C–H Activation

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Manganese(I)-Catalyzed C–H Aminocarbonylation of Heteroarenes

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Dedicated to Professor Paul Knochel on the occasion of his 60th birthday

Abstract: *A versatile manganese(I) catalyst was employed in C–H aminocarbonylation reactions of heteroarenes with aryl as well as with alkyl isocyanates using a removable directing group approach. Detailed experimental mechanistic studies were suggestive of an organometallic C–H manganesation step, followed by a rate-determining migratory insertion.*

The direct utilization of otherwise inert C–H bonds as latent functional groups has received considerable attention, because it avoids the use of prefunctionalized substrates.[1] In this context, over the last decade powerful transition-metal catalysts for C–H activation have been developed, which have enabled a streamlining of organic synthesis.[1] For instance, the step-economical assembly of aryl amides proved viable through C–H functionalizations using easily accessible isocyanates,[2] with key contributions by the groups of Kuninobu/Takai, Bergman/Ellman, Cheng, Li, and our group.[3] Reactions of this type could be successfully achieved using catalysts derived from the versatile, yet rather expensive, 4d or 5d transition metals rhodium, rhenium, or ruthenium. In contrast, only two very recent reports by us[4] and Ellman et al.[5] highlighted the potential of more naturally abundant 3d cobalt complexes for C–H aminocarbonylation reactions. Despite this considerable advance, the approach was limited to complexes employing the relatively expensive Cp^*Co^{III} motif (Cp^* = pentamethylcyclopentadienyl).

Although manganese is the third most abundant transition metal, organometallic[6–8] C–H functionalization reactions with manganese complexes are unfortunately scarce,[9] despite notable recent progress from the groups of Kuninobu/Takai[10] and Wang[11] as well as from our group.[12] Within our program on sustainable catalysis,[13] we have now developed an expedient chelation-assisted manganese-catalyzed C–H aminocarbonylation, on which we report herein. Notable features of our findings include: i) an unusually broad substrate scope featuring challenging sterically bulky alkyl isocyanates; ii) the use of synthetically useful removable directing groups (rDG);[14,15] and iii) a detailed mechanistic insight into the working mode of the catalysts (Figure 1).

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At the outset of our studies, we tested reaction conditions for the C–H aminocarbonylation of indole **1a** with isocyanate **2a** (Table 1). The desired product **3aa** could be obtained with $[Mn_2(CO)_{10}]$ as the catalyst using toluene as the solvent (entry 1). In contrast to recent cobalt-catalyzed approaches,[4,5] the manganese-catalyzed C–H aminocarbonylation also occurred in the absence of any additional ligands or additives. Although the catalytic efficacy was only slightly

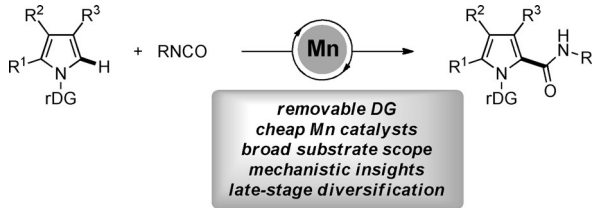
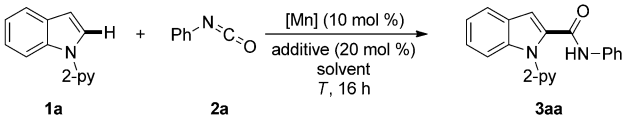


Figure 1. Manganese-catalyzed C–H aminocarbonylation.

Table 1: Optimization of the manganese-catalyzed C–H aminocarbonylation.[a]



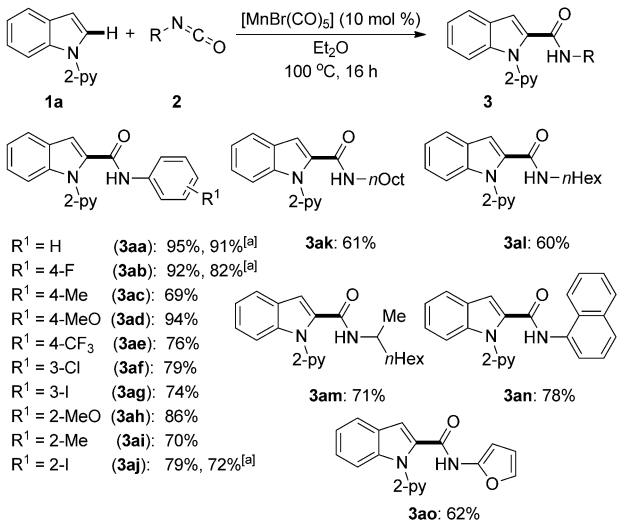
1a **2a** **3aa**

Entry	Catalyst	Additive	Solvent	*T* [°C]	Yield [%][b]
1	$[Mn_2(CO)_{10}]$	–	PhMe	120	56[c]
2	$[Mn_2(CO)_{10}]$	NaOAc	PhMe	120	47[c]
3	$[MnBr(CO)_5]$	NaOAc	PhMe	120	70[c]
4	$[MnBr(CO)_5]$	NEt_3	PhMe	120	79[c]
5	$[MnBr(CO)_5]$	PPh_3	PhMe	120	< 3[c]
6	$[Mn_2(CO)_{10}]$	NaOAc	Et_2O	100	76
7	$[Mn_2(CO)_{10}]$	NaOAc	1,4-dioxane	100	33[d]
8	$[Mn_2(CO)_{10}]$	NaOAc	DME	100	14[d]
9	$[MnBr(CO)_5]$	NaOAc	Et_2O	100	84
10	$[MnBr(CO)_5]$	–	PhMe	120	61
11	$[MnBr(CO)_5]$	–	THF	100	78
12	$[MnBr(CO)_5]$	–	MTBE	100	80
13	**$[MnBr(CO)_5]$**	**–**	***n*Bu_2O**	**100**	**91**
14	**$[MnBr(CO)_5]$**	**–**	**Et_2O**	**100**	**95**
15	$[MnBr(CO)_5]$	–	–	100	83
16	$[Mn_2(CO)_{10}]$	–	Et_2O	100	89
17	–	–	Et_2O	100	–
18	$MnCl_2$	–	Et_2O	100	–
19	$Mn(OAc)_2$	–	Et_2O	100	–

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.55 mmol), [Mn] (10 mol%), additive (20 mol%), solvent (1.0 mL), 100°C, 16 h. [b] Yield of isolated product. [c] **2a** (1.0 mmol). [d] NMR conversion with CH_2Br_2 as the internal standard. DME = 1,2-dimethoxyethane; MTBE = methyl-*tert*-butyl ether; py = pyridyl.

improved with $[MnBr(CO)_5]$ as the catalyst in the presence of a tertiary amine (entries 2–5), the most effective C–H aminocarbonylations were achieved with ethereal solvents (entries 6–13. Optimal results were, hence, obtained in ethers as the solvent with $[MnBr(CO)_5]$ as the catalyst of choice (entries 12–16). Furthermore, test reactions clearly showed that the C–H functionalization did not occur in the absence of the catalyst or when employing simple manganese salts (entries 17–19).

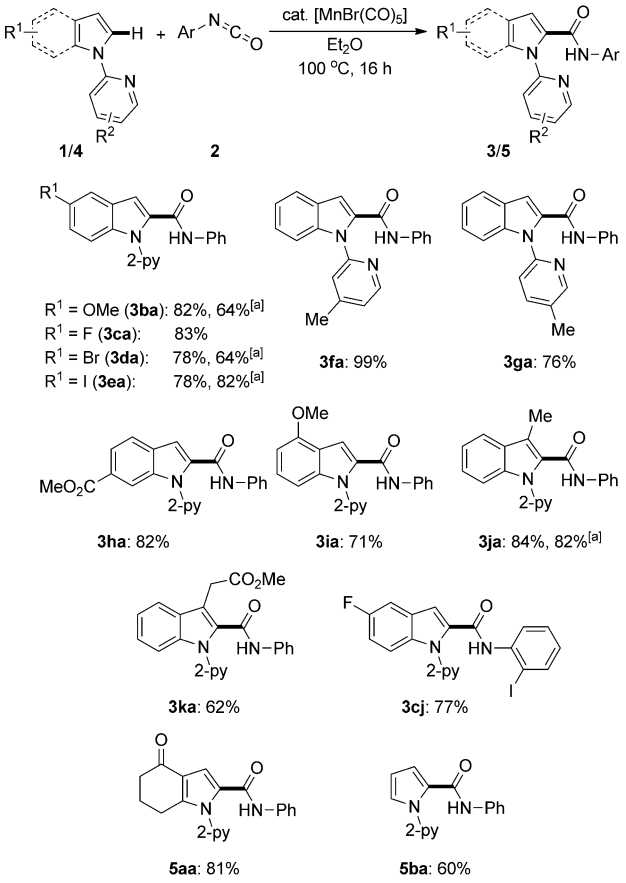
With the optimized catalytic system in hand (Table 1, entries 13 and 14), we explored its versatility in the C–H functionalization of indole **1a** (Scheme 1). Using these



Scheme 1. Manganese-catalyzed C–H aminocarbonylation with isocyanates **2**. [a] nBu_2O used as solvent.

reaction conditions, a variety of substituted aryl isocyanates **2** was smoothly converted into the corresponding products **3**. The reaction conditions demonstrated considerable tolerance of valuable functional groups, such as alkyl or aryl halides. It is important to note that the manganese(I) catalyst also proved applicable to more challenging electron-rich alkyl isocyanates **2**. Intriguingly, in contrast to the cobalt(III)-catalyzed reaction,[4,5] even isocyanate **2m** bearing a sterically hindered secondary alkyl group underwent the C–H functionalization, with the product obtained in a synthetically useful yield. Likewise, the congested *ortho*-substituted aryl isocyanate **2n** and the heteroaromatic substrate **2o** were converted with high catalytic efficacy.

Moreover, diversely decorated indoles **1** proved to be amenable for the site-selective C–H functionalization process (Scheme 2). The C–H aminocarbonylation reaction was shown to be highly chemoselective, as reflected by the smooth conversion of indoles bearing bromo, iodo, ester, or ketone groups, among others. Sterically encumbered substrates **1j** and **1k** featuring substituents in the C3 position were also found to be suitable substrates. Notably, the manganese(I) catalyst was not limited to indole substrates, but pyrroles **4** underwent the C–H functionalization with comparable levels of catalytic efficacy. It is noteworthy that

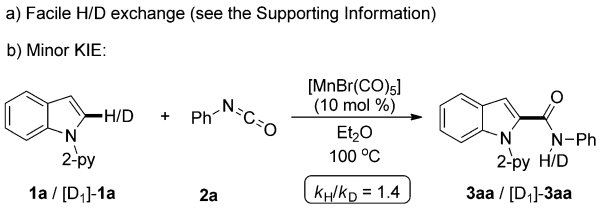


Scheme 2. Manganese-catalyzed C–H activation with indoles **1** and pyrroles **4**. [a] nBu_2O used as solvent.

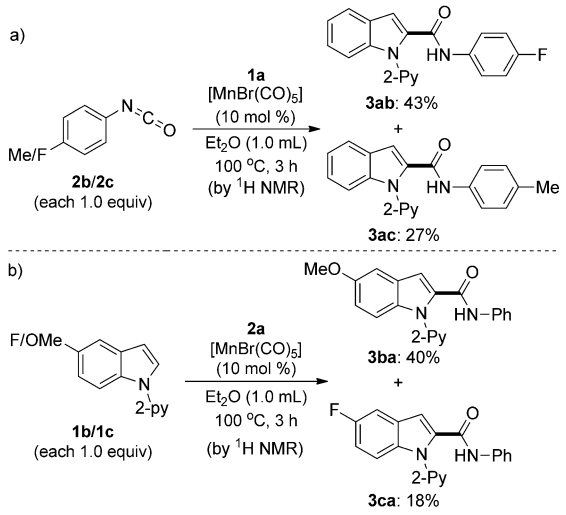
the aminocarbonylation of substrate **4b** chemoselectively delivered the mono-functionalized pyrrole **5ba** as the sole product.

In light of the unique features of the manganese-catalyzed C–H aminocarbonylation reaction, we sought to delineate the mode of action of the catalyst. To this end, we performed reactions with isotopically-labeled substrates (Scheme 3). First, we found that manganese-catalyzed H/D exchange was facile in this system.[16] In agreement with this finding, only a minor kinetic isotope effect (KIE) was found in independent reactions using either substrate **1a** or the monolabeled analogue $[D_1]$-**1a** (Scheme 3b). These observations are indicative of a fast and reversible C–H manganesation process.

Intermolecular competition experiments revealed electron-deficient isocyanates **2** and electron-rich indoles **1** to be



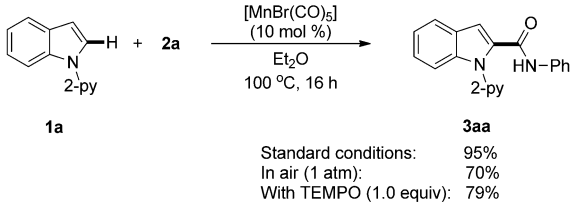
Scheme 3. Studies with isotopically labeled compounds.



Scheme 4. Intermolecular competition experiments.

inherently most reactive (Scheme 4), which can be rationalized in terms of a rate-determining nucleophilic attack of the metallated indole on the coordinated isocyanate electrophile **2**.

Additionally, evidence for an organometallic activation mode was gathered by successful manganese(I)-catalyzed C–H functionalizations under either an atmosphere of air or in the presence of stoichiometric amounts of the radical scavenger 2,2,6,6,-tetramethylpiperidine-*N*-oxide (TEMPO; Scheme 5).

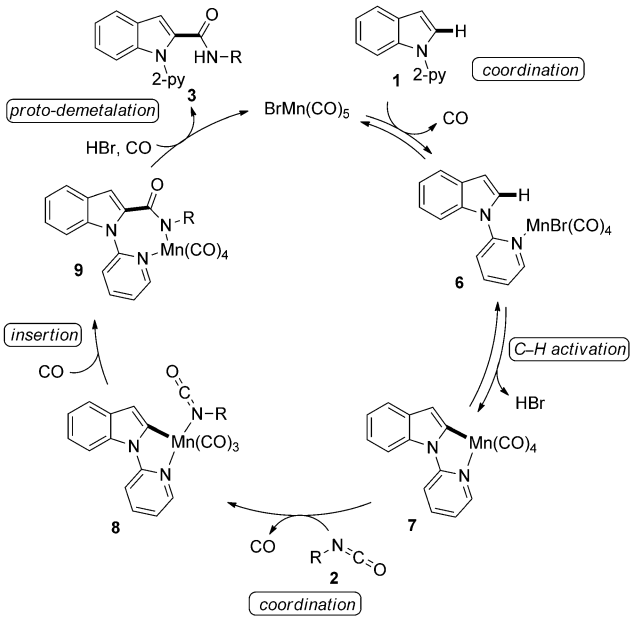


Scheme 5. Evidence supporting an organometallic activation mode for the C–H functionalization process.

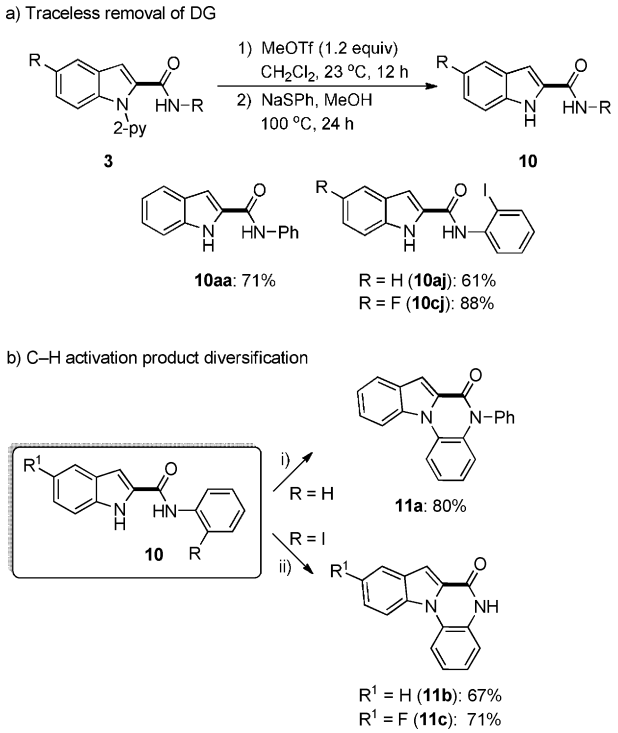
Overall, our experimental mechanistic studies are suggestive of a fast C–H manganesation, which is followed by coordination of the isocyanate **2** to the thus formed cyclometalated complex **7** (Scheme 6). Thereafter, coordination and rate-determining isocyanate insertion generates intermediate **9**. Finally, proto-demetalation liberates the desired product **3** and regenerates the catalytically active manganese(I) complex.

The synthetic utility of the manganese(I)-catalyzed C–H aminocarbonylation strategy was illustrated by devising a powerful procedure for the traceless removal of the pyridyl directing group (Scheme 7a). Moreover, the late-stage diversification of amides **10** provided versatile access to valuable quinoxalinones **11** in a step-economical manner (Scheme 7b).

In summary, we have reported the first manganese-catalyzed aminocarbonylation by C–H bond activation. The



Scheme 6. Proposed catalytic cycle.



Scheme 7. Diversification of C–H activation products. Reagents and conditions: i) 1-Fluoro-2-nitrobenzene, Cs_2CO_3, CH_3CN, 90 °C, 12 h. ii) CuI (cat.), L-proline (cat.), NaH, DMF, 150 °C, μw, 5 min.

optimized manganese(I) catalyst was highly functional-group tolerant and allowed for C–H functionalizations on synthetically useful heteroarenes with ample scope. Detailed mechanistic studies provided strong evidence for an organometallic C–H manganesation, along with a rate-determining migratory isocyanate insertion step.

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