Highly Enantioselective Imino Pinacol Coupling Leading to the Synthesis of 1,2-Diphenylethylenediamine Derivatives

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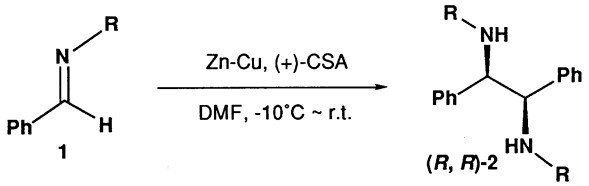
Enantioselective imino pinacol coupling of *p*-anisylbenzalimine was promoted by the use of Zn-Cu couple in the presence of (+)-camphorsulfonic acid to give (*R*,*R*)-1,2-diphenylethylenediamine derivative in high enantiomeric purity.

Chiral 1,2-diamino compounds such as 1,2-diphenylethylenediamine or *trans*-1,2-cyclohexanediamine have found considerable utility as a chiral auxiliary in the field of asymmetric synthesis, in particular catalytic asymmetric synthesis.[1] One of the most straightforward synthetic ways to such a class of compounds involves asymmetric reductive coupling of imines, although conventional methods utilizing resolution of racemic 1,2-diamines with certain chiral carboxylic acids have offered the procedures widely used.[1q,2] The pinacol coupling reaction has provided us with a short simple way of producing 1,2-diols,[3] and recently the imino version of such coupling procedure was reported to give 1,2-diamino compounds in a straightforward manner.[4] To the best of our knowledge, however, no method has been available for the imino coupling in an enantioselective manner. Difficulties associated with the stereocontrol in the imino coupling reaction involve the diastereofacial selectivity which reflects the *dl* vs. *meso* ratio and the enantiofacial selectivity of the *dl*-adduct. In conjunction with our recent interest in the reactivity of imino compounds in the addition reaction of enolate species,[5] we became interested in the reductive coupling of imino compounds, and now found that the reductive coupling reaction was promoted and controlled by the use of Zn-Cu couple and a suitable chiral sulfonic acid. We would like to report herein a facile approach to 1,2-diphenylethylenediamine derivatives in high enantiomeric purity.



a: R = *p*-MeOC$_6$H$_4$
b: R = C$_6$H$_5$
c: R = C$_6$H$_5$CH$_2$
d: R =(*p*-MeOC$_6$H$_4$)$_2$CH

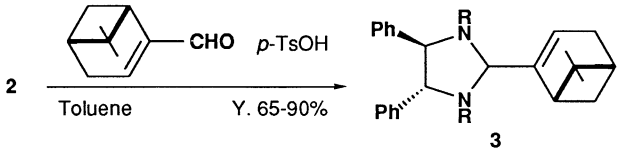
(+)-CSA = (+)-Camphorsulfonic acid

The imino coupling was carried out as follows: to a suspension of Zn-Cu couple (196 mg, 3 mmol) in DMF (10 mL) was added a solution of (+)-camphorsulfonic acid (696 mg, 3 mmol) in DMF (2 mL) at -10 °C. Then a solution of *p*-anisylbenzalimine (211 mg, 1.0 mmol) in DMF (2 mL) was added to the cooled mixture during 1 hr at -10 °C, and the reaction mixture was allowed to stand at room temperature for 30 hr. Sat aq NaHCO$_3$ (5 mL) was added at 0 °C, and the resulting mixture was filtered through a pad of Celite. The filtrate was extracted with ethyl acetate (5 mL x 3), and the combined extracts were washed with sat aq brine (10 mL x 2). Purification of the crude oil on preparative TLC gave a mixture of *dl*- and *meso*-1,2-diphenylethylenediamine (173 mg, 88%).[6] The ratio of *dl*- vs. *meso*-compounds was determined by ^{1}H NMR to be 70 : 30, and the optical purity of the *dl*-adduct was determined to be 97%ee with the (*R*,*R*)-enantiomer in excess by HPLC (Merck Hibar column) after transformation into aminal **3a** with (-)-myrtenal. The results of imino coupling reaction are summarized in Table 1.

Table 1. Coupling Reaction of Imime **1**[a]

Entry	Imine	(+)-CSA/eq	Yield/%[b]	*dl* : *meso*[c]	%ee[d]
1	**1a**	1.0	76	55 : 45	54
2	**1a**[e]	2.0	64	88 : 12	88
3	**1a**	2.0	74	75 : 25	84
4	**1a**	3.0	88	70 : 30	97
5	**1a**	4.0	63	81 : 19	97
6	**1a**	5.0	60	80 : 20	97
7	**1b**	3.0	64	50 : 50	52[f]
8	**1c**	3.0	54	53 : 47	34[f,g]
9	**1d**	3.0	64	50 : 50	0

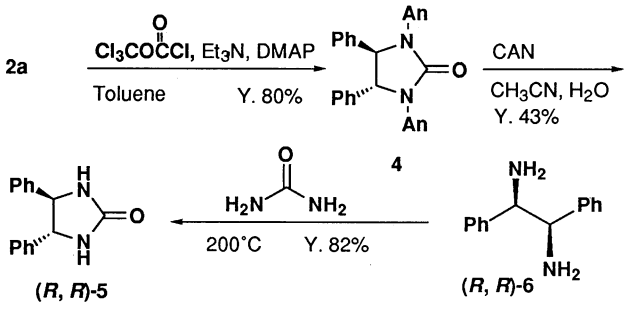
[a]The reaction was carried out according to the typical experimental procedure. [b]Isolated yield. [c]Ratio determined by ^{1}H NMR and/or HPLC. [d]Determined by HPLC analysis of aminal **3** prepared from **2** and (-)-myrtenal. For determination of the absolute configuration, see text. [e]Zn-Cu (2 eq) was used. [f]The absolute configuration was not determined. [g]Determined by HPLC analysis of **2** using chiral stationary column (Daicel OJ).



The reaction needed 3 equiv of Zn-Cu couple for reproducible results, and the use of less than 3 equiv did not always meet with completion of the reaction. When the reaction was carried out in the presence of 1 equiv of (+)-camphorsulfonic acid the enantiomeric excess of the diamine obtained was not high, and the use of an increased amount of the chiral source raised the enantioselectivity of the present reaction. The best result was obtained when the reaction was carried out in the presence of 3 equiv of (+)-camphorsulfonic acid, and the reaction gave enantiomers in 97%ee. The use of 4 or 5 equiv of camphorsulfonic acid did not substantially increase the optical purity of the coupling product, but decreased the chemical yield. The reaction usually gave a mixture of *dl*- and *meso*-compounds with *dl*-isomer being predominated. Separation of these isomers was carried out readily by silica gel chromatography after transformation into imidazolidinone **4** with trichloromethyl chloroformate. Separation of *dl*- from *meso*-isomer was also performed readily at aminal stage **3** by silica gel chromatography. Furthermore, enantiomerically pure diamine was readily obtained

by simple recrystallization of imidazolidinone **4**. Other imines besides *p*-anisyl derivative were examined, and simple phenyl derivative **1b** recorded moderate selectivity, whereas benzyl and di-*p*-anisylmethyl derivatives **1c, d** did not show satisfactory discrimination. Oxime and its derivatives such as *O*-benzyl or *O*-methyl ether did not produce the diamine in good enantiomeric purity under the present coupling conditions, and almost a 1:1 mixture of enantiomers was obtained.

The absolute configuration of the diamine **2a** was determined to be 1*R*,2*R* by transforming into imidazolidinone **4** followed by oxidative removal of anisyl group as the following equation shows, and comparison of the sign of the optical rotation with that of the authentic sample **5** prepared from commercially available (*R,R*)-1,2-diphenylethylenediamine **6**.



From **4**: $[\alpha]_D^{23}$ +60.3 (c 0.16, $CHCl_3$)

From **6**: $[\alpha]_D^{23}$ +58.6 (c 1.06, $CHCl_3$)

The imino pinacol coupling studied in the present work offers a rapid simple way of preparing 1,2-diphenylethylenediamine derivatives in high enantiomeric purity, and demonstrates that the relative and absolute strereochemistry of the resulting coupling product is highly dependent on the substituent on the aromatic ring. Since the reaction did not proceed in the absence of sulfonic acid, the key intermediate in the present reaction involved a chiral iminium salt formed from imine and (+)-camphorsulfonic acid,[7] which in turn underwent reductive coupling with Zn-Cu couple. This kind of construction of relatively rigid asymmetric environment around the imino functionality may offer practical C-C bond formation on the imino carbon in an enantioselective manner without the need for removal of chiral auxiliary on or around the nitrogen atom after the reaction.

References and Notes

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6 **2a** (*dl*): ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.65 (s, 6H), 4.42 (brs, 2H), 4.45 (s, 2H), 6.45 (d, *J* = 7.43, 4H), 6.65 (d, *J* = 7.43, 4H), and 7.08-7.19 (m, 10H); **2a** (*meso*): δ 3.65 (s, 6H), 4.20 (brs, 2H), 4.87 (s, 2H), 6.45 (d, *J* = 7.43, 4H), 6.65 (d, *J* = 7.43, 4H), and 7.09-7.20 (m, 10H).

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