Investigation of Additive Effects in Enantioselective Copper-Catalysed C–H Insertion and Aromatic Addition Reactions of α-Diazocarbonyl Compounds.

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Abstract: Significant enhancements in enantioselectivities and reaction efficiencies in asymmetric copper-catalysed C–H insertion and aromatic addition reactions of α-diazocarbonyl compounds in the presence of various group I salts are reported. For the first time in carbenoid chemistry, evidence for the critical role of the metal cation is described.

Key words: diazocarbonyl, copper catalysis, C–H insertion, Buchner reaction, bis(oxazoline) ligands,

Carbenoid C–H insertion and aromatic addition reactions of α-diazocarbonyl compounds are very important reactions in organic synthesis for the formation of C–C bonds.[1–4] While traditionally conducted in the presence of rhodium catalysts, chiral copper systems have also been shown to be highly effective catalysts for enantioselective C–H insertion[5–7] and Buchner reactions.[8,9] We[7,8] and Zhou[10,11] have recently demonstrated that the addition of NaBARF {BARF = tetrakis[3,5-bis (trifluoromethyl)phenyl] borate} to the catalytic complex comprising a copper source and a bis(oxazoline) ligand results in enhanced reaction efficiencies and enantioselectivities in X–H insertion reactions. However, to date the mechanistic role of NaBARF in carbenoid insertion reactions has not been discussed. Herein we report our findings on the key role of the additive in enantioselective C–H insertion and aromatic addition reactions.

Two α-diazosulfones [1-diazo-1-phenylsulfonyl-5-phenyl pentan-2-one **3** and methyl 2-diazo-2-(4-phenylbutylsulfonyl) acetate **5]** were chosen for this initial study. C–H insertion reactions of **3** and **5** were conducted in refluxing dichloromethane in the presence of a copper catalyst generated *in situ* from 5 mol% $CuCl_2$, 6 mol% bis(oxazoline) ligand (Figure 1) and 6 mol% additive. In general, *trans*-cyclopentanone **4** and *cis*-thiopyran **6** were the major products for the insertion reactions of **3** and **5**, respectively.

As was observed in our previous study examining CuCl- catalysed reactions,[7] C–H insertion of α-diazo-β-keto sulfone **3** in the presence of $CuCl_2$ and bis(oxazoline) ligand was seen to result in very low levels of enantioselectivity (Table 1, entry 1). Addition of NaBARF to the catalytic mixture was found to result in a dramatic increase in enantiocontrol (Table 1, entry 2), and this high level of asymmetric induction was largely maintained for reactions employing $NaPF_6$ as additive (Table 1, entry 3). In contrast, no significant enhancement in enantioselectivity was recorded for reactions in the presence of either $NaB(C_6H_5)_4$ or $NaBF_4$ (Table 1, entries 4 and 5).

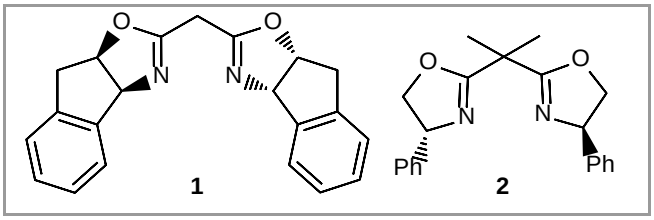
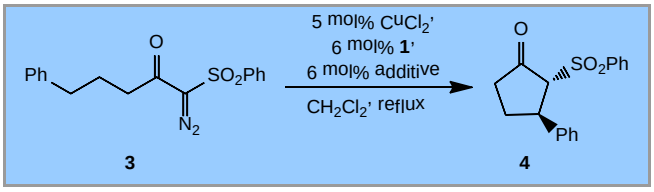


Figure 1 Bis(oxazoline) ligands.

A slight increase in enantioinduction (91% ee) was observed for insertion of **3** with KBARF (Table 1, entry 6) relative to cyclisation with NaBARF. Notably, this result represents the highest level of asymmetric induction recorded to date for cyclopentanone synthesis *via* C–H insertion.

Table 1 C–H insertion reactions of 1-diazo-1-phenylsulfonyl-5-phenylpentan-2-one **3**.



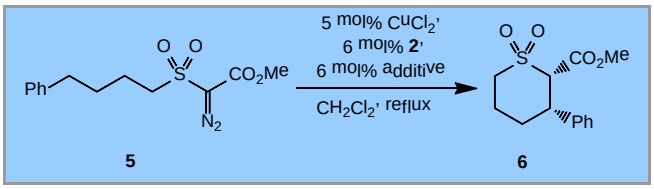
Entry	Additive	Yield[a] (%)	ee[b,c] (%)
1	–	62	14
2	NaBARF	87	89
3	$NaPF_6$	66	83
4	$NaB(C_6H_5)_4$	77	25
5	$NaBF_4$	63	11
6	KBARF	59	91
7	KPF_6	43	35
8	$LiPF_6$	78	71
9	NaBARF + 15-crown-5[d]	63	25

[a] Isolated after flash chromatography.
[b] Determined by chiral HPLC (see supporting information for details).
[c] Absolute configuration is (2*R*, 3*R*).
[d] 8 mol% 15-crown-5 added to catalytic mixture.

Reactions with the potassium and lithium salts KPF_6 and $LiPF_6$ resulted in decreased levels of enantioselectivity relative to reactions employing $NaPF_6$ (Table 1, entries 7 and 8 vs. 3).

From the results presented in Table 1, it is evident that the choice of additive has a significant effect on the level of enantioselectivity that can be achieved in the C–H insertion reactions of α-diazosulfone **3**. Highest enantiocontrol was achieved for reactions in the presence of $BARF^-$, which behaves as a very weakly-coordinating anion.[12] Reactions employing less weakly coordinating anions [PF_6^-, $B(C_6H_5)_4^-$, BF_4^-] resulted in decreased levels of asymmetric induction. Thus, as decreased anion coordination appears to correlate to an increase in enantioselectivity, it is probable that the main role of these additives is to provide a "naked" alkali metal cation in solution which may play a key role in permitting formation of a highly efficient catalytic complex. It is envisioned that the role of the metal cation is to effect complete or partial chloride abstraction[13–15] from the copper complex, thereby altering the active catalyst species. Evidence for this includes isolation of small amounts of sodium chloride which precipitate from the reaction mixture.[16] More significantly, when reactions were conducted in the presence of NaBARF and the crown ether 15-crown-5, which is known to effectively complex sodium cations, the enantioselectivity decreases substantially, reversing the enhancement previously seen for addition of the additive species (Table 1, entry 9 vs. 2).

Table 2 C–H insertion reactions of methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate **5**.



5 **6**

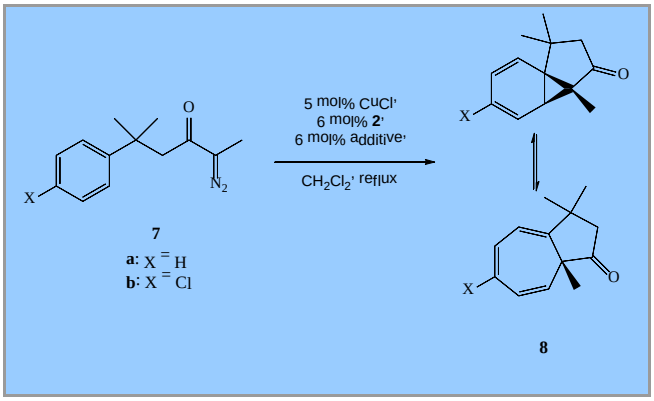
Entry	Additive	Yield[a] (%)	ee[b,c] (%)
1	–	48	79
2	NaBARF	61	95
3	$NaPF_6$	68	97
4	$NaB(C_6H_5)_4$	4	–[d]
5	$NaBF_4$	43	93
6	KBARF	46	98
7	KPF_6	45	92
8	$LiPF_6$	47	83

[a] Isolated after flash chromatography.
[b] Determined by chiral HPLC (see supporting information for details).
[c] Absolute configuration is (2*S*, 3*S*).
[d] Not determined.

Insertion reactions with methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate **5** were also conducted (Table 2). Although in this case the enantioselectivity achieved for cyclisation in the absence of additives (Table 2, entry 1) is much higher than the corresponding insertion with α-diazosulfone **3** (Table 1, entry 1), enhancement of asymmetric induction is still possible for reactions employing NaBARF, KBARF and $NaPF_6$ (Table 2, entries 2, 3 and 6). In this instance, high levels of enantiocontrol were observed for insertions in the presence of KPF_6 and $NaBF_4$ (Table 2, entries 5 and 7). This observation is in contrast with results recorded for insertion with α-diazo-β-keto sulfone **3** in which a decrease in ee was noted for insertion in the presence of KPF_6 and $NaBF_4$ (Table 1, entry 5 and 7). As was previously noted for cyclisation of **3**, reduced enantioselectivity was observed for insertion employing $LiPF_6$ (Table 2, entry 8). Suprisingly, use of $NaB(C_6H_5)_4$ as additive resulted in the formation of very little C-H insertion product, with several competing side reactions instead observed (Table 2, entry 4).

Enhancement of enantioselectivity in the presence of NaBARF has also been observed in copper-catalysed Buchner reactions of α-diazoketones.[8] As summarised in Table 3, alteration of the counterion has a significant effect on asymmetric induction in the intramolecular aromatic addition reactions of diazoketones **7a** and **7b**. In the absence of the sodium cation, little or no enantioselectivity is achieved using CuCl and bis(oxazoline) ligand **1** (Table 3, entries 1 and 7), while addition of NaBARF, KBARF or $NaPF_6$ to the catalytic mixture results in good enantioselectivity in each case (Table 3, entries 2–4 and 8–10). As was previously observed for the C–H

Table 3 Buchner reaction of diazoketones **7a** and **7b**.



7
a: X = H
b: X = Cl

8

Entry	X	Additive	Yield[a] (%)	ee[b] (%)
1	H	–	31	37
2	H	NaBARF[c]	57	78
3	H	$NaPF_6$	65	78
4	H	KBARF	55	80
5	H	$LiPF_6$	50	49
6	H	NaBARF + 15-crown-5[d]	47	56
7	Cl	–	49	0
8	Cl	NaBARF[c]	54	78
9	Cl	$NaPF_6$	56	73
10	Cl	KBARF	47	71
11	Cl	$LiPF_6$	66	54
12	Cl	NaBARF + 15-crown-5[d]	67	45

[a] Isolated after flash chromatography.
[b] Determined by chiral shift ^1H NMR experiments using (+)-Eu(Hfc)$_3$.
[c] Previously published results.[8]
[d] 8 mol% 15-crown-5 added to catalytic mixture.

insertion reactions of **3**, use of $LiPF_6$ as an additive is less effective than $NaPF_6$ in facilitating highly enantioselective reactions (Table 3, entries 5 and 11). Once again, addition of 15-crown-5, together with NaBARF, (Table 3, entries 6 and 12) resulted in a substantial decrease in asymmetric induction in line with results reported for C-H insertion of α-diazosulfone **3**.

In conclusion, we have demonstrated for the first time the key role of the alkali metal cation in producing highly enantioenriched products *via* C–H insertion and aromatic addition of α-diazocarbonyl compounds. Work is currently underway to further investigate the influence of additives in copper-catalysed carbenoid transformations.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(16) Presence of NaCl confirmed by PXRD analysis (see supporting information for details).