted in the original catalytic cycle, one must assume that this step also requires the presence of a mild base, such as a metal carbonate, to be thermodynamically feasible.

With the two complementary catalyst systems, Zhang et al. achieved high yields in the carboxylation of a broad range of aryl- and alkyl-substituted alkynes.

■ SILVER-CATALYZED CARBOXYLATION OF TERMINAL ALKYNES

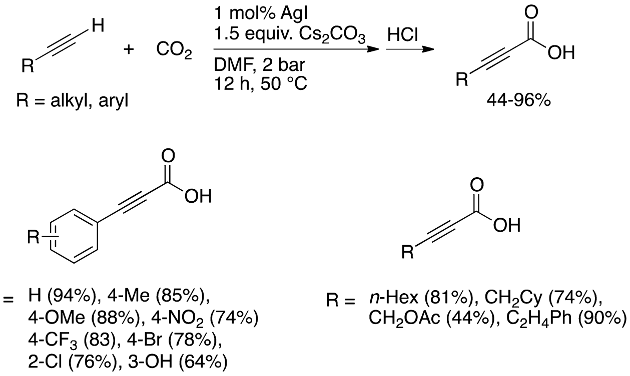
In continuation of the pioneering studies by Saegusa and Inoue, Lu and co-workers investigated the use of silver catalysts in the carboxylation of terminal alkynes. In 2011, they reported that 1 mol % of AgI or similar Ag(I) salts effectively promote the carboxylation of terminal alkynes in the presence of Cs_2CO_3 at 50 °C with 2 bar of CO_2 in DMF (Scheme 8).[84] No ligand was required to stabilize the Ag(I), but Cs_2CO_3 was once again critical for reaching high yields with low catalyst loadings.

This catalytic system showed a substrate scope similar to the copper-based catalysts, although the yields were somewhat lower. Interestingly, an increase in the catalyst loading led to a reduction rather than the expected improvement of the yields.

The key advantage of this reaction protocol is the simplicity of the catalyst, and its main drawback is its requirement of 2 bar CO_2 pressure. The authors postulate a mechanism analogous to that discussed for the copper systems with intermediate formation of a silver(I) acetylide and propiolate species.

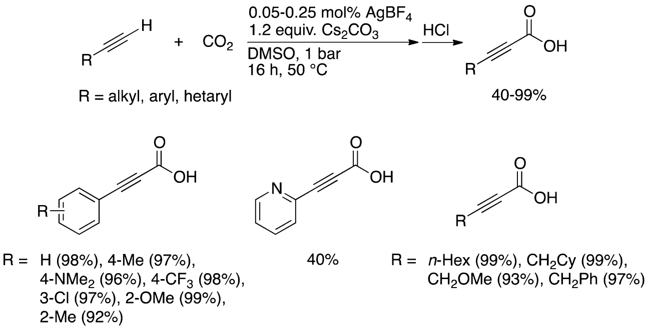
Our own approach to silver-catalyzed carboxylation reactions is based on established protodecarboxylation catalysts.[85] In contrast to copper-based systems, silver complexes had been found to be most effective as decarboxylation catalysts in combination with monodentate ligands, and the presence of dimethylsulfoxide (DMSO) had been observed to strongly increase the catalytic activity of silver salts.[86−88] Similar observations were also made for silver-catalyzed carboxylation reactions. Thus, in DMSO as the solvent, the catalytic activity of simple silver salts was increased to an extent that 500 ppm of $AgBF_4$ sufficed to promote the carboxylation of most terminal alkynes at 50 °C and ambient CO_2 pressure. Again, Cs_2CO_3 was found to be the most efficient base.[89] Remarkably, even aryl and heteroaryl alkynes could be converted in high yields albeit at slightly increased catalyst loadings (Scheme 9).

Scheme 8. Ligand-Free Ag-Catalyzed Carboxylation of Terminal Alkynes



The high efficiency of this catalyst system may be explained by a mechanism involving DMSO-ligated silver(I) carbonate as the actual catalytic species. Alternatively, the intermediacy of silver nanoparticles is in discussion, as these are known to form when silver salts are heated in DMSO solutions.[90,91] The

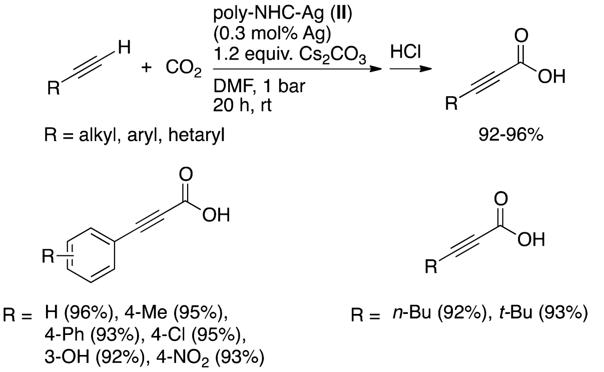
Scheme 9. Carboxylation of Alkynes by Low Loadings of Ag



excellent solubility of CO_2 and inorganic salts in this solvent may also contribute to the beneficial effect that DMSO has on the reaction outcome.[92] As can be seen from the examples in Scheme 9, excellent yields are thus achieved for a broad variety of substrates.

Once again, Zhang et al. almost simultaneously reported an alternative catalyst system with similar activity (Scheme 10).[93]

Scheme 10. Poly-NHC-Ag Catalyzed Synthesis of Propiolic Acids



They found that when heating silver nitrate in DMSO in the presence of a poly-NHC ligand similar to that previously employed in the copper-catalyzed reaction variant, silver nanoparticles deposited on the ligand material (Scheme 11). They proposed that some carbene centers coordinate to the silver particles, thus immobilizing them on this solid support. As before, the remaining free carbenes are believed to react with CO_2 gas with formation of NHC-carboxylates. Similarly to the corresponding copper system, the alkyne is activated by the silver nanoparticle with intermediate formation of a silver acetylide, CO_2 is transferred from NHC to silver, and salt metathesis in the presence of Cs_2CO_3 leads to formation of the propiolate salt. The catalyst has to be employed at a higher loading than the homogeneous silver propiolate DMSO system but can be recycled several times, so that overall, a similar catalyst productivity is achieved. Control experiments revealed that only in the presence of surplus NHC-centers, a high catalytic activity is reached that allows the conversion even of electron-deficient aryl-substituted alkynes. The key advantages of this approach are the recyclability of the heterogeneous catalyst and the negligible silver leaching. Its main drawbacks are the laborious ligand synthesis, and catalyst preformation.

METAL-FREE CARBOXYLATION OF TERMINAL ALKYNES

Hu and co-workers recently discovered that carboxylations of particularly C−H acidic heterocycles, for example, oxazoles, thiazoles, or oxadiazoles, are possible even in the absence of transition metal catalysts if Cs_2CO_3 is employed as the base.[94] Zhang et al. reported that this approach is effective also for the carboxylation of alkynes. When relatively forcing conditions (120 °C and 2.5 bar of CO_2) are used, various terminal alkynes are carboxylated in the presence of 1.2 equiv. of Cs_2CO_3 in DMF. Control experiments revealed that the carboxylate group originates from the CO_2 and not from the Cs_2CO_3. In view of the high catalytic activity of silver even at ppm levels, it might be worthwhile to also probe whether commercial cesium carbonate is free of trace metal impurities.

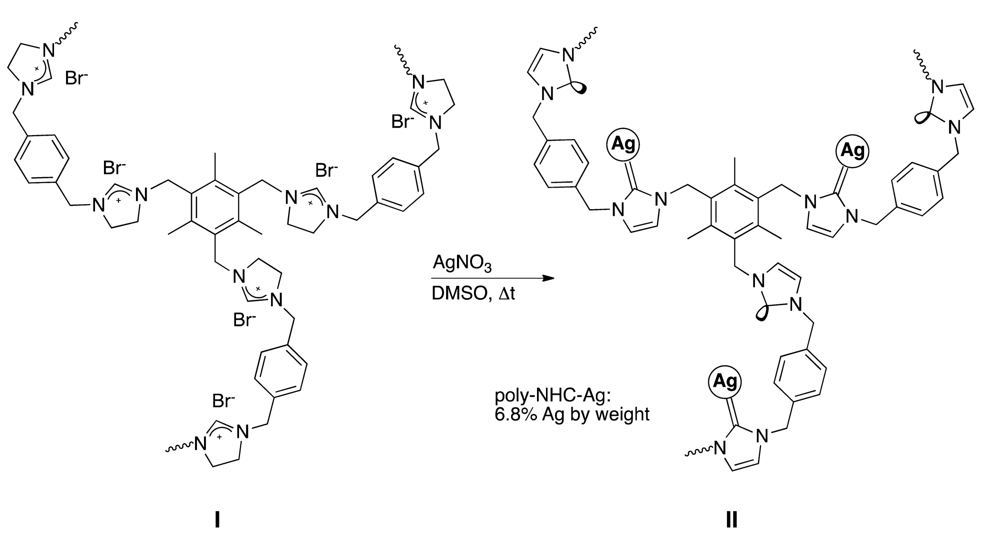
Kinetic studies showed that the reaction time strongly depends on the CO_2 pressure. It is remarkable that the equilibrium remains far to the side of the products at such high temperatures and moderate CO_2 pressures (Scheme 12).[95] One might speculate that the limited solubility of the propiolate salts in DMF may play a role in this.

Despite the harsh conditions, the resulting carboxylation process has a surprisingly good scope, which even extends to electron-deficient aryl-substituted alkynes. Its key advantage is that this noncatalytic reaction is robust and unaffected by the presence of moisture and oxygen. The drawbacks are the high reaction temperatures and the need for high-pressure equipment.

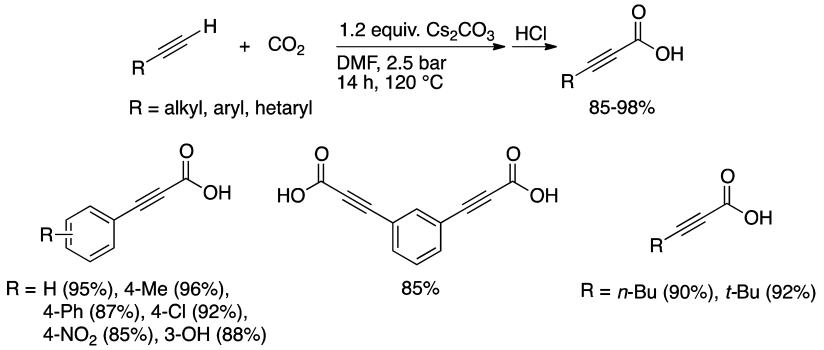
OUTLOOK

Overall, remarkable progress has been achieved in the C−H carboxylation of alkynes within the past few years. This elegant and sustainable transformation, which combines C−H bond functionalization with the utilization of CO_2 as a C_1 building block, is on its best way toward reaching synthetic maturity. Copper and silver have been discovered to be highly active catalyst metals, the effects of ligands, solvents, additives, and

Scheme 11. Synthesis of Poly-NHC-Ag



Scheme 12. Non-Catalytic Carboxylation of Terminal Alkynes with Carbon Dioxide



bases have been investigated, and strategies for catalyst immobilization have been devised. State-of-the-art catalysts allow using CO_2 at ambient pressure, at loadings below 1 mol %. The presence of free NHC centers has been demonstrated to widen the substrate scope of such carboxylation reactions, presumably by intermediate CO_2 adduct formation.

These discoveries lay a solid foundation for the development of a new catalyst generation that should combine the key findings of the research discussed above. Protocols allowing the carboxylation of terminal alkynes regardless of their electronic properties, at ambient CO_2 pressures, and using inexpensive sodium, calcium, or ammonium rather than cesium bases appear to be within close reach. It will be interesting to witness future advances in this topical field.

AUTHOR INFORMATION

Corresponding Author

*Fax: (+49) 631-205 3921. E-mail: goossen@chemie.uni-kl.de.

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Notes

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