Kumada–Corriu coupling of Grignard reagents, probed with a chiral Grignard reagent

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Received (in Cambridge, UK) 2nd January 2003, Accepted 29th January 2003 First published as an Advance Article on the web 19th February 2003

The Grignard reagent 2, in which the magnesium-bearing carbon atom is the sole stereogenic centre has been coupled with vinyl bromide under Pd(0) or Ni(0)-catalysis to give compound 3 with full retention of configuration. Coupling using $Fe(acac)_3$ or $Co(acac)_2$ as catalyst was accompanied by considerable racemisation. These findings are discussed with respect to a dichotomy between concerted polar and stepwise SET transmetallation pathways.

The transition metal catalyzed cross-coupling of Grignard reagents with vinylic and aryl halides was the subject of both the exploratory phase¹ of the cross-coupling reaction as well as of the ground breaking studies by Corriu² and by Kumada.^{3,4} After 30 years of expansion of the transition metal catalyzed crosscoupling to other organometallic reagents,⁵ the Grignard crosscoupling reactions are presently finding renewed interest.⁶ The principal mechanistic scenario of the cross-coupling reaction is by now common text-book material. However, especially the earlier contributions provided ample evidence that free radicals may be generated in the context of the transition metal catalyzed cross-coupling of Grignard reagents. This raises the question whether the generation of radicals is part of the catalytic cycle, or rather of related or unrelated side-reactions. Radicals could be generated, if electron motion precedes nuclear motion in the transmetallation step. Such an SET-step could be detected on transmetallation of an enantiomerically enriched chiral secondary Grignard reagent, as the secondary alkyl radical formed in such an oxidation step would be achiral on the time scale of the experiment.⁷ Hence, racemic coupling product should result in the case of an SET step. In the absence of such an electron transfer the coupling products should be formed with (full) retention of configuration.

We recently gained access to the enantiomerically enriched (*ca.* 91% e.e.) secondary Grignard reagent **2**, in which the magnesium bearing carbon atom is the sole stereogenic center.⁸ Reagent **2** is thus ideally suited to determine the mechanisms of Grignard reactions.⁹ The reagent **2** was generated from the sulfoxide **1** by addition of 5 equiv. of EtMgCl. We have to keep in mind that this reaction results in a cocktail of Grignard reagents and sulfoxides in which the reagent **2** of interest is only a constituent.



We report here on the stereochemistry of the transmetallation of this reagent to Ni(π), Pd(π), Fe(π ?), and Co(π ?) in the course of Kumada–Corriu coupling reactions with vinyl bromide. The latter reaction can be carried out at low temperature¹⁰ (-78 °C), at which reagent **2** is configurationally stable. Kumada–Corriucouplings were effected by reducing the pre-catalyst (0.1 equiv. rel. to total Mg) with EtMgCl at 0 °C, addition of vinyl bromide at -78 °C and reaction with **2** for 5 d at -78 °C. Workup furnished the coupling product **3** and the hydride-elimination product **4**. The results are compiled in Table 1.



The absolute configuration of the coupling product **3** was established by chemical correlation with the known¹¹ carboxylic acid **5**. The lengthy sequence from **5** to **3** was chosen because it did not involve any racemisation-prone intermediates. It provided the product **3** of 98% e.e as indicated by GC-analysis using a chiral stationary phase.



The results in Table 1 show that both Ni(0)- and Pd(0)mediated coupling reactions proceeded with essentially full retention of configuration establishing the transmetallation of **2** to Ni(π) or Pd(π) as a concerted S_E2-ret process.¹² The Grignard

Table 1 Kumada-type couplings of the Grignard reagent 2 of *ca*. 90% e.e. with vinyl bromide in THF at -78 °C

	Catalyst	3/4-ratio	3: yield (%)	e.e. (%) ^a
1	NiCl ₂ dppf	95:5	60	88
2	$NiCl_2(-)diop$	89:11	80	89 ^b
3	PdCl ₂ dppf	95:5	58	88
4	$PdCl_2(-)diop$	86:14	55	89 ^b
5	Fe(acac) ₃	>95:<5	35	53
6	$Co(acac)_2$	>95:<5	30	55

^{*a*} Determined by GC on a Chiral-Dex column. ^{*b*} Racemic **2** resulted in racemic **3** under these conditions.

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reagent **2** therefore behaves in this respect like secondary alkylboron¹³ and alkyl-zinc reagents.¹⁴.

In contrast, when the coupling was catalyzed by low-valent Fe or Co generated from $Fe(acac)_3$ or $Co(acac)_2$ in THF–NMP¹⁵ the e.e. of the coupling product **4** was significantly reduced.

This points to a situation, in which SET between 2 and 6, *e.g.* to give 8 and 9 *via* path (b), is involved in the transmetallation step. As the vinyl metal species 9 (with the oxidation state changed by one unit compared to 7) can be considered to be persistent at the time-scale of the experiment, the persistent radical effect¹⁶ would then guarantee an effective recombination of 8 and 9 to give (now racemic) 7. But a reaction sequence *via* path (b) is by no means established, especially since the oxidation state of the iron or cobalt species 6 in the catalytic cycle is not known⁶ and, hence, it is not known whether their oxidation potential would be high enough to oxidize a Grignard reagent.



Therefore an alternate mechanistic scenario should also be discussed, in which transmetallation could occur with full retention of configuration (path (a)). As the alkyl-cobalt or the alkyl-iron species 7 formed in this manner has a weak carbonmetal bond,¹⁷ reversible bond homolysis^{18,19} to 8 and 9 (equilibrium (c)) could then lead to racemisation of the alkyl residue. For this scenario to account for the observed partial racemisation in the cobalt or iron-mediated cross coupling of 2 to 3, it is necessary that spontaneous thermal bond homolysis of 7 would have to occur with a much higher rate than turnover in the catalytic cycle. It is quite uncertain, though, whether this condition will be met at the low temperature of -78 °C.¹⁹ For this reason we tend to ascribe the partial racemisation observed in the cross-coupling of 2 with vinyl bromide under iron- or cobalt catalysis to an SET process in the transmetallation step (*i.e.* path (b)).

We are grateful to the Deutsche Forschungsgemeinschaft (SFB 260 and Graduiertenkolleg Metallorganische Chemie) as well as the Fonds der Chemischen Industrie for support of this study.

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