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Palladium-Catalyzed Regio- and Enantioselective Synthesis of Allylic Amines Featuring Tetrasubstituted Tertiary Carbons

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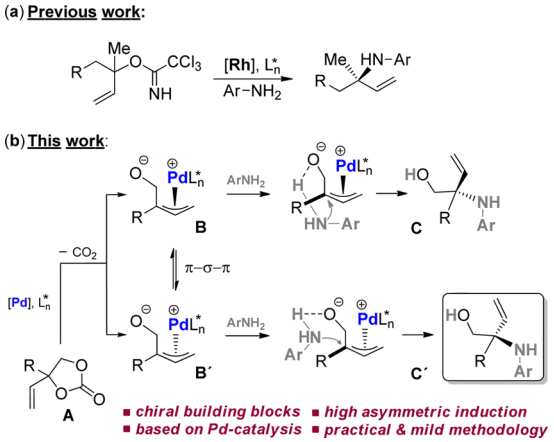
Supporting Information

ABSTRACT: The first asymmetric synthesis of α,α-disubstituted allylic *N*-arylamines based on a palladium-catalyzed allylic amination has been developed. The protocol uses highly modular vinyl cyclic carbonates and unactivated aromatic amine nucleophiles as substrates. The catalytic process features minimal waste production, ample scope in reaction partners, high asymmetric induction up to 97% *ee*, and operational simplicity.

Building chiral quaternary and/or tetrasubstituted tertiary carbons from simple and readily available starting materials under mild reaction conditions continues to be one of the most challenging and attractive research goals in modern synthetic chemistry.[1] Chiral allylic amines are fundamental building blocks in organic synthesis, and their preparation is of high synthetic and industrial interest.[2] Transition-metal-catalyzed allylic amination has up to now been used as the most powerful and convenient tool for constructing α-monofunctionalized chiral allylic amines,[3] with iridium-based catalysts representing privileged systems in this domain.[3a−n]

Despite significant progress in this area, the catalytic formation of chiral α,α-disubstituted allylic amines incorporating tetrasubstituted tertiary carbons attained through allylic amination has proven to be very challenging and remains a largely unexplored field of science.[4,5] In this respect, Arnold and Nguyen[5] recently reported the first general allylic amination toward chiral α,α-disubstituted allylic amines based on rhodium catalysis (Scheme 1a). However, the use of economically more attractive palladium catalysis in the context of allylic amination to provide products with chiral tetrasubstituted tertiary carbons continues to be an unsolved problem.[4] A key challenge is that nucleophilic attack on the sterically more crowded internal carbon center of the Pd−allyl species is much more challenging than the attack on the terminal carbon, resulting preferably in linear rather than branched allylic amine formation.[4a] New methodologies that can invert this selectivity bias should undoubtedly trigger general interest in the synthetic communities and revive the use of alternative strategies toward these important chiral allylic scaffolds. In a wider context, the asymmetric synthesis of α,α-disubstituted trifluoroacetimidates via intramolecular rearrangement[6] and the transition-metal-catalyzed synthesis of (*rac*)-α,α-disubstituted allylic amines[7] further show the limited progress and challenging nature of the asymmetric synthesis of α,α-disubstituted allylic amines.

Scheme 1. Methodological Approach toward Chiral Allylic Amines from Vinyl Carbonates and Amine Nucleophiles Using Pd Catalysis



Previous success in the Pd-catalyzed transformation of vinyl carbonates with various electrophiles showed wide potential toward the construction of enantioenriched compounds such as furans, tertiary vinyl glycols, and oxazolidinones.[8] A key to this success was the in situ formation of postulated zwitterionic π-allyl-Pd intermediates **B** and **B′** that result from Pd-catalyzed decarboxylation of vinyl cyclic carbonate **A** (Scheme 1b).

We hypothesized that in the presence of a suitable chiral ligand and amine nucleophile,[9] a dynamic kinetic asymmetric transformation (DYKAT) would be feasible if the isomerization of intermediates **B** and **B′** through π−σ−π interconversion occurs faster than subsequent nucleophilic attack.[2i] The asymmetric environment around the Pd center would then kinetically favor the formation of one of the possible allylic amine enantiomers **C** or **C′** (Scheme 1b) upon nucleophilic attack by amines. Herein we disclose the first regio- and enantioselective synthesis of α,α-disubstituted branched allylic arylamines based on a Pd-catalyzed allylic amination using substituted vinyl cyclic carbonates **A** and unactivated arylamine nucleophiles as reaction partners.

To challenge our mechanistic hypothesis, the reaction of phenyl-substituted vinyl cyclic carbonate **D** and aniline was selected as a model reaction (Table 1). Preliminary investigations (see Table S1 in the Supporting Information (SI)) suggested that

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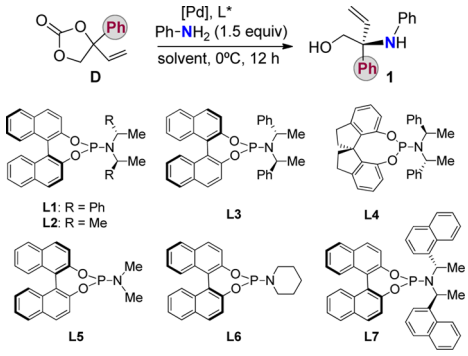
Table 1. Selected Screening Data toward the Formation of Chiral Allylic Amine 1 Using Vinyl Cyclic Carbonate D and Aniline as Substrates[a]



entry	L	solvent	yield[b] [%]	ee[c] [%]
1	**L1**	CH_2Cl_2	67	64 (*S*)
2	**L1**	toluene	52	59 (*S*)
3	**L1**	CH_3CN	52	76 (*S*)
4	**L1**	Et_2O	67	75 (*S*)
5	**L1**	THF	76	95 (*S*)
6	**L1**	DMF	37	84 (*S*)
7	**L2**	THF	39	68 (*S*)
8	**L3**	THF	60	73 (*S*)
9	**L4**	THF	<2	–
10	**L5**	THF	<2	–
11	**L6**	THF	<2	–
12	**L7**	THF	<2	–
13[d]	**L1**	THF	73	95 (*S*)
14[e]	**L1**	THF	38	91 (*S*)
15[f]	**L1**	THF	59	71 (*S*)
16[g]	**L1**	THF	<15	–
17[h]	**L1**	THF	63	71 (*S*)

[a]Reaction conditions, unless stated otherwise: carbonate (0.2 mmol, 1 equiv), aniline (1.5 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (1.25 mol %), **L** (5.0 mol %), solvent (0.20 mL), 0 °C, open to air, 12 h. [b]Isolated yields. [c]Determined by HPLC (see the SI for details). [d]Using $Pd(dba)_2$ (2.5 mol %) as the catalyst. [e]At room temperature. [f]Using 0.10 mL of THF. [g]Using 0.30 mL of THF. [h]Using 5 equiv of aniline.

a reaction temperature of 0 °C and a combination of $Pd_2(dba)_3{\cdot}CHCl_3$ and **L1** (Table 1) are key to obtain an appreciable yield of **1** (67%).[10] At this temperature the formation of a 1,4-but-2-ene diol byproduct[11] is significantly suppressed. A further decrease in the reaction temperature led to very low conversion.

Then the solvent and ligand effects were systematically optimized at 0 °C, and we were pleased to find that the yield of the branched allylic amine **1** further increased to 76% with excellent enantiocontrol (95% *ee*) when THF was used as the solvent (Table 1, entries 1–6). The other phosphoramidite ligands **L2**–**L7** gave inferior results compared with **L1** under similar conditions (entries 7–12). The use of $Pd(dba)_2$ was also productive (entry 13) but showed poor reproducibility. The room-temperature conversion gave lower *ee* (91%; entry 14) and a significantly lower isolated yield (38%). Similar erosion of the asymmetric induction was noted when the reaction was performed at higher concentration (71% *ee*; entry 15). Lowering the concentration of the reactants resulted in rather low conversion (entry 16). The use of a large excess of aniline also led to a decrease in the enantioselectivity (entry 17). The experimental observations reported in entries 14, 15, and 17 align well with the mechanistic hypothesis that the asymmetric induction should be less efficient if the nucleophilic attack by the amine is accelerated.[12] Notably, base additives are not required in this catalytic process, which is crucial to control the chemoselectivity of this transformation.[13]

With the optimized conditions in hand, we then investigated the scope of arylamines toward the formation of branched allylic amines **1**–**15** (Figure 1).[14] In general, the formation of these

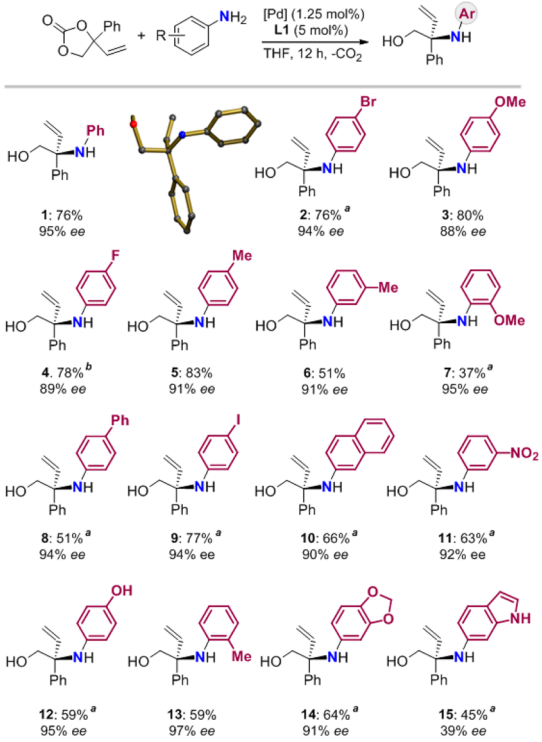


Figure 1. Scope of arylamine reaction partners. Reaction conditions: carbonate (0.2 mmol), arylamine (0.3 mmol), [Pd] = $Pd_2(dba)_3{\cdot}CHCl_3$ (1.25 mol %), **L1** (5.0 mol %), THF (0.20 mL), 0 °C, open to air, 12 h. Isolated yields after column purification are reported. In the X-ray structure of **1** (inserted at the top), only the alcohol H is shown. Notes: [a]$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), **L1** (10 mol %). [b]24 h.

products proceeded with excellent enantioselectivity of up to 97% (except for allylic amine **15**). The absolute configuration of allylic amine **1** (*S*) was unambiguously confirmed by X-ray diffraction studies (Figure 1).[15] The protocol is quite efficient for various arylamine reaction partners, including those having aryl groups with para (**2**–**5**, **8**, **9**, and **12**), meta (**6** and **11**), and ortho (**7** and **13**) substitutions. Both electron-donating (**3**, **5**–**7**, and **12**) and -withdrawing groups (**2**, **4**, and **9**) are tolerated. The *m*-nitro-substituted aniline was also tolerated, affording allylic amine **11** in 63% yield with 93% *ee*. The installation of indole (**15**) and 1,3-benzodioxole (**14**) fragments, which are frequently observed in relevant pharmaceutical compounds,[16] is also possible. The reaction with *o*-methoxyaniline gave a lower yield (**7**; 37%) indicating some steric limitations of the present methodology. The use of sterically demanding *N*-methylaniline resulted in quantitative linear product formation, while no reaction was observed under the optimized conditions utilizing indole or pyrrole nucleophiles. Further attempts to improve the enantioselectivity of products **15** and **25** using chloride additives failed.[17] Also, a linear carbonate analogue was tested but gave as the major product the linear allylic amine under the optimized

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conditions (51% yield; see the SI for details). This shows that vinyl cyclic carbonate substrates have different intrinsic reactivity.

We then focused on investigating the scope of vinyl carbonates (Figure 2). We gratifyingly noted that a wide range of aryl-

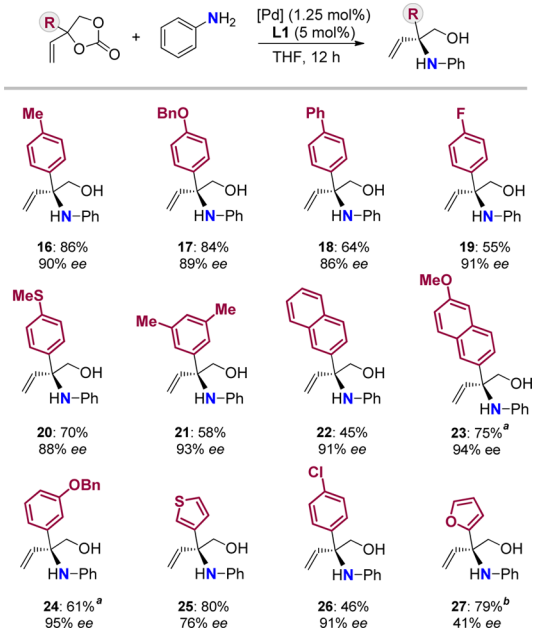

Figure 2. Scope of vinyl carbonate reaction partners. Reaction conditions: carbonate (0.2 mmol), aniline (0.3 mmol), [Pd] = $Pd_2(dba)_3{\cdot}CHCl_3$ (1.25 mol %), **L1** (5.0 mol %), THF (0.20 mL), 0 °C, open to air, 12 h. Isolated yields after column purification are shown. Notes: [a] $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), **L1** (10 mol %). [b] $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), **L7** (20 mol %).

substituted vinyl cyclic carbonates were tolerated under the reaction conditions, giving access to the corresponding enantioenriched allylic amines **16**–**27** in appreciable yields with good to excellent levels of enantioselectivity. It is worth noting that compounds **1**–**27** also represent chiral vicinal amino alcohols, which are of high synthetic interest and have important applications in biology.[18]

The presence of substituents with different steric and electronic effects in the vinyl carbonate were tolerated. Generally, vinyl carbonates equipped with electron-donating aryl groups gave more productive catalysis with high levels of enantioselectivity (**16**, **17**, and **20**–**24**; ≥88% *ee*). The carbonate substrate having an ortho-bromo substituent did not show any reactivity under the optimized conditions, while the meta-substituted isomer gave the allylic amine product with 88% *ee* (see the SI), though in low yield. Installation of a thiophene moiety in the allylic amine is feasible (**25**; 80% yield, 76% *ee*), albeit with a lower degree of enantiocontrol. This may be explained by the presence of an additional heteroatom that could interact with the Pd catalyst during the enantiodetermining stage of the reaction. Similar effects were noted when other reaction partners (arylamines or carbonates) incorporating heteroatoms were utilized (cf. the preparation of **15** and **27**). Under the optimized conditions using ligand **L1**, the use of a furyl-substituted carbonate afforded allylic amine **27** with only 12% *ee*. The enantioselectivity improved to 41% when the bulkier ligand **L7** was utilized at a higher catalyst/ligand loading. It is worth noting that in some cases the linear product was observed, and this resulted in a lower isolated yield of the branched product (cf. the syntheses of **7**, **15**, **22**, and **26**).

To further challenge the catalytic protocol, the enantioselective synthesis of methyl- and nonsubstituted (R = H) allylic amines **28** and **29** was probed (Figure 3). These products were

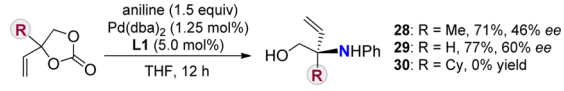

Figure 3. Preparation of methyl- and nonsubstituted chiral allylic amines **28** and **29** and attempted synthesis of **30**.

isolated in good yields (71–77%) with moderate enantioselectivity (46–60% *ee*); the use of ligand **L7** did not improve the enantioselectivity (see the SI). With a bulkier cyclohexyl group (**30**, R = Cy), no product was obtained.

In addition to the application potential of (chiral) allylic amines reported previously,[2] a further synthetic use of these branched allylic amines was exemplified by the preparation of chiral ether **31**, oxazolidinone **32**, diamine **33**, and carbamate **34** from **1** with retention of the original chirality (Figure 4).

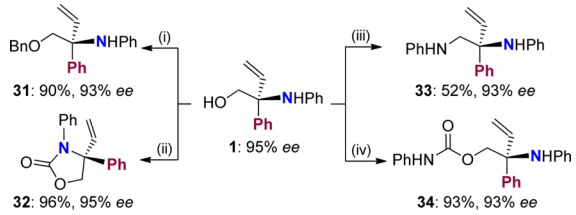

Figure 4. Conversion of allylic amine **1**. Reaction conditions: (i) BnBr (1.1 equiv), NaH (2.0 equiv), THF (1 mL), 0 °C to rt, 15 h; (ii) pyridine (4.0 equiv), triphosgene (0.50 equiv), CH_2Cl_2, 0 °C to rt, 3 h; (iii) see the SI for experimental details and further comments; (iv) phenyl isocyanate (1.3 equiv), Et_3N (10 equiv), CH_2Cl_2, rt, 10 min.

In summary, we have presented herein the first regio- and enantioselective synthesis of *α*,*α*-disubstituted allylic *N*-aryl-amines based on a palladium-catalyzed allylic amination protocol. This procedure utilizes readily available and modular substituted cyclic vinyl carbonates and unactivated arylamines as reactants, can be operated without any special precautions, and does not require any additives. Therefore, this user-friendly and efficient methodology marks a significant step forward in the challenging synthesis of these chiral allylic amine scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08841.

Experimental details and characterization data (PDF)

Crystallographic data for **1** (CIF)

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Notes

The authors declare no competing financial interest.

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(10) The choice to use chiral phosphoramidites was based on previous success with these ligands in asymmetric synthesis.[8a,b]

(11) Water can react with the vinyl cyclic carbonate in the presence of a suitable palladium catalyst to afford a 1,4-but-2-ene diol product. See: Guo, W.; Martínez-Rodríguez, L.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Angew. Chem., Int. Ed.* **2016**, *55*, 11037.

(12) Increasing the reaction temperature, concentration, or amount of aniline would give faster nucleophilic addition. This combined with a relatively slow equilibration between reactive species **B** and **B′** (Scheme 1) would consequently lead to lower enantiodiscrimination. For relevant observations and/or a more detailed explanation, see refs 4a and 9c.

(13) Addition of external base may lead to 1,2-diol or carbamate formation. See: (a) Guo, W.; Gónzalez-Fabra, J.; Bandeira, N. A. G.; Bo, C.; Kleij, A. W. *Angew. Chem., Int. Ed.* **2015**, *54*, 11686. (b) Laserna, V.; Fiorani, G.; Whiteoak, C. J.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 10416.

(14) Alkylamines can react with cyclic carbonates at room temperature to give carbamate compounds. Such aminolysis behavior has been well-documented. For example, see: (a) Blain, M.; Jean-Gérard, L.; Auvergne, R.; Benazet, D.; Caillol, S.; Andrioletti, B. *Green Chem.* **2014**, *16*, 4286. (b) Guo, W.; Laserna, V.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Chem. - Eur. J.* **2016**, *22*, 1722. (c) Sopeña, S.; Laserna, V.; Guo, W.; Martin, E.; Escudero-Adán, E. C.; Kleij, A. W. *Adv. Synth. Catal.* **2016**, *358*, 2172. No branched allylic amine product was observed using deactivated alkylamines of *p*-F- and *p*-NO_2-substituted benzylamines.

(15) For more details, see CCDC-1496759.

(16) (a) Bloom, J. D.; Dutia, M. D.; Johnson, B. D.; Wissner, A.; Burns, M. G.; Largis, E. E.; Dolan, J. A.; Claus, T. H. *J. Med. Chem.* **1992**, *35*, 3081. (b) Ali, A.; Wang, J.; Nathans, R. S.; Cao, H.; Sharova, N.; Stevenson, M.; Rana, T. M. *ChemMedChem* **2012**, *7*, 1217. (c) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620.

(17) Chloride can increase the rate of the $\pi-\sigma-\pi$ process (Scheme 1) and potentially improve the enantioselectivity. See: Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014. However, no conversion of the substrates toward **15** and **25** was observed in the presence of Bu_4NCl or $N(Hex)_4Cl$ (30 mol %).

(18) For recent relevant literature, see: (a) Shi, S.-L.; Wong, Z. L.; Buchwald, S. L. *Nature* **2016**, *532*, 353. (b) Orcel, U.; Waser, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 5250. Also see ref 8c.

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