

## Mischmetall, zinc–copper couple, and Dewarda alloy in the pinacol coupling of aldimines

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**Abstract.** New cheap reagents for the pinacol type coupling reaction of aldimines such as mischmetall, Zn–Cu couple, and Dewarda alloy are introduced. A relatively simple procedure for this reaction is described. Zn–Cu couple should be preferred because of economical considerations.

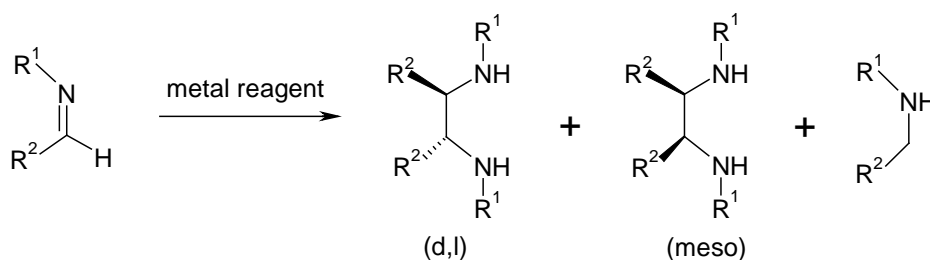
**Key words:** mischmetall, Zn–Cu couple, Dewarda alloy, imine, pinacol coupling.

Pinacol type coupling of carbonyl compounds and their aza-analogues became an interesting task in the 1990s [1]. The homochiral products of such couplings – 1,2-diols, 1,2-diamines, and 1,2-diaminoalcohols – are of particular interest. These valuable synthetic targets can be employed as efficient chiral C<sub>2</sub> auxiliaries for asymmetric synthesis or as ligands in asymmetric catalysis [2]. Moreover, these compounds are known to be highly biologically active and of therapeutic importance [3, 4].

A variety of metals and low valent metal reagents have been proposed to accomplish the coupling reaction of imines [5]. Despite the great number of such reagents, experimental data concerning the application of low cost and readily available potential reagents for this purpose are missing. The aim of the present work was to fill this gap and investigate the pinacol coupling of aldimines in the presence of mischmetall (Ce and La), Zn–Cu couple, and Dewarda alloy (50% Cu, 5% Zn, 45% Al). Both main components of mischmetall could potentially serve as highly coordinating metals for asymmetric diamine synthesis:

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The ratio of reductive dimerization and ordinary C=N reduction, as well as the diastereomeric ratio of 1,2-diamine, depends on both the metal reagent used and the structure of starting imine [5]. The mechanism and the influence of different factors on the yield and diastereomeric composition of products are not yet well understood [6].

It should be pointed out that there is only one report on the use of mischmetall for the pinacol coupling of aldehydes in the presence of a catalytic amount of SmI<sub>2</sub> in THF [7]. In the present work it was found that mischmetall powder (0.3–1.3 mm) is inactive toward aldimines even under reflux. For the initiation of a reaction in THF a set of different activators was studied: (CH<sub>3</sub>)<sub>3</sub>SiCl, TiCl<sub>4</sub>, ZnCl<sub>2</sub>, CuCl<sub>2</sub>, CoCl<sub>2</sub>, NiI<sub>2</sub>, Ni(OAc)<sub>2</sub>, I<sub>2</sub>, and mischmetall iodide (prepared according to the procedure in [8]). Trimethylsilyl chloride (TMSCl) was found to be the best activator, and other substances were less active even if accompanied by radiation in ultrasonic bath.

Only the use of Zn–Cu couple for the asymmetric coupling of aldimines in DMF is documented [9]. Unfortunately, this procedure was not reproducible. Therefore we employed Zn–Cu couple without alkali activation, prepared just before use according to the previously published procedure [10]. This reagent worked well in ethanol at 70–80°C, giving high yields within a relatively short reaction time. The mischmetall was not active under these conditions.

To the best of our knowledge Dewarda alloy has never been used for similar reactions. Because of the previously established low activity of the alloy in ethanol, TMSCl was introduced as activator while carrying out the coupling reaction with ground Dewarda alloy (~0.1–0.3 mm) in THF.

Data on the pinacol coupling of the model aldimines with three metal reagents used are presented in Table 1.

**Table 1.** Reductive coupling of aldimines

Imine	Reaction time, min			Yield, %			d,l/meso ratio		
	MM*	Zn–Cu	Dew	MM	Zn–Cu	Dew	MM	Zn–Cu	Dew
Ph–CH=N–Ph	30	40	120	72	77	89	1:1.1	1:3.4	1:2.4
<i>p</i> -MeO–Ph–CH=N–Ph	45	10	180	27	63	34	1:1.4	1:1.2	1:2.6
Ph–CH=N–Ph– <i>p</i> -OMe	60	25	105	15	47	7	1.6:1	1<99	1<99
Ph–CH=N–CH <sub>2</sub> –Ph	40	60	50	55	90	39	99>1	99>1	1<99
<i>o</i> -HO–Ph–CH=N–Ph	30	30	45	40	71	13	1:1.9	1:1.2	2.2:1
1-Naphthyl–N=CH–Ph	60	15	270	33	58	0	1.4:1	1:1.2	–

\*MM – mischmetall, Zn–Cu – zinc–copper couple, Dew – Dewarda alloy

The highest yields were obtained with Zn–Cu couple. When using the mischmetall reagent we observed partial decomposition of diamines, which resulted in the contamination of the product with the starting material, as determined by HPLC and NMR spectroscopy. A similar phenomenon was also described earlier in  $\text{Cp}_2\text{VCl}_2$  catalysed imine dimerization with Zn/TMSCl reagent [1]. It was confirmed recently that the cleavage of C–C bond in 1,2-diamines is caused by the atmospheric oxygen and accelerated by acids [11]. Hereby the experiments were carried out in inert atmosphere. Nevertheless, the formed lanthanide salts could act as Lewis acid, thus accelerating the decomposition of diamines during the work-up. Dewarda alloy in the presence of TMSCl was the least active reagent.

All the used reagents afforded the mixture of d,l and meso isomers mainly in comparable amounts – from 2.1:1 up to 1:3.4. The entries 3 and 4 were excellent exceptions, furnishing only the d,l or meso isomer depending on the compound and metal reagent used. These findings support the assumption that the structure of the substrate is the most important factor in the control of reaction diastereoselectivity. We could not observe the inversion of the diastereomeric ratio during the reaction or work-up procedures. The simple reduction was not observed in the majority of studied compounds. Only the naphthyl and salicyl derivatives gave substantial amounts (5–58%) of the corresponding monoamines as detected by  $^{13}\text{C}$  NMR spectroscopy. This can be explained by the relative bulkiness of the intermediate radical anion, hindering the dimerization and therefore increasing the extent of the ordinary C=N reduction. All obtained compounds are characterized by correct  $^1\text{H}$  and  $^{13}\text{C}$  NMR and FTIR spectra.

#### **PROCEDURES. THE USE OF MISCHMETALL OR DEWARDA ALLOY**

To the stirred suspension of 0.5 g (3.6 mmol) ground mischmetall (purchased from Riedel-deHäen) or Dewarda alloy in 10 mL THF under argon 0.35 mL (2.75 mmol) of TMSCl was added dropwise followed by 1.4 mmol of imine. The reaction was monitored by HPLC and/or TLC. After the coupling was complete, the hot reaction mixture was filtered through the pad of Celite<sup>®</sup> directly into the ice cold NaOH (10%) solution in order to minimize the contact with possibly acidic lanthanide salts. After separation of layers, the water layer was extracted 3 times with dichloromethane, the organic phase was washed to neutral, dried with  $\text{Na}_2\text{SO}_4$ , and evaporated to dryness. The yield and isomeric ratio were determined by NMR from the raw products. After recrystallization the structure of the products was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR and FTIR spectroscopy.

## THE USE OF ZN–CU COUPLE

To the freshly prepared suspension of Zn–Cu couple (from 2 g Zn powder and 0.5 g  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ ) in 10 mL of EtOH under argon imine (1.4 mmol) was added and stirred at 75–80 °C. After all the imine was consumed as monitored by TLC and HPLC, the reaction mixture was filtered through a thin silica pad and evaporated to dryness. The yield and isomeric ratio were determined by NMR from the raw products. After recrystallization the structure of the products was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR and FTIR spectroscopy.

## ACKNOWLEDGEMENT

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## REFERENCES

1. Hatano, B., Ogawa, A. & Hirao, T.  $\text{Cp}_2\text{VCl}_2$ -catalyzed meso-selective pinacol coupling reaction of aldimines in the presence of chlorosilane and zinc metal. *J. Org. Chem.*, 1998, **63**, 9421–9424 (and references cited therein).
2. Bennani, Y. L. & Hanessian, S. *trans*-Diaminocyclohexane derivatives as chiral reagents, scaffolds, and ligands for catalysis: applications in asymmetric synthesis and molecular recognition. *Chem. Rev.*, 1997, **97**, 3161–3195.
3. Pasini, A. & Zunino, F. Neue Cisplatin – Analoga auf dem Weg zu besseren Cancerostatica. *Angew. Chem.*, 1987, **99**, 632–641.
4. Lucet, D., Le Gall, T. & Mioskowski, C. The chemistry of vicinal diamines. *Angew. Chem. Int. Ed. Engl.*, 1998, **37**, 2581–2627.
5. Alexakis, A., Aujard, I. & Mangeney, P. Practical and efficient synthesis of  $\text{C}_2$  symmetrical diamines with  $\text{Zn}/\text{Me}_3\text{SiCl}$ . *Synlett*, 1998, 873–874.
6. Taluktar, S. & Banerji, A. Low valent titanium mediated imino-pinacol coupling: an improved and expeditious route to vicinal diamino-based ligands. *J. Org. Chem.*, 1998, **63**, 3468–3470.
7. Helion, F. & Namy, J.-L. Mischmetall: an efficient and low cost coreductant for catalytic reactions of samarium diiodide. *J. Org. Chem.*, 1999, **64**, 2944–2946.
8. Girard, P., Namy, J.-L. & Kagan, B. H. Divalent lanthanide derivatives in organic synthesis. 1. Mild preparation of  $\text{SmI}_2$  and  $\text{YbI}_2$  and their use as reducing or coupling agents. *J. Amer. Chem. Soc.*, 1980, **102**, 2693–2699.
9. Shimizu, M., Iida, T. & Fujisawa, T. Highly enantioselective imino pinacol coupling leading to the synthesis of 1,2-diphenylethylenediamine derivatives. *Chem. Lett.*, 1995, **24**, 609–610.
10. Mäeorg, U. & Timotheus, H. Zinc–copper couple as a reducing agent. 2. The modification of catalyst and study of medium effects on reduction of triple bond. *Proc. Acad. Sci. Estonian SSR. Chem.*, 1985, **34**, 180–185 (in Russian).
11. Shimizu, M. & Makino, H. Oxidative carbon–carbon bond cleavage reaction of 1,2-diamines and 1,2-amino alcohols under an oxygen atmosphere. *Tetrahedron Lett.*, 2001, **42**, 8865–8868.

## **Segametall, tsink–vask-paar ja Dewarda sulam aldimiinide pinakoolkondensatsioonil**

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Uuriti segametalli, tsink–vask-paari ja Dewarda sulami kasutamist aldimiinide pinakoolkondensatsioonil. Parimaks reagentiks osutus tsink–vask-paar. Segametalli ja Dewarda sulami korral tekitas probleemi 1,2-diamiinide liiga kiire oksüdeerumine lähteimiinideks.