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Synthesis of Chiral Vicinal Diamines by Highly Diastereoselective Three-Component Phenolic Mannich Reaction: Temperature-Dependent Stereodivergency

Christophe Rondot and Jieping Zhu*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

zhu@icsn.cnrs-gif.fr

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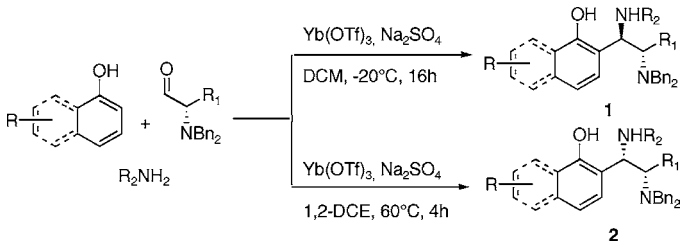
ABSTRACT



A diastereoselective three-component synthesis of chiral *o*-1,2-diaminoalkyl phenols from an electron-rich phenol, an amine, and a chiral α-*N*,*N*-dibenzylamino aldehyde is developed. The diastereoselectivity of this phenolic Mannich reaction is temperature-dependent,and either *anti* or *syn* diastereomer can be prepared by controlling the reaction conditions. Low reaction temperature (–20 °C) favors the formation of *anti* adduct 1, whereas higher temperature (60 °C) under otherwise identical conditions produces mainly the *syn* isomer.

Chiral vicinal diamines are frequently found as a subunit in a large number of bioactive natural products, biotin (vitamin H) and penicillins being notable examples.[1] This functionality can also be found in various medicinally relevant compounds including anticancer drugs such as 1,2-diaminoplatinum complexes.[2] In addition, the 1,2-diamine is also considered as a privileged structural element[3] in the search for chiral catalysts.[1,4]

Many elegant synthetic routes have been developed to obtain the chiral 1,2-diamine unit.[1] Among them, nucleophilic addition to α-*N*,*N*-dibenzylamino aldimine, amino oxime, amino nitrone, and amino hydrazone is particularly attractive since the starting materials are readily available.[5,6] A variety of organometallic reagents have been successfully used, and the diastereoselective Strecker reaction[5] and Mannich reaction[5,7] have also been developed to reach a diverse set of functionalized chiral diamines. Interestingly, while asymmetric phenolic aldol reaction between chiral α-amino aldehyde and phenol is well-known,[8] the asymmetric phenolic Mannich reaction or imino Friedel−Crafts reaction of

(1) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627.
(2) Reedijk, J. *J. Chem. Soc., Chem. Commun.* **1996**, 801−806.
(3) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691−1693.
(4) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vols. 1 and 2.
(5) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162.
(6) For recent general reviews on the nucleophilic adition to imine, see: (a) Enders, D.; Reinhold, U. *Tetrahedon: Asymmetry* **1997**, *8*, 1895−1946. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (d) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651−673.
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(8) (a) Casiraghi, G.; Cornia, M.; Rassu, G. *J. Org. Chem.* **1988**, *53*, 4919−4922. (b) De Paolis, M.; Blankenstein, J.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2002**, *4*, 1235−1238. (c) De Paolis, M.; Chiaroni, A.; Zhu, J. *J. Chem. Soc., Chem. Commun.* **2003**, 2896−2897.

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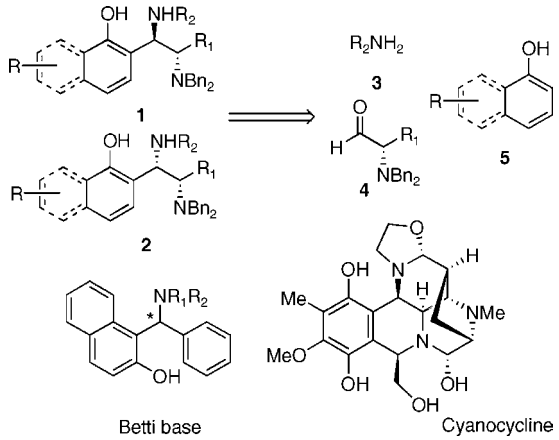
chiral α-amino aldimine was unknown.[9,10] Indeed, the reduced electrophilicity of imine in conjunction with its higher tendency to undergo imine−enamine tautomerization leading to racemization made this transformation particularly challenging. In this regard, the elegant three-component synthesis of chiral Betti base from phenol, aldehyde, and chiral amine developed by the Chan group is a notable exception.[11,12] However, in this case, the chirality was induced by the chiral amine, which is less prone to racemization upon formation of iminium intermediate. We report herein the first examples of diastereoselective three-component synthesis of chiral *o*-1,2-diaminoalkyl phenols (**1**, **2**) from an amine (**3**), a chiral α-*N*,*N*-dibenzylamino aldehyde (**4**), and a phenol (**5**) and document that both *syn* and *anti* diastereomers are readily accessible in a stereoselective fashion by simply changing the reaction temperature (Scheme 1). [13−15] Diamines of type **1** and **2** are subunits of

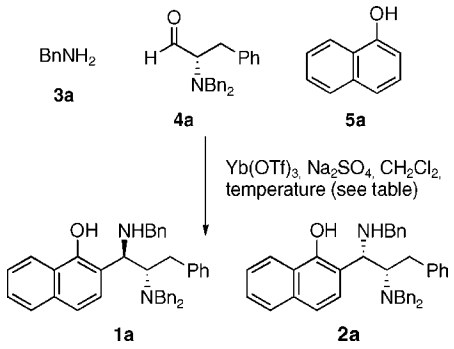
Scheme 1. Stereoselective and Stereodivergent Syntheses of Chiral *o*-1,2-Diaminoalkyl Phenols by a Three-Component Phenolic Mannich Reaction



a number of natural products such as cyanocycline C.[16]

The three-component condensation of benzylamine (**3a**), L-α-*N*,*N*-dibenzylaminophenylalaninal (**4a**), and α-naphthol (**5a**) was used as a model for the survey of reaction conditions. After screening of catalysts ($InCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$),[17] additives (Na_2SO_4, tertiary amines, molecular sieves 4 Å), and solvents (MeCN, CH_2Cl_2, dichloroethane), the best conditions we found consisted of performing the reaction in dichloromethane in the presence of a catalytic amount of $Yb(OTf)_3$ (0.1 equiv) and sodium sulfate (Scheme 2). It is noteworthy that the same reaction

Scheme 2. Three-Component Synthesis of Diamino Phenol



took place even in the absence of Lewis acid, albeit with a longer reaction time and lower yield.[18] Interestingly, the diastereoselectivity was found to be temperature-dependent (Table 1). At −20 °C, the reaction produced mainly the *anti*

Table 1. Three-Component Reaction of α-Naphthol, Benzylamine, and L-α-*N*,*N*-Dibenzylaminophenylalaninal: Temperature-Dependent Stereodivergency[a]

entry	*T* (°C)	reaction time (h)	yield[b] (%)	**1a/2a**[c]
1	−20	20	88	14/1
2	0	20	79	9/1
3	20	5	75	7/1
4	20	16	84	1/1
5	60[d]	4	44	1/18

[a] Reaction was run in dichloromethane (concentration: 0.5 M) in the presence of ytterbium triflate (0.1 equiv) and sodium sulfate. [b] Isolated yield of major isomer. [c] Determined by analysis of ^{1}H NMR spectrum. [d] The reaction was performed in 1,2-dichloroethane.

diastereomer (**1a**, entry 1, vide supra for the stereochemical issue), the diastereoselectivity decreased as the temperature went from −20 to 0 °C and to 20 °C. The reaction became *syn*-selective when the same reaction was run at 60 °C (*syn*/*anti* = 18/1, entry 5). Carefully monitoring the reaction course indicated that the *anti*/*syn* ratio is changing gradually in favor of the *syn* adduct at 20 °C (entries 3 vs 4). Furthermore, the control experiment shows that *syn* adduct (**2a**) was produced by simply heating a $CDCl_3$ solution of diastereomerically pure *anti* adduct (**1a**). We thus speculated that the temperature-dependent stereodivergency did not

(9) Diastereoselective Passerini reaction with chiral *N*,*N*-dibenzylamino aldehyde: Cuny, G.; Gamez-Montano, R.; Zhu, J. *Tetrahedron* **2004**, *60*, 4879−4885.

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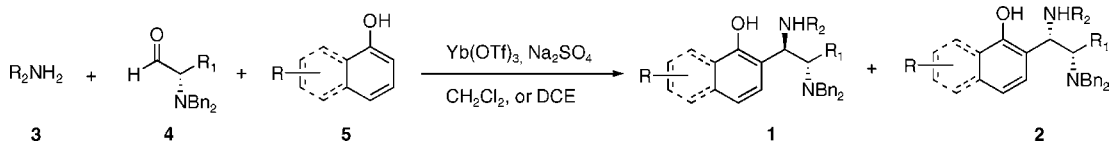
Table 2. Stereodivergent Three-Component Synthesis of Chiral *o*-1,2-Diaminoalkylphenols **1** and **2**



entry 1	phenol	amine	α-amino aldehyde	T (°C)	yield[a] (%)	anti/syn
1	α-naphthol (**5a**)	R_2 = Bn (**3a**)	R_1 = CH_2Ph (**4a**)	−20	88	**1a/2a** = 14/1
2	**5a**	**3a**	**4a**	60	48	**1a/2a** = 1/18
3	**5a**	**3a**	R_1 = Me (**4b**)	−20	52	**1b/2b** = 17/1
4	**5a**	**3a**	**4b**	20	100	**1b/2b** = 0/100
5	**5a**	**3a**	R_1 = CH_2OTBS (**4c**)	−20	31	**1c/2c** = 6/1
6	**5a**	R_2 = $TBSOCH_2CH_2$ (**3b**)	R_1 = CH_2Ph (**4a**)	−20	95	**1d/2d** = 100/0
7	**5a**	R_2 = 4-MeO-phenyl (**3c**)	**4a**	−20	64	**1e/2e** = 6/1
8	β-naphthol (**5b**)	**3a**	**4a**	−20	51	**1f/2f** = 100/0[b]
9	4-MeO-1-naphthol (**5c**)	**3a**	**4a**	−20	43	**1g/2g** = 6/1
10	sesamol (**5d**)	**3a**	**4a**	−20	70	**1h/2h** = 12/1
11	**5d**	**3a**	**4a**	60	25	**1h/2h** = 0/100
12	**5d**	**3a**	*N*-Boc-phenylalaninal (**4d**)	rt	0	

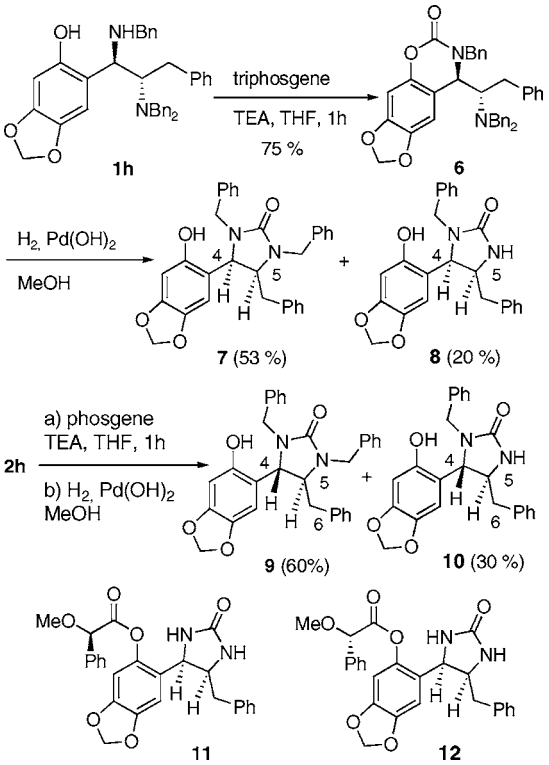
[a] Isolated yield of major diastereomer. [b] Addition occurred at C-1 position.

result from the change of the facile selectivity during the nuclephilic addition of phenol to imine[19] but was a consequence of equilibrium of these two isomers.

The scope of this three-component phenolic Mannich reaction is examined with various inputs including four phenols, three amines, and four protected amino aldehydes derived from phenylalanine, alanine, and serine, respectively.[20] As is seen from Table 2, the reaction was quite general and gave either *syn* or *anti* adduct, depending on the reaction temperature, in good chemical yield and good to excellent diastereoselectivity. Functionalized amines such as β-amino alcohol (**3b**) as well as 4-methoxyaniline (**3c**) took part in this reaction. However, secondary amine failed to produce the desired phenolic Mannich base (data not shown). As expected, only electron-rich phenol can participate in this reaction to afford the desired adduct. While *N*,*N*-dibenzylamino aldehyde was initially selected on the basis of the diastereoselectivity issue, it turns out that the *N*-protective group played a decisive role for the present Mannich reaction since no reaction took place with L-*N*-Boc phenylalanal (**4d**, entry 12) under otherwise identical conditions.

The stereochemistry of the *syn* and *anti* adducts was determined by their conversion to the rigid imidazolidinones (Scheme 3). Thus, treatment of **1h** with triphosgene in the presence of triethylamine produced the cyclic carbamate **6**. Interestingly, when **6** was submitted to hydrogenolysis conditions (H_2, $Pd(OH)_2$, MeOH), a sequence of partial debenzylation followed by transacylation occurred to afford directly two imidazolidinones **7** and **8**, differing only in the level of *N*-substitution. The coupling constant (J_{H4-H5} = 8.5 Hz)[21] together with the observation of a NOE cross-peak between the protons H-4 and H-5 of **7** and **8** indicated the *cis* relationship of these two protons and, hence, the *anti* stereochemistry of **1h**. Similarly, the stereochemistry of **2h** (*syn*) was deduced from imidazolidinones **9** and **10** whose

Scheme 3. Determination of Relative Stereochemistry and Enantiomeric Purity of Adducts **1h** and **2h**



(19) $Yb(OTf)_3$ may coordinate to imino nitrogen. However, we surmised that five-membered chelate was not formed under our reaction conditions.

(20) Synthesized following literature precedents: (a) Beaulieu, P. L.; Wernic, D.; *J. Org. Chem.* **1996**, *61*, 3635−3645. (b) Laïb, T.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1998**, *63*, 1709−1713.

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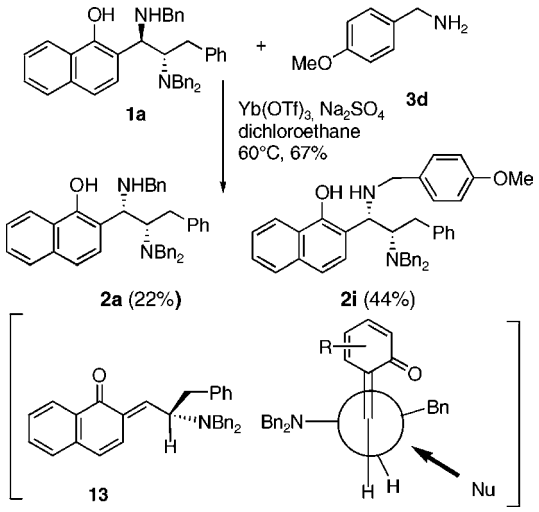
spectroscopic property (J_{H4-H5} = 5.5 Hz, NOE: H-4/H-6) is in accord with the *trans* stereochemistry. The enantiomerical purity of **7**, hence that of **1h**, was determined to be higher than 93% by its transformation to the diastereomeric mandelates **11** and **12**.[22] This result demonstrated that little, if any, racemization occurred during the present phenolic Mannich and subsequent transformations.

While the nucleophilic addition of phenol onto the *N*,*N*-dibenzylaminoaldimine leading predominantly to the *anti* adduct is readily explained on the basis of the Felkin−Ahn model,[23] the facile isomerization of *anti* to *syn* adduct is intriguing. Two crossover experiments were performed in order to probe the mechanism of epimerization (Scheme 4).

Scheme 4. Mechanistic Hypothesis for the Thermal Isomerization of *Anti* Adduct **1** to *Syn* Adduct **2**



Heating a 1,2-dichloroethane (DCE) solution of *anti* adduct (**1a**) and sesamol (**5d**) to 60 °C afforded only the *anti* isomer **2a** without concurrent formation of **1h** or **2h** indicating that retro-Mannich reaction did not take place and was not responsible for the therml isomerization of **1** to **2**. On the other hand, heating a DCE solution of **1a** and 4-methoxybenzylamine (**3d**, 2 equiv) led not only to the formation of *syn* adduct **2a** but also to **2i** in which the 4-methoxybenzylamine was incorporated (Scheme 4). On the basis of this observation, the following mechanistic hypothesis was advanced to account for thermal isomerization: 1,4-elimination of the benzylic amine assisted by the neighboring phenoxyl group and possibly the basicity of the benzylamino function that may act as an internal base would provide the *o*-quinone methide intermediate **13**. Michael addition of available amine onto **13**[24] according, once again, to the Felkin−Ahn model would give the observed *syn* adduct **2**.

In summary, we reported a three-component synthesis of chiral *o*-1,2-diaminoalkylphenol from readily available starting materials. The synthesis is diastereoselective and stereodivergent allowing the access to four possible enantiomers by simply changing the absolute configuration of the amino aldehyde and reaction temperature. It represents one of the shortest routes to access this type of chiral entity.

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Supporting Information Available: Experimental details and physical data for compounds **1**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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