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

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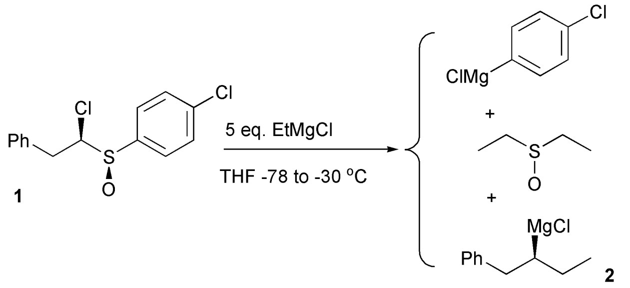
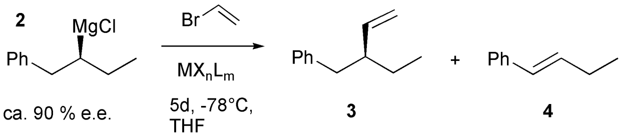
The Grignard reagent 2, in which the magnesium-bearing carbon atom is the sole stereogenic centre has been coupled with vinyl bromide under Pd(0) or Ni(0)-catalysis to give compound 3 with full retention of configuration. Coupling using Fe(acac)$_3$ or Co(acac)$_2$ as catalyst was accompanied by considerable 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 phase[1] of the cross-coupling reaction as well as of the ground breaking studies by Corriu[2] and by Kumada.[3,4] After 30 years of expansion of the transition metal catalyzed cross-coupling to other organometallic reagents,[5] the Grignard cross-coupling 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.

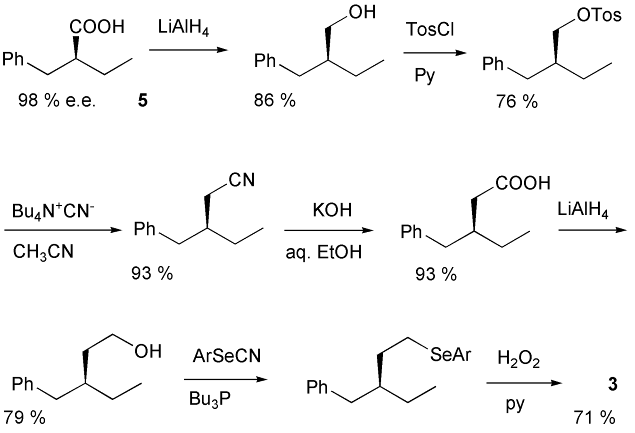
We recently gained access to the enantiomerically enriched (*ca.* 91% e.e.) secondary Grignard reagent **2**, in which the magnesium bearing carbon atom is the sole stereogenic center.[8] Reagent **2** is thus ideally suited to determine the mechanisms of Grignard reactions.[9] The reagent **2** was 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(II), Pd(II), Fe(II?), and Co(II?) in the course of Kumada–Corriu coupling reactions with vinyl bromide. The latter reaction can be carried out at low temperature[10] (−78 °C), at which reagent **2** is configurationally stable. Kumada–Corriu-couplings 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 known[11] 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.



Ar = o-O$_2$N-C$_6$H$_4^-$

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(II) or Pd(II) as a concerted S$_E$2-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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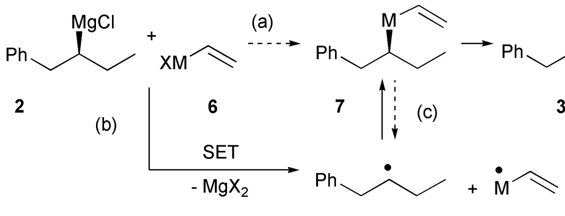
reagent **2** therefore behaves in this respect like secondary alkylboron[13] and alkyl-zinc reagents.[14].

In contrast, when the coupling was catalyzed by low-valent Fe or Co generated from Fe(acac)$_3$ or Co(acac)$_2$ in THF–NMP[15] 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 effect[16] 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 known[6] and, hence, it is not known whether their oxidation potential would be high enough to oxidize a Grignard reagent.



M = Fe or Co species of
unknown oxidation state

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 carbon–metal 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)).

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Notes and references

1 (*a*) M. S. Kharash and C. F. Fields, *J. Am. Chem. Soc.*, 1943, **65**, 504; (*b*) M. S. Kharash and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice Hall, New York, 1954; (*c*) M. Tamura and J. K. Kochi, *J. Am. Chem. Soc.*, 1971, **93**, 1487.

2 R. J. P. Corriu and J. P. Masse, *J. Chem. Soc., Chem. Commun.*, 1972, 144.

3 K. Tamao, K. Sumitani and M. Kumada, *J. Am. Chem. Soc.*, 1972, **94**, 4374.

4 The historical aspects have recently been reviewed: K. Tamao, T. Hiyama and E.- i. Negishi, *J. Organomet. Chem.*, 2002, **653**, 1; and following papers.

5 *Metal-catalyzed Cross-coupling Reactions*, ed. F. Diederich and P. J. Stang, Wiley-VCH, Weinheim, Germany, 1998.

6 A. Fürstner, A. Leitner, M. Méndez and H. Krause, *J. Am. Chem. Soc.*, 2002, **124**, 13856.

7 D. Griller, K. U. Ingold, P. J. Krusic and H. Fischer, *J. Am. Chem. Soc.*, 1978, **100**, 6750.

8 R. W. Hoffmann, B. Hölzer, O. Knopff and K. Harms, *Angew. Chem.*, 2000, **112**, 3206; R. W. Hoffmann, B. Hölzer, O. Knopff and K. Harms, *Angew. Chem., Int. Ed.*, 2000, **39**, 3072.

9 (*a*) R. W. Hoffmann and B. Hölzer, *Chem. Commun.*, 2001, 491; (*b*) R. W. Hoffmann, B. Hölzer and O. Knopff, *Org. Lett.*, 2001, **3**, 1945–1948; (*c*) R. W. Hoffmann and B. Hölzer, *J. Am. Chem. Soc.*, 2002, **124**, 4204.

10 G. Consiglio and C. Botteghi, *Helv. Chim. Acta*, 1973, **56**, 460.

11 W. Kirmse, P. Feyen, W. Gruber and W. Kapmeyer, *Chem. Ber.*, 1975, **108**, 1839.

12 R. E. Gawley, *Tetrahedron Lett.*, 1999, **40**, 4297.

13 (*a*) B. H. Ridgeway and K. A. Woerpel, *J. Org. Chem.*, 1998, **63**, 458; (*b*) K. Matos and J. A. Soderquist, *J. Org. Chem.*, 1998, **63**, 461.

14 (*a*) A. Boudier, C. Darcel, F. Flachsmann, L. Micouin, M. Oestreich and P. Knochel, *Chem. Eur. J.*, 2000, **6**, 2748; (*b*) A. Boudier, E. Hupe and P. Knochel, *Angew. Chem.*, 2000, **112**, 2396; A. Boudier, E. Hupe and P. Knochel, *Angew. Chem., Int. Ed.*, 2000, **39**, 2294.

15 G. Cahiez and H. Avedissian, *Tetrahedron Lett.*, 1998, **39**, 6159.

16 (*a*) A. Studer, *Chem. Eur. J.*, 2001, **7**, 1159; (*b*) H. Fischer, *Chem. Rev.*, 2001, **101**, 3581.

17 (*a*) B. G. Daikh and R. G. Finke, *J. Am. Chem. Soc.*, 1991, **113**, 4160; (*b*) J. Halpern, *Acc. Chem. Res.*, 1982, **15**, 238.

18 B. G. Daikh and R. G. Finke, *J. Am. Chem. Soc.*, 1992, **114**, 2938.

19 Walling[20] presented arguments that homolytic cleavage of $(RCH_2)_2Fe$ is unimportant even for reactions of Grignard reagents with Fe(II) carried out at room temperature. Of course, secondary $(R_2CH)_2Fe$ species are thermally much less stable[21].

20 C. Walling, *J. Am. Chem. Soc.*, 1988, **110**, 6846.

21 W. Lau, J. C. Huffman and J. K. Kochi, *Organometallics*, 1982, **1**, 155.