

TRANSITION METAL CATALYSIS

Nothing gets between Me and nitrogen

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Tertiary amides are useful solvents and synthetic intermediates, but their syntheses typically have poor atom economy and require functionalized precursors. In light of these problems, it would be desirable to prepare tertiary amides from CO and tertiary amines — a carbonylation using only sustainable materials. CO is reluctant to insert into strong N–C bonds in amines, but a team led by Thibault Cantat has avoided this insertion and developed an expeditious route to tertiary amides. Writing in *Angewandte Chemie International Edition*, the team describe how catalytically acylating a tertiary amine activates it towards dealkylation to give a tertiary amide.

Beyond their roles as Brønsted and/or Lewis bases and reductants, one might be hard pressed to find synthetic applications of tertiary

amines, much less conceive how carbonylation is possible without ring strain or proximal activating groups. Cantat and co-workers took NMe₂Ph as their model substrate and subjected it to high pressures of CO in the presence of the activator MeI and different low-valent Fe catalysts. In each case, the desired tertiary amide Me(O)CNMePh formed with 100% atom economy. Of the catalysts tried, $[(C_5H_5)Fe^I(CO)_2]_2$, $[Fe^0(CO)_5]$, $[Fe^0(CO)_{12}]$ and $[Fe^{-II}(CO)_4]^{2-}$, the electron-rich complex $[Fe^{-II}(CO)_4]^{2-}$ emerged as the best, which is unsurprising given that an earlier isoelectronic catalyst $[Co^{-I}(CO)_4]^-$ had been shown to carbonylate NMe₃ and give MeC(O)NMe₂. Despite the similarities between the Co^{-I} and Fe^{-II} experiments, even at the screening stage it became clear that the dianionic Fe^{-II} species is more nucleophilic and can thus operate under more practical conditions (8 bar versus 30 bar CO).

Catalyst nucleophilicity is important because a key step is the methylation (‘promotion’) of $[Fe^{-II}(CO)_4]^{2-}$ with MeI to give the intermediate $[MeFe^0(CO)_4]^-$. One CO ligand in this complex inserts into the Me–Fe bond as Fe picks up an additional CO ligand — also a reaction that may benefit from having a more electron-rich metal site. The acetyl ligand in the product $[Me(O)CFe^0(CO)_4]^-$ undergoes nucleophilic attack from the NMe₂Ph substrate to give $[Me(O)CNMe_2Ph]^+$ and regenerate $[Fe^{-II}(CO)_4]^{2-}$. Although NMe₂Ph is not liable to lose Me⁺, the cationic species $[Me(O)CNMe_2Ph]^+$ can undergo such

an S_N2 reaction with I⁻ to regenerate MeI. Thus, one obtains the tertiary amide Me(O)CNMePh — formally a CO insertion product — without CO ever getting between N and Me (or Ph) in the substrate. “CO has carbene character and our idea was to use this to facilitate insertion into C–N bonds,” says Cantat of the overall reaction.

Not satisfied with their yields, Cantat and colleagues exploited Lewis acid co-catalysts to bind coordinated CO to encourage insertion and polarize the acetyl ligand to make it a stronger electrophile for the tertiary amine. The team arrived at their optimal $[Fe^{-II}(CO)_4]^{2-}/MeI/Nd^{III}(O_3SCF_3)_3$ system for the carbonylation of NMeR₂ substrates (MeCN, 200 °C, 8 bar CO), an approach they extended to the ethylamine derivative NEt₂Ph by using EtI as the promoter.

Alkyl iodide promoters can conceivably sequester an amine substrate in its unreactive quaternary ammonium form. Such deleterious chemistry can only be reversed at higher temperatures, which explains the need for relatively harsh reaction conditions — a limitation of the present methodology. “We aim to better understand the mechanism and design second-generation catalysts that are more reactive and can transform CO at lower (<100 °C) temperatures,” concludes Cantat.

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Credit: David Schilter/Springer Nature Limited

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