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Palladium-Catalyzed Regio- and Enantio-Selective Synthesis of Allylic Amines Featuring Tetra-Substituted Tertiary Carbons

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Supporting Information

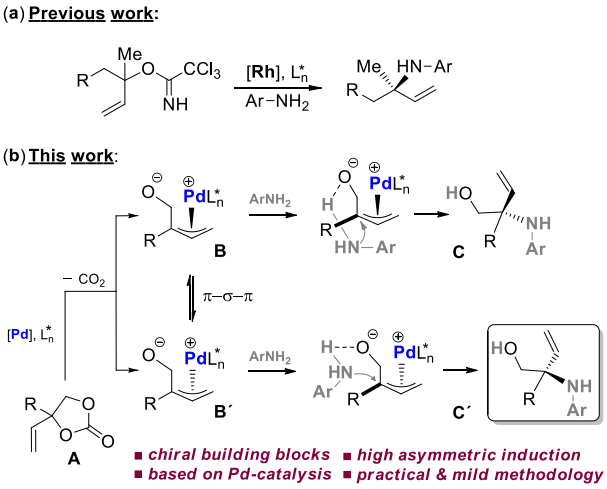
ABSTRACT: The first asymmetric synthesis of α,α-disubstituted allylic N-arylamines based on a palladium-catalyzed allylic amination has been developed. The protocol uses highly modular vinyl cyclic carbonates and unactivated aromatic amine nucleophiles as substrates. The catalytic process features minimal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

Building chiral quaternary and/or tetra-substituted 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 construction of α-mono-functionalized chiral allyl 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 tetra-substituted 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, Nguyen *et al*. recently reported the first general allylic amination towards chiral α,α-disubstituted allylic amines based on rhodium catalysis (Scheme 1a).[5] However, the use of economically more attractive palladium catalysis in the context of allylic amination providing products with chiral tetra-substituted 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 towards 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.

Previous success in the palladium-catalyzed transformation of vinyl carbonates with various electrophiles showed wide potential towards the construction of enantio-enriched 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 palladium intermediates **B** and **B´** that result from a Pd-catalyzed decarboxylation of vinyl cyclic carbonate **A** (Scheme 1b).

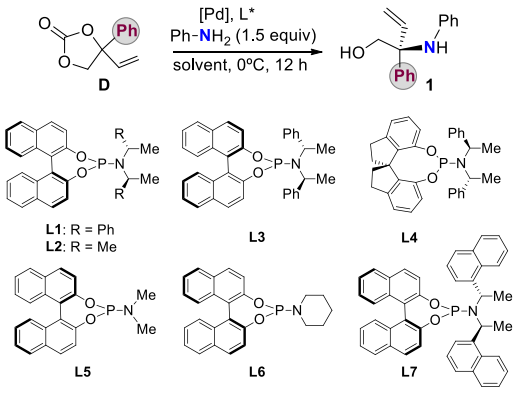
Scheme 1. Methodological Approach towards Chiral Allylic Amines from Vinyl Carbonates and Amine Nucleophiles using Pd-Catalysis



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 aryl amine 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 SI, Table S1) suggested that a reaction temperature of 0ºC and a combination of $Pd_2(dba)_3{\cdot}CHCl_3$/**L1** (Table 1) is key to obtain an appreciable yield of **1** (67%).[10] At this temperature the formation of a 1,4-but-2-ene diol by-product[11] is significantly suppressed. Upon further decreasing the reaction temperature, very low conversion was noted.

Table 1. Selected Screening Data towards 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: 0.2 mmol (1 equiv) of carbonate, aniline (1.5 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (1.25 mol%), **L** (5.0 mol%), 0.20 mL of solvent, 0ºC, open to air, 12 h. [b]Isolated yield. [c]Determined by HPLC (see SI for details). [d]Using $Pd(dba)_2$ (2.5 mol%) as catalyst. [e]Reaction at rt. [f]0.10 mL of THF. [g]0.30 mL of THF. [h]5 equiv of aniline used.

Then the solvent and ligand effect was systematically optimized at 0ºC, and we were pleased to find that the yield of the branched allylic amine **1** further increased to 76% with excellent enantiocontrol (95% *ee*) using THF as solvent (Table 1, entries 1–6). The other phosphoramidite ligands **L2**–**L7** gave inferior results compared to the use of **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 (entry 15, 71% *ee*). Lowering the concentration of the reactants resulted in rather low conversions (entry 16). The use of a large excess of aniline also led to a decrease of the enantioselectivity (entry 17). The experimental observations reported in entries 14, 15 and 17 align well with the mechanistic hypothesis that the asymmetric induction would 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]

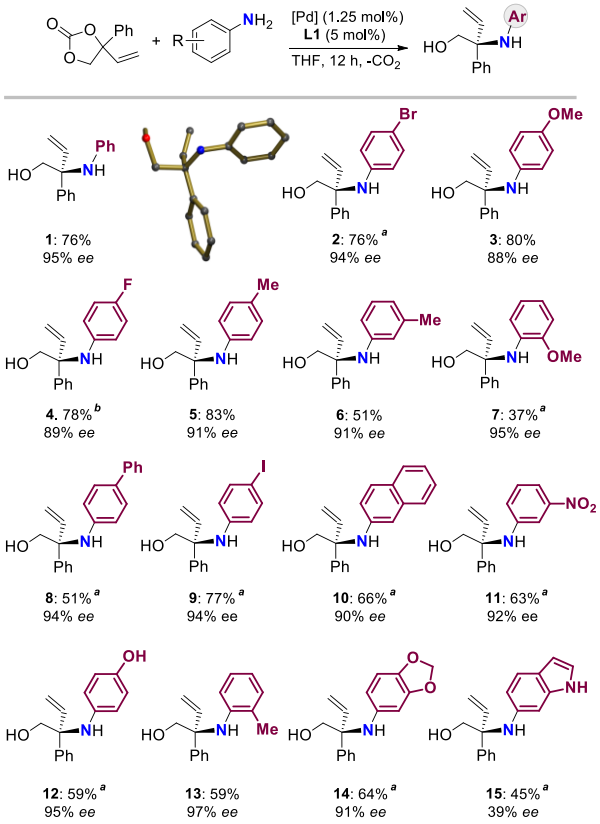


Figure 1. Scope in aryl amine reaction partners. Reaction conditions: 0.2 mmol carbonate, 0.3 mmol of arylamine, [Pd] = $Pd_2(dba)_3{\cdot}CHCl_3$ (1.25 mol%), **L1** (5.0 mol%), 0.20 mL THF, 0ºC, open to air, 12 h. All reported yields are isolated ones after column purification. [a]$Pd_2(dba)_3{\cdot}CHCl_3$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

With the optimized conditions in hand, we then investigated the scope in aryl amines towards the formation of the branched allylic amines **1**–**15** (Figure 1).[14] In general, the formation of these products proceeds 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 aryl amine 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 *meta*-nitro substituted aniline was also tolerated affording allylic amine **11** in 63% yield and 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 the *ortho*-methoxy-aniline gave a lower yield (**7**: 37%) indicating some steric limitations of present methodology. The use of sterically demanding N-methyl aniline resulted in quantitative linear product formation, while no reaction was observed under the opti-

mal 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 major product the linear allylic amine under the optimized conditions (yield: 51%; see the SI for details). This shows that vinyl cyclic carbonate substrates have different intrinsic reactivity.

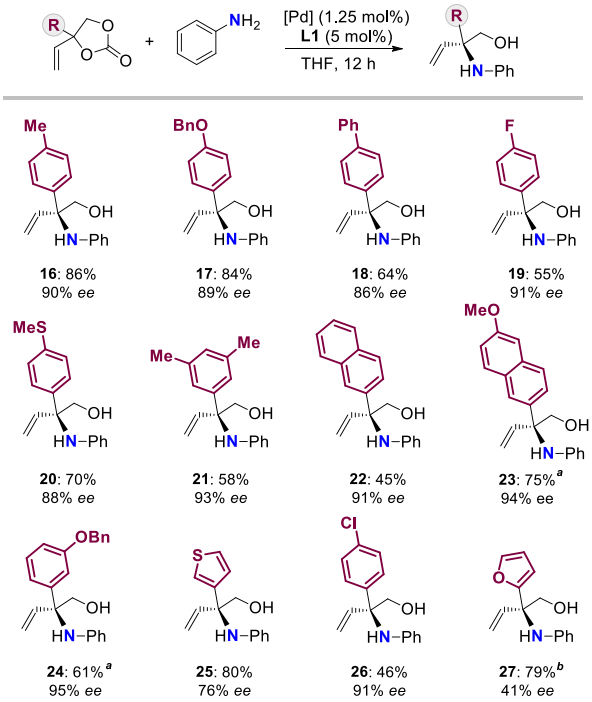


Figure 2. Scope in vinyl carbonate reaction partners. Reaction conditions: 0.2 mmol carbonate, 0.3 mmol of aniline, [Pd] = $Pd_2(dba)_3{\cdot}CHCl_3$ (1.25 mol%), **L1** (5.0 mol%), 0.20 mL THF, 0°C, open to air, 12 h. All reported yields are isolated ones after column purification. [a] $Pd_2(dba)_3{\cdot}CHCl_3$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

We then focused on the investigation of the scope in vinyl carbonates (Figure 2). We gratifyingly noted that a wide range of aryl-substituted vinyl cyclic carbonates were tolerated under the reaction conditions giving access to the corresponding enantioenriched allylic amines **16**–**27** in appreciable yields and 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 proved to be useful reaction partners. Generally, vinyl carbonates equipped with electron-donating aryl groups gave more productive catalysis with high levels of enantioselectivity (**16**–**17**, **20**–**24**; ≥ 88% ee). The carbonate substrate having an *ortho*-Br substituent did not show any reactivity under the optimized conditions, while the *meta*-substituted isomer gave the allylic amine product in 88% *ee* (see Supporting information) though in low yield. Installation of 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 hetero-atom that could interact with the Pd catalyst during the enantiodetermining stage of the reaction. Similar effects were noted when other reaction partners (aryl amines or carbonates) incorporating heteroatoms were utilized (*cf*., 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 could be improved to 41% when bulkier ligand **L7** was utilized at 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*., syntheses of **7**, **15**, **22** and **26**).

In order to further challenge the catalytic protocol, the enantioselective synthesis of methyl- and non-substituted (R = H) allylic amines **28** and **29** was probed (Figure 3). Both allylic amine products were 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). The introduction of a bulkier cyclohexyl group (**30**: R = Cy) was not feasible.

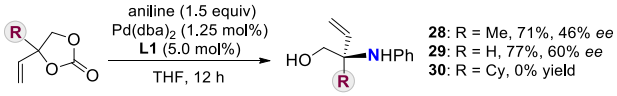


Figure 3. Preparation of methyl- and non-substituted chiral allylic amines **28** and **29**, and attempted synthesis of **30**.

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 allylic amine **1** retaining the original chirality (Figure 4).

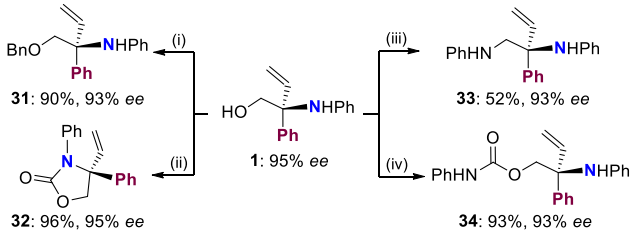


Figure 4. Conversion of allylic amine **1**. Reaction conditions: (i) BnBr (1.1 equiv), NaH (2.0 equiv), THF (1 mL), 0–rt, 15 h; (ii) pyridine (4.0 equiv), triphosgene (0.50 equiv), CH_2Cl_2, 0–rt, 3 h; (iii) See SI for experimental details and further comments; (iv) phenylisocyanate (1.3 equiv), Et_3N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

In summary, we herein present the first regio- and enantioselective synthesis of α,α-disubstituted allylic N-arylamines based on a palladium-catalyzed allylic amination protocol. This procedure utilizes readily available and modular substituted cyclic vinyl carbonates and unactivated aryl amines 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

Complete experimental details, spectral data and HPLC analysis for all new compounds. This material is available free of charge on the ACS Publications website at DOI: 10.1021/jacs###.

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Notes

The authors declare no competing financial interests.

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(10) The choice for using chiral phosphoramidites was based on previous success with these ligands in asymmetric synthesis, refer to refs. 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) The increase of reaction temperature, concentration or aniline amount would give faster nucleophilic addition. This combined with a relatively slow equilibration between reactive species **B** and **B´** (Scheme 1) will consequently lead to lower enantio-discrimination. For relevant observations and/or a more detailed explanation please refer to 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) Alkyl amines can react with cyclic carbonates at room temperature giving carbamate compounds. Such aminolysis behavior has been well-documented, see for instance: (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 alkyl amines of *p*-F and *p*-NO_2 substituted benzylamines.

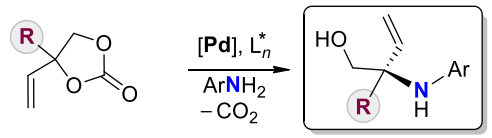
(15) For more details see: CCDC-1496759.

(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 π–σ–π 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 towards **15** and **25** was observed in the presence of Bu_4NCl or $N(Hex)_4Cl$ (30 mol%).

(18) For recent relevant literature: (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; See also ref. 8c.

SYNOPSIS TOC:



- ee up to 97%
- yield up to 86%
- 29 examples, mild
- no additives needed