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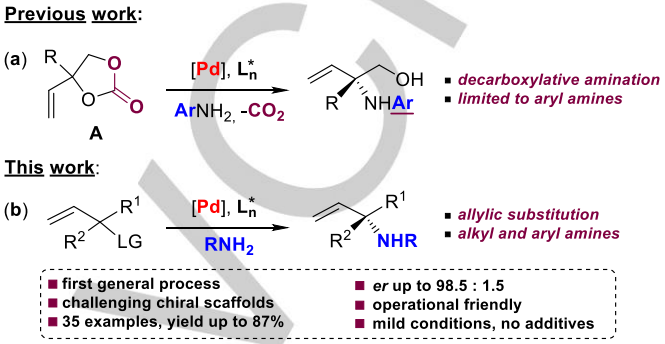
Asymmetric Synthesis of α,α-Disubstituted Allylic Amines via Pd-Catalyzed Allylic Substitution

Wusheng Guo,[a][+] Aijie Cai,[a][+] Jianing Xie,[a] and Arjan W. Kleij*[a][b]

Abstract: *The first asymmetric synthesis of important α,α-disubstituted N-alkyl allyl amine scaffolds via allylic substitution is reported. This approach is based on palladium catalysis and features ample scope in both allylic precursor and amine reagent, and high asymmetric induction with the enantiomeric ratio (er) up to 98.5:1.5. The use of less reactive anilines is also feasible providing enantioenriched α,α-disubstituted N-aryl allylic amines*.

Controlling the regioselectivity in Pd-catalyzed allyl substitution towards branched allylic amines has traditionally been extremely challenging. The nucleophilic attack of the amine on the less crowded terminal carbon of the Pd(allyl) intermediate is favored over the attack on the sterically hindered internal carbon thus giving the linear derivative as the major product. In this context, rather few examples succeeded in the preparation of sterically demanding (*rac*)-α,α-disubstituted allylic amines *via* Pd-catalyzed allylic substitution with limitations in the α,α-disubstitution pattern (often two methyl groups) and functional group diversity.[1,2]

Chiral α,α-disubstituted allylic amines represent a class of amines featuring a tetrasubstituted tertiary carbon center which have found important applications in biology and pharmaceutical industry,[3] and their synthesis is thus of high significance.[4] Despite notable success in the preparation of allylic amines via transition metal (TM) catalyzed allylic substitution in the last decade,[1-2,4-7] the asymmetric synthesis of α,α-disubstituted allylic amines based on allylic substitution using palladium catalysis has remained extremely challenging and to date underdeveloped.[8,9] We recently reported a Pd-catalyzed decarboxylative amination process toward the synthesis enantioenriched α,α-disubstituted allylic *N*-**aryl** amines from substituted vinyl cyclic carbonates and anilines (Scheme 1a).[10] Although successful, the cyclic carbonate precursor **A** was found to be a requisite,[11] and as a consequence this decarboxylative approach was limited to the use of aryl amines only as the more nucleophilic aliphatic amines quickly convert the cyclic carbonate into undesired carbamate through ring-opening aminolysis.[12,13] To the best of our knowledge, there is still no approach available for the asymmetric synthesis of α,α-disubstituted allylic *N*-**alkyl** amines based on TM-catalyzed allylic substitution.[14]



Scheme 1. Enantioselective synthesis of α,α-disubstituted allylic amines. LG stands for leaving group.

Based on our previous success with the Pd-catalyzed decarboxylative amination protocol (Scheme 1a),[10] we reasoned that in the presence of a suitable palladium precursor and a chiral ligand, the conversion of allylic precursors with an appropriate leaving group (LG) into α,α-disubstituted allylic amines (Scheme 1b) could be achieved. Such an approach would offer a general and tunable route towards chiral α,α-disubstituted allylic amines.

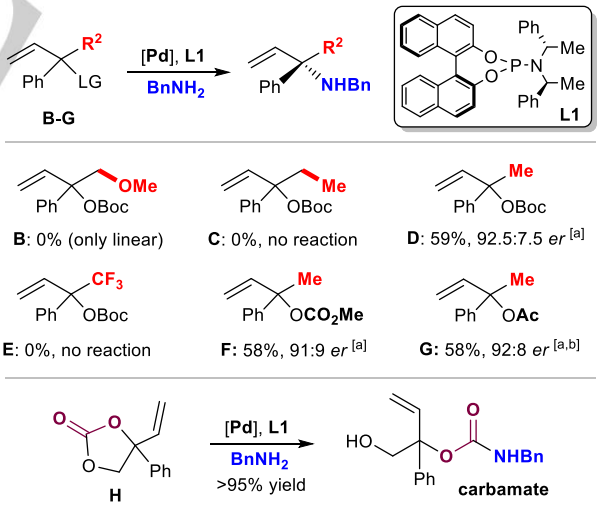


Figure 1. Preliminary screening of allylic precursors: **B–G** and **H** (0.15 mmol), $BnNH_2$ (0.23 mmol, 1.5 equiv), THF (150 μL), $Pd_2(dba)_3{\cdot}CHCl_3$ (3.5 mol %), **L1** (14 mol%), open to air, rt, 12 h. [a] Isolated yield, *er* determined by UPC2 (see Supporting information (SI) for details). [b] 36 h.

Therefore, we started our investigation using the model reaction between benzyl amine and a series of highly substituted allylic precursors **B**–**G** (Figure 1). In the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (3.5 mol %) and phosphoramidite ligand **L1** (14 mol %),[15] allylic

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precursor **B** (a Me-protected linear analogue of carbonate **A**, Scheme 1a), was converted quantitatively into a linear allylic amine[10] affirming the challenging nature of α,α-disubstituted allylic amine formation.

We reasoned that the steric impediment in the allylic precursor would probably be crucial to bias the regio-selectivity towards the branched product. A less bulky, ethyl-substituted precursor (**C**) was then tested but no reaction (conversion) was noted. To our delight, by decreasing the bulkiness of the alkyl group to methyl, conversion of allyl precursor **D** resulted in substantial amount of branched product (59% isolated yield) with a high enantiomeric ratio (*er* 92.5:7.5).[16] No reaction was observed when the Me was replaced by a CF_3 group (**E**). Changing the leaving group from OBoc to OCO_2Me did not significantly affect the reaction outcome (**F** *vs.* **D**), while the presence of an OAc leaving group (**G**) slowed down the reaction. A control reaction using vinyl cyclic carbonate **H** under similar conditions gave virtually quantitatively formation of a carbamate product (Figure 1).[12]

Then, the phosphoramidite ligand (**L1–L7**) and the solvent were systematically optimized using allyl precursor **D** and benzyl amine as reaction partners (see Table S1; Supporting Information). The use of CH_2Cl_2 and acetonitrile (ACN) increased the yield of the branched allylic amine but with slightly lower enantioselectivity (Table S1, entries 1-4). A higher (80%) isolated yield was achieved when the reaction was performed in a mixed solvent system consisting of THF/ACN (*er* 86:14, entry 5). Upon increasing the amount of THF in the mixed solvent medium (THF/ACN, 3:1) the enantioselectivity could be improved without affecting the overall reactivity (entries 5-7). Other phosphoramidite ligands **L2**–**L7** proved to be less efficient under these conditions (entry 5 *vs* 8–13). The increase of the amount of solvent and decreasing the amount of amine reagent (entry 14) or catalyst loading (entry 15) did not significantly change the reaction outcome. The reaction was further optimized using more diluted conditions and lowering the reaction temperature to 0 ºC giving the allylic amine target in 78% yield and with an *er* of 95.5:4.5 (entries 16-18).

The scope of allyl Boc-protected precursors was then examined under the optimized conditions (Figure 2, products **1**-**13**). The absolute configuration for **1** (*S*) was unambiguously confirmed by X-ray analysis of its HCl salt (Figure 2).[17] Both electron-donating (**6**, **8**, **9**, **12** and **13**) and withdrawing (**2**, **3**, **5** and **11**) groups in the aryl substituents were tolerated while providing high levels of enantio-induction with *er*´s up to 98.5:1.5. The presence of *meta*-, *para*- or *ortho*-substitutions in the aryl group proved to be feasible (**2**-**6**, **9**, **11**–**13**). The presence of larger aromatic fragments did not affect the efficiency of the catalysis (**7** and **8**), while the preparation of enantioenriched allylic amines with two α-alkyl substituents was also endorsed as exemplified by the synthesis of compound **10** though with a moderate *er* value.

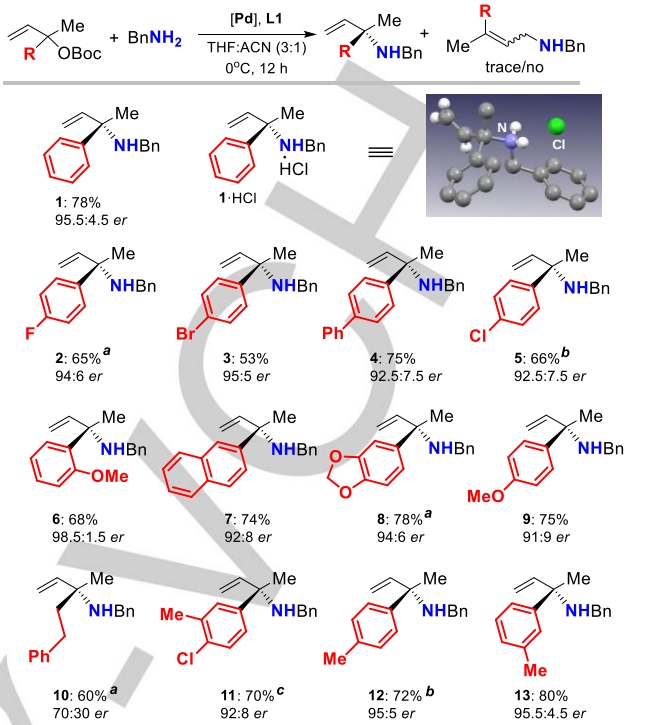

Figure 2. Scope in allyl precursors: allylic precursor (0.15 mmol), $BnNH_2$ (0.17 mmol, 1.1 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (2 mol %), **L1** (10 mol%), THF/ACN (3:1; 0.35 mL), 0ºC, open to air, 12 h. Isolated yields are reported, and the *er* values were determined by UPC2. [a] The *er* values were determined by using a chiral shift reagent (SI for details). [b] 24 h. [c] 36 h.

Various highly functionalized alkyl amines were found to be suitable reaction partners (Figure 3, **14**–**29**). Importantly, more functional amines showed appreciable reactivity and provided good to high *er* values (**18**, **22**-**26**) unlike in previous reports.[9] The presence of a thiophene group did not hamper the successful preparation of **21** despite the potential for catalyst poisoning in the presence of sulfur-containing compounds.[18] Although the use of a propargylic amine reagent resulted in a sluggish reaction,[19] amine **25** may be useful for *in vivo* bio-orthogonal applications through the use of click chemistry.[20] The amine products comprising of an indole (**27**) or 1,3-benzodioxole fragment (**8** and **20**) are of interest for pharmaceutical development.[21] It is interesting to note that in most cases only trace amounts of the corresponding linear allylic amine product were observed (Figures 2 and 3). However, in some cases (Figure **2**; for **14**, **17** and **29**) substantial amount of a 1,3-diene elimination product[22] was detected under the optimized reaction conditions thus resulting in a poorer yield of the desired allylic amine. This side-reaction could be suppressed by addition of CsF which significantly improved the yield of the branched product though with somewhat lower enantio-induction.[22]

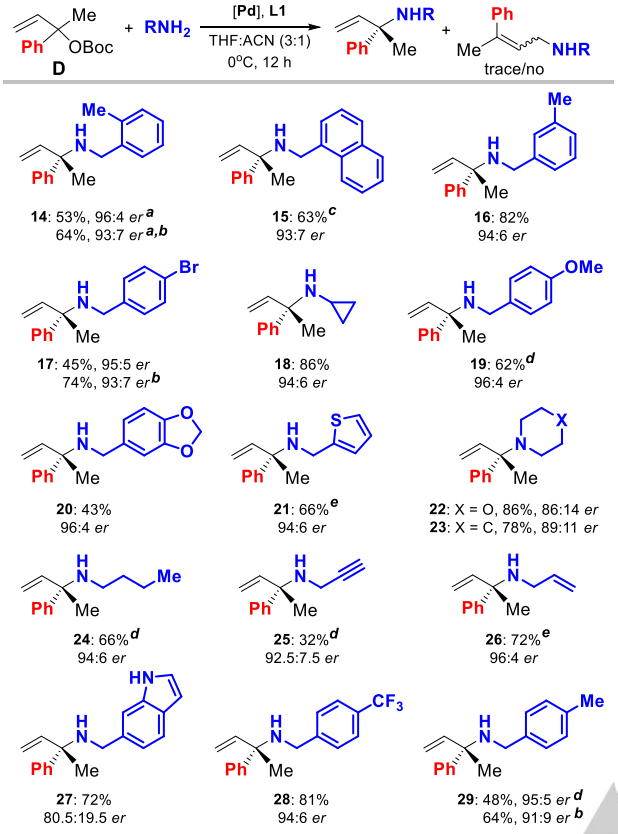

Figure 3. Scope in aliphatic amines: allylic precursor **D** (0.15 mmol), amine (0.17 mmol, 1.1 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (2 mol %), **L1** (10 mol %), THF/ACN (3:1; 0.35 mL), 0ºC, open to air, 12 h; isolated yields are reported and the *er* values were determined by UPC2. [a] 24 h. [b] CsF (3 equiv) was added, THF/ACN/H_2O (3:1:0.4). [c] Amine (1.5 equiv). [d] 36 h. [e] The *er* values were determined by using a chiral shift reagent (SI for details).

Encouraged by the asymmetric synthesis of various *N*-**alkyl** allyl amines (Figures 2 and 3), the preparation of α,α-disubstituted *N*-**aryl** allylic amines was then probed (Figure 4). The reaction of allylic precursor **D** and aniline gave product **30** with an *er* of 80:20 under the optimized conditions (Table 1, entry 17). By further optimization (see Table S2 in the SI) the *er* could be improved to 88:12 when the reaction was performed in THF and with a lower catalyst loading (1.25 mol% Pd precursor and 5 mol% **L1**). Subsequently, both the aniline and allylic precursor with either electron-donating (**31**, **34** and **35**) or withdrawing (**32** and **33**) aryl substituents were tested, and afforded the allylic amine products in good isolated yields and appreciable enantioselectivities. The use of *N*-methyl aniline, however, resulted in quantitative formation of the linear product.

The catalytic system could be easily performed on a 5 mmol scale which was exemplified by the successful isolation of 1.24 g (75% yield) of allylic amine **1** with high enantioselectivity (*er* 95:5). The synthetic potential of these allylic amines was demonstrated by further transformation of **1** into enantioenriched amide **36**, allylic nitrone **37**, asymmetric urea **38** and epoxide **39** via simple procedures (Figure 5) retaining the chiral integrity of the starting allylic amine. The α,α-disubstituted allylic amines can also be transformed into highly functionalized aziridines as reported previously.[23]

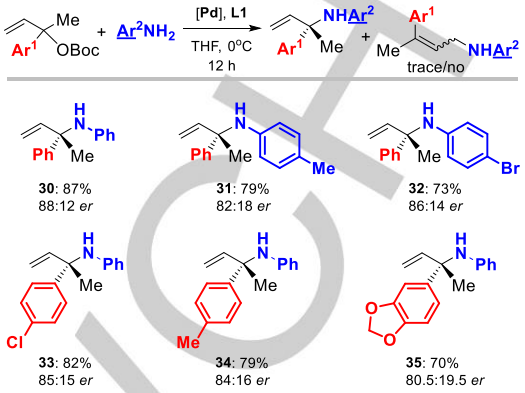

Figure 4. Scope in allylic precursors and anilines: allylic precursor (0.15 mmol), aniline reagent (0.23 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (1.25 mol %), **L1** (5 mol %), THF (0.2 mL), 0ºC, open to air, 12 h. Isolated yields are reported.

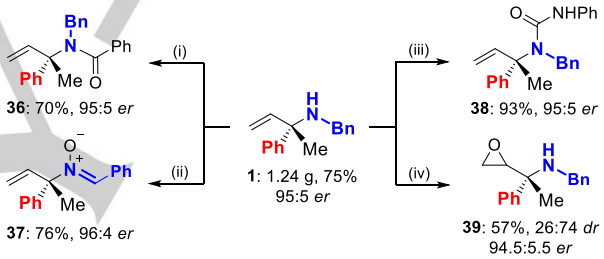

Figure 5. Various conversions of allylic amine **1**: (i) Benzoyl chloride (1.3 equiv), NEt_3 (5 equiv), CH_2Cl_2, rt, 50 min. (ii) *m*-CPBA (2.3 equiv), CH_2Cl_2, 0-rt, 2 h. (iii) Phenyl isocyanate (1.3 equiv), NEt_3 (10 equiv), CH_2Cl_2, rt, 10 min. (iv) TsOH (1.02 equiv), *m*-CPBA (1.2 equiv), CH_2Cl_2, 0-rt, 3 h; see SI for details.

In summary, chiral α,α-disubstituted allylic *N*-alkyl amines are important building blocks in organic synthesis and medicinal chemistry, but to date no general approach has been developed regarding their synthesis. The regio- and enantioselectivity of Pd-catalyzed allylic substitution toward α,α-disubstituted allylic *N*-alkyl amines has been a long-standing challenge. Our contribution represents a first, huge step forward in this area. Despite the fact that some substrate combinations deliver moderately high asymmetric induction levels and some limitations are pertinent to the allylic precursors, this new catalytic approach represents the most effective method reported to date. Our work here also highlights the key role of the steric modulation in the allylic substrate to prepare challenging chiral allylic amines via attractive palladium catalysis.

Acknowledgements

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A.C.) and the Chinese Research Council (CSC-2016-06200061) for support. We also thank Dr. Eva Raluy and Dr. Luca Buzzetti for help with UPC2 analyses. Eduardo C. Escudero-Adán and Dr. Eddy Martin are acknowledged for the X-ray analysis of **1**·HCl.

Keywords: Allylic amines • palladium • allylic substitution • enantioselectivity • regioselectivity

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[11] The use of a Me-protected linear carbonate analogue of cyclic carbonate **A** (Scheme 1) in this decarboxylative process resulted mainly in linear allylic amine formation pointing toward a privileged selectivity for branched product when using vinyl cyclic carbonate and aromatic amines. See for more details reference 10.

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[16] Allylic precursor **D** represents a linear carbonate and unlike the reactivity of cyclic carbonate **H**, no reaction is observed for **D** in the presence of 4 equiv of $BnNH_2$ or $BuNH_2$ at rt for 20 h.

[17] For more details see the SI and CCDC-1554683.

[18] J. E. Gómez, W. Guo, A. W. Kleij, *Org. Lett.* **2016**, *18*, 6042.

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Entry for the Table of Contents:

COMMUNICATION

Widen up: The first asymmetric synthesis of invaluable α,α-disubstituted *N*-alkyl allylic amines is reported using an allylic substitution approach. The catalytic method relies on Pd-catalysis, is user-friendly and can be accomplished under mild and additive-free conditions. The product scope for these challenging allylic amine scaffolds is the widest reported to date with *er* values of up to 98.5:1.5.

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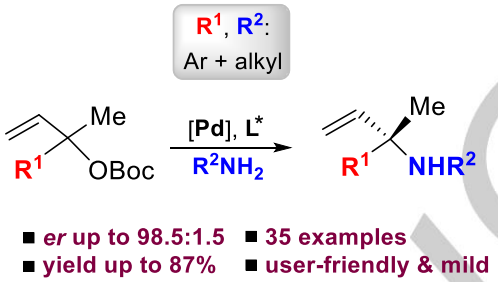

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