

# Mischmetall and Zn–Cu couple as efficient reagents for the pinacol coupling of aldimines

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The reductive pinacol coupling of aldimines was studied in respect to different coupling-mediators such as mischmetall, Zn–Cu couple and Devarda alloy. High diastereoselectivity was achieved for three substrates. A simple procedure for the preparation of 1,2-diamines is described.

**Keywords:** Mischmetall, Zn–Cu couple, imine, pinacol coupling

1,2-Diols, 1,2-diamines and 1,2-aminoalcohols are valuable synthetic targets, and versatile auxiliaries for asymmetric synthesis.<sup>1</sup> They are biologically active and of therapeutic importance.<sup>2,3</sup> A modern approach to these compounds is based on the pinacol type coupling of carbonyl compounds<sup>4,5</sup> and their *aza*-analogues<sup>6</sup> and has been extensively studied during the last twenty years.<sup>7</sup> The synthesis of 1,2-diamines starts from imines and is mediated by a variety of metals and reduced metal compounds. Under the typical conditions, two diastereomeric 1,2-diamines and the reduction product of C=N bond are obtained as shown on Scheme 1.

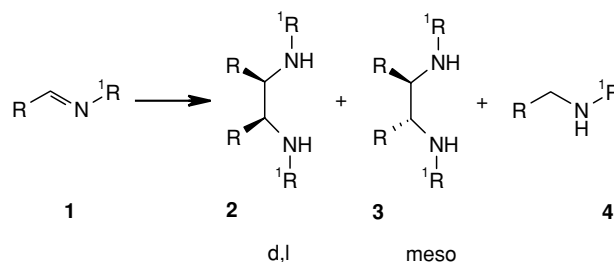
Unfortunately, most reagents are expensive<sup>8</sup> and environmentally unfriendly,<sup>9</sup> and a convenient coupling procedure is still absent.

Despite the fact that lanthanides and their salts found many applications,<sup>8,9</sup> there are only three reports on the use of mischmetall in organic synthesis.<sup>10–12</sup> This cheap and readily available industrial material was combined with SmI<sub>2</sub> for the pinacol coupling of aldehydes and aldimines. Zinc is another potential coupling-mediator. However, due to variable quality of zinc dust the reproducibility is questionable,<sup>13,14</sup> thus requiring certain modifications to be introduced. For example, Zn–Cu couple, prepared *in situ*,<sup>15,16</sup> was reported to induce imine coupling in nonprotic solvents.<sup>13</sup> The third easily available reagent could be Devarda alloy, which contains both Zn and Al as active components (5% Zn, 45% Al, 50% Cu), but surprisingly has not yet found any synthetic applications in this area.

Our work was aimed at the comparison of the above-mentioned coupling mediators and development of simple reproducible technique for the synthesis of 1,2-diamines.

## Result and discussion

Despite of relatively high reduction potential of mischmetall components (50% Ce, 25% La, 16% Nd, 6% Pr),<sup>17</sup> no reaction was observed with refluxing benzalaniline in THF for several hours. For initiation of the coupling process a set of different



Scheme 1

activators were studied: TiCl<sub>4</sub>, CoCl<sub>2</sub>, ZnCl<sub>2</sub>, (CH<sub>3</sub>)<sub>3</sub>SiCl, CuCl<sub>2</sub>, NiI<sub>2</sub>, Ni(OAc)<sub>2</sub>, I<sub>2</sub>, Ce(OBu)<sub>4</sub>, ultrasonic waves and mischmetall iodide (prepared according to the procedure in reference 18). Trimethylsilyl chloride (TMSCl) was found to be the most potent activator and the reactivity of the other compounds was evidently lower or totally absent. From among the solvents tested here (CH<sub>3</sub>CN, CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, hexane, toluene and Et<sub>2</sub>O) THF afforded the fastest conversion in the absence of any side products.

The results of the pinacol coupling of several aldimines mediated by mischmetall, Zn–Cu couple and Devarda alloy under the appropriate reactions conditions are outlined in the Table 1. In addition to the activator mischmetall also requires 1.0 eq of H<sub>2</sub>O for the initiation of the coupling process.

In order to understand the reaction pathway better, the coupling reaction was studied with D<sub>2</sub>O instead of H<sub>2</sub>O. When the conversion was complete, the product was isolated and characterised by <sup>1</sup>H, <sup>13</sup>C NMR and FTIR spectroscopy. The spectroscopic data were in agreement with those of the product obtained in typical work-up with H<sub>2</sub>O. Evidently, H<sub>2</sub>O reacts only with TMSCl and the formed HCl is responsible for mischmetall activation. To confirm the assumption, an equivalent amount of HCl in dioxane was used instead of water and that resulted in full conversion.

**Table 1** Pinacol coupling of aldimines with different reagents

| Compound                                  | Reaction time/min |       |                  | Crude yield/% (2+3) |       |     | d,l: meso ratio |       |       |
|---|-------------------|-------|------------------|---------------------|-------|-----|-----------------|-------|-------|
|   | MM <sup>a</sup>   | Zn/Cu | Dev <sup>b</sup> | MM                  | Zn/Cu | Dev | MM              | Zn/Cu | Dev   |
| Ph–CH=N–Ph ( <b>1a</b> )                  | 90                | 40    | 120              | 100                 | 77    | 89  | 1,1:1           | 1:3.4 | 1:2.4 |
| <i>p</i> -MeO–Ph–CH=N–Ph ( <b>1b</b> )    | 60                | 10    | 180              | 87                  | 63    | 37  | 1,2:1           | 1:1.2 | 1:2.6 |
| Ph–CH=N–CH <sub>2</sub> –Ph ( <b>1c</b> ) | 40                | 60    | 50               | 40                  | 90    | 39  | 1:11            | 99>1  | 1<99  |
| <i>m</i> -MeO–Ph–N=CH–Ph ( <b>1d</b> )    | 90                | 60    | –                | 89                  | 100   | –   | 1,1:1           | 1:2.7 | –     |
| Ph–CH=N–Ph– <i>p</i> -OMe ( <b>1e</b> )   | 90                | 25    | 100              | 87                  | 47    | 6   | 1:2             | 1<99  | 99>1  |
| <i>o</i> -OH–Ph–CH=N–Ph ( <b>1f</b> )     | 60                | 30    | 45               | 14                  | 71    | 13  | 99:1            | 1.2:1 | 2.2:1 |
| Nf–N=CH–Ph ( <b>1g</b> )                  | 90 <sup>c</sup>   | 15    | 360              | 11                  | 58    | 0   | 1,1:1           | 1:1.2 | –     |

<sup>a</sup>MM, mischmetall.

<sup>b</sup>Devarda alloy.

<sup>c</sup>The experiment was finished after 90 min.

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The separation technique was found to be crucial. Common liquid–liquid extraction caused a noticeable decomposition of the 1,2-diamines back to imines probably due to their prolonged contact with mischmetall chlorides left in the solution. The cleavage of a C–C bond in 1,2-diamines is known to be induced by the atmospheric oxygen in the presence of Lewis acids.<sup>19</sup> In order to reduce the decomposition and to retain the diastereomeric ratio of product, the product was purified by column chromatography to improve the yield. No inversion of the diastereomeric ratio was ever noticed during the reaction or work-up.

Under the employed conditions, mixtures of d,l- and meso-isomers were obtained in comparable amounts, from 1.2 : 1 up to 1 : 1.1. Compounds **1c**, **1e**, **1f** afforded excellent diastereoselectivity, furnishing only d,l- or meso-isomer depending on the compound and metal reagent used. These experimental facts support the assumption that the structure of substrate and the nature of reducing agent are the most important factors in the control of reaction diastereoselectivity.

The simple C=N reduction was not typical for the majority of studied aldimines, except for **1g** and **1f** where it afforded amines as detected by <sup>13</sup>C NMR spectroscopy (58 and 5% respectively). This can be explained by the relative bulkiness of the intermediate radical anion, hindering the dimerisation and therefore increasing the extent of the ordinary C=N reduction.

From the experimental results we conclude that both mischmetall and Zn–Cu couple are efficient mediators for the fast and clean pinacol coupling of aldimines. Extremely simple, cheap and reproducible protocol is reported.

## Experimental

The reactions were monitored by TLC (toluene–EtOAc 12:1 or toluene–EtOAc 10:1) or HPLC (Separon SX C18, MeOH–H<sub>2</sub>O 75:25 or 85:15). <sup>1</sup>H and <sup>13</sup>C NMR spectra were determined on a Bruker AC200P instrument operating at 200 and 50MHz respectively.

### Reductive coupling with mischmetall

To the stirred suspension of finely ground mischmetall 0.1 g (0.85 mmol) (purchased from Riedel-de-Häen) in THF 5 ml (1.4 mmol) TMSCl 180 μl was added dropwise followed by the imine (0.8 mmol). When the conversion was complete, the solvent and excess of the TMSCl were removed under reduced pressure. The crude product was purified on the short silica column using dichloromethane as eluent.

### Reductive coupling with Zn–Cu couple

To the freshly prepared suspension of Zn–Cu couple<sup>16</sup> (from 1 g Zn powder and 0.25 g CuCl<sub>2</sub> · 2H<sub>2</sub>O) in EtOH (5 ml) imine (0.8 mmol) was added and stirred at ~80 °C. After all the imine was consumed, the reaction mixture was filtered through a thin silica pad and evaporated to dryness.

### Reductive coupling with Devarda alloy

To the stirred suspension of Devarda alloy 0.25 g (5.3 mmol) in THF 5 ml of TMSCl 0.18 ml (1.4 mmol) was added dropwise followed by imine 0.8 mmol. After the conversion was complete, the hot reaction mixture was filtered through a pad of Celite® directly into the ice-cold NaOH (10%) solution in order to minimise the contact with possibly acidic lanthanide salts. Aqueous layer was extracted 3 times with dichloromethane; organic extracts were washed to neutral, dried with Na<sub>2</sub>SO<sub>4</sub>, and evaporated to dryness.

### Spectral data of the products

<sup>1</sup>H and <sup>13</sup>C NMR spectral data of **2a** + **3a** and **2c** + **3c** were identical to previously published.<sup>20</sup>

**2b** + **3b**: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 3.74/3.75 (s, 6H, OMe), 4.48 (overlapping signals, 4H, CH and NH), 4.87 (broad signal, 1H, NH), 6.4–7.1 (m, 18H, Ar). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 55.2 (OMe), 61.7 (meso-CH), 63.3 (dl-CH), 113.77, 113.87, 114.2, 117.8, 118.0, 120.9, 128.5, 128.7, 129.1, 129.2, 130.4, 132.0, 146.8, 147.2, 159.0, 159.05 (Ar). FTIR (cm<sup>-1</sup>): 3398 (ν N–H), 1248 (ν<sub>as</sub> C–O–C), 1032 (ν<sub>s</sub> C–O–C).

**2d** + **3d**: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 3.58/3.60/3.67 (s, 6H, OMe), 4.2/4.5 (2H, CH), 4.95 (broad signal, 1H, NH), 6.4–7.1 (m, 18H, Ar). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 54.89/55.25 (OMe), 62.1 (meso-CH), 63.9 (dl-CH), 123.65, 127.45, 128.25, 138.31, 140.01, 147.97, 148.24, 149.98 (Ar). FTIR (cm<sup>-1</sup>): 3396 (ν N–H), 1210 (ν<sub>as</sub> C–O–C), 1040 (ν<sub>s</sub> C–O–C).

**2e** + **3e**: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 3.64/3.65 (s, 6H, OMe), 4.25/4.42 (broad signals, 2H, CH), 6.4–7.9 (m, 18H, Ar). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 55.7 (OMe), 55.8 (OMe), 63.2 (meso-CH), 65.1 (dl-CH), 114.2, 114.5, 114.8, 115.0, 115.2, 115.5, 122.2, 127.1, 127.4, 127.46, 127.53, 127.7, 128.2, 128.3, 128.6, 128.7, 131.0, 136.6, 138.8, 140.5, 140.9, 141.4, 145.1, 158.3, 158.4. FTIR (cm<sup>-1</sup>): 3382 (ν N–H), 1244 (ν<sub>as</sub> C–O–C), 1030 (ν<sub>s</sub> C–O–C).

**2f** + **3f**: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 1.71 (broad signal, 2H, NH), 4.73/4.78 (s, 2H, CH), 6.6–7.3 (m, 20H, Ar ja OH). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 63.6 (meso-CH), 64.3 (dl-CH), 115.3, 116.5, 116.9, 117.7, 120.5, 120.5, 120.8, 121.3, 122.9, 124.3, 129.0, 129.25, 129.31, 129.5, 129.8, 146.1, 147.0, 155.6, 156.6. FTIR (cm<sup>-1</sup>): 3522 (O–H), 3398, 3372, 3326, 3262 (ν N–H), 1268, 1226 (ν C–O).

**2g** + **3g**: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 4.9–5.5 (broad signal, 4H, NH ja CH), 6.3–6.4 (m, 2H, Ar), 7.0–7.5 (m, 18H, Ar), 7.7–7.9 (m, 4H, Ar). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 62.8 (meso-CH), 64.2 (dl-CH), 107.2, 118.3, 119.9, 124.2, 125.1, 125.7, 127.4, 127.5, 127.9, 128.5, 128.7, 128.8, 128.9, 134.4, 134.5, 138.2, 139.7, 141.7, 142.0. FTIR (cm<sup>-1</sup>): 3386 (ν N–H).

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