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Stereoselective cyclizations mediated by functionalized organomagnesium reagents and catalyzed by cobalt or copper salts

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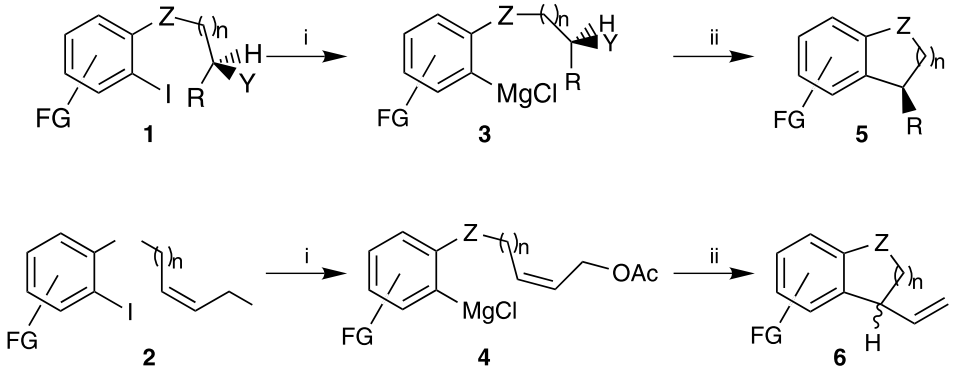
Abstract—The iodine–magnesium exchange reaction with *i*-PrMgCl allows a mild preparation of functionalized arylmagnesium compounds bearing a leaving group in the molecule. With the appropriate transition-metal catalyst (a copper or cobalt salt), cyclization reactions occur leading to five- or six-membered ring systems in good yields.

Recently, we have shown that the iodine–magnesium exchange reaction is a general method for preparing functionalized aryl-, heteroaryl- and alkenyl-magnesium reagents.[1,2] Since this method allows the preparation of a wide range of Grignard reagents bearing electrophilic functionalities, we envisioned the preparation of heterocycles from substrates of type **1** or **2**. Reaction with *i*-PrMgCl should selectively afford the corresponding organomagnesium reagents of type **3** and **4**, which may undergo a ring closure reaction either directly or in the presence of a transition-metal catalyst,[3] leading to products of type **5** or **6** (Scheme 1).

First, we examined the reaction of the three aromatic iodides **7**–**9**. In all cases, the iodine–magnesium exchange in the presence of *i*-PrMgCl (1.0 equiv.) was fast and complete at −30°C within 1 h. Upon warming of the intermediate Grignard reagent to room temperature, the cyclized product **10** or **11** was obtained in variable yields, depending on the reaction conditions (Scheme 2). Thus, the magnesium species derived from the bromide **7** furnishes 2,3-dihydrobenzofuran **10**[4] in 42% yield. When the diiodide **8** was subjected to the same reaction conditions the heterocycle **10** was obtained in 65% yield. Addition of a 1 M solution of



Scheme 1. *Reagents and conditions*: (i) THF, *i*-PrMgCl, −20°C; (ii) transition-metal catalysis (copper or cobalt salt).

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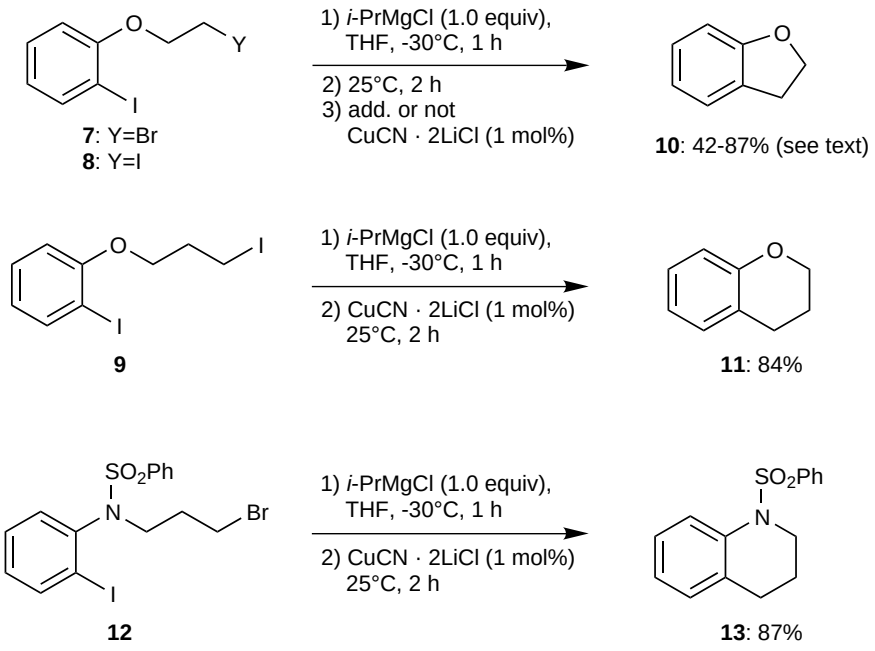


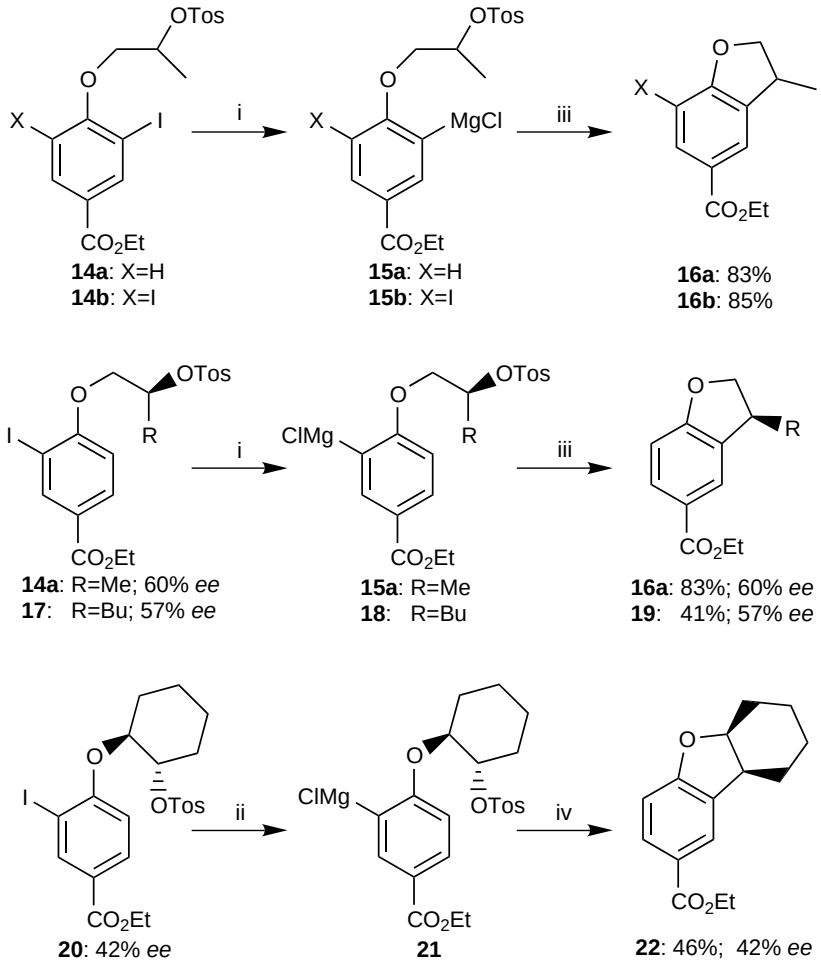
Scheme 2.

the THF soluble copper salt CuCN·2LiCl[5] (1 mol%) promoted a smooth cyclization, affording **10** in 79% yield starting from **7** and 87% yield starting from the diiodide **8**, demonstrating the efficient catalysis of copper salts in these intramolecular S_N2 reactions.[6,7] These results confirm that the substitution reactions are more efficient with alkyl iodides than with alkyl bromides.

In the presence of CuCN·2LiCl (1 mol%), the Grignard reagent derived from **9** underwent ring closure to chroman **11** in 84% yield (Scheme 2). Interestingly, these conditions could be used with nitrogen-functionalized substrates. The iodosulfonamide **12** was converted under standard conditions to the corresponding intermediate Grignard reagent (*i*-PrMgCl, THF, −30°C, 1 h). After treatment with CuCN·2LiCl (1 mol%) a smooth cyclization occurred (25°C, 2 h) leading to the sulfonylated 1,2,3,4-tetrahydro-quinoline **13** in 87% yield. We have examined functionalized substrates such as the readily available tosylates **14a**–**b** which contain an ester functionality. In both cases, the I–Mg exchange reaction proceeded smoothly at −20°C within 1 h, leading to the corresponding Grignard reagents **15a**–**b**. In the case of the diiodide **14b**, only a mono I–Mg exchange is observed.

The ester and tosylate functions of both substrates are compatible with the conditions of the iodine–magnesium exchange; 10 mol% of the catalyst (CuCN·2LiCl) was used. In a preliminary experiment with **14a**,[8] the reaction was kept at 0°C for 12 h after the addition of CuCN·2LiCl and **16a** was obtained in 50% yield. By performing the same reaction and warming up to room temperature the yield of the cyclized product could be increased to 65% and even to 83% at 45°C, showing that under these conditions, the sensitive ethyl ester function does not react with the Grignard reagent. We have also studied the stereochemistry of the cyclization step. We prepared the tosylates **14a**, **17** and **20** in optically enriched form in, respectively, 60, 57 and 42% ee, by using the method of Jacobsen.[9] After cyclization induced by the addition of CuCN·2LiCl (10–25 mol%), the products **16a**, **19** and **22** were obtained in 83, 41 and 46% yield and in 60, 57 and 42% ee, showing that the reaction occurs with complete inversion of configuration[6,7,10] (Scheme 3). Next, we turned our attention toward the cyclization of substrates of type **23** bearing an allylic acetate as leaving group. We prepared *cis*-**23**, *trans*-**23** and *trans*-**24** using the method of Bäckvall.[11] Thus, the sodium salt of the sulfonamide **25a** was treated (25°C, 16 h) with the allylic chloride **26** in the presence of $Pd(dba)_2$ (10 mol%) and PPh_3 (40 mol%), affording the precursor *cis*-**23** in 76% yield. On the other hand, treatment of **25a**–**b** with the allylic chloride **26** in the presence of K_2CO_3 (1.2 equiv.) in DMSO (80°C, 22 h) gave the corresponding acetates *trans*-**23** and *trans*-**24** in 89 and 35% yield, respectively.

The treatment of *cis*-**23** and *trans*-**23** with *i*-PrMgCl (1.1 equiv. in THF, −10°C, 16 h) furnished the corresponding Grignard reagent as expected. Whereas *trans*-**23** underwent cyclization leading quantitatively to the *cis* carbazole derivate **27**, the Grignard reagent derived from *cis*-**23** did not undergo ring closure. However, the addition of CuCN·2LiCl (50 mol%) led to cyclization (25°C, 15 h) in quantitative yield.



Scheme 3. *Reagents and conditions*: (i) THF, *i*-PrMgCl, −20°C, 1 h; (ii) THF, *i*-PrMgCl, −10°C, 10 h; (iii) CuCN·2LiCl (10 mol%), −20°C to 25°C or 45°C, 12 h; (iv) CuCN·2LiCl (25 mol%), −10°C to 45°C, 12 h.

Alternatively, we found that by adding $Co(acac)_2$ (10 mol%) instead of CuCN·2LiCl, a similar ring closure reaction occurred (−10°C, 17 h) leading to **27** in >95% yield.

Similarly, the ester-substituted substrate *trans*-**24** was converted into the *cis*-tetrahydrocarbazole **28**, after successive treatment with *i*-PrMgCl (1.1 equiv., −10°C, 1 h) and a catalytic amount of CuCN·2LiCl (50 mol%, −20°C, 4 h), in 69% yield. In the absence of CuCN·2LiCl, the heterocycle **28** was obtained in 56% yield (Scheme 4). These results indicate that an intramolecular *anti*-S_N2'-substitution reaction has a low activation energy. In the case of the *cis*-substrate **23**, *anti*-substitution would provide a carbazole containing a higher energy *trans*-ring junction. This explains the preferential cyclization of the *trans*-isomers **23** and **24**. An estimate of the *cis*/*trans* energy difference using Boltzmann-averaged enthalpies for all conformers within a 40 kJ/mol window leads to a preference for *cis*-**27** of 20.6 kJ/mol. Provided that this energy difference is also descriptive of the S_N2 transition states leading to **27**, this corresponds to a *cis*/*trans* product ratio of 150 000:1.[12] This also explains the preferential cyclization of the *trans*-isomers **23** and **24**.

In summary, we have shown that polyfunctionalized arylmagnesium compounds bearing a primary halide or a secondary tosylate can be readily prepared by an iodine–magnesium exchange. A smooth cyclization reaction occurs after the addition of a catalytic amount of CuCN·2LiCl. These ring closures occur with complete inversion of configuration. In the case of allylic acetates, an *anti*-substitution (S_N2') occurs directly from the Grignard intermediate. The cyclization of the substrate requiring *syn*-substitution only took place in the presence of copper or cobalt salts.

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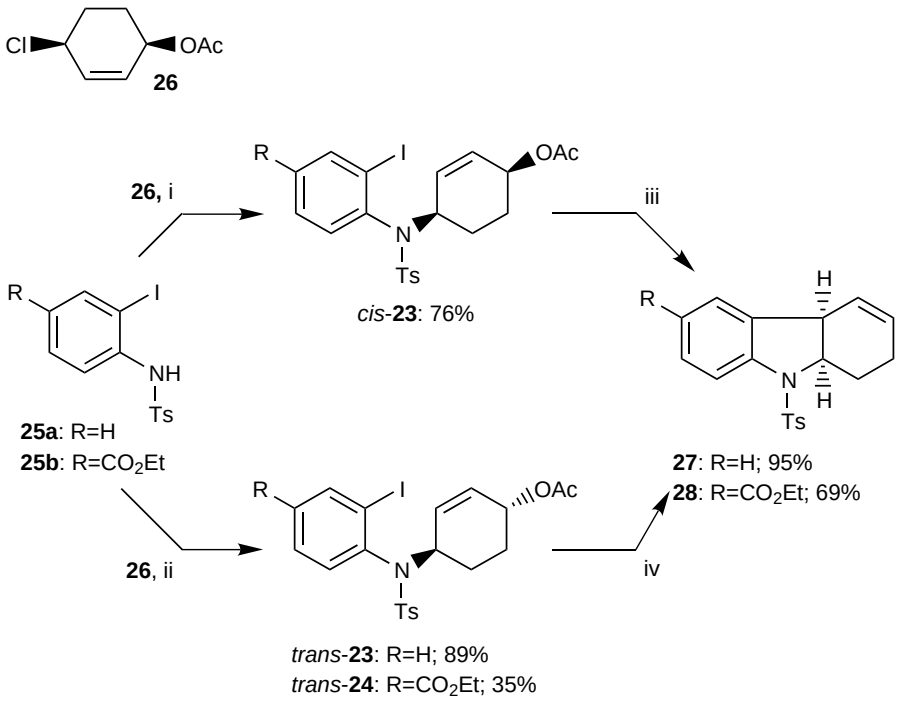

Scheme 4. *Reagents and conditions*: (i) $Pd(PPh_3)_4$ (10 mol%), rt, 16 h; (ii) K_2CO_3, DMSO, 80°C, 22 h; (iii) *i*-PrMgCl, CuCN·2LiCl or $Co(acac)_2$ cat.; (iv) *i*-PrMgCl, −10°C to rt, *anti*-substitution.

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8. The tosylates **14a**–**b** were prepared starting from ethyl 4-hydroxybenzoate. The first step was an iodination following an analogous literature procedure (Sy, W.-W. *Synth. Commun.* **1992**, *22*, 3215–3219). The second step was an etherification following an analogous literature procedure (Buisson, J.-P.; Demerseman, P. *J. Heterocyclic Chem.* **1995**, *32*, 17–24) using 2-chloroacetone as the electrophile. The keto function was reduced with 1.0 equiv. $NaBH_4$ at −25°C in MeOH. Tosylation of the alcohol with toluene-4-sulfonic anhydride in dichloromethane in the presence of NEt_3 at room temperature resulted in the formation of **14a** and **14b**.
9. Enantiomerically enriched cyclization precursors **14a**, **17** and **20** were prepared as described in Ref. 8, see also: Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086–6087.
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