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Palladium-Catalyzed Three-Component Transformation of Homoallenols: A Regio- and Stereoselective Route to 1,5-Amino Alcohols

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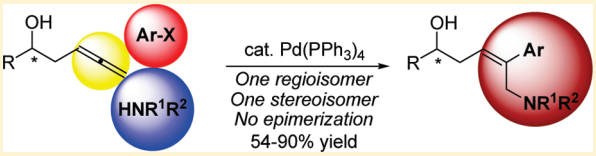
Supporting Information

ABSTRACT: A palladium-catalyzed three-component transformation of enantioenriched homoallenols with aryl halides and amines has been developed to selectively afford (*Z*)-configured 1,5-amino alcohols in good-to-excellent yields without any epimerization.



The high π-coordination ability of allenes toward transition metals, combined with the capacity of such complexes to undergo a wide range of transformations, has enabled the straightforward synthesis of structurally diverse molecules from simple allenes.[1] Although extensive efforts have been devoted to devise more selective and higher-yielding transformations, new developments in the functionalization of allenes remain the focus of many research groups. In particular, the metal-catalyzed intermolecular functionalization of allenes bearing a nucleophilic functionality (e.g., alcohols, amines) remains a challenging task due to the propensity of these substrates to undergo intramolecular cyclization[2] or fragmentation in the presence of a metal.[3] To date, only a few reports have succeeded in the selective intermolecular functionalization of allenes bearing a nucleophilic group.[4] In an important contribution to this field, Ma has reported the highly regio- and stereoselective synthesis of 1,2- and 1,4-amino alcohols through a palladium-catalyzed multicomponent reaction of 2,3-allenols.[5] During a recent study of the application of tridentate bis(oxazoline) ligands in Cr-catalyzed C−C bond forming processes[6] we discovered the first regio- and enantioselective synthesis of homoallenols **1**.[7] We envisioned that these would be useful substrates to investigate in a novel route for preparing enantioenriched 1,5-amino alcohols **2** (Scheme 1),[8] interesting building blocks for the synthesis of bioactive compounds, novel synthetic materials, and catalysts.[9]

We describe herein the successful implementation of this multicomponent functionalization strategy and, significantly, this represents the first general method for the preparation of enantioenriched 1,5-amino alcohols, which are difficult to access through single-step synthetic routes.[10]

Scheme 1. Palladium-Catalyzed Preparation of 2

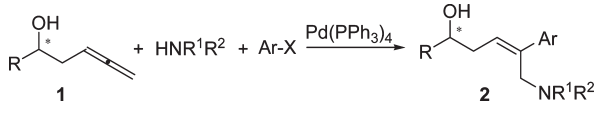
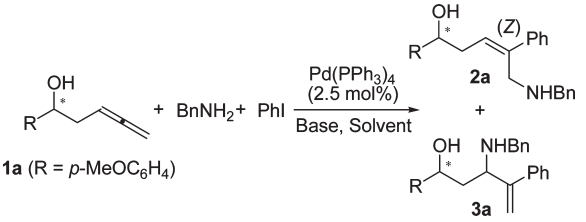


Table 1. Initial Screening Results[a]



entry	solvent	base	yield (%)	**2a**/**3a**[b]
1	Et_3N		65	71/29
2	DMF[c]	Et_3N (2 equiv)	n.r.	n.d.
3	CCl_4	Et_3N (2 equiv)	70	92/8
4	1,4-dioxane	Et_3N (2 equiv)	80	75/25
5	toluene	Et_3N (2 equiv)	76	71/29
6	CH_2Cl_2[d]	Et_3N (2 equiv)	75	100/0

[a] Reaction conditions: **1a** (1 equiv), PhI (1.25 equiv), $BnNH_2$ (1.5 equiv), $Pd(PPh_3)_4$ (2.5 mol %), reflux, 40 h. [b] Ratio determined by ^1H NMR spectroscopy of the crude. [c] Reaction performed at 70 °C. [d] 16 h reaction time.

Because of the lack of a method allowing for the straightforward preparation of racemic 1,5-amino alcohols, we first investigated the reaction of racemic homoallenol **1a** with benzylamine and iodobenzene as coupling partners (Table 1). Our initial

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Table 2. Scope of the Palladium-Catalyzed Synthesis of 2[a]

entry	R	R^1	R^2	ArX	yield (%)	product
1	*p*-$MeOC_6H_4$	Bn	H	PhI	75	**2a**
2	*p*-$MeOC_6H_4$	*n*-Bu	H	PhI	90	**2b**
3	*p*-$MeOC_6H_4$	*n*-Bu	*n*-Bu	PhI	70	**2c**
4	*p*-$MeOC_6H_4$	Bn	H	2-naphthylI	72	**2d**
5	*p*-$MeOC_6H_4$	Bn	H	*p*-MeC_6H_4I	70	**2e**
6	*p*-$MeOC_6H_4$	Bn	H	*m*-BrC_6H_4I	54	**2f**
7	*p*-$MeOC_6H_4$	Bn	H	*p*-$NO_2C_6H_4Br$	73	**2g**
8	*p*-ClC_6H_4	Bn	H	PhI	74	**2h**
9	*p*-ClC_6H_4	Bn	H	2-naphthylI	79	**2i**
10	*p*-ClC_6H_4	Bn	Bn	PhI	84	**2j**
11	$PhCH_2CH_2$	Bn	H	PhI	90	**2k**
12	$PhCH_2CH_2$	Bn	Bn	PhI	80	**2l**

[a] Reaction conditions: **1** (1 equiv), ArX (1.25 equiv), amine (1.5 equiv), Et_3N (2 equiv), $Pd(PPh_3)_4$ (2.5 mol %), CH_2Cl_2, reflux, 16 h.

attempts at changing solvent and additive yielded a mixture of isomeric products **2a** and **3a** (entries 1 and 3−5). We subsequently identified dichloromethane and 2 equiv of triethylamine as particularly effective for this reaction as, under these conditions, the desired compound **2a** was obtained in 75% yield as a pure diastereomer without any trace of regioisomer **3a** (entry 6).[11,12] Furthermore, cycloetherification of **1a** was not observed under these conditions.[13]

With these optimized catalytic reaction conditions in hand, we then explored the scope of this three-component transformation by reacting a range of homoallenols **1** with a focused selection of amines and aryl halides (Table 2). Regardless of the coupling partners, the desired products **2** were obtained as pure diastereomers in 54−90% yields without any trace of the 1,3-amino alcohols **3**. Both primary and secondary amines proved to be suitable nucleophiles for this transformation. With respect to aryl iodide substitution, para- and meta-substituents were tolerated, even the presence of a *m*-bromo substituent (entry 6). No products were obtained when ortho-substituted aryl iodides were employed as substrates. Apart from aryl iodides, only a highly electrophilic aryl bromide, *p*-nitrobromobenzene, turned out to be a suitable substrate for this transformation (entry 7).

We next focused our attention on the synthetic potential of this three-component transformation for creating chiral building blocks **2** from enantioenriched homoallenols **1** (Table 3). No epimerization at the stereogenic center was observed during the transformations and consequently, the desired 1,5-amino alcohols (*Z*)-**2** were obtained as optically enriched compounds from the corresponding homoallenols **1**.

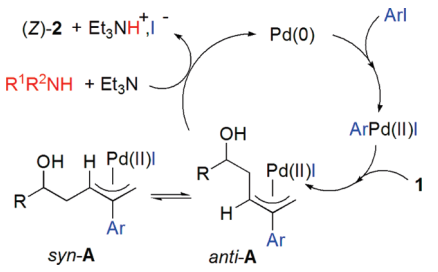
A proposed catalytic cycle helps to explain the regio- and stereochemical course of this transformation (Scheme 2). First, oxidative addition of the aryl iodide to palladium(0), followed by insertion of this species to allene **1** would afford the thermodynamically more stable η^3-allyl complex *anti*-**A**.[14] In this intermediate, the allene substituent ($RCH(OH)CH_2$) would be in the *anti*-position relative to the aryl group in order to minimize steric interactions, even if the presence in solution of *syn*-**A** cannot be ruled out at this stage. Then, *anti*-**A** would undergo a nucleophilic attack by the amine preferably at the terminal carbon for steric reasons to provide (*Z*)-**2** as the unique regio- and stereoisomer.[15]

Table 3. Synthesis of Chiral 1,5-Amino Alcohols 2[a]

entry	% ee **1**[b,c]	product	% ee **2**[c]	yield (%)
1	96	**2a**	96	73
2	96	**2d**	96	84
3	97	**2h**	97	79
4	97	**2i**	97	80
5	97	**2j**	97	86
6	95	**2k**	95	90

[a] Reaction conditions: **1** (1 equiv), ArX (1.25 equiv), amine (1.5 equiv), $Pd(PPh_3)_4$ (2.5 mol %), Et_3N (2 equiv), CH_2Cl_2, reflux, 16 h. [b] Optically enriched homoallenols **1** were synthesized following our procedure, see ref 7. [c] The ee value was determined by chiral HPLC.

Scheme 2. Proposed Catalytic Cycle



In summary, we have disclosed a regio- and stereoselective palladium-catalyzed three-component transformation allowing a simple access to optically enriched 1,5-amino alcohols **2** from readily available homoallenols **1**. This reaction possesses the ability to generate valuable chiral building blocks **2**, merging an allene, an amine, and an alcohol into the same molecule in an atom-economic fashion. We anticipate that this transformation will find many applications in different areas of organic chemistry.

EXPERIMENTAL SECTION

General Procedure for the Palladium-Catalyzed Synthesis of 2. A flame-dried Schlenk tube flushed with nitrogen was charged with homoallenol **1** (0.52 mmol), the corresponding electrophile (0.65 mmol), and amine (0.78 mmol). To this mixture was added Et_3N (1.04 mmol), anhydrous CH_2Cl_2 (2.5 mL), and $Pd(PPh_3)_4$ (13 μmol). The tube was allowed to reflux under nitrogen for the appropriate length of time. The solvent was removed in vacuo. The crude mixture was then purified by flash column chromatography on silica gel with pentane:EtOAc as the eluent to give the corresponding 1,5-amino alcohol **2**. Characterization data for **2a**: TLC: R_f 0.58 (EtOAc:pentane 3:2). $[\alpha]^{20}_D$ +34.0 (*c* 0.2, $CHCl_3$) for 96% ee (*R*). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.27 (m, 12H), 6.87 (d, J = 8.5 Hz, 2H), 5.93 (t, J = 8.5 Hz, 1H), 4.80 (app dd, J = 7.5, 3.8 Hz, 1H), 3.81 (s, 2H), 3.79 (s, 3H), 3.64 (d, J = 12.0 Hz, 1H), 3.56 (d, J = 12.0 Hz, 1H), 2.70−2.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6 (1C), 141.8 (1C), 140.0 (1C), 138.9 (1C), 137.5 (1C), 129.0 (1C), 128.5 (4C), 128.4 (2C), 127.2 (1C), 127.1 (1C), 126.7 (2C), 126.0 (2C), 113.6 (2C), 71.9 (1C), 55.2 (1C), 53.8 (1C), 47.1 (1C), 39.6 (1C). IR (neat): ν 3414, 2092, 1644, 1512, 1443 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{28}NO_2$ [M + H] 374.2120, found 374.2120. Enantiomeric excess has been determined by HPLC analysis, using an IA column (heptane/ethanol 90/10, 1.0 mL/min), t_r = 23.7 min for (*S*) and t_r = 25.4 min for (*R*).

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■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and compound characterization including NMR spectra and relevant HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The geometry of **2a** has been determined by NOE experiments, see the Supporting Information.

(12) It is worthwhile noting that under similar reaction conditions, functionalization of 2,3-allenols can selectively afford 1,2- or 1,4-amino alcohols depending on the substitution of 2,3-allenols. See: ref 5.

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(15) We have ruled out the potential importance of an intramolecular interaction between the hydroxyl group and palladium by carrying out the reaction using homoallenol **1a** protected as its *tert*-butyl dimethyl silyl ether and obtained silyl-protected (*Z*)-**2a** as the sole product.