# Highly Chemoselective Crossed Imino Pinacol Coupling Reaction Using the Synergetic Effect of Boron Trifluoride Etherate and Trichloromethylsilane

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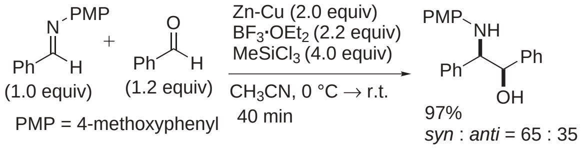
**Abstract:** Use of boron trifluoride etherate and trichloromethylsilane in the presence of zinc-copper couple effects a crossed imino pinacol coupling reaction to give 1,2-diamines in good yields with high diastereoselectivities.

**Key words:** crossed imino pinacol coupling, boron trifluoride etherate, trichloromethylsilane, 1,2-diamines, zinc-copper couple



**Scheme 1**

Widespread use of 1,2-diarylethylenediamines coupled with some difficulties associated with their preparations prompted us to investigate highly efficient methods for their synthesis. 1,2-Diamines are useful units for the synthesis of many biologically important natural products as well as drugs for therapeutic purpose. They also serve as chiral auxiliaries or metal ligands in catalytic asymmetric synthesis.[1]

Several strategies have been employed to construct such units, e.g., introduction of diamino functionalities into olefins, diols, or their derivatives[2] and creation of diamines with simultaneous construction of the interconnecting carbon-carbon bonds.[3] Among such processes, the crossed imino pinacol coupling of two different imino compounds is a direct way to synthesize unsymmetrical 1,2-diamines, and therefore, it is one of the most attractive and useful methods. However, due to the competing homo-coupling reactions, control of chemoselectivity is the most difficult problem. Although there exist only limited examples on intermolecular crossed pinacol coupling between carbonyl compounds and imines,[4] no example is available for crossed imino pinacol versions due to difficulty to discriminate the subtle difference of reactivity.

Recently, we have found that a simple combination of two different Lewis acids discriminates the difference of reactivity between aldehydes and imines (Scheme 1).[5] We, therefore, consider that the synergetic use of boron trifluoride etherate and trichloromethylsilane also recognizes the difference of reactivity between two imino species. This paper describes an easy way to the discrimination of two different imines in imino pinacol coupling, leading to the chemoselective synthesis of 1,2-diamines.

We initially investigated the reaction conditions for the crossed imino pinacol coupling using the reaction of *N*-benzylidene-*p*-anisidine (**1**) and *N*-benzylidene-*p*-chlorophenyl aniline (**2**) as substrates possessing an electron-donating and an electron-withdrawing substituents on the aromaic rings, respectively, and the results are summarized in Table 1.

As shown in Table 1, the combined use of $BF_3$·$OEt_2$ and $MeSiCl_3$ promoted the desired crossed coupling reaction. The use of an increased amount of trichloromethylsilane gave the unsymmetrical 1,2-diamine **3** in good yield with high diastereoselectivity (entries 1–4). The reaction carried out for a long reaction time decreased the yield of the product because 1,2-diamine readily underwent cleavage reaction (entry 5).[8] The reactions carried out at lower reaction temperatures decreased diastereoselectivities of the products, although the product yields were increased (entries 7 and 8).

Control experiments were carried out as shown in Schemes 2– 4. In the absence of $BF_3$·$OEt_2$ and $MeSiCl_3$, the reaction did not proceed (Scheme 2). While in the presence of $MeSiCl_3$ the coupling reaction gave the crossed adduct **3** in only 10% yield in a low stereoselective manner with a concomitant formation of homo-adducts **1′** and **2′**(Scheme 3), the presence of $BF_3$·$OEt_2$ effected the formation of the desired adduct **3** with good diastereoselectivity but in low yield (Scheme 4). Thus, the synergetic use of $BF_3$·$OEt_2$ and $MeSiCl_3$was proved to be necessary for the formation of the crossed coupling product **3** in acceptable yields.

We next examined the crossed imino pinacol coupling between the imines, one possessing an electron-donating and the other an electron-withdrawing substituent on the aromatic rings, under the best conditions found as in the above cases, and the results are summarized in Table 2.

As shown in Table 2, the use of halogen as an electron-withdrawing substituent on the aromatic ring gave the unsymmetrical 1,2-diamines **6** in good yield with high diastereoselectivities (entries 1–4). The use of the imine possessing a 2,4-dichlorophenyl moiety gave the crossed coupling product in low yield with low diasteroselectivity (entry 5). In this case the homo-coupling product **4′** was

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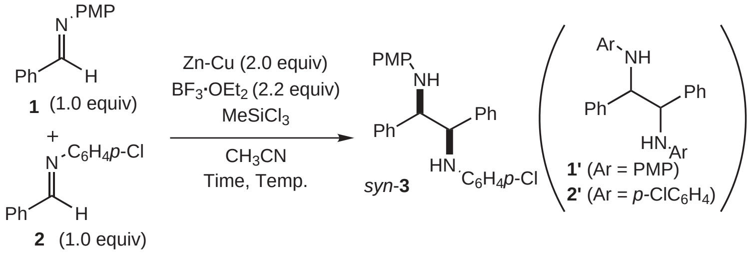
**Table 1** The Reaction of *N*-Benzylidene-*p*-anisidine with *N*-Benzylidene-*p*-chlorophenyl Aniline[a]



| Entry | $MeSiCl_3$/equiv | Time/h | Temp/°C | **3**(%)[b] | *syn*:*anti*[c,d] | **1′**(%)[b] | **2′** (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | 3.5 | 1.0 | 0–r.t. | 54 | 93:7 | 23 | 23 |
| 2 | 4.0 | 1.0 | 0–r.t. | 63 | 90:10 | 15 | 18 |
| 3 | 4.5 | 1.0 | 0–r.t. | 65 | 90:10 | 14 | 17 |
| 4 | 5.0 | 1.0 | 0–r.t. | 71 | 93:7 | 12 | 14 |
| 5 | 5.0 | 24.0 | 0–r.t. | 53 | 93:7 | 15 | 14 |
| 6 | 5.0 | 0.5 | 0–r.t. | 63 | 87:13 | 13 | 11 |
| 7 | 5.0 | 5.8 | –45–0 | 83 | 81:19 | 6 | 5 |
| 8 | 5.0 | 1.0 | 0 | 75 | 89:11 | 11 | 11 |
| 9[e] | 5.0 | 1.0 | 0–r.t. | 62 | 74:26 | 12 | 16 |

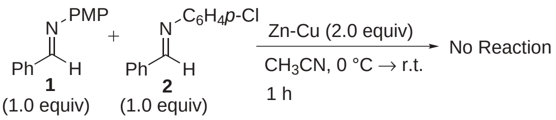
[a] The reaction was carried out according to the typical experimental procedure.[6]

[b] Isolated yield.

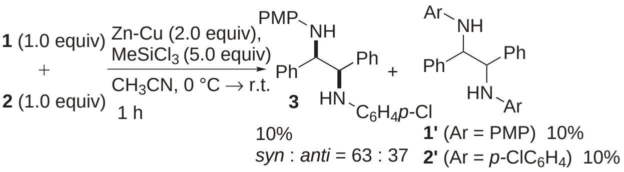
[c] Determined by HPLC.

[d] Determination of the relative stereochemistry, see ref.[7,]

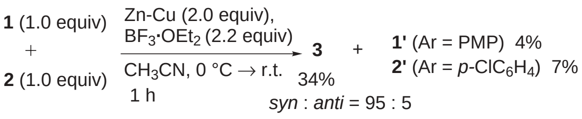
[e] EtCN was used as a solvent.



**Scheme 2**



**Scheme 3**

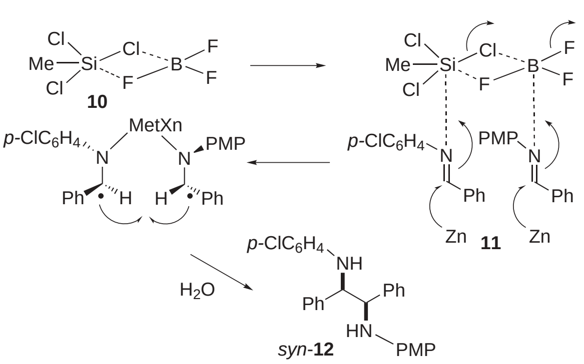


**Scheme 4**

obtained in 33% yield, presumably because the 2-chloro moiety prevented the nitrogen atom from coordinating with the Lewis acidic species. The reaction of various imines with *N*-benzylidene-*p*-bromophenyl aniline was next investigated, and the results are summarized in Table 3.

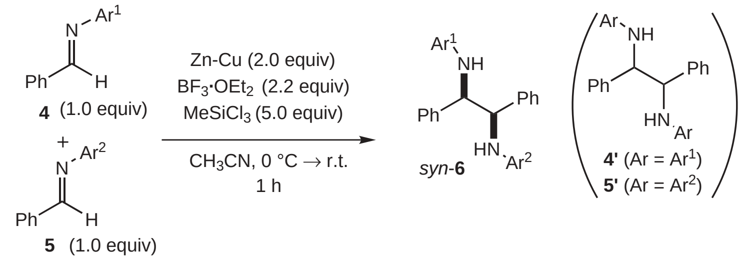
In general, the reaction usually proceeded to give the crossed coupling products in good yields. The use of $CH_2Cl_2$ as a co-solvent decreased the diastereoselectivities (entries 2 and 5). However, use of aliphatic and α,β-unsaturated aldimines did not give the desired coupling products.

On the basis of the previously reported results from the crossed pinacol coupling between imines and aldehydes as well as the present results, we propose a possible reaction mechanism as shown in Scheme 5.



**Scheme 5**

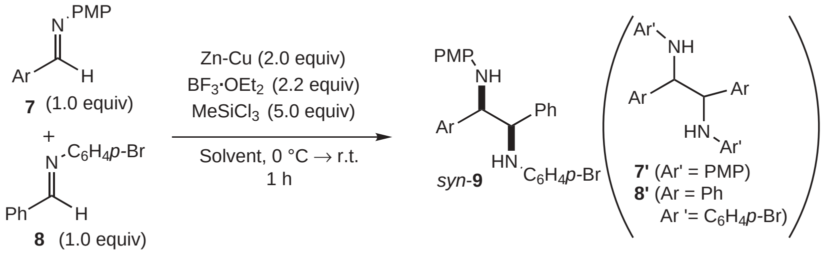
**Table 2** The Crossed Imino Pinacol Coupling[a]



| Entry | Ar[1] | Ar[2] | **6** (%)[b] | *syn*:*anti*[c] | **4′**(%)[b] | **5′** (%)[b] |
|---|---|---|---|---|---|---|
| 1 | 4-MeOC$_6$H$_4$ | 4-FC$_6$H$_4$ | 69 | 87:13 | 10 | 15 |
| 2 | 4-MeOC$_6$H$_4$ | 4-ClC$_6$H$_4$ | 71 | 93: 7 | 12 | 14 |
| 3 | 4-MeOC$_6$H$_4$ | 4-BrC$_6$H$_4$ | 74 | 92: 8 | 10 | 13 |
| 4 | 4-MeOC$_6$H$_4$ | 4-IC$_6$H$_4$ | 64 | 86:14 | 11 | 15 |
| 5 | 4-MeOC$_6$H$_4$ | 2,4-Cl$_2$C$_6$H$_3$ | 34 | 54:46 | 33 | 23 |
| 6 | 4-MeOC$_6$H$_4$ | 4-CF$_3$C$_6$H$_4$ | 41 | 87:13 | 15 | 27 |
| 7 | 4-MeOC$_6$H$_4$ | 4-EtO$_2$CC$_6$H$_4$ | 48 | 94: 6 | 12 | 22 |
| 8 | 4-MeSC$_6$H$_4$ | 4-ClC$_6$H$_4$ | 54 | 98: 2 | 9 | 7 |

[a] The reaction was carried out according to the typical experimental procedure.[6]
[b] Isolated yield.
[c] Determined by HPLC.

**Table 3** The Reaction of Various Imines with *N*-Benzylidene-*p*-bromophenyl Aniline[a]



| Entry | Ar | Solvent | **9** (%)[b] | *syn*:*anti*[c] | **7′** (%)[b] | **8′** (%)[b] |
|---|---|---|---|---|---|---|
| 1 | 1-Naphthyl | MeCN | 61 | 83:17 | 9 | 12 |
| 2 | 4-ClC$_6$H$_4$ | MeCN/CH$_2$Cl$_2$(9/1) | 64 | 83:17 | 11 | 18 |
| 3 | 3-ClC$_6$H$_4$ | MeCN | 59 | 93: 7 | 14 | 18 |
| 4 | 2-ClC$_6$H$_4$ | MeCN | 59 | 92: 8 | 12 | 18 |
| 5 | 4-MeOC$_6$H$_4$ | MeCN/CH$_2$Cl$_2$(9/1) | 33 | 78:22 | 23 | 29 |
| 6 | 4-MeC$_6$H$_4$ | MeCN | 68[d] | 93: 7 | 12 | 16 |

[a] The reaction was carried out according to the typical experimental procedure.[6]
[b] Isolated yield.
[c] Determined by HPLC.
[d] The reaction time was 5 h.

A mixture of boron trifluoride etherate and trichloromethylsilane would form a bimetallic complex **10**. On the basis of reactivity, the nitrogen atom of more basic imine possessing an electron-donating substituent is coordinated with the boron atom of boron trifluoride etherate, whereas the nitrogen atom of less basic imine possessing an electron-withdrawing substituent is coordinated with the silicon atom of trichloromethylsilane. Therefore, the bimetallic complex discriminates a subtle difference of reactivity between imino compounds and coordinates to them. Imines are reduced with zinc via a SET mechanism, and the subsequent coupling of the radical species to avoid the repulsion of aromatic rings gives the *syn*-**12**.

In conclusion, we have developed a new convenient crossed imino pinacol coupling reaction of various imines using inexpensive and readily accessible reagents, where use of the synergetic effect of plural Lewis acids is crucial for the crossed coupling. This reaction offers a useful method for a rapid assembly of unsymmetrical *syn*-1,2-diamines using an operationally simple procedure.

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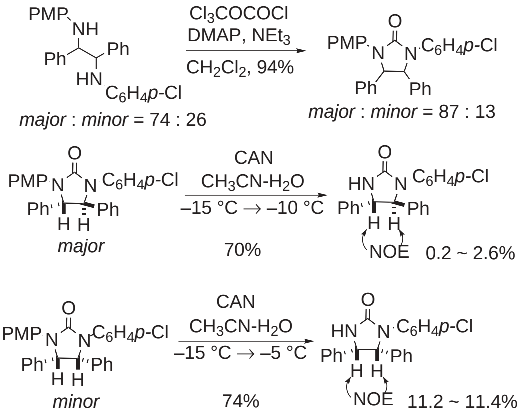
(6) A typical experimental procedure is as follows: To a suspension of Zn-Cu (32.7 mg, 0.50 mmol) in MeCN (0.25 mL) was added a mixture of $BF_3 \cdot OEt_2$ (78.1 mg, 0.55 mmol) and $MeSiCl_3$ (0.147 mL, 1.25 mmol) in MeCN (1.0 mL) at 0 °C under an argon atmosphere. To the resulting mixture was added a solution of *N*-benzylidene-*p*-anisidine (52.8 mg, 0.25 mmol) and *N*-benzylidene-*p*-chlorophenyl aniline (53.9 mg, 0.25 mmol) in acetonitrile (1.25 mL) at 0 °C. After being stirred at room temperature for 1 h, the reaction was quenched with sat. aqueous $NaHCO_3$. Usual work-up followed by purification on preparative silica gel TLC[9] deactivated with phosphate buffer gave 1-(4-chlorophenylamino)-2-(4-methoxyphenylamino)-1,2-diphenylethane (76.2 mg, 71%) as a yellow amorphous.

(7) The relative stereochemistry of the product was determined using $^1H$ NMR (NOE) after transforming into the corresponding imidazolidinone as in the following examples (Scheme 6).



**Scheme 6**

(8) Shimizu, M.; Makino, H. *Tetrahedron Lett.* **2001**, *42*, 8865.

(9) The buffered silica gel TLC was used for the purification. The buffered silica gel was prepared by suspending 93 g of silica gel (Merck $60F_{254}$) in 230 mL of phosphate buffer solution (pH 7.0) for 2 h and dried.