# Decarboxylative Generation of 2-Azaallyl Anions: 2-Iminoalcohols via a Decarboxylative Erlenmeyer Reaction

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S *Supporting Information*

ABSTRACT: Condensation between the tetrabutylammonium salt of 2,2-diphenylglycine and aldehydes results in a decarboxylative Erlenmeyer reaction, affording 1,2-diaryl-2-iminoalcohols as a mixture of diastereomers in good yields. The diastereomeric ratio shifts over time, with the *anti* diastereomer and the *syn* oxazolidine tautomer serving as the kinetic and thermodynamic products, respectively. Addition of Lewis acids can catalyze the rates of reaction and product equilibration. The results highlight the stereochemical promiscuity of 1,2-diaryl-2-iminoalcohols in the presence of Lewis acids and Brønsted bases.
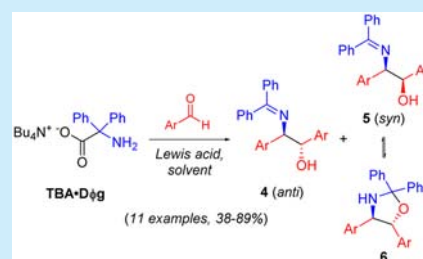
Decarboxylation can serve as a gentle alternative to anion generation via deprotonation with a strong base. Transition metal catalyzed decarboxylative alkylations in particular have arisen as powerful and relatively mild options for nucleophilic carbanion generation and functionalization.[1] In this arena, we previously reported palladium-catalyzed decarboxylative allylation,[2] interceptive decarboxylative allylation,[3] and decarboxylative benzylation[4] reactions, all of which proceed via the intermediacy of an 2-azaallyl anion (α-imino anion). Importantly, we noted that these anionic intermediates, generated via decarboxylation of 2,2-diphenylglycinate (Dφg) imines under ambient reaction conditions, could be intercepted with electrophilic aldehydes prior to allylation by the π-allylPd(II) species (Scheme 1).[2a] An unresolved question at

Scheme 1. Previous Interception of 2-Azaallyl Anions with Aldehydes[2a]
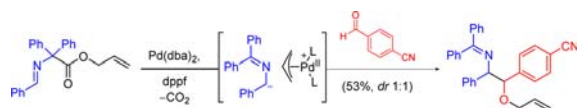
the time was the importance of the Pd catalyst in the actual decarboxylation event.[5] Computational studies suggest that the relatively poor oxophilicity of the π-allylPd(II) cation allows for formation of a solvent-separated ion pair, a necessary step in the rate-limiting decarboxylation event.[6] Recently, Zhao provided additional evidence that palladium is not required for the decarboxylative generation of α-imino anions from Dφg imines under ambient conditions.[7] Specifically, his group reported that lithium Dφg imine salts (**1**), stable in MeOH, will decarboxylate in THF to generate the corresponding 2-azaallyl anions which are then intercepted by *N*-tosylarylimines to afford 1,2-diaryl-1,2-diamines as a mixture of diastereomers (Scheme 2a). Addition of
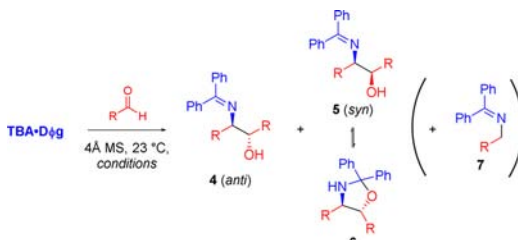
Scheme 2. Decarboxylative Couplings from Dφg Salts

a Brønsted acid (e.g., 3-nitrobenzoic acid) favored formation of *syn*-**3**. Very recently, Han and Soloshonok reported similar findings employing homochiral *N-tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine as an electrophile for the *syn* diastereoselective synthesis of 1-trifluoromethyl-1,2-diamines (Scheme 2b).[8] They proposed that decarboxylation occurs during or after C−C bond formation, with the protonated carboxylic acid **TS-1** representing the most plausible transition state. These findings encouraged us to report herein our own observations gleaned from the exploration of a related decarboxylative Erlenmeyer reaction[9] between tetrabutylammonium 2,2-diphenylglycinate (TBA·DφG) and aromatic aldehydes to form 1,2-diaryl-2-iminoalcohols (Table 1). Current evidence suggests that the C−C bond formed in our process is sensitive to reversible scission under the reaction conditions, resulting in a transition from the kinetically formed *anti* diastereomer **4** to the

Table 1. Decarboxylative Erlenmeyer Reaction

entry	R	4/5/6	conditions	yield[a] (anti:syn)[b]
1	4-NC-C₆H₄	a	PhCH₃, 20h	0% (n/a)
2	" "	a	Yb(OTf)₃ (30 mol %), PhCH₃, 18h	86% (1:2.1)
3	" "	a	CH₂Cl₂. 6h	82% (1:1.1)
4	" "	a	Sc(OTf)₃ (30 mol %), CH₂Cl₂, 20h	76% (1:1.1)
5	4-Br-C₆H₄	b	Yb(OTf)₃ (10 mol %), CH₂Cl₂, 18h	66% (1:1.2)
6	4-F-C₆H₄	c	In(OTf)₃ (10 mol %), CH₂Cl₂, 18h	77% (1:1.4)
7	C₆H₅	d	In(OTf)₃ (10 mol %), CH₂Cl₂, 24h	89% (1:1.9)
8	2-naphthyl	e	In(OTf)₃ (10 mol %), CH₂Cl₂, 15h	47% (1:1.6)
9	3-pyridyl	f	Yb(OTf)₃ (10 mol %), CH₂Cl₂, 18h	46% (1.5:1)
10	benzodioxole-Br	g	In(OTf)₃ (13 mol %), CH₂Cl₂, 15.5h	83% (1.7:1)
11	2-thienyl	h	In(OTf)₃ (10 mol %), CH₂Cl₂, 13h	38% (1:1.9)
12	4-O₂N-C₆H₄	i	In(OTf)₃ (10 mol %), CH₂Cl₂, 20h	0% (n/a)[c]
13	4-Me₂N-C₆H₄	j	In(OTf)₃ (10 mol %), CH₂Cl₂, 22h	0% (n/a)
14	Br-salicyl-OAc	k	PhCH₃, 50min (no 4Å MS)	53%[d] (n.d.)

[a]Isolated yield of diastereomeric mixture. [b]Determined from ¹H NMR of a single crude reaction mixture; dr values varied significantly depending on reaction time (*vide infra*). [c]Only imine 7i isolated. [d]Combined isolated yield of 9 (43%) and 8 (10%).

thermodynamically preferred oxazolidine 6. These results lend mechanistic insight into other efforts involving 2-azaallyl anions.[5,10,21]

Initial interest in Dφg as an amine transfer reagent arose from reports that it will undergo direct decarboxylative imination of α-ketoesters in aqueous solutions containing alkylated polyethylenimine catalysts.[11] To further investigate the ability of Dφg imines to decarboxylate under mild conditions we combined

TBA·DφG with a variety of aldehydes (2 equiv). There was no significant reaction between TBA·DφG and the relatively electrophilic 4-cyanobenzaldehyde in toluene (Table 1, entry 1). Simply adding Lewis acids to the reaction mixture, changing the solvent to dichloromethane, or both resulted in formation of the expected 2-iminoalcohol as a mixture of diastereomers (Table 1, entries 2−4). Molecular sieves were added to the reaction mixture to reduce the amount of benzylimine 7 generated. As expected, *syn* 5a (but not *anti* 4a) exists in equilibrium with its oxazolidine tautomer (6a).[12] Overall, this transformation represents a decarboxylative variant of the tandem imine condensation/anion generation/C−C bond formation process originally described by Erlenmeyer.[9] The procedure was successfully applied to a variety of aryl and heteroaryl aldehydes (Table 1, entries 5−11). Nitro groups proved incompatible, resulting in exclusive formation of benzylimine 7i (Table 1, entry 12). Electron-rich aldehydes were also incompatible with the reaction conditions, as can be expected for a reaction in which decarboxylation is the rate-limiting step (Table 1, entry 13). Acetyl 4-bromosalicylaldehyde reacted rapidly with TBA·DφG in PhCH₃ (Table 1, entry 14). From the resulting complex reaction mixture, we were able to isolate and obtain X-ray single crystal structures for two of the products, *syn* diastereomers 8 and 9 (Figure 1). In both products, an acetyl group migrated to the secondary alcohol from the nearby phenolic oxygen.[13,14]
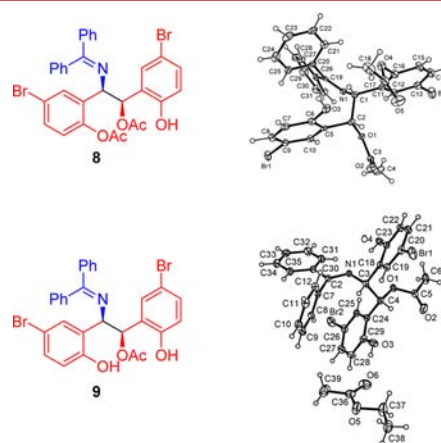
Figure 1. X-ray crystal structures of 8 (top) and 9 (bottom, cocrystallized with EtOAc).

Further investigation of the Lewis acid mediated transformation revealed that the diastereomeric ratio (*dr*) was highly dependent on reaction time. Addition of chiral ligands (e.g., Jacobsen's ligand[15]) to the reaction mixture did not dramatically alter the final *dr* values, but their ability to fully solubilize the Lewis acid catalyst did facilitate reaction monitoring by ¹H NMR spectroscopy. Accordingly, we monitored the reaction between TBA·DφG and 3-bromo-4-methoxybenzaldehyde (2 equiv) in CD₂Cl₂. As shown in Figure 2, key peaks corresponding to products 4l−7l were readily distinguished from each other. The four tetrabutylammonium methyl groups (set at 12H) were used as an internal standard to determine yields for each product relative to TBA·DφG. In the absence of a Lewis acid or ligand, the reaction proceeded to 61% yield over ∼6 days with a final *dr* of roughly 1:1 (Table 2A). At lower conversions, *anti* 4l predominated and none of the *syn* oxazolidine tautomer 6l was observed. As the reaction progressed, the *dr* shifted toward unity,

Figure 2. ^{1}H NMR for a mixture of **4–7l** in CD$_2$Cl$_2$.

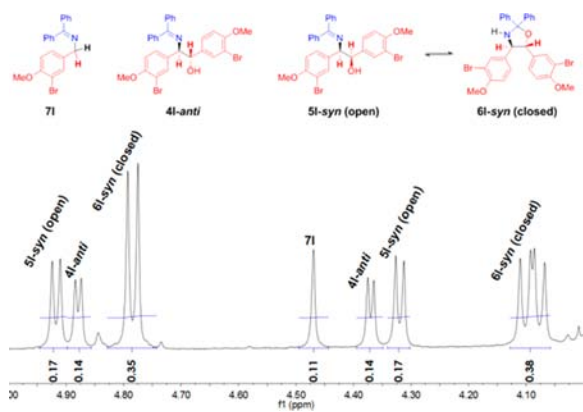**Table 2. Changes in *dr* over Time As Determined by ^{1}H NMR**

A. Conditions: No Lewis acid or ligand				
time	conversion	**4l**	**5l**	**6l**	anti:syn
9 min	8%	6%	2%	0%	3:1
18.6 h	44%	29%	12%	2%	2.1:1
42.3 h	53%	31%	14%	6%	1.6:1
66.3 h	57%	31%	15%	9%	1.3:1
138.8 h	60%	29%	16%	14%	~1:1

B. Conditions: Sc(OTf)$_3$ (16 mol %), (R,R)-Jacobsen's ligand (14 mol %)				
time	conversion	**4l**	**5l**	**6l**	anti:syn
2.5 h	38%	23%	9%	3%	1.9:1
6 h	49%	27%	12%	6%	1.5:1
27.3 h	64%	22%	15%	19%	1:1.5
45.5 h	72%	19%	16%	26%	1:2.2
93.5 h	72%	13%	17%	32%	1:3.8
167.5 h	77%	13%	18%	35%	1:4.1

C. Conditions: (R,R)-Jacobsen's ligand (20 mol %), no Lewis acid				
time	conversion	**4l**	**5l**	**6l**	anti:syn
30 min	8%	6%	2%	0%	3:1
23.5 h	38%	21%	10%	5%	1.4:1
47.8 h	46%	19%	11%	13%	1:1.3
71.5 h	48%	16%	12%	16%	1:1.8
95.5 h	47%	13%	12%	18%	1:2.3
167.8 h	51%	11%	13%	23%	1:3.3

with the concentration of **6l** increasing steadily. When the reaction was conducted in the presence of Sc(OTf)$_3$ and (R,R)-Jacobsen's ligand the overall yield as well as the rates at which the oxazolidine **6l** formed and the *dr* switched in favor of the *syn* isomer all increased dramatically (Table 2B). The *dr* at equilibrium was significantly shifted in favor of the *syn* products, with **6l** becoming the predominant species within 2 days. A similar trend was seen using Sc(OTf)$_3$ alone (no ligand), but poor peak resolution in this circumstance precluded accurate peak integration.[16] Remarkably, using Jacobsen's ligand alone, without any additional Lewis acid, had similar impacts on the *dr* over time, but the overall conversion was significantly lower (Table 2C).[17]

There are at least two possible explanations for these observations: either the crucial C−C bond-forming event is actively reversible under the reaction conditions, with the *anti* diastereomer **4** representing the kinetic product and the *syn* oxazolidine tautomer **6** serving as the thermodynamic minimum, or **4**-*anti* is epimerizing to the more stable **5/6**-*syn* via deprotonation−reprotonation of either benzylic C−H. In contrast to the related system described by Han and Soloshonok,[8] the presence of benzylic imine **7l** and its increasing concentration throughout the reaction strongly suggest that decarboxylative formation of a 2-azaallyl anion occurs *prior* to C−C bond formation. The possibility of an alternative *ene*-type reaction mechanism was excluded by the failure of imine **10** and 3-bromo-4-methoxybenzaldehyde to form the corresponding 2-iminoalcohols **4−6l** under conditions otherwise identical to our Lewis acid catalyzed decarboxylative Erlenmeyer procedure (Scheme 3).

**Scheme 3. Attempted Lewis Acid Catalyzed *ene*-Type Addition**
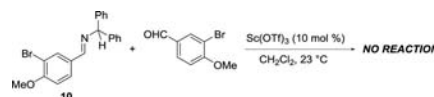
Combining pure *anti* diastereomer **4l** with 10 mol % Sc(OTf)$_3$ in CH$_2$Cl$_2$ at 20 °C for 36 h resulted in absolutely no change, indicating that Lewis acid alone is not sufficient to affect the observed equilibration to the *syn* diastereomer **5/6l**.[16] Deprotonation of benzhydrilimine **10** (2 equiv) with either KHMDS or *n*-BuLi followed by addition of the resulting 2-azaallyl anion to a solution of **4l**-*anti* and 10 mol % Sc(OTf)$_3$ in CH$_2$Cl$_2$ resulted in formation of 3-bromo-4-methoxybenzaldehyde at the expense of the starting 2-iminoalcohol **4l** (Scheme 4).[18]

Scheme 4. Decomposition of 4l-*anti* with 2-Azaallyl Anions
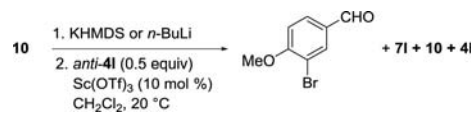
Importantly, the *syn* isomer **5/6l** was not detected in the ^{1}H NMR spectra of the concentrated crude reaction mixture.[16] This suggests that (1) the hydroxylic, and not benzylic, proton of **4l** is more sensitive to deprotonation and (2) the potassium and lithium 2-azaallyl anion salts are not as reactive as the "naked" tetrabutylammonium salt. This observation implies that, for our method, the 2-azaallyl anion intermediate can either attack the aldehyde to form the products or deprotonate the hydroxylic (and not benzylic) proton of the products resulting in C−C bond cleavage, thus setting up an equilibrating process (Scheme 5). The presence of Lewis or mild Brønsted acids ("M" in Scheme 5) could accelerate the rate of this equilibration by increasing the

Scheme 5. 2-Azaallyl Anion-Mediated Equilibration
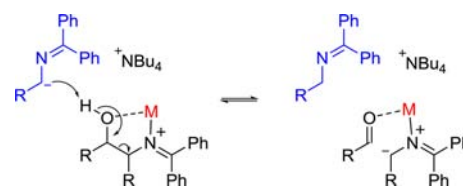
acidity of the hydroxylic proton via complexation to the imine and hydroxyl moieties in **4−6**. The exact mode of C−C bond formation is not clear, as we are currently unable to discount the possibility that the oxazolidine tautomer **6** may also be a product of a Lewis acid catalyzed [3 + 2] cycloaddition between the aldehyde and the corresponding azomethine ylide (Scheme 6).[19]

Scheme 6. Possible [3 + 2] Cycloaddition
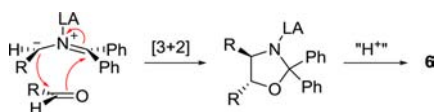
The import of these discoveries extends beyond simply providing a new strategy for constructing 2-iminoalcohols. For example, the observed reversibility of the key C−C bond-forming step should serve as a clear warning about the relative stereochemical instability of 2-iminoalcohols (particularly those with anion stabilizing substituents) when combined with both Lewis acids and Brønsted bases! This is most relevant to procedures in which 1,2-diaryl-2-iminoalcohols are used as chiral ligands for Lewis acids.[20] In summary, we reported a decarboxylative variant of the Erlenmeyer reaction for the construction of 1,2-diaryl-2-iminoalcohols. Our results provide further validation that the decarboxylative formation of 2-azaallyl anions from amino acid Schiff bases can proceed readily in the absence of a transition metal catalyst. Most importantly, the process is reversible and Lewis acids can accelerate equilibration toward the thermodynamically favored syn oxazolidine tautomer. The reactivity of semistabilized 2-azaallyl anions is an area of significant interest.[5,7−10,21] The mechanistic insights gained from our studies are readily applicable to some of these other reaction manifolds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General reaction procedures, compound characterization, transition state model, and CIF files for **8** and **9**. 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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(14) Condensation between the potassium salt of Dϕg and 3,5-di(*tert*-butyl)salicylaldehyde in EtOH forms an imine that is remarkably resistant to decarboxylation: (a) Waser, J.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 8294. (b) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693.

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(16) See Supporting Information for representative ^{1}H NMR spectra of all mechanistic investigations.

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