

Crossed Pinacol Coupling Reaction between Aldehydes and Imines: A Rapid Access to 1,2-Amino Alcohols

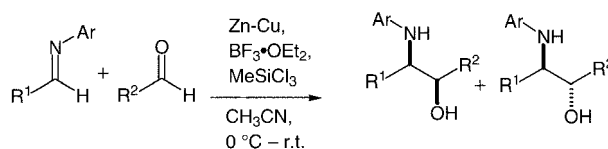
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Abstract: In the presence of zinc, boron trifluoride etherate, and methyltrichlorosilane, aldehydes and imines underwent a crossed pinacol coupling reaction to give 1,2-amino alcohols in good to excellent yields.

Key words: crossed pinacol coupling, 1,2-amino alcohols, methyltrichlorosilane, boron trifluoride etherate, zinc-copper couple



Scheme 1

1,2-Amino alcohol moieties have been found in many of biologically important natural products. In recent years several synthetic 1,2-amino alcohol derivatives have also been employed as drugs for therapeutic purpose as well as chiral auxiliaries or metal ligands in catalytic asymmetric synthesis.¹

So far, several strategies have been employed to construct such units. For example, amino alcohol entities are introduced without altering the carbon skeleton of a molecule.² Alternatively, the 1,2-amino alcohol array is elaborated with the simultaneous construction of the interconnecting carbon-carbon bond.³ Among such processes, the crossed pinacol coupling between carbonyl and imino compounds is one of the most direct ways to synthesize 1,2-amino alcohols, and therefore, it is an attractive and useful reaction for the synthesis of such valuable materials. However, it is not trivial to control the chemoselectivity in the crossed pinacol coupling due to simultaneous homo-couplings. There are only limited examples reported on intermolecular crossed pinacol coupling between imines and carbonyl compounds.⁴ There still appear to be some room for further improvements, regarding starting materials and reagents. We have now found that a simple combination of two different Lewis acids induces discrimination of subtle difference of reactivity between aldehydes and imines, and herein, we wish to report a convenient method for the crossed pinacol coupling of various imines with aldehydes using inexpensive and readily accessible reagents, zinc, boron trifluoride etherate, and chlorosilane (Scheme 1).

We initially investigated the effect of halosilanes for crossed pinacol coupling using the reaction of *N*-benzylidene-*p*-anisidine **1** and benzaldehyde **2**, and the results are summarized in Table 1.⁵

As shown in Table 1, among the halotrialkylsilanes used chlorotrimethylsilane and its triethyl counterpart promoted the desired crossed coupling most effectively, whereas the use of the bulky *t*-butyldimethyl derivative slightly decreased the product yield (entries 1–5). In order to increase the Lewis acidity of the chlorosilanes, dichloro- and trichlorosilyl derivatives were next used. As expected the use of methyltrichlorosilane recorded the best result, where the desired crossed coupling product, 1,2-diphenyl-

Table 1 Effects of the Silicon Reagents^a

Entry	Silicon reagent	3 (%) ^b	<i>syn:anti</i> ^c	4 (%) ^b	5 (%) ^b
1	Me ₃ SiCl	66	62:38	10	0
2	Me ₃ SiBr	22	21:79	4	9
3	Me ₃ SiI	8	13:87	0	14
4	Et ₃ SiCl	69	65:35	11	6
5	<i>t</i> -BuMe ₂ SiCl	50	68:32	8	0
6	Me ₂ SiCl ₂	76	64:36	1	2
7	Ph ₂ SiCl ₂	61	66:34	1	2
8	MeSiCl ₃	85	65:35	1	0

^a The reaction was carried out according to the typical experimental procedure (ref.⁷).

^b Isolated yield.

^c Determined by 270 MHz ¹H NMR.

2-(4-methoxy-phenylamino)ethanol **3**⁶ was obtained in 85% yield and moderate diastereoselectivity along with a negligible amount of the homo-coupling product (entry 8). We next examined the range of aldehydes employable for the present crossed coupling using the reaction with *N*-benzylidene-*p*-anisidine under the best conditions found as in the above cases, and the results are summarized in Table 2.

The use of a slightly increased amount of benzaldehyde gave the 1,2-amino alcohol **7** in excellent yield (entries 1–3) and, therefore, 1.2 equivalents of aldehydes were used throughout the examples in Table 2. In general, the reaction with the aldehydes possessing electron-withdrawing substituents gave the adducts in high yields, in which the use of 4-chlorobenzaldehydes gave the best yield (entry 5), whereas the reaction with acetylene derivative gave the adduct with moderate selectivity in lower yield (entry 12). Use of other aliphatic aldehydes such as 3-phenylpropanal did not give the desired product, but gave a homo-coupling product arising from the imine. The reaction of benzaldehyde with various imines was

Table 2 The Reaction of *N*-Benzylidene-*p*-anisidine with Various Aldehydes^a

Entry	R	Yield of 7 (%) ^b	<i>syn:anti</i> ^c
1	Ph	85 ^d	62:38
2	Ph	90 ^e	65:35
3	Ph	97	65:35
4	4-BrC ₆ H ₄	93	68:32
5	4-ClC ₆ H ₄	97	70:30
6	2-ClC ₆ H ₄	81	61:39
7	4-FC ₆ H ₄	76	58:42
8	4-CF ₃ C ₆ H ₄	72	69:31
9	4-MeOC ₆ H ₄	50	82:18
10	4-MeC ₆ H ₄	82	54:46
11	1-Naphtyl	95	62:38
12	Phenylethynyl	29	65:35 ^f

^a The reaction was carried out according to the typical experimental procedure (ref. ⁷).

^b Isolated yield.

^c Determined by 270 MHz ¹H NMR.

^d Zn-Cu (3.0 equiv), BF₃·Et₂O (2.0 equiv), and aldehyde (1.0 equiv) were used.

^e BF₃·Et₂O (2.0 equiv) and aldehyde (1.2 equiv) were used.

^f Major:minor.

next investigated, and the results are summarized in Table 3.

Table 3 The Reaction of Benzaldehyde with Various Imines^a

Entry	Ar	R	Yield of 9 <i>syn:anti</i> ^c (%) ^b	
1	2-MeOC ₆ H ₄	Ph	74	52:48
2	2,4-(MeO) ₂ C ₆ H ₃	Ph	60	63:37
3	4-MeSC ₆ H ₄	Ph	87	60:40
4	4-Me ₂ NC ₆ H ₄	Ph	72	56:44
5	Ph	Ph	74	54:46
6	4-ClC ₆ H ₄	Ph	76	45:55
7	4-MeOC ₆ H ₄	<i>cyclo</i> -Pr	25	57:43
8	4-MeOC ₆ H ₄	<i>cyclo</i> -Hex	62	77:23
9	4-MeOC ₆ H ₄	2-Phenylethyl	39	56:44
10	4-MeOC ₆ H ₄	Phenylethynyl	85 ^d	56:44 ^e
11	4-MeOC ₆ H ₄	Ethoxycarbonyl	45	54:46

^a The reaction was carried out according to the typical experimental procedure (ref. ⁷).

^b Isolated yield.

^c Determined by 270 MHz ¹H NMR.

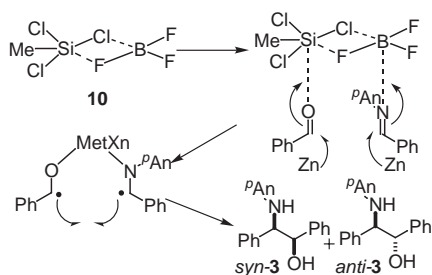
^d CH₃CN–CH₂Cl₂ (9:1) was used as a solvent.

^e Major:minor.

In general, the effect of the substituents at the nitrogen atom was not prominent, and the reaction usually proceeded to give the coupling products in good yields (entries 1–6). The reaction with the imine possessing a phenylacetylene moiety gave the adducts in good yield (entry 10). A lower yield was observed in the reaction of *N*-cyclopropylmethylene-*p*-anisidine with benzaldehyde (entry 7). In this case reduction product of the imine, diol, and *p*-anisidine were isolated as by-products. The in situ preparation of a relatively unstable imine followed by the coupling reaction also afforded the desired amino alcohol but in moderate yield (entry 9).

Although there are several arguments on the reaction pathways, a possible reaction mechanism is shown in Scheme 2.

A mixture of boron trifluoride etherate and methyltrichlorosilane would form a bimetallic complex **10**. On the basis of affinity and steric repulsion, the oxygen atom is coordinated with the more Lewis acidic silicon atom of methyltrichlorosilane, whereas the nitrogen atom is coordinated with the boron atom of boron trifluoride. Imine and aldehyde are reduced with zinc via a SET mechanism,



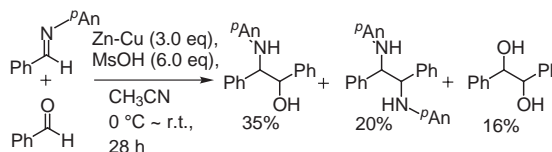
Scheme 2

and the subsequent coupling of the radical species gives the adduct **3**.

In conclusion, we have developed a new convenient crossed pinacol coupling reaction of various imines with aldehydes using inexpensive and readily accessible reagents, where the use of more than one Lewis acid is crucial for the crossed coupling. Although the diastereoselectivity is not high, this reaction offers a useful method for a rapid assembly of 1,2-amino alcohols using an operationally simple procedure.

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- (5) Control experiments indicate that the presence of plural Lewis acids is crucial for the chemoselective addition. The following example (in Scheme 3) shows one of the examples. (Since no coupling reaction was observed in the absence of acid additives, the reaction was conducted in the presence of methanesulfonic acid.)



Scheme 3

- (6) (a) Alcaide, B.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1649. (b) Burton, R. D.; Bartberger, M. D.; Zhang, Y.; Eyley, J. R.; Schanze, K. S. *J. Am. Chem. Soc.* **1996**, *118*, 5655.
- (7) A typical experimental procedure is as follows: To a suspension of zinc-copper couple (65 mg, 1.0 mmol) in acetonitrile (0.5 mL) was added a mixture of boron trifluoride diethyl etherate (156 mg, 1.1 mmol) and methyltrichlorosilane (0.24 mL, 2.0 mmol) in acetonitrile (1.5 mL) at 0 °C under an argon atmosphere. To the resulting mixture was added a solution of N-benzylidene-p-anisidine (106 mg, 0.5 mmol) and benzaldehyde (64 mg, 0.60 mmol) in acetonitrile (3.0 mL) at 0 °C. After being stirred at r.t. for 40 min, the reaction was quenched with sat. aqueous NaHCO₃. The mixture was filtered through a Celite pad. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with sat. aqueous NaHCO₃ and brine, and then dried over anhydrous Na₂SO₄. Purification on preparative silica gel TLC gave 1,2-diphenyl-2-(4-methoxyphenylamino)ethanol (155 mg, 97%) as a colorless oil.