ChemInform Abstract: C-H Activation/Functionalization Catalyzed by Simple, Well-Defined Low-Valent Cobalt Complexes.

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Communication

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C–H activation/functionalization catalyzed by simple, well-defined low valent cobalt complexes

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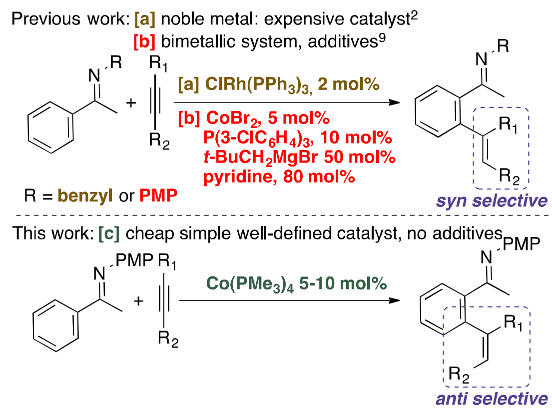
Supporting Information Placeholder

ABSTRACT: A facile C–H activation and functionalization of aromatic imines is presented using low-valent cobalt catalysts. Using $Co(PMe_3)_4$ as catalyst we have developed an efficient and simple protocol for the C–H/hydroarylation of alkynes with an *anti* selectivity. Deuterium-labeling experiments, DFT calculations coupled with the use of a well-defined catalyst have for the first time shed light on the elusive black box of cobalt catalyzed C−H functionalization.

The last decade has seen a rapid development in the field of C–H bond functionalization, and within this area *ortho*-directed C–H bond cleavage has proven to be a broadly applicable strategy for the regioselective functionalization of otherwise unreactive C–H bonds.[1] While much work focused on second-row transition metals such as palladium, ruthenium and rhodium[2] (Scheme 1, a) there is an obvious need to develop alternatives using the more naturally abundant and cheaper first-row transition metals.[3] Pioneering work in 1955 by Murahashi demonstrated the ability of cobalt to participate in C–H functionalization.[4] Some notable contributors to this field include Klein who demonstrated that the use of stoichiometric electron-rich cobalt(I) species, particularly $MeCo(PMe_3)_4$, were capable of promoting cyclometalation of aromatic substrates such as aryl ketones, imines and thioketones at low temperatures (–70 °C).[5] Despite these cobalt complexes demonstrating their potential utility in *ortho* C−H functionalization, no catalytic activity was reported. Kisch reported a series of *anti*-additions of diarylacetylenes into C−H bonds of azobenzenes catalyzed by $HCo(N_2)(PPh_3)_3$ or $HCo(H_2)(PPh_3)_3$. Unfortunately this reaction had a very limited scope and the mechanism remains ambiguous.[6] The last five years has seen an explosion of interest in C–H functionalization catalyzed by iron and cobalt.[7, 8] Of particular interest is the cobalt based quaternary system consisting of $CoBr_2$, $P(3\text{-}ClC_6H_4)_3$, neopentyl-magnesium bromide and pyridine developed by Yoshikai to promote the addition of internal alkynes to aromatic imines through chelation-assisted C–H activation (Scheme 1, b).[9]

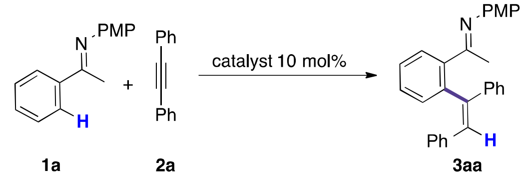
Despite these impressive results the use of bimetallic combinations as catalytic systems for direct C–H functionalization suffers limitations; the nature of the active catalytic species and the precise role of additives remain largely unknown. Furthermore it is difficult to gain mechanistic insight due tothe complex reaction mixture.

Scheme 1. Hydroarylation of alkynes *via* directed C−H activation.



We reasoned that well-defined electron-rich cobalt catalysts could offer the possibility to achieve C–H functionalization without reducing agents or additives and thus allow us to address some of these issues. Based on recent results published within our laboratory on the dimerization of arylacetylenes *via* a C–H activation/hydroalkynylation pathway using $Co(PMe_3)_4$ and $HCo(PMe_3)_4$ we postulated these catalysts could have the potential to participate in the C–H activation/functionalization of aromatic imines.[10, 11] Table 1 summarizes our initial screening of reaction conditions. We chose imine **1a** and diphenylacetylene **2a** as our model substrates. No conversion was observed at rt for $Co(PMe_3)_4$, $HCo(PMe_3)_4$, or $HCo(N_2)(PPh_3)_3$ (Entries 1-3). Heating the reaction to 80 °C using $HCo(PMe_3)_4$ and $Co(PMe_3)_4$, product **3aa** could be isolated in 50 and 60% yield respectively (Entries 4-5). Much to our surprise however, and in sharp contrast with Yoshikai's results, **3aa** was isolated exclusively as the (*Z)*-isomer, as determined by X-ray crystallography (see SI). Increasing the reaction temperature to 110 °C in toluene showed no significant improvement in yield (Entry 6). On switching from thermal to microwave conditions a reduction of the reaction time was observed (Entry 7). Using the catalyst previously reported by Kish (Entry 9) a very low yield of 10% was achieved further emphasizing the specificity of this catalyst to hydroarylation of azobenzenes.

Table 1. Optimization of reaction conditions[a]

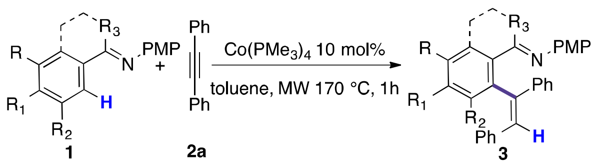


entry	catalyst[a]	time (h)	temp (°C)	solvent	yield[b] (%)
1	$Co(PMe_3)_4$	18	rt	THF	0
2	$HCo(PMe_3)_4$	18	rt	THF	0
3	$HCo(N_2)(PPh_3)_3$	18	rt	THF	0
4	$HCo(PMe_3)_4$	18	80	THF	50
5	$Co(PMe_3)_4$	18	80	THF	60
6	$Co(PMe_3)_4$	18	110	Toluene	68
7[c]	$Co(PMe_3)_4$	1	180	THF	72
8[c]	$HCo(PMe_3)_4$	1	180	THF	60
9[c]	$HCo(N_2)(PPh_3)_3$	1	180	THF	10
10[c]	$Co(PMe_3)_4$	1	180	MeCN	60
11[c]	$Co(PMe_3)_4$	1	180	Acetone	50
12[c]	$Co(PMe_3)_4$	1	170	Toluene	90[e]
13[c]	$HCo(PMe_3)_4$	1	170	Toluene	71
14[d]	$Co(PMe_3)_4$	1	170	Toluene	86

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol). [b] Isolated yield of **3aa**. [c] Reaction carried out in microwave. [d] Reaction carried out in sealed tube. [e] Same yield was obtained in the presence of 10 mol% of TEMPO.

Further exploration of solvents and reaction temperature led to the optimal conditions of 1 h at 170 °C (MW) with $Co(PMe_3)_4$ (Entry 12). Only a small decrease in yield was observed on switching to thermal conditions in a sealed tube showing no significant microwave effect (Entry 14).

Table 2. Scope of the aryl-imine[a]

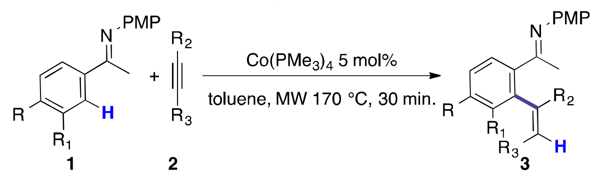


entry	1	R	R_1	R_2	R_3	3	yield[b] (%)
1	**1a**	H	H	H	Me	**3aa**	90(73)[c]
2	**1b**	H	Me	H	Me	**3ba**	82(60)[c]
3	**1c**	H	OMe	H	Me	**3ca**	90
4	**1d**	H	*t*-Bu	H	Me	**3da**	90[d](60)[c]
5	**1e**	H	F	H	Me	**3ea**	80[e](67)[c]
6	**1f**	Me	H	H	Me	**3fa**	61[e]
7	**1g**	H	H	OMe	Me	**3ga**	60[e]
8	**1h**	H	H	F	Me	**3ha**	85[e](67)[c]
9	**1i**	H	H	CN	Me	**3ia**	84[e](63)[c]
10	**1j**	H	OCH_2O		Me	**3ja**	70[e](61)[c]
11	**1k**	H	C_4H_4		Me	**3ka**	80[e, f](65)[c, f]
12	**1l**	H	H	H	Et	**3la**	61[g, h]
13	**1m**	H	H	H	$-(CH_2)_3-$	**3ma**	82

[a] Unless otherwise stated reaction carried out on: **1** (0.5 mmol), **2a** (1 mmol). [b] Isolated yield of **3**. [c] Isolated yield using $HCo(PMe_3)_4$ as catalyst. [d] Reaction carried out on 1 gram of **1d**. [e] Reactions carried out using 1.2 equiv. of **2a**. [f] Isolated as a 75/25 mixture of regioisomers. [g] **3la** obtained as the ketone after acidic treatment. [h] Stereoselectivity of addition (96/4) determined by ^{1}H NMR.

With our optimal conditions in hand, we sought to explore the potential scope of the hydroarylation reaction on a variety of imines and diphenylacetylene **2a** (Table 2). The reaction proceeded in good yields for *para*-substituted imines (Entries 1-5). Electron-donating (e.g., OMe), neutral and electron-withdrawing groups (e.g., F) were all tolerated. The reaction ran smoothly on gram-scale with an identical yield to the standard reaction conditions (Entry 4). Substrates bearing a methyl group in *meta* position (Entry 6) showed complete selectivity for the less hindered *ortho* position which could be expected based on sterics, while substrates bearing a methoxy, fluoro and cyano group in the same position (Entries 7-9) reacted preferentially at the more hindered *ortho* position. Presumably this is due to the secondary directing effect previously reported for cobalt, ruthenium and iridium catalysis.[12] A similar secondary group effect was observed for the methylenedioxy product (Entry 10). The imine derived from 2-acetonaphthone also participated in the reaction to afford the desired product in good yield and reasonable regioselectivity of 75/25 for both catalysts (Entry 11). Imines derived from propiophenone and tetralone also yielded the desired compound (Entries 12-13).

Table 3. Scope of the alkynes



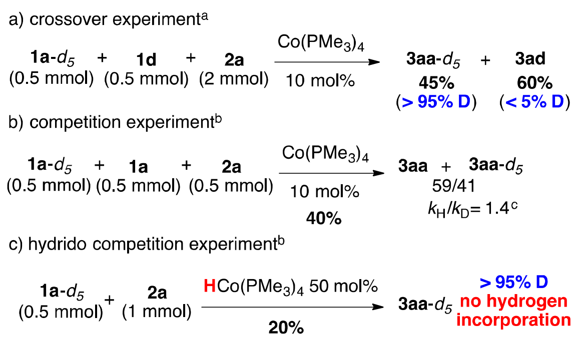
entry	1	R	R_1	2	R_2	R_3	3	yield[b] (%)
1	**1a**	H	H	**2b**	Ph	TMS	**3ab**	85
2	**1b**	Me	H	**2b**	Ph	TMS	**3bb**	63
3	**1c**	OMe	H	**2b**	Ph	TMS	**3cb**	55
4	**1d**	*t*-Bu	H	**2b**	Ph	TMS	**3db**	85
5	**1h**	H	F	**2b**	Ph	TMS	**3hb**	81
6	**1d**	*t*-Bu	H	**2c**	*p*-MeC_6H_4	TMS	**3dc**	38
7	**1d**	*t*-Bu	H	**2d**	*p*-$MeOC_6H_4$	TMS	**3dd**	79[c, g]
8	**1d**	*t*-Bu	H	**2e**	*p*-$CF_3C_6H_4$	TMS	**3de**	90
9	**1d**	*t*-Bu	H	**2f**	*m*-$MeOC_6H_4$	TMS	**3df**	62
10	**1d**	*t*-Bu	H	**2g**	*n*-C_3H_7	TMS	**3dg**	45[d, g]
11	**1d**	*t*-Bu	H	**2h**	Ph	*n*-C_3H_7	**3dh**	50[e, f]
12	**1d**	*t*-Bu	H	**2i**	*n*-C_3H_7	*n*-C_3H_7	**3di**	96[h, i]
13	**1d**	*t*-Bu	H	**2j**	*p*-*n*BuC_6H_4	*p*-*n*BuC_6H_4	**3dj**	75

[a] Unless otherwise stated reaction carried out on 0.5 mmol of **1** using 1.2 equiv. of **2**. [b] Isolated yield of **3**. [c] Stereoselectivity of addition (85/15). [d] Stereoselectivity of addition (89/11) determined by ^{1}H NMR. [e] Regioselectivity of insertion (86/14) determined by ^{1}H NMR. [f] **3dh** was obtained as the ketone after acidic treatment. [g] Reaction time 1h. [h] Reaction carried out with 2 equiv. of **2**. [i] Obtained as a mixture of mono- and dialkenylated product.

Having explored the scope of the reaction in terms of imine variation we then focused on other acetylenes (Table 3). Interestingly, non-diarylic acetylenes proved to be much more active thus lower catalyst loadings and reaction times were possible. The reaction of TMS protected phenylacetylene with a variety of *para*-substituted imines proceeded in moderate to good yields (Entries 1-4). The insertion showed complete *anti*-stereoselectivity and regioselectivty which was proven by ^{1}H NMR after removal of the TMS protecting group by TBAF (see SI). As seen previously with the addition of diphenylacetylene, *meta*-fluoro substituted imines preferentially reacted in the more hindered position (Entry 5). We chose imine **1d** as the model substrate for the proceeding reactions due to the ease at which we could follow the reaction by ^{1}H NMR. *Para* and *meta*-substituted TMS-protected phenylacetylene reacted in moderate to good yields with the same regio- and stereoselectivity as seen before (Entries 6-9). TMS protected pentyne (Entry 10) produced a modest yield of 45 % with reasonable stereoselectivity of addition (89/11). Due to stability issues, the product **3dh** of 1-phenyl-1-pentyne addition could not be isolated purely as the imine derivative but instead was hydrolyzed by 3M HCl (see SI) to afford the corresponding ketone in 50% yield with a lower regioselectivity of the addition (Entry 11). Next the reactivity of 4-octyne was explored. It proved to be the most active of all substrates but the regioselectivity of the C–H activation was difficult to control. The C–H functionalized product was isolated in 96% yield as a (70/30) mixture of mono- and dialkenylated compounds (Entry 12). Finally for this series the *bis*-butyl substituted diphenylacetylene was shown to efficiently undergo addition (Entry 13). It is worth mentioning that using $HCo(PMe_3)_4$ as catalyst allows the formation of same compounds in slightly lower yields.

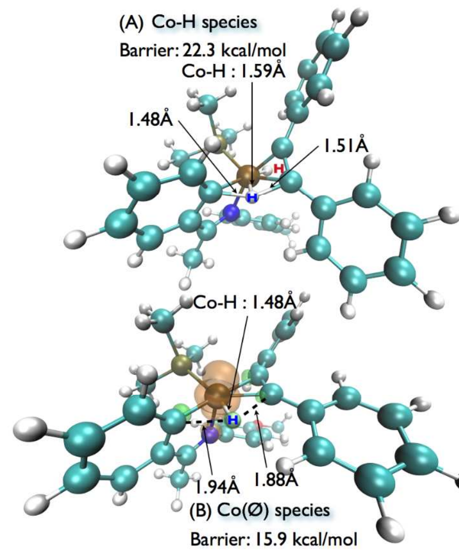
To probe the reaction mechanism we initially carried out a series of experiments using deuterium-labeled imine **1a-*d*$_5$** (Scheme 2). Firstly, combining an equimolar mixture of **1a-*d*$_5$** and **1d** no evidence of H/D crossover in the final products was observed (Scheme 2a). This unambiguously proves that the olefinic hydrogen atom is a product of intramolecular hydrogen transfer excluding any deprotonation step. Secondly, competition experiment between an excess of **1a-*d*$_5$** and **1a** compared to **2a** was ran to determine the kinetic isotopic effect (Scheme 2b). Values of 1.4 and 1.7 were obtained respectively for $Co(PMe_3)_4$ and $HCo(PMe_3)_4$ in agreement with the KIE (1.05 and 1.65) of the transition states calculated using the Bell kinetic theory. However, these values are not significant enough to suggest that the C–H activation is the rate limiting step. Thirdly, combining imine **1a-*d*$_5$** with two equivalents of diphenylacetylene in the presence of 50 mol% of $HCo(PMe_3)_4$ under standard reaction conditions, we saw no incorporation of hydrogen in the final product with **3aa-*d*$_5$** isolated in a 20% yield as the sole compound (Scheme 2c). Moreover, no evidence of oxidative addition was observed by ^{1}H NMR when heating $HCo(PMe_3)_4$ in the presence of the imine. From these observations we postulated that the C–H bond activation and functionalization proceed in a concerted manner for the hydro-complex.

Scheme 2. Deuterium labeling and KIE experiments



[a] Reaction conditions: MW 170°C, 1 h. [b] Reaction conditions: MW 170°C, 30 min. [c] KIE for the $HCo(PMe_3)_4$ was determined to be 1.7.

To further substantiate this claim a series of computational studies namely, DFT calculations were performed on the key step of the catalytic process (the C–H activation). The Turbomole program was used in conjunction with the B3LYP functional complemented by an empirical scheme to describe dispersion and a double-zeta polarized basis set (see SI). To find a relevant transition state, it was mandatory to remove three phosphines from the metallic centre in order to accommodate simultaneously imine and alkyne. The two catalysts $Co(PMe_3)_4$ and $HCo(PMe_3)_4$ were investigated and led to globally similar transition state (TS) structures (Figure 1). It is noteworthy to mention the following observations. Firstly, the barrier with $Co(PMe_3)_4$ is found to be smaller than with $HCo(PMe_3)_4$ which is in line with the experimental observations.



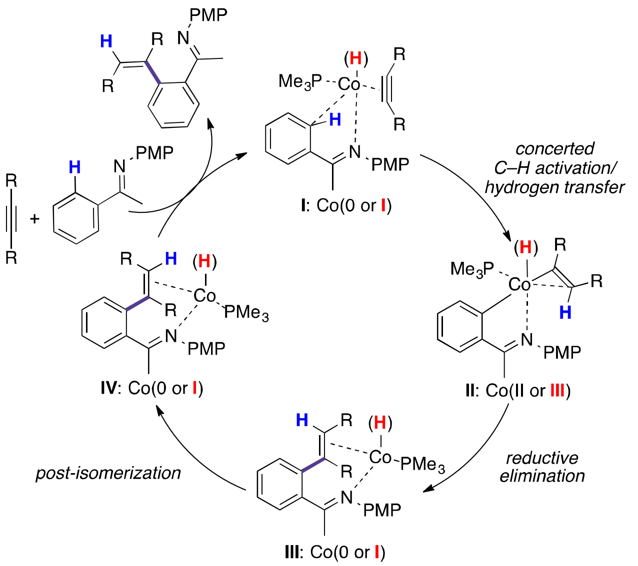
(**A**) For $HCo(PMe_3)_4$ catalyst, (**B**) For $Co(PMe_3)_4$ catalyst. On structure **B**, the spin density iso-surface is also shown

Figure 1. DFT calculated transition state structures for the C–H activation

Secondly, the structural similarity between the two transition states can be explained by the fact that the orbital involving the unpaired electron (namely d_z2) in the Co(0) species shows no interaction with the migrating hydrogen. Nevertheless, the cobalt-hydrogen distance is shorter in the Co(0) species. Thirdly, to understand the mechanism of C–H activation, topological analyses were performed, namely using AIM and ELF schemes. It appears that, according to AIM, there is a bonding between cobalt and hydrogen during the transfer. According to ELF methodology, one electron is always associated to the proton during hydrogen transfer (see SI). Thus, this C–H activation pattern can be designated as a metal-assisted σ bond metathesis, also termed in a more general way ligand-to-ligand hydrogen transfer (LLHT) as coined by Eisenstein and Hall.[13]

Putting together the closeness of the KIE values, the same regioselectivity[14] for the naphthalene compound **3ka** and the similarity of the calculated TS, we can propose the following common catalytic cycle for both catalysts (Scheme 3).[15] Ligand exchange between trimethylphosphine, the imine and alkyne leads to the formation of intermediate (**I**). A concerted hydrogen transfer *via* an oxidative pathway generates intermediate (**II**). Intermediate (**II**) undergoes a reductive elimination leading to the formation of intermediate (**III**). A subsequent isomerization would account for the observed *anti* selectivity. Indeed, we calculated that at 170°C ***anti*-3aa** is 2.27 kcal more stable than ***syn*-3aa,** high enough to achieve complete isomerization. Indeed, the ability of cobalt to participate in the isomerization of double bonds is well known.[16] Shibata reported a simple cationic iridium-catalyzed addition of aryl ketones to alkynes which allowed us access to the ketone with *syn*-stereochemistry.[17] Introduction of this ketone into our catalytic system resulted in an isomerization of 55 % to our observed *anti* product suggesting that the post- isomerization is a feasible pathway. Complete isomerization was not observed in this case presumably due to the weaker anchoring group effect of ketones compared to imines.[11, 18]

Scheme 3. Proposed catalytic cycle



In conclusion we have demonstrated the utility of simple well-defined low-valent cobalt catalysts to carry out C–H functionalization without the need for reducing agents or additives. Moreover, for a wide scope of substrates *anti*-selectivity was observed for this hydroarylation process. Additionally deuterium-labeling studies and computational studies of our simple catalysts have allowed us to gain greater mechanistic insight than previously reported for cobalt catalyzed C–H functionalization.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and physical properties of compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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(14) In our previous work (ref 10) we observed the same tendency.

(15) Stability of the catalysts was explored (see SI).

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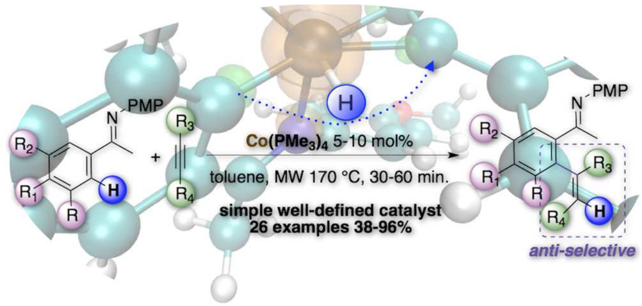
PMP
N
R2
R1
R
H
R3
R4
+
Co(PMe3)4 5-10 mol%
toluene, MW 170 °C, 30-60 min.
simple well-defined catalyst
26 examples 38-96%
anti-selective