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Aminative Umpolung Synthesis of Aryl Vicinal Diamines from Aromatic Aldehydes

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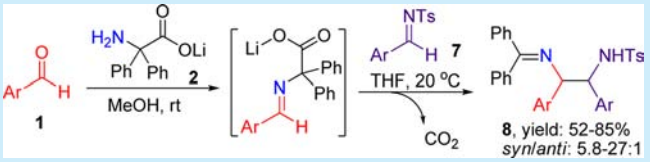
Supporting Information

ABSTRACT: In this paper an aminative umpolung synthesis of aryl vicinal diamines from aldehydes and *N*-Ts imines is described. Electrophilic aromatic aldehydes were smoothly converted into delocalized 2-azaallylanions via condensation with 2,2-diphenylglycine in methanol and subsequent decarboxylation in THF and underwent further reaction with *N*-Ts imines to give a variety of 1,2-diamine derivatives in good yields with high *syn*/*anti* diastereoselectivity.



Vicinal diamines are very important motifs that have been broadly employed as key functional elements in various bioactive compounds and numerous powerful catalysts.[1−3] Although many efforts have been contributed to the synthesis of vicinal diamines,[1,4,5] the development of a new synthetic methodology is still highly desirable. Addition of α-amino anions to electrophiles has been developed into an intriguing strategy to access various amines.[6] However, it is not easy to obtain α-amino anions under mild conditions.[6] Recently, Tunge[7] and Chruma[8] demonstrated that α-amino anion equivalents could be in situ generated under mild conditions via decarboxylation of *N*-imino amino acid allylic esters in the presence of Pd catalyst. Very recently, we also reported an efficient method for generating delocalized α-imino anions **4** by decarboxylation of lithium salts of 2,2-diphenylglycinate imines **3** in the aprotic solvent THF. The Schiff base lithium salts **3** could be obtained from electrophilic aldehydes **1** via condensation with lithium 2,2-diphenylglycinate (**2**)[9] in methanol (Scheme 1a).[10] The α-imino anions have shown high reactivity and excellent regioselectivity in Pd-catalyzed allylation with allylic electrophiles **5**,[11,12] providing a nontraditional and efficient way to synthesize homoallylic amines. In this transformation, the 2,2-diphenylglycine not only provides the amino group but also Umpolungs the reactivity of the aldehydes.[13,14] Encouraged by these results, we envisioned that the strategy could be extended to the synthesis of vicinal diamines **8** if imines **7** were used as the electrophiles instead of compounds **5** to react with the in situ generated α-imino anions **4** (Scheme 1b). Herein, we wish to report the preliminary results on this project.

As anticipated, the reaction of the Schiff base lithium salt **3a** with *N*-Ts imine **7a** proceeded smoothly in THF at 20 °C, to give the corresponding diamine derivative **8a** in 66% yield with a *syn*/*anti* (*dl*/*meso*) ratio of 5.4:1 (Table 1, entry 1). Compound *syn*-**8a** was mostly precipitated out of the reaction solution as a white solid when the reaction was over and thus could be obtained by simple filtration.[15] Diamine derivative *anti*-**8a** was isolated by careful column chromatography. The structures of the compounds *syn*-**8a** and *anti*-**8a** were determined by X-ray analysis (for the X-ray structures, see Supporting Information and Figure 1). ^{1}H NMR data were also collected for the two diastereoisomers (for ^{1}H NMR data and the corresponding spectra, see Supporting Information). The NH signal of *syn*-**8a** (a doublet at 6.25 ppm) is more downfield than that of *anti*-**8a** (a doublet at 4.98 ppm), and the coupling constant between the two methenyl protons for *syn*-**8a** (2.4 Hz)

Scheme 1. Aminative Umpolung Synthesis of Homoallylic Amines (6) and 1,2-Diamines (8) from Aldehydes

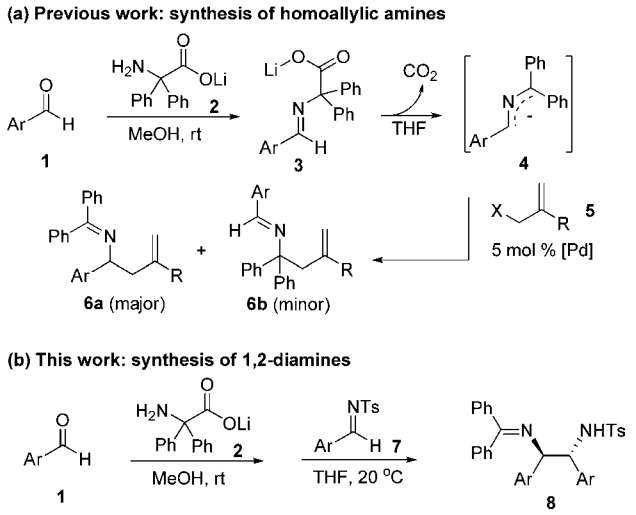


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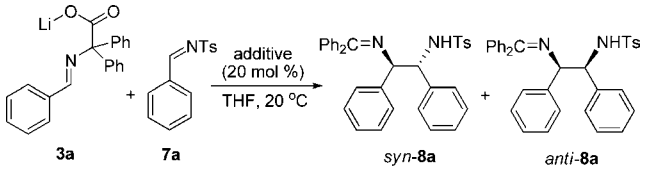
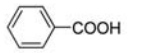
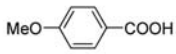
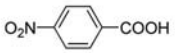
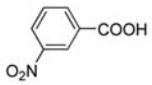
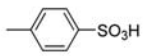
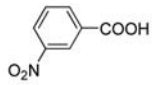
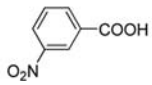
Table 1. Studies on Optimization of the Reaction of Schiff Base Lithium Salt 3a and *N*-Ts Imine 7a[a]



3a 7a *syn*-8a *anti*-8a

entry	conditions	additive	yield[b] (*syn*:*anti*)[c]
1	THF, 20 °C	-	66% (5.4:1)
2	toluene, 20 °C	-	47% (4.5:1)
3	DCM, 20 °C	-	40% (8.7:1)
4	MeOH, 20 °C	-	0%
5	THF, 20 °C		76% (9.2:1)
6	THF, 20 °C		84% (6.9:1)
7	THF, 20 °C		71% (11:1)
8	THF, 20 °C		86% (12:1)
9	THF, 20 °C		83% (7.9:1)
10	THF, 20 °C	NEt_3	39% (4.8:1)
11	THF, 5 °C		77% (12:1)
12	THF, 25 °C		73% (8.8:1)

[a]All reactions were carried out with lithium salt **3a** (0.44 mmol), *N*-Ts imine **7a** (0.40 mmol), and additive (0.080 mmol) in dry THF (2 mL) at 20 °C under Ar overnight unless otherwise stated. For entries 1−4, no additive was added. [b]Yield based on **7a** and determined by ^{1}H NMR analysis of the crude reaction mixture. [c]The ratio of *syn*-**8a** to *anti*-**8a** was determined by ^{1}H NMR analysis of the crude reaction mixture.

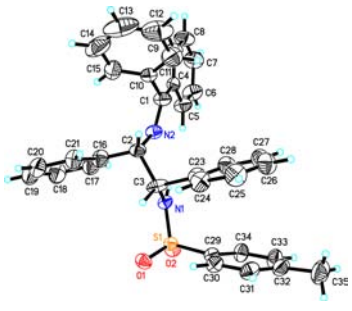


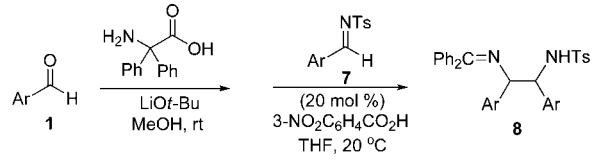
Figure 1. X-ray structure of compound *syn*-**8a**.

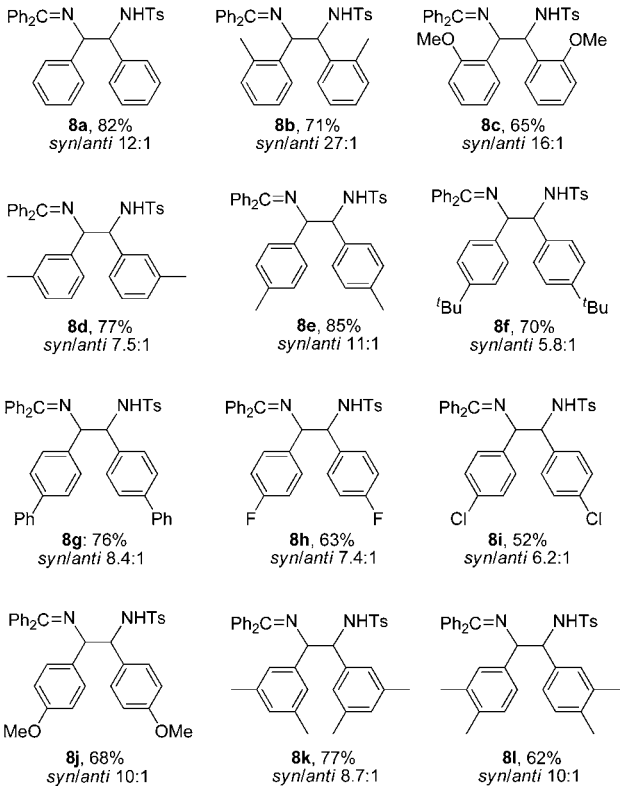
is obviously smaller than that for *anti*-**8a** (6.8 Hz). These spectroscopic differences between the diastereoisomers were used to judge *syn*/*anti* selectivity in the following studies.

When the reaction of Schiff base lithium salt **3a** and *N*-Ts imine **7a** was carried out in methanol under otherwise identical conditions, no diamine product was observed (Table 1, entry 4). This is consistent with the fact that the Schiff base lithium salt **3a** is relatively stable in methanol but can undergo decarboxylation in an aprotic solvent such as THF, indicating that the reaction was likely initiated by the generation of the α-imino anion intermediate **4** via decarboxylation. Introducing a Brønsted acid such as benzoic acid resulted in an obvious increase in selectivity for *syn*-diamine product **8a** (Table 1, entry 5 vs 1), whereas an organic base such as NEt_3 slightly favors the *anti*-isomer (Table 1, entry 10 vs 1). The reason for the additive effect is not yet clear at this point. Further optimization showed that the reaction could be improved to 86% yield and 12:1 *syn*/*anti* ratio by using 3-nitrobenzoic acid as the additive (Table 1, entry 8).

On the basis of the optimized reaction conditions, substrate scope including aromatic aldehydes **1** and *N*-Ts imines **7** was investigated for the transformation. As shown in Scheme 2,

Scheme 2. Aminative Umpolung Synthesis of 1,2-Diamine Derivatives 8[a]





[a]All reactions were carried out with aromatic aldehydes **1** (0.44 mmol), 2,2-diphenylglycine (0.44 mmol), LiO*t*-Bu (0.44 mmol), 3 Å molecular sieves (0.10 g), methanol (0.5 mL), *m*-nitrobenzoic acid (0.080 mmol), *N*-Ts imines **7** (0.40 mmol), and dry THF (2 mL) under Ar.[15] Isolated yield based on **7**. The ratio of *syn*-**8** to *anti*-**8** was determined by ^{1}H NMR analysis of the crude reaction mixture.

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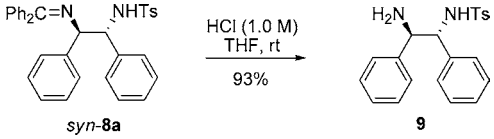
various aldehydes were readily converted into the corresponding Schiff base lithium salts by stirring with 2,2-diphenylglycine and lithium *tert*-butoxide in methanol, which then reacted with *N*-Ts imines **7** in THF in the presence of 20 mol % of 3-nitrobenzoic acid, giving a variety of diamine products in good yields with high *syn*/*anti* diastereoselectivity.[15] 2-Substituted substrates displayed higher selectivity for *syn*-diamine products (**8b** and **8c**), likely due to steric effect. No obvious electronic effect was observed in the transformation. Both electron-rich and electron-deficient substrates gave the corresponding diamines with good *syn*/*anti* selectivity. This transformation is not effective for the synthesis of unsymmetric diamines, since the reaction between unsymmetric aldehydes and *N*-Ts imines is somewhat messy as judged by ^{1}H NMR analysis of the crude reaction mixture.

The diphenylketimine protecting group on the diamine product **8** is stable enough to carry out purification on silica gel without special cautions but also can be facilely removed to release the NH_2 group under mild conditions. For example, treatment of *syn*-**8a** with HCl in THF at room temperature gave the monotosylated diamine **9** in 93% yield (Scheme 3).

Scheme 3. Deprotection of the Diamine Product



syn-**8a** **9**

In summary, we have demonstrated a new strategy for the synthesis of aryl 1,2-diamines by using electrophilic aldehydes **1** and *N*-Ts imines **7** as the starting materials. Aromatic aldehydes were converted to various α-imino anions **4** under mild conditions via condensation with 2,2-diphenylglycine to form Schiff base lithium salts **3** and subsequent decarboxylation of **3**. The in situ generated α-imino anions are highly reactive in the reaction with *N*-Ts imines **7**, to give a variety of diamine products **8** in good yields with high *syn*/*anti* diastereoselectivity. The diamine product can be selectively deprotected to give a monotosylated diamine in high yield.

■ ASSOCIATED CONTENT

Supporting Information

Procedures for the synthesis of diamine derivatives **8** and deprotection, characterization data, and NMR spectra along with the X-ray data of compounds *syn*- and *anti*-**8a**. 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.

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(15) Representative procedure for the synthesis of 1,2-diamine derivatives (Scheme 2, diamine derivative **8a**). To a 5 mL vial equipped with a magnetic stirrer bar were added 2,2-diphenylglycine (0.1000 g, 0.44 mmol), LiO*t*-Bu (0.0353 g, 0.44 mmol), and 3 Å molecular sieves (0.100 g). The sealed vial was evacuated and refilled with Ar three times, followed by addition of anhydrous methanol (0.5 mL). After the mixture was stirred at room temperature for 30 min, benzaldehyde (0.0467 g, 0.44 mmol) was added. After stirring at room temperature for 24 h, the reaction mixture was submitted to filtration. The solid was washed with anhydrous methanol (1 mL × 3). The combined filtrate was concentrated via rotary evaporation at 50 °C under reduced pressure to give a white solid. The solid was further vacuumed by oil pump for 1 h. To the solid were added *m*-nitrobenzoic acid (0.0134 g, 0.080 mmol), *N*-benzylidene-4-methylbenzenesulfamide (**7a**) (0.1036 g, 0.40 mmol), and THF (2.0 mL). The mixture was stirred under argon atmosphere at 20 °C overnight, and a white precipitate appeared. The reaction mixture was filtered. The filter cake was washed with THF (0.2 mL × 2) to give *syn*-**8a** (0.1430 g) as a white solid. The combined filtrate was submitted to flash chromatography (eluent, petroleum ether/ethyl acetate = 10:1) to give another part of the diamine products *syn*/*anti*-**8a** (0.0310 g, total yield 82%) as a white solid. The polarities of the two diastereoisomers are very close. We ran column chromatography several times to separate the mixture of the *syn*/*anti* isomers to get pure *anti*-**8a** for ^{1}H NMR spectroscopy and X-ray analysis. In order to determine the *syn*/*anti* selectivity, a parallel experiment was carried out. Additional CH_2Cl_2 was added to dissolve the precipitate before ^{1}H NMR analysis of the crude reaction mixture. The *syn*/*anti* ratio for the current reaction is 12:1.