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Pd-Catalyzed Stereodivergent Allylic Amination of α-Tertiary Allylic Alcohols towards α,β-Unsaturated γ-Amino Acids

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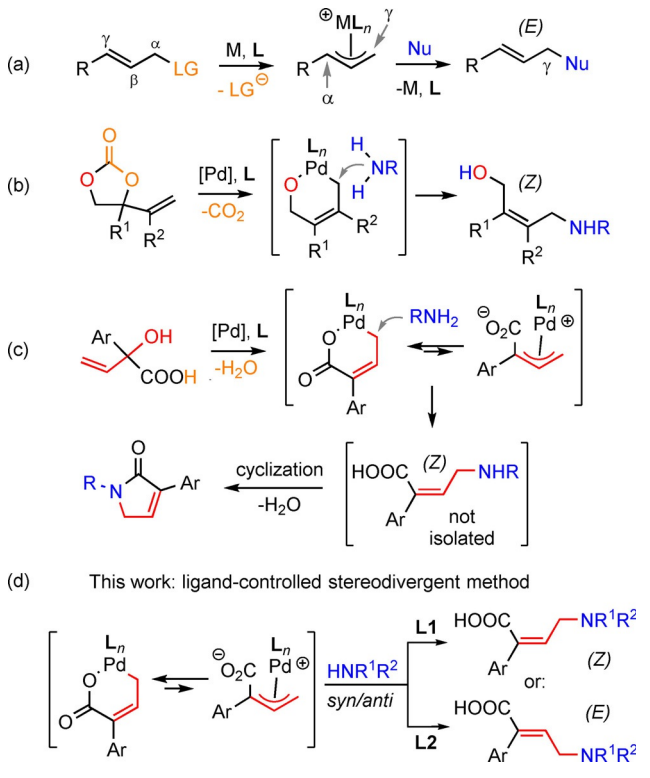
Tertiary allylic alcohols were conveniently converted into either (*Z*)- or (*E*)-configured α,β-unsaturated γ-amino acids by treatment with secondary amines under Pd catalysis at ambient conditions. The key to control the stereochemical course of these formal allylic aminations was the presence of a suitable diphosphine ligand, with dppp [1,3-bis(diphenylphosphino)-propane, **L12**] providing high yields and selectivities for the (*Z*) isomers, whereas the bis[(2-diphenylphosphino)phenyl]ether (DPEPhos) derivative **L1′** allowed for selective formation of the corresponding (*E*) isomeric products. This ligand-controlled, stereodivergent protocol thus shows promise for the stereoselective preparation of allylic amine products from a common substrate precursor.

Introduction

Stereoselective construction of functionalized polysubstituted olefin scaffolds plays an important role in numerous synthetic transformations.[1] Metal-catalyzed allylic substitution processes provide a potential route for stereodivergent olefin synthesis by nucleophilic attack onto the least hindered carbon terminus (γ-position, Scheme 1 a) of the in situ-formed metal–allyl unit. Generally, the preparation of (*E*) and (*Z*) isomeric olefins requires either the synthesis of two different sets of precursors,[2] or the use of different synthetic routes and/or catalysts. Although challenging, the stereodivergent synthesis of olefins from the same starting material has been realized, for example, in alkene cross metathesis,[3] semi-reduction of alkynes,[4] and reductive cross-coupling reactions with alkynes.[5] Despite notable progress in this area, the development of a stereodivergent methodology for polysubstituted olefins based on metal-mediated allylic substitution presents a challenge and remains scarce.[6]

Allylic amination is one of the most efficient synthetic methods to rapidly construct amine derivatives.[7] Allylic amine groups are frequently encountered in a wide range of natural products and biologically active molecules, and thus their preparation has aroused broad interest spanning several de-



Scheme 1. (a) Typical regio- and stereocontrol in metal-catalyzed allylic substitutions. (b) (*Z*)-selective allylic aminations in highly substituted vinyl cyclic carbonates acting as allylic surrogates. (c) Carboxyl chelation effect leading to (*Z*)-selective amination and cyclization to lactams by using primary amines. (d) This work: ligand-controlled amination leading to either (*Z*)- or (*E*)-configured γ-amino α,β-unsaturated carboxylic acids. **L1** and **L2** stand for two arbitrary ligands.

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cades.[8] Although efficient methodologies have been developed for the construction of the thermodynamically (typically) more stable (*E*)-configured, γ-mono-substituted allylic amine scaffolds (Scheme 1 a),[9] reports pertaining to stereodivergent allylic amination affording either a (*Z*)- or (*E*)-configured product from a single substrate are scarce.[6a]

Our laboratory recently developed a methodology for the stereoselective synthesis of (*Z*)-configured allylic amines based on a Pd/bis[(2-diphenylphosphino)phenyl]ether- (DPEPhos)-catalyzed decarboxylative amination of vinyl cyclic carbonates.[10] The key to the success of this approach was the in situ formation of a six-membered palladacyclic intermediate (computed by DFT; Scheme 1 b). Although the efficiency and stereoselectivity of Pd-catalyzed allylic substitutions may be significantly affected by the electronic and steric features of the intermediate π-(allyl) Pd^{II} species, the selective formation of the (*E*)-configured allylic amine isomers was not feasible.

Particularly, allylic amine synthesis by direct amination of allylic alcohols is attractive and offers both environmental and economic advantages with water as the sole byproduct.[11] In this context, we recently disclosed a protocol for α,β-unsaturated γ-lactam synthesis through Pd-mediated stereoselective amination of α-tertiary allylic alcohols under ambient conditions without the requirement of any additives.[12]

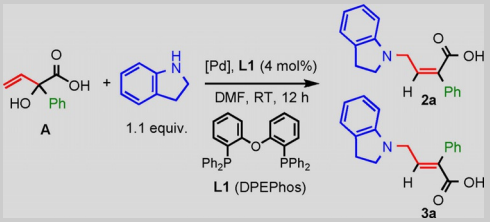
In this process, there is a crucial role for the carboxyl group present in the substrate, which allows activation of the allylic alcohol and directs the stereochemical course of the reaction through chelation (Scheme 1 c). We wondered whether the strength of this Pd–O coordination could be controlled by the use of appropriate ligands and conditions (i.e., solvent polarity, additives)[13] to increase its dynamic character, thus allowing for well-established π–σ–π interconversion and switching between *syn* and *anti* Pd(allyl) species.[14] Such ligand-controlled reactivity would facilitate allylic amination and result in either a (*Z*)- or (*E*)-configured γ-amino acid as the product. Stereodivergent access to both isomeric products (Scheme 1 d) from a single allylic alcohol precursor by using secondary amine reagents represents a step forward in the area of allylic amination, combining improved stereocontrol, facile operation, and attractive eco-friendly features.

Moreover, α,β-unsaturated γ-amino acids (and their corresponding esters) are of considerable significance owing to their functionality, allowing for further manipulations such as their transformation into γ-amino amides, γ-amino alcohols, and γ-lactams.[15] In addition, α,β-unsaturated γ-amino acids may have further value as key structural building blocks in peptide-based natural products and related congeners, which display interesting pharmaceutical activities.[16] Herein, we report a stereodivergent allylic amination route that establishes the preparation of both stereoisomers (*E* and *Z*) from carboxyl-functionalized allylic alcohols by a judicious choice of a supporting phosphine ligand.

Results and Discussion

To test our working hypothesis illustrated in Scheme 1 d, we chose substrates **A** and indoline (Table 1) for the screening

Table 1. Allylic amination of substrate **A** and indoline in the presence of different Pd-precursors and **L1**.[a]



Entry	[Pd]	Solvent	Conv.[b] [%]	Yield[c] **2a**+**3a** [%]	*Z*/*E*[c]
1	$[allylPdCl]_2$	DMF	18	10	70:30
2	$Pd_2(dba)_3{\cdot}CHCl_3$	DMF	52	19	94:6
3	$Pd(dba)_2$	DMF	34	17	97:3
4	$Pd(PPh_3)_4$	DMF	42	22	74:26
5	Pd/bis-sulf	DMF	35	14	64:36
6	$Pd(OAc)_2$	DMF	28	14	49:51
7	$Pd(TFA)_2$	DMF	41	25	42:58
8	$Pd(acac)_2$	DMF	24	13	50:50
9	$Pd(TFA)_2$	CH_3CN	38	10	58:42
10	$Pd(TFA)_2$	CH_2Cl_2	35	9	62:38
11	$Pd(TFA)_2$	MeOH	36	16	61:39
12	$Pd(TFA)_2$	HFIP	97	79	99:1
13	$Pd(TFA)_2$	DMSO	75	60	45:55

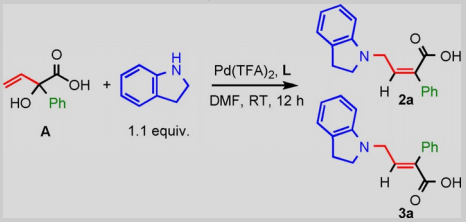
[a] Reaction conditions unless stated otherwise: **A** (0.15 mmol), indoline (0.165 mmol, 1.1 equiv.), solvent (0.15 mL; 1 M), [Pd] (4.0 mol%), **L1** (4.0 mol%), 12 h, RT. [b] Conversion of **A** determined by ^1H NMR spectroscopy in $CDCl_3$ by using CH_2Br_2 as an internal standard. [c] Determined from the crude ^1H NMR spectrum by signal integration. Pd/bis-sulf stands for the White catalyst precursor [bis-sulfoxide-ligated $Pd(OAc)_2$].

phase, which should allow access to either (*Z*)- or (*E*)-configured γ-amino acid products **2a** and **3a**, respectively. As an initial ligand, DPEPhos was selected because we recently observed that **L1** was an effective ligand system for Pd-catalyzed allylic amination.[10a]

Various Pd^0 and Pd^{II} precursors were scrutinized (entries 1–8, Table 1), showing, however, only modest variation in the conversion levels. Because the use of $Pd(TFA)_2$ (TFA = trifluoroacetic acid) provided a slightly higher selectivity towards products **2a** and **3a** (entries 4 and 7),[17] we decided to further use this precursor and to vary the solvent (entries 9–13). Interestingly, although most solvents did not improve the reactivity, the presence of HFIP (hexafluoro isopropanol) afforded the γ-amino acid products in 79% yield and with a high *Z*/*E* ratio of 99:1 (entry 12). Although HFIP and DMSO provided overall higher yields of the targeted products, we further focused on the use of DMF for optimization because it gave the highest amount of (*E*) isomer. Additionally, in a second optimization phase, the use of DMF allowed for a direct comparison of ligand effects under otherwise identical reaction conditions (see below, Table 2).

To improve the overall reactivity, chemoselectivity, and stereoselectivity bias for the process, an additional set of 18 phosphine ligands were evaluated (see Figure 1). Introduction of *ortho*-methoxy substituents in the DPEPhos ligand structure (**L1′**) provided a catalyst system that gave, after increasing both the Pd precursor and ligand amount to 10 mol% and

Table 2. Allylic amination of substrate **A** and indoline in the presence of $Pd(TFA)_2$ and various phosphine ligands **L** in DMF.[a]



Entry	[Pd] [mol%]	L [mol%]	Conv.[b] [%]	Yield[c] 2a+3a [%]	Z/E[c]
1	4.0	**L1′**, 4.0	60	42	21:79
2	6.0	**L1′**, 6.0	85	60	18:82
3	10.0	**L1′**, 10.0	100	83	16:84
4[d]	10.0	**L1′**, 10.0	100	82	14:86
5	4.0	**L2**, 4.0	38	16	80:20
6	4.0	**L3**, 4.0	16	4	>99:1
7	4.0	**L4**, 4.0	37	9	80:20
8	4.0	**L5**, 4.0	56	38	>99:1
9	4.0	**L6**, 4.0	88	51	92:8
10	4.0	**L7**, 4.0	100	74	62:38
11	4.0	**L8**, 4.0	63	42	99:1
12	4.0	**L9**, 4.0	26	10	95:5
13	4.0	**L10**, 4.0	42	20	>99:1
14	4.0	**L11**, 4.0	17	10	>99:1
15	4.0	**L12**, 4.0	100	94	>99:1
16	4.0	**L13**, 4.0	100	90	98:2
17	4.0	**L14**, 4.0	67	38	73:27
18	4.0	**L15**, 4.0	84	65	69:31
19	4.0	**L16**, 4.0	83	56	95:5
20	4.0	**L17**, 4.0	80	54	90:10
21	4.0	**L18**, 4.0	28	14	99:1
22	4.0	**L19**, 4.0	16	4	>99:1

[a] Reaction conditions unless stated otherwise: **A** (0.15 mmol), indoline (0.165 mmol, 1.1 equiv.), solvent (0.15 mL; 1 M), amount of [Pd] and **L** indicated, 12 h, RT. [b] Conversion of **A** determined by ^{1}H NMR spectroscopy in $CDCl_3$ by using CH_2Br_2 as an internal standard. [c] Determined from the crude ^{1}H NMR spectrum by signal integration. [d] Concentration was 0.5 M in DMF (0.30 mL).

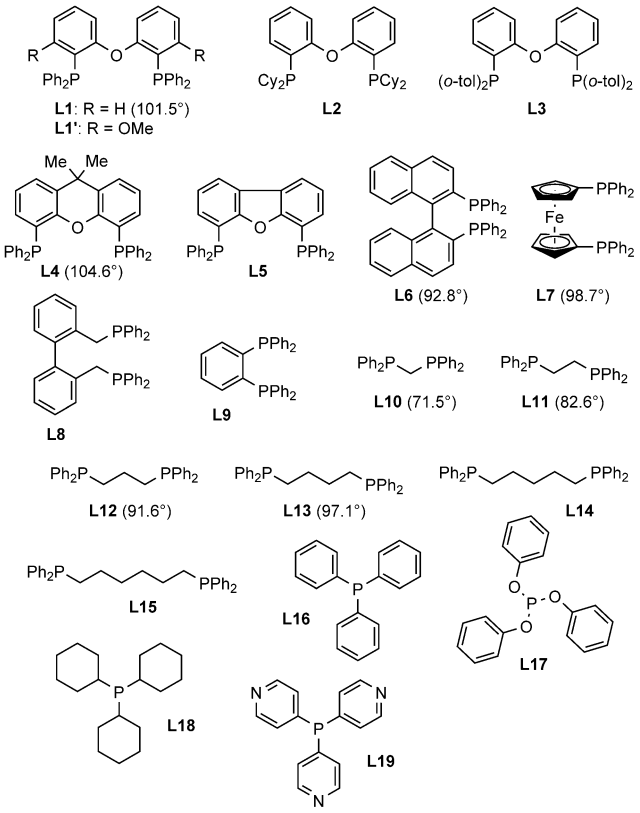


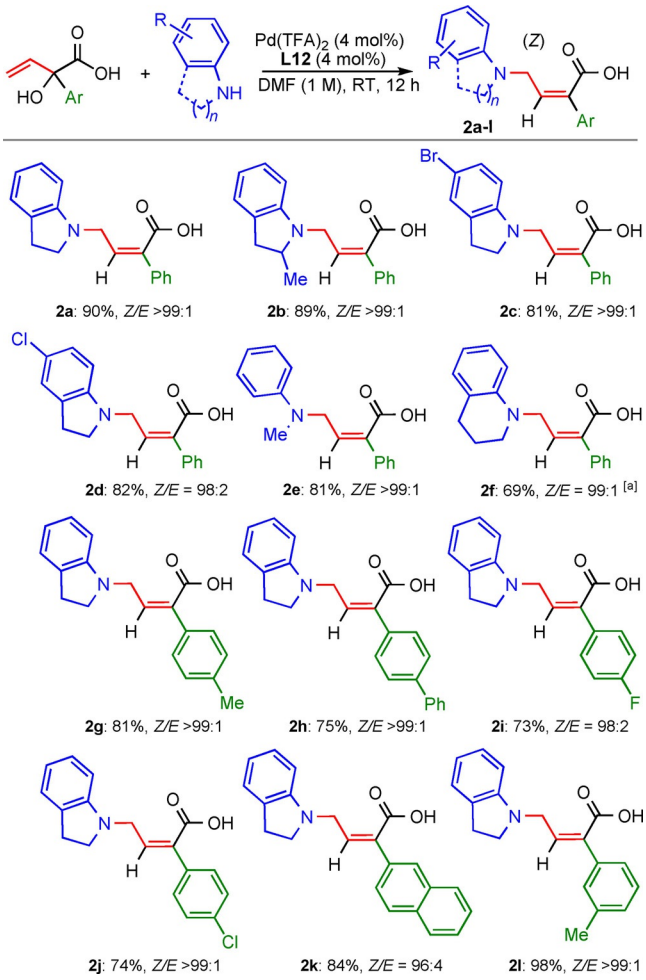
Figure 1. Phosphine ligands **1**–**16** and **18**–**19**, and phosphite **17** used in the optimization process towards either **2a** or **3a** and related to Table 2. In parentheses, some of the diphosphine bite angles are also provided.

using 0.5 M dilution (Table 2, entries 1–4), the highest *E*/*Z* ratio of approximately 6:1, providing the amino acid products in a combined 82% yield.

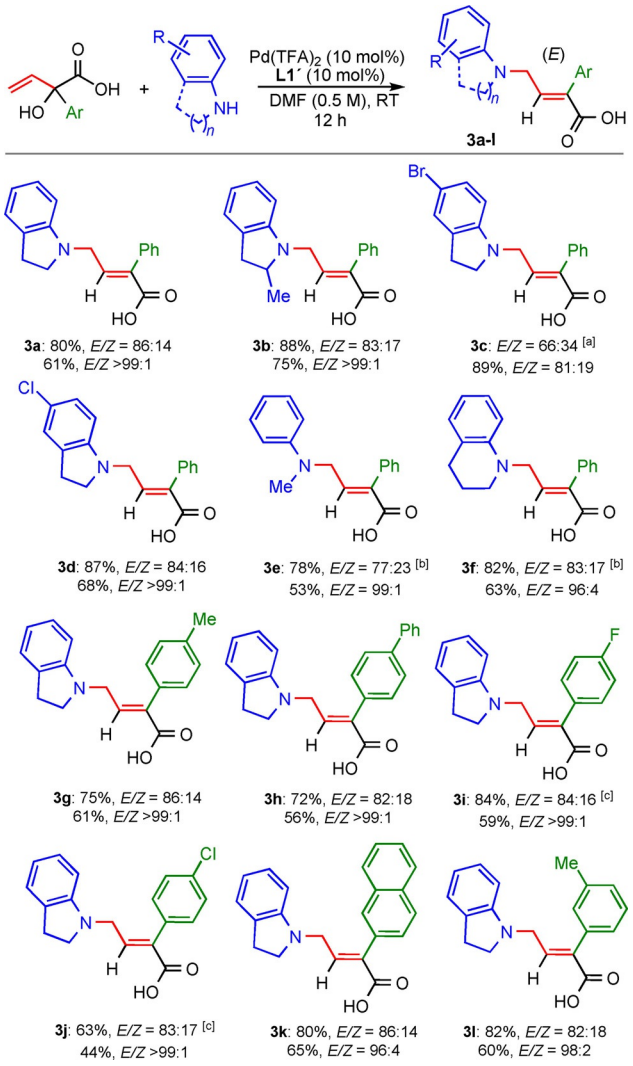
Although the selectivity towards the (*E*) product could not be further improved,[18] further experiments then focused on achieving an optimal yield and stereocontrol towards the (*Z*)-configured product (entries 5–22). Various ligands, including **L7** [1,1′-bis(diphenylphosphino)ferrocene, dppf],[12] **L13** [1,4-bis(diphenylphosphino)butane, dppb], and **L15** [1,6-(diphenylphosphino)hexane, dpph] proved to be efficient catalyst systems for the conversion of **A**, although **L12** [1,3-bis(diphenylphosphino)propane, dppp] was outstanding in terms of substrate conversion (quantitative), product yield (94%), and stereocontrol towards **2a** (>99:1). These conditions differ markedly from those previously found to be optimal for the formation of α,β-unsaturated γ-lactams from **A** [**L7**, $Pd_2(dba)_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone), CH_3CN, RT; Scheme 1c].[12]

With these optimized conditions in hand for both the (*Z*)-(**2a**) and the (*E*)-stereoisomer (**3a**), the scope of this stereodivergent allylic amination process was examined, focusing first on the synthesis of the (*Z*)-stereoisomers by using the conditions reported in entry 15 of Table 2 (Scheme 2). The indoline-based amino acid **2a** was isolated in high yield (90%) under excellent stereocontrol (*Z*/*E* > 99:1). Other substituted indolines proved to be productive substrates upon combination with **A** (Ar = Ph), giving smooth access to (*Z*) amino acids **2b**–**d** in good yields and with high *Z*/*E* values. Apart from indolines, the use of secondary amines such as *N*-methylaniline and 1,2,3,4-tetrahydroquinoline gave easy access to the targeted amino acids **2e** (81%) and **2f** (69%), preserving a high stereoinduction. Next, we examined the use of other tertiary allylic alcohol derivatives by variation of the Ar group. Good-to-excellent yields of the amino acids **2g**–**2l** were obtained, and all products were isolated with high *Z*/*E* ratios of at least 96:4. Electron-withdrawing and -donating groups did not significantly influence the outcome of the allylic amination protocol, and a larger aromatic group (naphthyl; preparation of **2k**) in the substrate was also tolerated.

The synthesis of the (*E*)-configured analogues of **2a**–**2l** (Scheme 3; **3a**–**3l**) was then also probed by using the optimal conditions found for the preparation of **3a** (Table 2, entry 4). All substrate substitutions and variations scrutinized in the scope presented for the (*Z*) amino acids (Scheme 2) were kept the same for the sake of comparison and to allow for investigation of the generality of the stereodivergent protocol. In



Scheme 2. Synthesis of (*Z*)-configured products **2a**–**2l** by using the reaction conditions from entry 15 in Table 2: **A** (0.15 mmol), amine (0.165 mmol, 1.1 equiv.), DMF (0.15 mL), $Pd(TFA)_2$ (4.0 mol%), **L12** (4.0 mol%), 12 h, RT. [a] $Pd(TFA)_2$ (8.0 mol%) and **L12** (8.0 mol%), 24 h. Yields reported are of the isolated product after column purification.



Scheme 3. Synthesis of (*E*)-configured products **3a**–**3l** by using the reaction conditions from entry 4 in Table 2: **A** (0.15 mmol), amine (0.165 mmol, 1.1 equiv.), DMF (0.30 mL), $Pd(TFA)_2$ (10.0 mol%), **L1′** (10.0 mol%), 12 h, RT; both the combined isolated yield of the *E*/*Z* mixture and the purified (*E*) compounds were determined, alongside their respective *E*/*Z* ratios by ^{1}H NMR spectroscopy. [a] The (*E*) and (*Z*) isomers could not be (fully) separated by column chromatography; after isolation, the product was isolated with an *E*/*Z* ratio of 81:19. [b] DPEPhos **L1** (10.0 mol%) was used as ligand. [c] Reaction time was 24 h.

general, the products **3a**–**3l** were isolated in good yields of up to 89% (**3c**) with *E*/*Z* ratios up to 6:1. Fortunately, all (*E*) isomers (with the exception of **3c**) could be separated from these isomer mixtures by column chromatography to afford the virtually pure stereoisomers with typical yields in the range 60–70%. Neither the substitution pattern in the secondary amine reagent nor in the tertiary allylic alcohol affected the overall yield or stereoinduction.

These results (Scheme 3) combined with those reported in Scheme 2 demonstrate that both stereoisomers can be readily obtained from the same allylic alcohol precursor by simply switching from **L1′** [giving the (*E*) isomer as the major product] to **L12** [favoring the (*Z*) isomer] at ambient temperature under rather comparable reaction conditions. Suitable crystals of **2a** and **3a** were obtained, and the molecular structures of these stereoisomers were determined by X-ray crystallography (Figure 2). These data therefore provide unambiguous proof of the proposed connectivity present in the (*Z*) as well as (*E*) isomers obtained from the reaction between substrate **A** and indoline. Their NMR spectroscopic features provided a useful reference to determine the stereochemistry of the other products (**2b**–**2l** and **3b**–**3l**).

To rationalize the experimental observations, we first performed a closer inspection of the nature of the diphosphine ligand needed to favor the formation of the (*E*) isomer. This revealed that a slightly more-bulky ligand such as **L1′** (a bis-*ortho*-substituted DPEPhos analogue, see Figure 1) is required. This is reasonable because coordination of such a bulky ligand may disfavor the stability of the in situ-formed palladacycle (Scheme 4; after initial loss of H_2O) and allow for isomerization of the Pd(allyl) species through π–σ–π interconversion. From this point on, an electrostatic interaction of the carboxyl group and the Pd center in the *anti*-isomer may increase the overall 1,3-allylic strain, allowing for some degree of *anti*/*syn* intercon-

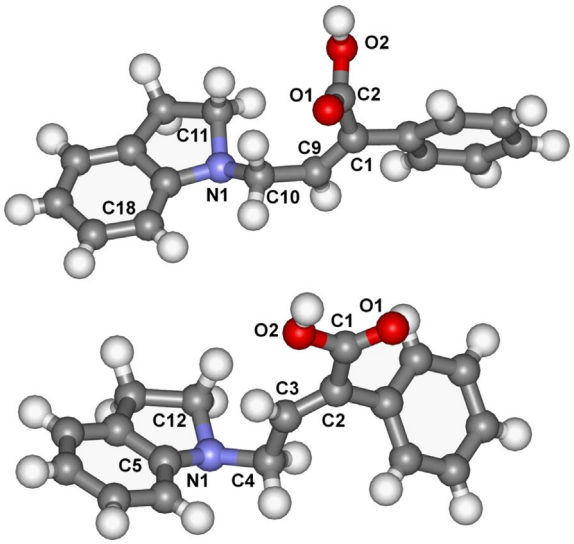
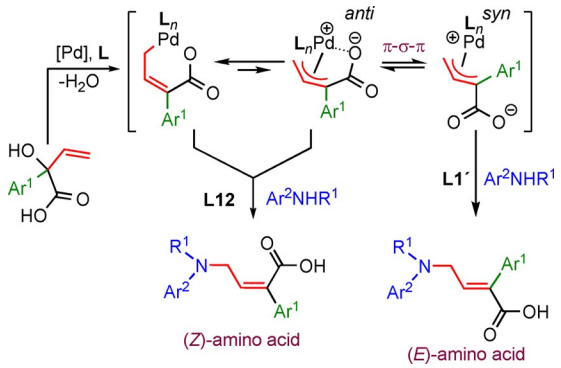


Figure 2. X-ray molecular structures determined for **2a** (*Z*; upper part) and **3a** (*E*; lower part). Selected bond lengths [Å] and angles [°] for **2a** with estimated standard deviations in parentheses: N(1)–C(10) = 1.4753(14), N(1)–C(11) = 1.4926(15), N(1)–C(18) = 1.4343(14), C(1)–C(9) = 1.3362(15), C(1)–C(2) = 1.5023(16), C(2)–O(1) = 1.2159(13); C(11)–N(1)–C(18) = 105.22(9), O(1)–C(2)–O(2) = 124.16(11), C(2)–C(1)–C(9) = 119.79(10). Selected bond lengths [Å] and angles [°] for **3a** with estimated standard deviations in parentheses: N(1)–C(4) = 1.475(3), N(1)–C(5) = 1.441(3), N(1)–C(12) = 1.491(3), C(2)–C(3) = 1.342(3), C(1)–C(2) = 1.498(3), C(1)–O(1) = 1.217(3); C(5)–N(1)–C(12) = 105.43(18), O(1)–C(1)–O(2) = 123.1(2), C(1)–C(2)–C(3) = 119.3(2).



Scheme 4. Proposed mechanistic rationale for the stereodivergent Pd-catalyzed synthesis of (*E*) and (*Z*) amino acids from tertiary allylic alcohols and amines. L_n refers to a diphosphine ligand.

version and increased steric shielding of the allyl carbon terminus. The *syn*-isomer is likely to be thermodynamically less stable, but it is believed to be kinetically more competent (i.e., following the Curtin–Hammett principle). As a consequence, the (*E*) isomer is preferentially formed if a more rigid, wide-bite-angle diphosphine ligand such as **L1′** is present.

Alternatively, if a more flexible, smaller-bite-angle ligand such as **L12** is used, the stereoselectivity is fully reversed towards the formation of the (*Z*) product. The diphosphine ligands that result in the highest conversion rates [Table 2, **L6**: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP); **L7**; **L12**; **L13**; **L15**] demonstrate that the diphosphine bite angle indeed plays an important role, with **L12** (bite angle ≈ 91.6°, Figure 1)[19] resulting in both quantitative conversion of the tertiary allylic alcohol and the highest selectivity towards the (*Z*)-configured product (*Z*/*E* > 99:1). Therefore, diphosphines comprising a semi-flexible alkyl spacer (propyl/butyl, **L12** and **L13**) between the two P-donors provide optimal steric and electronic control towards the formation of the (*Z*)-configured amino acid with the amine reagent proposed to attack either the palladacyclic intermediate or the *anti* Pd(π-allyl) intermediate.

Conclusions

A new stereodivergent protocol is reported for the Pd-mediated formation of either (*Z*)- or (*E*)-configured α,β-unsaturated γ-amino acids from easily accessed tertiary allylic alcohols and secondary amines. The key to the observed stereocontrol is the presence of a suitable diphosphine ligand that triggers, most likely through steric control, the attack of the amine onto either a *syn* or *anti* Pd(allyl) intermediate. The scope of this protocol demonstrates reasonable generality,[20] with the (*Z*) isomers isolated in good-to-excellent yield under excellent stereocontrol, and the corresponding (*E*) isomers produced with *E*/*Z* ratios of up to 6:1 and in good yields. This work may thus be regarded as a useful step forward in stereodivergent allylic amination chemistry.

Experimental Section

General procedure for the (*Z*)-selective allylic aminations

In a screw-capped vial, vinyl glycolic acid (0.0267 g, 0.15 mmol, 1 equiv.) was combined with $Pd(TFA)_2$ (0.0020 g, 4.0 mol%), dppp (0.0025 g, 4.0 mol%), and indoline (0.165 mmol, 1.1 equiv.) in DMF (0.15 mL). The reaction mixture was stirred at RT for 12 h, after which CH_2Cl_2 (15 mL) was added. The organic phase was washed with water (2×30 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under vacuum. The pure product (**2a**) was isolated by flash chromatography (37.7 mg, 90%, *n*-hexane/ethyl acetate = 3:1, R_f = 0.1). All purified (*Z*)-configured products were fully characterized by NMR spectroscopy (^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H}), IR spectroscopy, and high-resolution MS techniques. Full data and relevant spectra are provided in the Supporting Information.

General procedure for the (*E*)-selective allylic aminations

$Pd(TFA)_2$ (0.0050 g, 10.0 mol%) and the methoxy-substituted DPE-Phos **L1′** (0.0090 g, 10.0 mol%) were added to a screw-capped vial equipped with a magnetic stirring bar. The vial was then charged with DMF (0.30 mL) and stirred at RT for 1 h. Vinyl glycolic acid (0.0267 g, 0.15 mmol, 1 equiv.) and indoline (0.165 mmol, 1.1 equiv.) were added, and then the reaction mixture was stirred at RT for 12 h. Thereafter, CH_2Cl_2 (15 mL) was added. The organic phase washed with water (2×30 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under vacuum. The pure product (**3a**) was isolated by flash chromatography (25.5 mg, 61%, *n*-hexane/ethyl acetate = 3:1, R_f = 0.18). All purified (*E*)-configured products were fully characterized by NMR spectroscopy (^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H}), IR spectroscopy, and high-resolution MS techniques. Full data and relevant spectra are provided in the Supporting Information.

X-ray crystallographic studies

The measured crystals of **2a** and **3a** were stable under atmospheric conditions; nevertheless, they were treated under inert conditions by immersion in perfluoro-polyether as a protecting oil for manipulation. Data collection: measurements were made with a Bruker-Nonius diffractometer equipped with an APPEX II 4 K CCD area detector, a FR591 rotating anode with MoK_α radiation, Montel mirrors, and a Kryoflex low-temperature device ($T=-173\,^\circ$C). Full-sphere data collection was used with ω and φ scans. Programs used: data collection Apex2 V2011.3 (Bruker-Nonius 2008), data reduction Saint+Version 7.60A (Bruker AXS 2008), and absorption correction SADABS V. 2008-1 (2008). Structure solution: SHELXTL Version 6.10 (Sheldrick, 2000) was used.[21] Structure refinement: SHELXTL-97-UNIX VERSION.

Crystal data for 2a: $C_{18}H_{17}NO_2$; $M_r=279.32$; monoclinic; $P2/n$; $a=5.6162(3)$, $b=27.9447(13)$, $c=9.4836(4)$ Å; $\alpha=90$, $\beta=91.4146(14)$, $\gamma=90^\circ$; $V=1487.93(3)$ Å^3; $Z=4$; $\rho=1.247$ mg M^{-3}; $\mu=0.081$ mm^{-1}; $\lambda=0.71073$ Å; $T=100(2)$ K; $F(000)=592$; crystal size $=0.20\times0.10\times0.01$ mm^3; $\theta(\min)=2.268$, $\theta(\max)=31.693^\circ$; 12702 reflections collected, 4604 reflections unique ($R_{int}=0.0285$); GoF = 1.025; $R1=0.0474$ and $wR2=0.1167$ [$I>2\sigma(I)$]; $R1=0.0628$ and $wR2=0.1261$ (all indices); min/max residual density $=-0.235/0.472$ [e Å^{-3}]; completeness to $\theta(31.693^\circ)=91.4\,\%$. For further details: CCDC number 1895598.

Crystal data for 3a: $C_{9.5}H_{9.5}N_{0.5}OCl$; $M_r=182.13$; triclinic; $P\bar{1}$; $a=7.4617(13)$, $b=11.272(2)$, $c=11.3361(18)$ Å; $\alpha=72.069(5)$, $\beta=77.994(5)$, $\gamma=78.711(5)^\circ$; $V=878.4(3)$ Å^3; $Z=4$; $\rho=1.377$ mg M^{-3}; $\mu=0.380$ mm^{-1}; $\lambda=0.71073$ Å; $T=100(2)$ K; $F(000)=380$; crystal size $=0.10\times0.05\times0.03$ mm^3; $\theta(\min)=1.912$, $\theta(\max)=32.411^\circ$; 8818 reflections collected, 5094 reflections unique ($R_{int}=0.0353$); GoF = 1.066; $R1=0.0616$ and $wR2=0.1641$ [$I>2\sigma(I)$]; $R1=0.0964$ and $wR2=0.1829$ (all indices); min/max residual density $=-0.449/0.427$ [e Å^{-3}]; completeness to $\theta(32.411^\circ)=80.8\,\%$. For further details: CCDC number 1895597.

CCDC 1895597 and 1895598 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Conflict of interest

The authors declare no conflict of interest.

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[1] a) *Comprehensive Organic Synthesis, Vol. 4* (Ed.: M. F. Semmelhack), Pergamon Press, Oxford, **1991**; b) A. B. Flynn, W. W. Ogilvie, *Chem. Rev.* **2007**, *107*, 4698 – 4745.

[2] B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863 – 927.

[3] a) W. E. Crowe, D. R. Goldberg, *J. Am. Chem. Soc.* **1995**, *117*, 5162 – 5163; b) A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360 – 11370; c) J. Cossy, S. BouzBouz, A. H. Hoveyda, *J. Organomet. Chem.* **2001**, *634*, 216 – 221.

[4] a) S. Fu, N.-Y. Chen, X. Liu, Z. Shao, S.-P. Luo, Q. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 8588 – 8594; b) E. Richmond, J. Moran, *J. Org. Chem.* **2015**, *80*, 6922 – 6929.

[5] M. K. Armstrong, M. B. Goodstein, G. Lalic, *J. Am. Chem. Soc.* **2018**, *140*, 10233 – 10241.

[6] Pioneering examples using N-based nucleophiles have been explored, although resulting in products with poor *Z*/*E* ratios: a) B. Åkermark, S. Hansson, A. Vitagliano, *J. Am. Chem. Soc.* **1990**, *112*, 4587 – 4588; for allylic alkylations using C-based nucleophiles, see: b) B. M. Trost, C. Heinemann, X. Ariza, S. Weigand, *J. Am. Chem. Soc.* **1999**, *121*, 8667 – 8668; c) M. P. T. Sjögren, S. Hansson, B. Åkermark, A. Vitagliano, *Organometallics* **1994**, *13*, 1963 – 1971.

[7] a) M. Johannsen, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 1689 – 1708; for original work, see: b) P. A. Evans, E. A. Clizbe, *J. Am. Chem. Soc.* **2009**, *131*, 8722 – 8723; c) K.-Y. Ye, Q. Cheng, C.-X. Zhuo, L.-X. Dai, S.-L. You, *Angew. Chem. Int. Ed.* **2016**, *55*, 8113 – 8116; *Angew. Chem.* **2016**, *128*, 8245 – 8248; d) I. Dubovyk, I. D. G. Watson, A. K. Yudin, *J. Am. Chem. Soc.* **2007**, *129*, 14172 – 14173; e) B. M. Trost, D. R. Fandrick, T. Brodmann, D. T. Stiles, *Angew. Chem. Int. Ed.* **2007**, *46*, 6123 – 6125; *Angew. Chem.* **2007**, *119*, 6235 – 6237; f) D. Banerjee, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 13049 – 13053; *Angew. Chem.* **2014**, *126*, 13265 – 13269.

[8] a) E. M. Skoda, G. C. Davis, P. Wipf, *Org. Process Res. Dev.* **2012**, *16*, 26 – 34; b) *Chiral Amine Synthesis* (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**; c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921 – 2944; d) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395 – 422; e) L. Huang, M. Arndt, K. Gooßen, H. Heydt, L. J. Gooßen, *Chem. Rev.* **2015**, *115*, 2596 – 2697; f) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675 – 704; g) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795 – 3892.

[9] For allylic substitution reactions, see: a) N. A. Butt, W. Zhang, *Chem. Soc. Rev.* **2015**, *44*, 7929 – 7967; b) J. S. Arnold, Q. Zhang, H. M. Nguyen, *Eur. J. Org. Chem.* **2014**, 4925 – 4948; c) A. Leitner, C. Shu, J. F. Hartwig, *Org. Lett.* **2005**, *7*, 1093 – 1096; d) S. Shekhar, B. Trantow, A. Leitner, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 11770 – 11771; e) B. Plietker, *Angew. Chem. Int. Ed.* **2006**, *45*, 6053 – 6056; *Angew. Chem.* **2006**, *118*, 6200 – 6203. For other methodologies to prepare allylic amines, see: f) D. Banerjee, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 1630 – 1635; *Angew. Chem.* **2014**, *126*, 1656 – 1661; g) D. Banerjee, K. Junge, M. Beller, *Org. Chem. Front.* **2014**, *1*, 368 – 372; h) S. A. Reed, M. C. White, *J. Am. Chem. Soc.* **2008**, *130*, 3316 – 3318; i) S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller, M. C. White, *Nat. Chem.* **2015**, *7*, 987 – 994.

[10] a) W. Guo, L. Martínez-Rodríguez, R. Kuniyil, E. Martin, E. C. Escudero-Adán, F. Maseras, A. W. Kleij, *J. Am. Chem. Soc.* **2016**, *138*, 11970 – 11978. For an overview of other examples of (*Z*)-configured products derived from cyclic vinyl carbonates, see: b) W. Guo, J. Gómez, A. Cristofol, J. Xie, A. W. Kleij, *Angew. Chem. Int. Ed.* **2018**, *57*, 13735 – 13747; *Angew. Chem.* **2018**, *130*, 13928 – 13941.

[11] Pd-catalyzed allylic amination: a) F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami, M. Yoshifuji, *J. Am. Chem. Soc.* **2002**, *124*, 10968 – 10969; b) F. Ozawa, T. Ishiyama, S. Yamamoto, S. Kawagishi, H. Murakami, *Organometallics* **2004**, *23*, 1698 – 1707; c) H. Hikawa, Y. Yokoyama, *J. Org. Chem.* **2011**, *76*, 8433 – 8439; d) R. Ghosh, A. Sarkar, *J. Org. Chem.* **2011**, *76*, 8508 – 8512; e) D. Banerjee, R. V. Jagadeesh, K. Junge, H. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2012**, *51*, 11556 – 11560; *Angew. Chem.* **2012**, *124*, 11724 – 11728; f) D. Banerjee, R. V. Jagadeesh, K. Junge, H. Junge, M. Beller, *ChemSusChem* **2012**, *5*, 2039 – 2044; g) Y. Gumrukcu, B. de Bruin, J. N. H. Reek, *ChemSusChem* **2014**, *7*, 890 – 896; h) G. Hirata, H. Satomura, H. Kumagae, A. Shimizu, G. Onodera, M. Kimura, *Org. Lett.* **2017**, *19*, 6148 – 6151; i) J. Jing, X. Huo, J. Shen, J. Fu, Q. Meng, W. Zhang, *Chem. Commun.* **2017**, *53*, 5151 – 5154; Ni-catalyzed allylic amination: j) M. Utsunomiya, Y. Miyamoto, J. Ipposhi, T. Oshima, K. Mashima, *Org. Lett.* **2007**, *9*, 3371 – 3374; k) M. Salah Azizi, Y. Edder, A. Karim, M. Sauthier, *Eur. J. Org. Chem.* **2016**, 3796 – 3803; l) Y. Kayaki, T. Koda, T. Ikariya, *J. Org. Chem.* **2004**, *69*, 2595 – 2597; m) J. B. Sweeney, A. K. Ball, P. A. Lawrence, M. C. Sinclair, L. J. Smith, *Angew. Chem. Int. Ed.* **2018**, *57*, 10202 – 10206; *Angew. Chem.* **2018**, *130*, 10359 – 10363; Pt-catalyzed allylic amination: n) T. Ohshima, Y. Miyamoto, J. Ipposhi, Y. Naka-

hara, M. Utsunomiya, K. Mashima, *J. Am. Chem. Soc.* **2009**, *131*, 14317 – 14328; o) K. Das, R. Shibuya, Y. Nakahara, N. Germain, T. Ohshima, K. Mashima, *Angew. Chem. Int. Ed.* **2012**, *51*, 150 – 154; *Angew. Chem.* **2012**, *124*, 154 – 158.

[12] J. Xie, S. Xue, E. C. Escudero-Adán, A. W. Kleij, *Angew. Chem. Int. Ed.* **2018**, *57*, 16727 – 16731; *Angew. Chem.* **2018**, *130*, 16969 – 16973.

[13] For reviews, see: a) G. Consiglio, M. Waymouth, *Chem. Rev.* **1989**, *89*, 257 – 276; b) P. S. Pregosin, R. Salzmann, *Coord. Chem. Rev.* **1996**, *155*, 35 – 68; see also ref. [8d].

[14] The π–σ–π process in η-allyl palladium complexes has been shown to be controlled by the proper choice of a (bis)phosphine ligand, see: a) M. Ogasawara, K. Takizawa, T. Hayashi, *Organometallics* **2002**, *21*, 4853 – 4861; b) M. Kranenburg, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **1998**, 25 – 27; c) R. J. van Haaren, G. P. F. van Strijdonck, H. Oevering, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **2001**, 837 – 843.

[15] a) F. Palacios, D. Aparicio, J. García, E. Rodríguez, A. Fernández-Acebes, *Tetrahedron* **2001**, *57*, 3131 – 3141; b) A. K. Ghosh, M. Brindisi, J. Tang, *J. Neurochem.* **2012**, *120*, 71 – 83; c) S. Chandrasekhar, M. V. Reddy, *Tetrahedron* **2000**, *56*, 1111 – 1114; d) C. Xia, J. Shen, D. Liu, W. Zhang, *Org. Lett.* **2017**, *19*, 4251 – 4254; e) M. T. Reetz, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531 – 1546; *Angew. Chem.* **1991**, *103*, 1559 – 1573.

[16] a) N. Schaschke, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 855 – 858; b) Y. Nakao, M. Fujita, K. Warabi, S. Matsunaga, N. Fusetani, *J. Am. Chem. Soc.* **2000**, *122*, 10462 – 10463; c) T. Conroy, J. T. Guo, R. G. Linington, N. H. Hunt, R. J. Payne, *Chem. Eur. J.* **2011**, *17*, 13544 – 13552; d) J. A. Nieman, J. E. Coleman, D. J. Wallace, E. Piers, L. Y. Lim, M. Roberge, R. J. Andersen, *J. Nat. Prod.* **2003**, *66*, 183 – 199.

[17] Apart from products **2a** and **3a**, some other unidentified minor by-products were observed.

[18] Further variation of the reaction conditions and use of additives did not improve this result; see the Supporting Information for details.

[19] a) P. Dierkes, P. W. N. M. van Leeuwen, *J. Chem. Soc. Dalton Trans.* **1999**, 1519 – 1529; b) P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741 – 2769.

[20] Other potential substrates such as aniline (a primary amine) and a γ-substituted tertiary allylic alcohol were also probed. Despite the clear observation of the formation of the targeted amino acid products, both the yield according to NMR spectroscopy and the chemoselectivity of these reactions were much lower than observed for the products reported in Schemes 2 and 3. See the Supporting Information for more details.

[21] G. M. Sheldrick, *SHELXTL Crystallographic System*, version 6.10; Bruker AXS, Inc.: Madison, WI, **2000**.

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