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Phosphoric Acid Catalyzed Diastereo- and Enantioselective Synthesis of Substituted 1,3-Diaminotetralins

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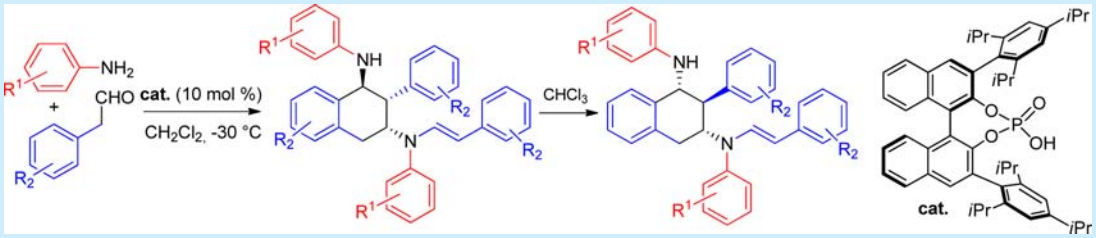
S *Supporting Information*



ABSTRACT: The reaction of anilines and phenylacetaldehydes in the presence of chiral phosphoric acid afforded optically active 1,2-*trans*, 2,3-*cis* 1,3-diaminotetralins in high yields with excellent diastereo- and enantioselectivities. The *trans*/*cis* product was readily isomerized to a *trans*/*trans* stereoisomer with no significant loss of enantiomeric purity.

The medicinal importance of the aminotetralins has been known for a long time. For instance, sertraline is a much studied antidepressant,[1] and 2-aminotetralins such as [(*S*)-(−)-5-OH-DPAT] and [(*R*)-(+)-7-OH-DPAT] are popular targets in asymmetric synthesis because of their dopamine agonist activity (Figure 1).[2] Surprisingly, the great majority of existing routes for the synthesis of these compounds are generally limited to classical methods such as catalytic hydrogenation[3] or reductive amination,[4] using the corresponding tetralone derivatives as starting materials.[5]

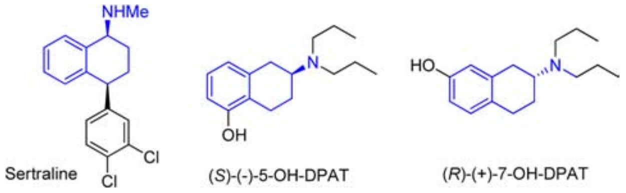


Figure 1. Examples of bioactive aminotetralins.

Only rare examples of aminotetralin syntheses are based on the construction of the saturated cycle. For example, Zard developed a racemic synthesis of 4-substituted 2-aminotetralins via a radical-based multistep route.[6] The development of an enantioselective one-pot synthesis of substituted aminotetralins via the construction of the saturated cycle is therefore highly desirable. Being involved in the enantioselective synthesis of aza-heterocycles,[7] we report herein the development of a short and rapid one-pot domino synthesis of enantioenriched substituted 1,3-diaminotetralins from easily available starting materials.

In our previous studies on the phosphoric acid catalyzed[8] three-component reaction of anilines **1**, aldehydes **2**, and enecarbamates **3**, we have provided convincing evidence that this reaction went through a stepwise[7a−d,9] process involving the *N*-acyliminium intermediate **4.**[10] Therefore, we thought that it might be possible to interrupt[9−11] the Povarov process by trapping the iminium function in **4** by the aromatic ring of the phenylacetaldehyde derivative **2** (Ar^2 = R^2-C_6H_4) rather than that of the aniline, which would lead to 1,3-diaminotetralins **5** (Scheme 1).

We therefore first investigated the three-component reaction of 4-nitroaniline **1a** (1.1 equiv), phenyl-acetaldehyde **2a** (1.0 equiv), and enecarbamate **3a** (1.0 equiv) in CH_2Cl_2 in the presence of phosphoric acid **6a** (0.1 equiv, Scheme 1). The reaction was carried out at −30 °C to avoid the potential isomerization of aliphatic *N*-arylimines as described in previous works.[12] To our surprise, we observed the formation of neither desired 1,3-diaminotetralin **5a** nor the Povarov adduct, even when a large excess of **3a** (5.0 equiv) was used. Instead, 1,3-diaminotetralin **7a** was produced in 61% yield as one diastereomer with a 1,2-*trans*, 2,3-*cis* relative stereochemistry assigned by NOESY experiments.[13] The formation of **7a** is postulated to arise from a tandem sequence described in Scheme 2. After condensation of the aniline **1a** with phenylacetaldehyde **2a**, the resulting imine **8a** would partially isomerize into enamine **9a** even at −30 °C, probably due to the great stability of its C=C double bond conjugated with the aromatic ring. Then, nucleophilic attack of the enamine **9a** onto imine **8a** would afford a new iminium intermediate **10a** with

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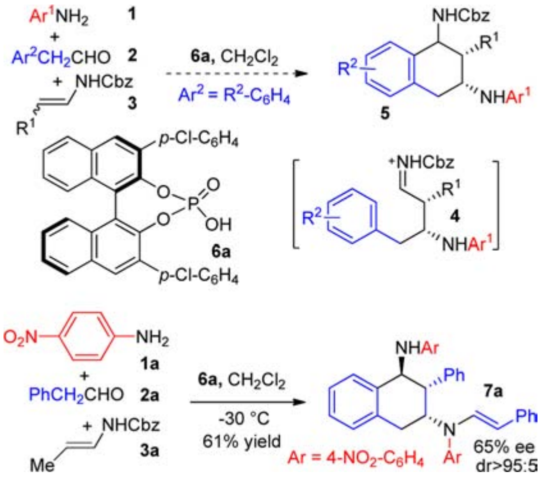
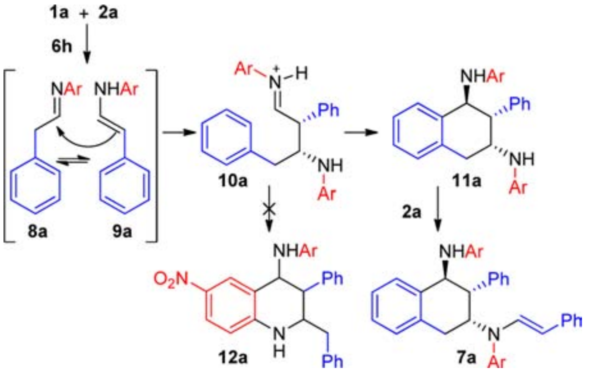
Scheme 1. A Proposed Route for the Synthesis of 1,3-Diaminotetralins *via* Intramolecularly Interrupted Povarov Reaction



Scheme 2. Plausible Mechanism of the Reaction

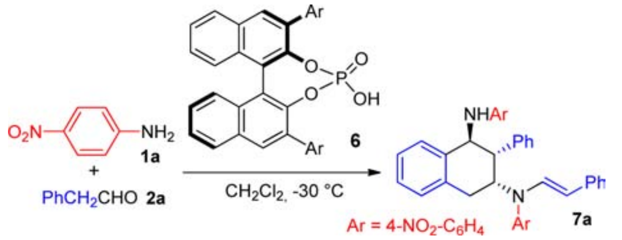


concurrent creation of two stereocenters. Subsequent intramolecular trapping of the Mannich-type adduct **10a** would lead to diaminotetralin **11a**, and its condensation with another molecule of phenylacetaldehyde **2a** would finally afford 1,3-diaminotetralin **7a**, having an enamine function on the 3-N position. Notably, the Doebner–von Miller[14] tetrahydroquinoline **12a** obtained from the aza-Friedel–Crafts reaction of the aromatic ring of aniline onto **10a** was never observed.

Encouraged by the promising enantioselectivity (65% ee) observed in this reaction, we further investigated the asymmetric synthesis of 1,3-diaminotetralins **7** (Table 1). A large number of phosphoric acid derivatives were tested, and the best enantioselectivity was obtained with catalyst **6h** having a bulky 2,4,6-triisopropylphenyl (TRIP) group on the 3,3′ positions (88% ee, entry 8). The yield could also be improved to 91% by adding **2a** (1.5 equiv) within 12 h by means of a syringe pump. We were also pleased to see that the catalyst loading could be decreased to 1 mol % without any significant loss of enantioselectivity or reactivity (entry 11).

The scope of this Brønsted acid catalyzed reaction was next investigated using our optimized conditions. In order to avoid the formation of the Doebner–von Miller tetrahydroquinoline **12** (Scheme 2), only electron-poor anilines were screened.[15] As shown in Table 2, all kinds of electron-poor *meta-* or *para-*substituted anilines were appropriate substrates, affording various diaminotetralins **7** in good to excellent yields with high enantioselectivities. Diastereoselectivities were generally very high (>95:5 dr) in favor of the *trans*/*cis* diastereomer, even though the *trans*/*trans* diastereomer could sometimes be isolated in small quantities (8:1 < dr < 17:1, entries 2, 5, 6, and 9). Reactions with *ortho*-substituted anilines did not proceed, probably due to steric reasons. Several *ortho-* or *para-*substituted electron-poor or -rich phenylacetaldehydes were also suitable reaction partners, leading to the corresponding diaminotetralins **7j–l** in good to high yields with good diastereoselectivities and excellent enantioselectivities (up to 96% ee, entries 10–12). Notably, when *meta*-methylphenylacetaldehyde was used, only one regioisomer bearing the methyl group in position 7 of the tetralin was isolated in 77% yield with good selectivites (dr = 7:1 and ee = 95%, entry 13), with no trace of the 9-methylated regioisomer. Based on our previous work, the phosphoric acid may act as a bifunctional catalyst activating both **8** and **9** to allow a pseudointramolecular *si*-face attack of enamine **9**. Then, the intramolecular Friedel–Crafts reaction would occur to form (1*S*,2*S*,3*R*)-1,3-diaminotetralins **7** (Scheme 3).

Table 1. Synthesis of 1,3-Diaminotetralins: A Survey of Phosphoric Acid Catalysts[a]



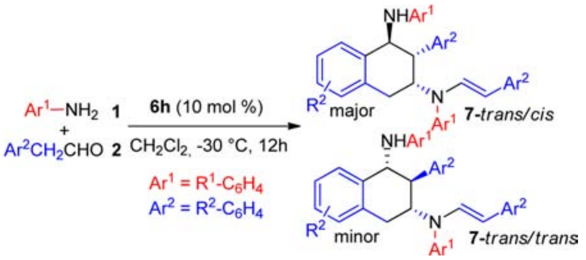
entry	Ar/**6**	loading of **6** (mol %)	yield **7a** (%)[b]	ee (%)[c]
1	4-ClC_6H_4/**6a**	10	61	65
2	Ph/**6b**	10	85	65
3	4-$MeOC_6H_4$/**6c**	10	90	60
4	4-$^tBuC_6H_4$/**6d**	10	57	20
5	*β*-Naph/**6e**	10	72	28
6	$CH(Ph)_2$/**6f**	10	56	72
7	$CH(4\text{-}MeOC_6H_4)_2$/**6g**	10	37	66
8	2,4,6-(iPr)$_3C_6H_2$/**6h**	10	65	88
9[d]	**6h**	10	91	88
10[d]	**6h**	2.5	90	87
11[d]	**6h**	1	86	87
12[d]	**6h**	0.5	81	84

[a] General conditions: aniline **1a** (0.10 mmol), aldehyde **2a** (0.15 mmol), and **6** in CH_2Cl_2 (1.0 mL). [b] Yields referred to a chromatographically pure product. [c] Enantiomeric excess was determined by chiral HPLC analysis (see Supporting Information). [d] The reaction was performed with the slow addition of **2a** within 12 h.

During the NMR analysis of these diaminotetralins, we also observed in some cases partial degradation and isomerization of $7_{trans/cis}$ into $7_{trans/trans}$ in $CDCl_3$. We thought that this isomerization could come from the slight acidity of this solvent, which would probably enable a retro-Friedel–Crafts reaction as shown in Scheme 4, leading to the thermodynamically more stable diastereomer $7_{trans/trans}$.

We then tried to optimize this reaction of isomerization (Table 3). We first let the reaction mixture warm to room temperature, hoping that the phosphoric acid itself could catalyze this isomerization process. Unfortunately, even if some desired product was obtained, we could only recover 53% of

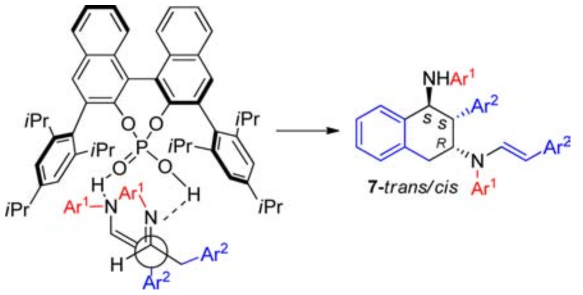
Table 2. Scope of the Enantioselective Phosphoric Acid Catalyzed Synthesis of 1,3-Diaminotetralins[a]



entry	R^1	R^2	7	yield (%)[b]	dr[c] $7_{\text{trans/cis}}$: $7_{\text{trans/trans}}$	ee (%)[d]
1	4-NO_2	H	**7a**	91	>95:5	88
2	4-CO_2Et	H	**7b**	99	16:1	90
3	3,5-di-Br	H	**7c**	90	>95:5	75
4	4-CF_3	H	**7d**	95	>95:5	84
5	4-Cl	H	**7e**	82	11:1	94
6	4-Me-3-NO_2	H	**7f**	68	17:1	89
7	3-NO_2	H	**7g**	85	>95:5	81
8	3-I	H	**7h**	98	8:1	88
9	4-Br	H	**7i**	95	10:1	94
10	4-Br	4-OMe	**7j**	92	7:1	93
11	4-Br	4-Br	**7k**	71	>95:5	95
12	4-Br	2-Br	**7l**	92	>95:5	96
13	4-Br	3-Me	**7m**	77	7:1	95

[a] General conditions: amine **1** (0.10 mmol), **6h** (0.005 mmol) in CH_2Cl_2 (1.0 mL), and slow addition of aldehyde **2** (0.15 mmol). [b] Yields referred to a chromatographically pure mixture of diastereomers. [c] Diastereomeric ratio was determined by NMR spectra analysis. [d] Enantiomeric excess was determined by chiral HPLC analysis (see Supporting Information).

Scheme 3. Activation Model and Possible Reaction Mechanism



Scheme 4. Mechanistic Proposal for the Isomerization of 7

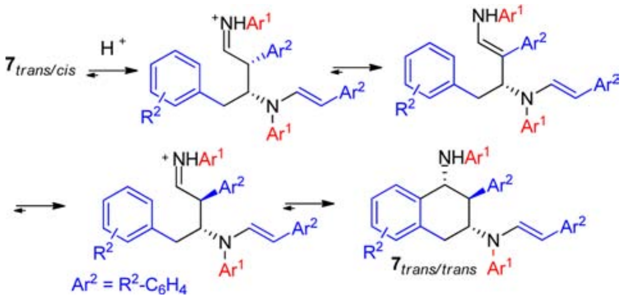
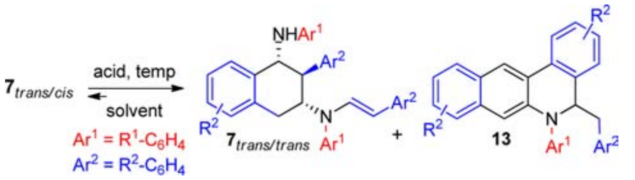


Table 3. Optimization of the Isomerization of 7



entry	R^1	R^2	7	yield of **13** (%)[e]	yield of 7 (%)[e]	dr[f] $7_{\textit{trans/trans}}$: $7_{\textit{trans/cis}}$	ee (%)[g]
1[a]	4-Cl	H	**7e**	25	53	9:1	90
2[b]	4-Cl	H	**7e**	traces	95	1:2	90
3[c]	4-Cl	H	**7e**	48	traces	9:1	ND
4[d]	4-Cl	H	**7e**	traces	86	9:1	90
5[d]	4-Br	H	**7i**	traces	82	8:1	90
6[d]	4-Br	4-OMe	**7j**	5	70	8:1	89

[a] Solvent: CH_2Cl_2; temp: 25 °C; acidic conditions: **6h** (0.1 equiv), 24 h. [b] Solvent: CH_2Cl_2; temp: −30 °C; acidic conditions: **6h** (0.1 equiv), 48 h. [c] Solvent: CH_2Cl_2; temp: −30 °C; acidic conditions: HCl (2M, 0.1 equiv), 2 h. [d] Solvent: $CHCl_3$; temp: 25 °C; 15 h. [e] Yields referred to a chromatographically pure mixture of diastereomers. [f] Diastereomeric ratio was determined by NMR spectra analysis. [g] Enantiomeric excess was determined by chiral HPLC analysis (see Supporting Information). ND: not determined.

$7_{\textit{trans/trans}}$ (entry 1) because of the formation of byproduct **13** (Table 3), coming from an intramolecular Friedel–Crafts reaction/aromatization sequence of compound **7**. We then tried to keep the temperature at −30 °C in order to avoid this side reaction, but, in this case, the isomerization was incomplete ($7_{\text{trans/trans}}$:$7_{\text{trans/cis}}$ = 1:2, entry 2). Finally, the best conditions included dissolving the diaminotetralin into chloroform and letting the solution stir overnight at room temperature. Using these conditions, we were pleased to see that isomerization readily took place in good yields and with only a slight loss of enantioselectivity (entries 4–6).

In summary, chiral phosphoric acid **6h** successfully catalyzed the enantioselective reaction between two molecules of aniline **1** and three molecules of phenylacetaldehyde **2**, to provide enantioenriched 1,2-*trans*, 2,3-*cis* 2-aryl-1,3-diaminotetralins **7**. By simply stirring a $CHCl_3$ solution of **7**, it isomerized readily to the 1,2-*trans*, 2,3-*trans* diastereomer in high yields without loss of enantiopurities.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Catalysis optimization, spectroscopic data, and ee measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(15) When mixing aniline (R^1 = H) with **2a** under optimized conditions, a 1:1 mixture of products **7**:**12** was observed by ^{1}H NMR.