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Aminative Umpolung of Aldehydes to α-Amino Anion Equivalents for Pd-Catalyzed Allylation: An Efficient Synthesis of Homoallylic Amines

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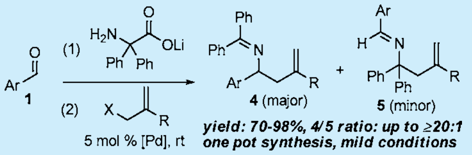
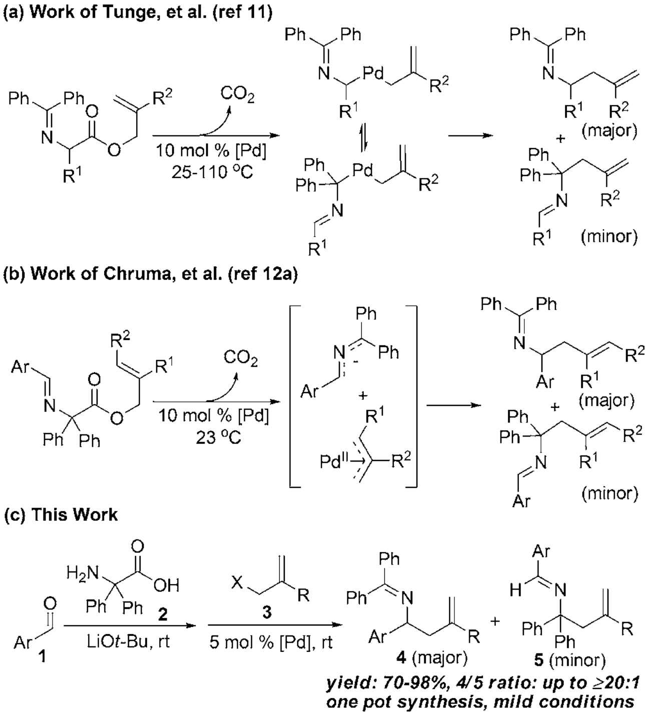
Supporting Information

ABSTRACT: An attractive strategy for generation of α-amino anions from aldehydes with applications in synthesis of homoallylic amines is described. Aromatic aldehydes can be converted to α-amino anion equivalents via amination with 2,2-diphenylglycine and subsequent decarboxylation. The in situ generated α-imino anions are highly reactive for Pd-catalyzed allylation, forming the corresponding homoallylic amines in high yields with excellent regioselectivity.



Homoallylic amines are important compounds and have served as valuable precursors for the synthesis of a variety of heterocycles, natural products, and pharmaceutical compounds.[1] Its synthesis has attracted much attention.[1,2] Traditional synthetic routes to homoallylic amines have relied on the addition of nucleophilic allylic organometallics to imines.[1,2] Conversely, addition of α-amino anions to electrophilic allylic cations has afforded a complementary approach. However, it is not easy to obtain α-amino anion equivalents directly from amines.[3] Since the past decade, decarboxylative alkylation[4,5] has been developed into one of the most powerful synthetic methodology by Stoltz,[6] Tunge,[7] Trost,[8] and others.[9,10] Application of this reaction into amino acid allylic esters has resulted in an interesting protocol to construct homoallylic amines via connecting α-amino anions to allylic cations.[11,12] By using this strategy elegantly, Tunge[11] developed a Pd-catalyzed decarboxylative coupling of allylic esters of *N*-(diphenylmethylene)-α-amino acids in 2006 (Scheme 1a), and Chruma[12a] also reported a Pd-catalyzed decarboxylative alkylation of allyl diphenylglycinate imines in 2007 (Scheme 1b). Both of the reactions were proposed to be initiated by oxidative addition of the allyl ester to Pd catalyst, followed by in situ generation of an α-imino anion and a Pd(II)−π-allyl moiety, which underwent further reaction to give the homoallylic amines.

Scheme 1. α-Amino Anion Routes for the Synthesis of Homoallylic Amines



Given the ready availability of aldehyde feedstocks, generation of nucleophilic α-amino anions directly from aldehydes would be particularly appealing. Further reaction of these α-amino anions with electrophiles, e.g., Pd(II)−π-allyl species, can provide an efficient access to various amines (including homoallylic amines Scheme 1c). We envisioned that the metal carboxylate salt of 2,2-diphenylglycine imine (**6**), which could be obtained from aldehyde (**1**) by condensation with 2,2-diphenylglycine (**2**), might undergo decarboxylation to generate a resonance-delocalized 2-azaallylanion **7** (Scheme 2).[11,12] The 2-azaallylanion **7** attacks an allylic electrophile to give homoallylic imines **4** and **5**. The desired *N*-diphenylketimine **4** can be formed predominantly in the reaction owing to steric preference and conjugation effect. In this scenario, the diphenylglycine not only provides the amino group but also umpolungs the reactivity of the aldehyde in the trans-

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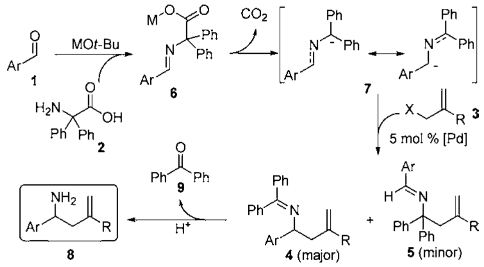
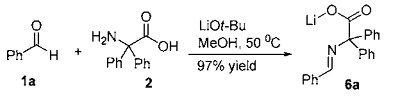
Scheme 2. Strategy for the Synthesis of Homoallylic Amines from Aldehydes



formation.[13] Treatment of the amination product **4** with HCl at room temperature would give the primary homoallylic amine **8** and cogenerate benzophenone (**9**). Herein, we wish to report the preliminary results on this project.

Studies started with the synthesis of the lithium salt of diphenylglycinate imine **6a**, obtained in high yield via condensation of benzaldehyde and 2,2-diphenylglycine (**2**) in the presence of lithium *tert*-butoxide (LiO-*t*-Bu) (Scheme 3).

Scheme 3. Synthesis of Lithium Salt 6a

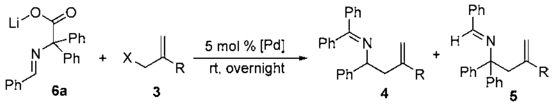


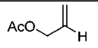
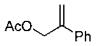
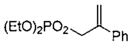
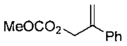
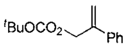
Lithium salt **6a** is a white solid that is relatively stable in the solid state and can be handled without special caution to moisture and oxygen; however, it undergoes decarboxylation in aprotic solvent such as THF. When NaO-*t*-Bu or KO-*t*-Bu was used instead of LiO-*t*-Bu, the condensation was a little messy as judged by ^{1}H NMR analysis of the crude reaction mixture. Without base, the corresponding Schiff base was hardly observed in the reaction of benzaldehyde and diphenylglycine.

With lithium salt **6a** in hand, we then investigated its reaction with allylic electrophiles **3** using a Pd−phosphine complex as the catalyst (Table 1). In the presence of 2.5 mol % of $Pd_2(dba)_3$−dppb, the reaction of **6a** and allyl acetate (**3a**) proceeded smoothly under room temperature to afford the product in excellent substrate conversion with a high regioselectivity for the desired *N*-diphenylketimine **4a** (entry 1). The Pd catalyst is important for the reaction in terms of reactivity and regioselectivity (entries 1−11). Further optimization showed that $Pd_2(dba)_3$−dppe was optimal catalyst, and THF was the choice of solvent (entry 6). The leaving group of the allylic electrophile was also examined by using 2-phenyl allyl alcohol derivatives **3b1−b4** as the substrate (entries 12−15). Although all of the substrates exhibited high reactivity and excellent regioselectivity, allyl carbonates **3b3** and **3b4** gave better isolated yields; thus, we chose allyl methyl carbonates as substrates in the following studies.

Under the optimized conditions, allyl methyl carbonates **3** were screened for allylation by using the preprepared lithium salt **6a** as the α-amino anion precursor (Table 2). In the presence of Pd catalyst, various alkyl- and aryl-substituted allyl methyl carbonates reacted efficiently with **6a** to give the desired *N*-diphenylketimines **4** in high yields with excellent regioselectivity. Functional groups such as C−C double bond, acetal, and Br are well tolerated by the reaction (Table 2, entries 4, 6, and 8). Substrates with electron-withdrawing groups have lower regioisomeric ratios of **4** to **5** (Table 2, entries 8 and 17). Substituted allyl methyl carbonates **3b3−3t** exhibited higher selectivity for **4** over **5** than allyl acetate (**3a**) (entries 2−20 vs 1), indicating that steric hindrance has a favorable effect on the formation of diphenyl ketimines **4**.

Table 1. Optimization Studies on the Reaction of Schiff Base Lithium Salt 6a and Allylic Electrophile 3[a]

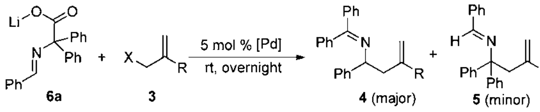


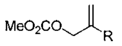
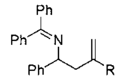
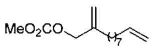
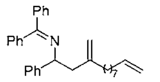
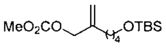
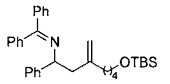
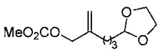
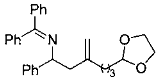
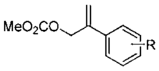
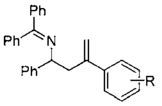
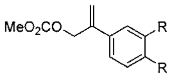
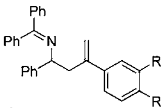
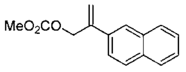
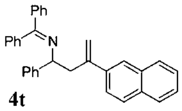
entry	3	conditions	conv[b] (**4**/**5**)[c]
1	 **3a**	Pd_2(dba)3-dppb, THF	93% (6.0:1)
2	**3a**	no catalyst, THF	0
3	**3a**	$Pd(OAc)_2$-dppb, THF	32% (6.7:1)
4	**3a**	$[Pd(C_3H_5)Cl]_2$-dppb,THF	71% (6.7:1)
5	**3a**	$Pd(PPh_3)_4$, THF	87% (3.5:1)
6	**3a**	**$Pd_2(dba)_3$-dppe, THF**	**95% (11:1)**
7	**3a**	$Pd_2(dba)_3$-dppf, THF	≥95% (6.1:1)
8	**3a**	$Pd_2(dba)_3$-BINAP, THF	90% (4.9:1)
9	**3a**	$Pd_2(dba)_3$-PBu_3, THF	≥95% (4.7:1)
10	**3a**	$Pd_2(dba)_3$-dppe, CH_3CN	trace
11	**3a**	$Pd_2(dba)_3$-dppe, DCM	51% (10:1)
12	 **3b1**	$Pd_2(dba)_3$-dppe, THF	≥95% (84%)[d] (≥20:1)
13	 **3b2**	$Pd_2(dba)_3$-dppe, THF	≥95% (80%)[d] (≥20:1)
14	 **3b3**	$Pd_2(dba)_3$-dppe, THF	≥95% (94%)[d] (≥20:1)
15	 **3b4**	$Pd_2(dba)_3$-dppe, THF	≥95% (94%)[d] (≥20:1)

[a] All reactions were carried out with **6a** (0.24 mmol), **3** (0.20 mmol), [Pd] (0.010 mmol, 5 mol %), and ligand (0.012 mmol for bidentate ligand and 0.024 mmol for PBu_3) in dry THF (0.50 mL) at room temperature. [b] Conversion was based on **3** and determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The ratio of **4** to **5** was determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The value in parentheses is the isolated yield based on **3**.

As shown in Scheme 3, Schiff base lithium salts can be readily obtained from aldehydes by stirring with 2,2-diphenylglycine (**2**). The simple manipulation provides opportunity to develop a one-pot procedure for the synthesis of homoallylic imines **4** directly from aldehydes. For example, condensation of benzaldehyde with **2** in methanol at room temperature, followed by solvent removal and Pd-catalyzed allylation with methyl 2-methylallyl carbonate (**3c**) in dry THF, gave the corresponding homoallylic imines in 85% yield with a ≥20:1 ratio of **4c** to **5c** (Table 3, entry 1). The yield and regioselectivity are similar to those obtained from the reaction using the preprepared lithium salt **6a** (Table 2, entry 2). Following the one-pot procedure, various aromatic aldehydes were examined in the allylation with allyl methyl carbonates **3b3** and **3c** (Table 3). Substituted benzaldehydes (entries 2−8 and 10−14), 2-naphthyl aldehyde (entry 9), and heteroaromatic aldehydes (entries 15−16) were all highly effective for the reaction, providing various homoallylic imines in high yields. In all these cases, the desired ketimines **4** were formed predominantly. Electron-deficient aldehydes exhibited higher regioselectivity for **4** over **5** than electron-rich ones (Entries 4, 10, 12, and 14 vs 6−7 and 13), probably due to electron-withdrawing group shifting the electron density toward the

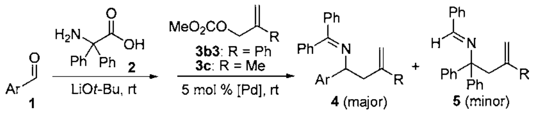
Table 2. Pd-Catalyzed Allylation of Allyl Methyl Carbonates 3 with Schiff Base Lithium Salt 6a[a]

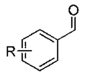
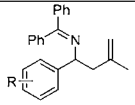
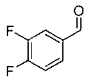
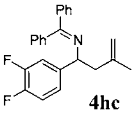
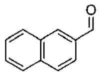
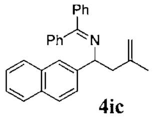
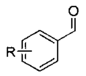
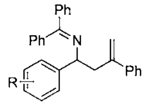
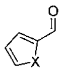
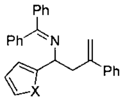


entry	substrate (3)	product (4)	yield[b] (4/5)[c]
1	**3a**	**4a**	74% (11:1)
		 **4c-d**	
2	**3c**: R = Me		88% (≥20:1)
3	**3d**: R = Et		89% (≥20:1)
4	 **3e**	 **4e**	90% (≥20:1)
5	 **3f**	 **4f**	88% (≥20:1)
6	 **3g**	 **4g**	92% (≥20:1)
			
7	**3b3**: R = H	**4b, 4h-q**	94% (≥20:1)
8	**3h**: R = 2-Br		91% (14:1)
9	**3i**: R = 3-Me		82% (≥20:1)
10	**3j**: R = 3-OMe		80% (≥20:1)
11	**3k**: R = 3-F		77% (≥20:1)
12	**3l**: R = 4-Me		89% (≥20:1)
13	**3m**: R = 4-*t*-Bu		91% (≥20:1)
14	**3n**: R = 4-Ph		95% (≥20:1)
15	**3o**: R = 4-OMe		89% (≥20:1)
16	**3p**: R = 4-F		87% (≥20:1)
17	**3q**: R = 4-CF_3		91% (14:1)
			
18	**3r**: R = F	**4r-s**	91% (≥20:1)
19	**3s**: R = OMe		90% (≥20:1)
20	 **3t**	 **4t**	91% (≥20:1)

[a] All reactions were carried out with **6a** (0.22 mmol), **3** (0.20 mmol), $Pd_2(dba)_3$ (0.0050 mmol), and dppe (0.012 mmol) in dry THF (0.50 mL) at rt overnight unless otherwise stated. For entries 1–2 and 4–5, **6a** (0.24 mmol) was used. [b] Isolated yield based on **3**. [c] The ratio of **4** to **5** was determined by ^1H NMR analysis of the crude reaction mixture.

Table 3. One-Pot Synthesis of Homoallylic Imines[a]



entry	aldehyde (1)	3	product (4)	yield[b] (4/5)[c]
				
1	**1a**: R = H	**3c**	**4c**	85% (≥20:1)
2	**1b**: R = 2-Me	**3c**	**4bc**	96% (17:1)
3	**1c**: R = 4-F	**3c**	**4cc**	90% (≥20:1)
4	**1d**: R = 4-CF_3	**3c**	**4dc**	87% (≥20:1)
5	**1e**: R = 4-Ph	**3c**	**4ec**	80% (≥20:1)
6	**1f**:R = 4-*t*-Bu	**3c**	**4fc**	92% (12:1)
7	**1g**:R =4-OMe	**3c**	**4gc**	86% (6.3:1)
8	 **1h**	**3c**	 **4hc**	81% (≥20:1)
9	 **1i**	**3c**	 **4ic**	80% (≥20:1)
				
10	**1j**: R = 2-Cl	**3b3**	**4jb**	80% (≥20:1)
11	**1k**: R = 3-Me	**3b3**	**4kb**	98% (≥20:1)
12	**1l**: R = 3-Cl	**3b3**	**4lb**	78% (≥20:1)
13	**1m**:R = 4-Me	**3b3**	**4mb**	98% (13:1)
14	**1n**: R = 4-Cl	**3b3**	**4nb**	90% (≥20:1)
				
15	**1o**: X = O	**3b3**	**4ob**	70% (≥20:1)
16	**1p**: X = S	**3b3**	**4pb**	95% (≥20:1)

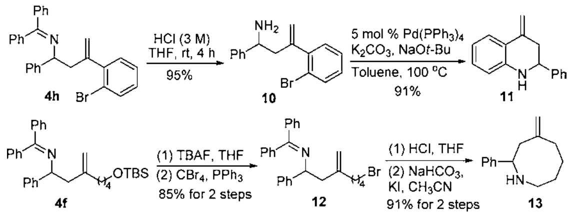
[a] All reactions were carried out with **1** (0.48 mmol), **2** (0.48 mmol), 3 Å molecular sieve (100 mg), LiO-*t*-Bu (0.48 mmol), **3** (0.40 mmol), $Pd_2(dba)_3$ (0.010 mmol), and dppe (0.024 mmol) at room temperature unless otherwise stated. For entries 10 and 14, **1** (0.44 mmol), **2** (0.44 mmol), and LiO-*t*-Bu (0.44 mmol) were used. [b] Isolated yield based on **3**. [c] The ratio of **4** to **5** was determined by ^1H NMR analysis of the crude reaction mixture.

carbon center adjacent to the aryl group in the delocalized 2-azaallyl anion **7** (Scheme 2) and thus favoring the formation of ketimine product. However, aliphatic aldehydes such as butyraldehyde are ineffective for this transformation under the current conditions.

The resulting homoallylic imines **4** can be utilized to synthesize various nitrogen-containing compounds. For example, primary homoallylic amine **10** could be obtained in 95% yield from ketimine **4h** by deprotection with HCl, which was further converted to bioactive tetrahydroquinoline[14] **11** in 91% yield via intramolecular coupling (Scheme 4). Eight-membered cyclic amine **12** also could be conveniently prepared in 77% total yield in four steps from ketimine **4f** (Scheme 4).

Although a precise mechanism awaits further studies, we have compared the allylation of lithium salt **6a** with **3b3** and Chruma's reaction of the correponding allyl diphenylglycinate imine (Scheme 1b)[12a] via ^1H NMR spectroscopic studies (Supporting Information). The current allylation was much slower than Chruma's reaction under similar conditions. In monitoring the reaction of **6a** and **3b3**, we did not observe any signals asigned to Chruma's reactant, which could be generated if the reaction first undergoes allylic substitution to form an allyl diphenylglycinate imine and then follows Chruma's sequence.

Scheme 4. Synthetic Transformation of Homoallylic Imines



In summary, we have demonstrated an attractive strategy to convert aldehydes to α-amino anions by using 2,2-diphenylglycine as an amination−Umpolung reagent. The in situ generated α-imino anions **7** are highly reactive for Pd-catalyzed allylation to give various homoallylic imines **4** in high yields with excellent regioselectivity. The transformation employs two readily available electrophiles (aldehydes and allylic electrophiles) as the starting materials to make the homoallylic amines and can be carried out under very mild conditions, providing a nontraditional, versatile, and complementary method for the synthesis of homoallylic amines. Further studies on mechanisms and development of an asymmetric process are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Procedures for the allylation and the synthesis of compounds **6a** and **10−13** and characterization data along with NMR spectra. 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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