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Stereochemistry of the Transmetalation of Grignard Reagents to Copper (I) and Manganese (II)

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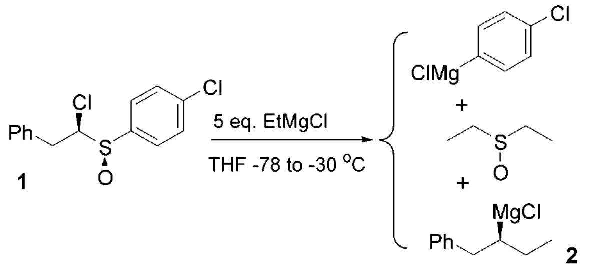
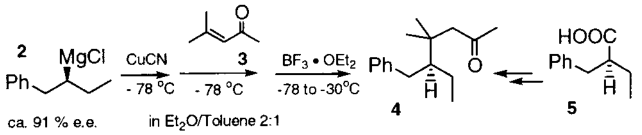
Transmetalation of an organo-(main-group)metal compound to an organo-transition-metal compound is an obligatory step in a multitude of transition-metal catalyzed coupling reactions. There is comparatively little information on the mechanistic details of this transformation. Does it occur with retention or inversion of configuration at carbon?[1] Is electron transfer to give intermediary free radicals involved? The latter mechanistic scenario would manifest itself by a loss of stereochemical information (racemization or epimerization) at the metal-bearing stereogenic center, because alkyl radicals have a very low (<0.5 kcal mol^{-1}) barrier toward racemization.[2]

The present-day picture regarding transmetalation of configurationally stable[3] organo-lithium compounds to copper (I) is anything but uniform; cases of full retention of configuration (signaling concerted transmetalation)[4] are confronted with cases of complete or predominant racemization.[5] Transmetalation of organo-zinc compounds, however, to copper (I) can be considered as established[6] to proceed with full retention of configuration.[7] The tendency of an organo-lithium (or an organo-zinc) reagent to enter transmetalation via a single electron transfer (SET) process depends on the reduction potential of the transition-metal reagent and on the oxidation potential of the starting organometallic compound. An organometallic compound will be easier to oxidize the more ionic and less covalent the carbon−metal bond is. The ionic character of the carbon−metal bond is for Grignard reagents intermediate between that of organo-lithium and organo-zinc compounds. Hence, it is an open question, do Grignard reagents undergo concerted transmetalation as the organo-zinc compounds or do they tend more strongly to enter SET processes? [8] Given the importance of Grignard reagents in Gilman (copper (I)) couplings, the lack of such information is surprising.

We recently gained access to the enantiomerically enriched (ca. 91% ee) secondary Grignard reagent **2**, in which the magnesium-bearing carbon atom is the sole stereogenic center.[9] This reagent is configurationally stable below −10 °C and thus ideally suited to determine the mechanisms of Grignard reactions.[10] We report here on the stereochemistry of the transmetalation of this reagent to Cu(I) and Mn(II). The reagent **2** was generated from the sulfoxide **1** by addition of 5 equiv of EtMgCl. It should be noted that this results in a cocktail of Grignard reagents and sulfoxides in which the reagent **2** of interest is only a constituent.



We then looked at the transmetalation of the Grignard reagent **2** (−78 to −30 °C in THF) with 1 equiv (relative to total Mg) of a copper (I) salt (CuCN, $Li_2CuCNCl_2$, CuCN·TMSCl, CuCN, BF_3·OEt_2, CuI·PBu_3, CuBr·PBu_3, CuBr·SMe_2). This met with a uniform result. Whatever the trapping reagent was (PhCOCl, $CH_2{=}CH{-}CH_2Cl$, $CH_2{=}C{=}CHOMe$, $Ph{-}C{\equiv}C{-}COOEt$, $Me_2C{=}CH{-}CO{-}Me$/BF_3·OEt_2), the adducts were obtained as racemates. This held also in those instances when the reaction was carried out in Et_2O/toluene (2:1) as solvent. From the work of Knochel[6] it is clear, that secondary alkyl cuprates are configurationally stable under the reaction conditions used here and that they can be trapped with retention of configuration. Hence, it is the transmetalation of **2** that leads to racemization.



Further experiments, however, showed the situation to be more complex. When less than 1 equiv of CuCN was applied in the coupling of **2** to the enone **3**, compare Table 1, a low degree of retention of configuration of the product **4** could be recorded, which increased on decreasing the amount of CuCN applied. A similar result was seen when $[(MeCN)_4Cu]^+$ PF_6^- was used. The absolute configuration of the product **4** was secured[11] by chemical correlation with the acid **5**.

These findings could be explained by a mechanistic scenario in which two transmetalation cycles with different stereochemical outcomes are involved. The reaction is initiated by a fast transmetalation of **2** with CuCN to furnish RCuCN·MgCl (**6**), a process that occurs with complete racemization. If less than 1 equiv of CuCN is present, a considerably slower second transmetalation of **6** with **2** to give R_2Cu^- $MgCl^+$ (**7**) follows, a process which is characterized by (partial or complete?) retention of configuration. In the case of $[(MeCN)_4Cu]^+$ PF_6^- the rates of the two transmetalation cycles appear to be similar to one another. This would account for an ee > 0 in the reaction with 1 equiv of $[(MeCN)_4Cu]^+$ PF_6^-.

The concept of the two transmetalation cycles suggests that transmetalation of **2** to preformed RCuCN·MgCl, such as EtCuCN·MgCl, should lead to a higher ee in the product **4**. This is indeed borne out by the experiments 5 and 6 in Table 1.

What makes for the mechanistic difference between the two transmetalation cycles that is manifested in the different stereo-

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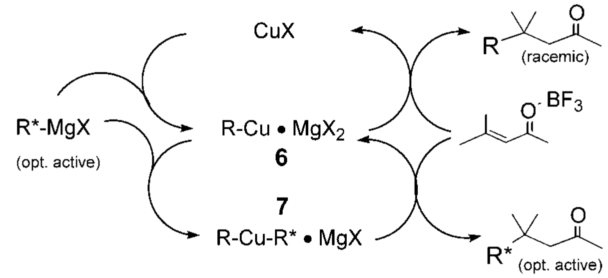
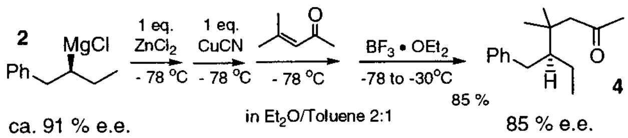
Table 1: Copper-Mediated Couplings of **2** in Et_2O/Toluene

entry	copper salt	equiv	**4**: yield (%)	**4**: ee (%)
1	CuCN	1.00	80	0
2	CuCN	0.50	75	12
3	CuCN	0.10	70	30
4	CuCN	0.05	50	34
5	$EtCuCN\cdot MgCl$	1.00	61	23
6	$EtCuCN\cdot MgCl$	0.10	48	60
7	$[(MeCN)_4Cu]PF_6$	1.00	66	31
8	$[(MeCN)_4Cu]PF_6$	0.10	53	65
9	$[(MeCN)_4Cu]PF_6$	0.05	50	66



chemical outcomes? A possible explanation focuses on the reduction potential of CuCN and of $RCuCN\cdot MgCl$ (**6**). It seems reasonable that the former is a stronger oxidant than the latter. Hence, CuCN can cause SET, whereas **8** might not! That subtle differences in the redox potentials may control the stereochemical result is seen from the following experiment: That is, transmetalation of **2** with $ZnCl_2$ to form an organo-zinc chloride is not compromised by an SET reaction. The same holds for the subsequent transmetalation of the organo-zinc chloride with stoichiometric CuCN.[6] Hence, essentially complete retention of configuration may be attained by *sequential* transmetalation of **2** first to $ZnCl_2$ and then to CuCN.



Finally, we briefly examined the transmetalation of **2** with manganese (II) salts (1 equiv relative to total Grignard) in THF, compare Table 2. Trapping of the resulting organo-manganese intermediates[13] was effected with benzoyl chloride to give the ketone **9** The absolute configuration of the product **9** was again secured[11] by chemical correlation with the acid **5**.

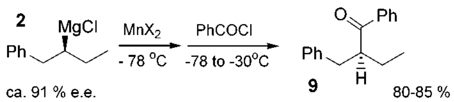


Table 2: Manganese-Mediated Couplings of **2**

entry	manganese salt	**10**: yield (%)	**10**: ee (%)
1	$MnCl_2$	78	53
2	MnI_2	80	58
3	$MnCl_2\cdot 2LiCl$	85	55
4	$EtMnCl\cdot MgCl_2$	59	69

The ee of the resulting ketone **9** (retention of configuration) was slightly above 50% regardless of the manganese (II) salt used. This renders coincidental reasons, such as limited configurational stability of the organo-manganese intermediates less likely and invites the speculation that again two transmetalation cycles could be involved, the first one to give $RMnCl\cdot MgCl_2$ with racemization and the second one to $R_2Mn\cdot MgCl_2$ with predominant retention of configuration. If this time the second transmetalation cycle proceeded faster than the first one, an ee of 50% should result in the product.

As a test (not a proof) of this suggestion, we transmetalated **2** with "preformed" $EtMnCl\cdot MgCl_2$.[12] This indeed resulted in a higher ee of the resulting ketone **9**.

While a definitive explanation for the results reported here is not yet at hand, we propose for further consideration that the transmetalation of Grignard reagents to copper (I) or to manganese (II) involves an intricate interplay between SET and concerted formation of the carbon−metal bond.

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(12) We have no information whether this contains an equilibrium mixture of $Et_2Mn\cdot MgCl_2 + MnCl_2 \rightleftarrows 2\ EtMnCl\cdot MgCl$.
(13) Normant, J.-F.; Cahiez, G. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Salle & Sauerländer: Aarau, 1983; Vol. 3; pp 173−216. That transmetalation from **2** to Mn has occurred follows from the high yield of **9.** In the absence of MnX_2 hardly any **9** is formed on reaction of **2** with benzoyl chloride.

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