

## Chapter 12

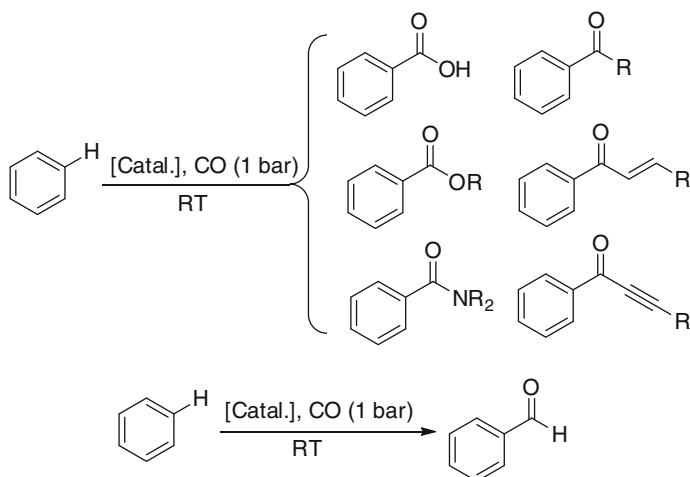
# Summary and Outlook

We have discussed developments in the area of transition metal catalyzed carbonylative coupling reactions of C–X bonds. Starting from the original work of Heck and his group's use of oxygen and nitrogen nucleophiles, various novel carbonylation reactions have been developed over the past decades. Due to the advancements in "classical" coupling methodology, these days a plethora of transition metal catalysts is also available for the carbonylative activation of C–X bonds and related substrates. Although cross-coupling reactions have become reliable transformations for all kinds of sophisticated natural product syntheses, this is only partly true for catalytic carbonylation reactions. The necessity to use carbon monoxide still hinders more applications of carbonylation reactions, because most synthetic organic chemists are reluctant to use high pressure equipment, even though most carbonylative coupling reactions can be run at ambient or low pressure (1–5 bar).

Notably, often a high pressure of CO retards the oxidative addition of the metal center to the C–X compound due to the  $\delta$ -acidic nature of CO as a ligand. Hence, catalytic performance is in general superior under milder conditions. It should also be noted that nowadays commercially available apparatuses exist that conveniently allow for parallel carbonylations, typically 6–16 fold.

What are the goals for the coming years in carbonylation reactions?

In the case of carbonylative coupling reactions, for example, catalyst efficiency (activity and productivity) in such reactions is still low compared to the more famous Suzuki or Heck reactions. In addition, substrates—especially (nitrogen) heteroarenes and more functionalized coupling partners—still represent significant challenges. Here, the development of better catalysts (ligands) will be a key issue. Clearly, such new catalyst systems should be tested initially in simpler benchmark reactions; however, this should be only the start and not the end of a catalyst development as it has often been in the past. With regard to sustainability, a major challenge will be the development of catalytic carbonylation reactions by directly employing arenes via C–H activation processes. The advantages of such methods are obvious: cheaper substrates and less waste. Obviously, these reactions would also be of principal interest to bulk chemicals.



**Scheme 12.1** Dream reactions

In the case of oxidative carbonylation reactions, air or other green oxidants should be applied more often in these reactions, especially in the industrially relevant direct carbonylation of arenes. For the more functionalized substrates which are interesting in organic synthesis, more selective catalyst systems are needed and directing groups might be omitted in the future.

Regarding the CO source, alternative CO sources should be discovered and applied in organic synthesis. Besides  $M(CO)_x$ , formic acid and aldehyde, can we use  $CO_2$  in carbonylation by in situ reduction?

Regarding the catalysts, the performance of palladium in carbonylative coupling is outstanding. But the other cheap potential catalysts like Fe and Cu have not yet been explored.

More specifically, we have several dream reactions. Can they be realized in the near future (Scheme 12.1)?