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β-Regioselective intermolecular Heck arylation of *N,N*-disubstituted allylamines

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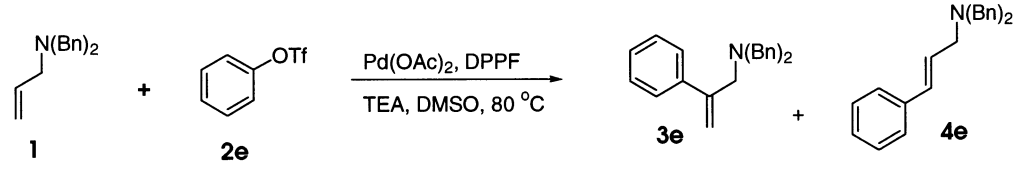
Abstract—β-Regioselectivity has been demonstrated for the Heck arylation of *N,N*-disubstituted allylamines. The scope and limitations of the reaction were demonstrated by the coupling of *N,N*-dibenzylallylamine with a variety of substituted aryl triflates. This methodology represents a straightforward approach for the efficient preparation of a variety of primary β-aryl allyl amines.

The palladium-catalyzed arylation and vinylation of olefins via the Heck reaction is a synthetically useful and convenient method for the preparation of substituted alkenes.[1] Substitution at the terminal position (γ position) of the olefin is usually favored when acrylate, acrylamide, acrylonitrile, styrene, or allyl alcohol are used as coupling partners. Mixtures of regioisomers are obtained when vinyl acetates, vinyl ethers, homoallylic alcohols, and simple alkenes are reacted. Complementary methodology was later developed by Cabri in which good β-selectivity was observed through the use of aryl triflates and various chelating bidentate phosphorus and nitrogen ligands.[2,3] Under those conditions, β-arylation occurred for allyl alcohol, *t*-butyl vinyl ether, and *N*-vinyl pyrrolidinone. Mixtures of β and γ-regioisomers were obtained in the case of styrene, homoallylic alcohol, and simple alkenes. Good β-regioselectivities have also been reported for couplings between allyl amides and aryl halides in both intermolecular[4] and intramolecular Heck reactions.[5] More recently, Hallberg reported the regioselective arylation of *N,N*-dimethylallylamine at the internal position.[6] The drawback of using *N,N*-dimethylallylamine is that it precludes the possibility of subsequent deprotection to the primary amine. To the best of our knowledge, intermolecular β-selective arylation of allyl amines that are substituted with groups amenable to deprotection has not yet been achieved. Herein, we report the intermolecular coupling of various substituted aryl triflates with *N,N*-dibenzylallylamine in moderate to good yields with excellent β-selectivity (Scheme 1).

For our initial studies, we examined the role of the base on regioselectivity. Heck couplings between phenyl triflate **2e** (1 equiv.) and *N,N*-dibenzylallylamine[7] **1** (1.75 equiv.) were performed using 4 mol% $Pd(OAc)_2$ and 6 mol% DPPF in DMSO at 80°C for 18 h using a variety of bases (Table 1). DPPF was chosen as ligand based on prior work reported by Cabri in which he used DPPF to achieve good β-selectivities in similar systems.[2] We were pleased to find that in our case DPPF similarly afforded excellent β-selectivities. The role of the base in Heck couplings is generally thought to be solely to scavenge the triflic acid that is formed during the reaction.[2] However, the results reported in Table 1 clearly demonstrate that the base does have a significant role in the determination of regioselectivity. While it is still unclear exactly what that role may be, steri-



Scheme 1.

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Table 1. Effect of base in the palladium-catalyzed arylation of *N*,*N*-dibenzylallylamine

Entry	Base	**3e**/**4e** branched/linear[a]	Assay yield[b] of **3** (%)
1	Triethylamine	13.6/1	52
2	DABCO	11.5/1	56
3	Diisopropylethylamine	5.7/1	47
4	Triisopropylamine	30/1	45
5	*N*,*N*-Diethylaniline	60/1	18
6	Di-*t*-Butylamine	1.5/1	20
7	2,2,6,6-Tetramethylpiperidine	3.5/1	50
8	Piperidine	–	0

[a] Based on HPLC assay[8] and ^{1}H NMR.
[b] Based on HPLC assay determined from an analytically pure sample of the final product.

cally crowded tertiary amines (entries 1–4) as well as amine bases that serve as poor nucleophiles (entry 5) gave the best selectivities. The bulky secondary amine 2,2,6,6-tetramethylpiperidine (entry 7) gave comparable yield but with lower selectivity while di-*t*-butylamine (entry 6) afforded poor yield and poor selectivity. Piperidine (entry 8) failed to yield product. Increasing the catalyst and ligand loading does not increase yield or selectivity.

The role of the ligand was examined in the next set of experiments in which the olefin **1** was coupled with **2e** using 3 mol% $Pd(OAc)_2$ and 6 mol% ligand (Table 2). DABCO was used as the base since it afforded a slightly superior yield compared to TEA. It has been previously reported that DPPF, DPPP, and neocuproine all react to give excellent β-selectivities for the arylation of a variety of allyl substrates with 1-naphthyl triflate.[2,3] In our case, DPPF gave the best yield and selectivity (Table 2, entry 1), followed by DPPP (entry 2). BINAP and neocuproine (entries 3 and 4) both showed poor selectivities and yields while DPPE did not give any product at all (entry 5). The monodentate ligand triphenylphosphine gave both poor yield and poor selectivity (entry 6).

The coupling of phenyl triflate with various *N*,*N*-substituted allylamines including *N*,*N*-dimethylallylamine, 1-[bis(*t*-butoxycarbonyl)amino]-2-propene,[9] *N*-TBDPS allylamine,[10] and the STABASE[11] adduct (3-tetramethyldisilylazacyclopentane-2-propene) was also investigated. Under the optimized conditions, only *N*,*N*-dimethylallylamine **5a** and 1-[bis(*t*-butoxycarbonyl)amino]-2-propene **5b** afforded product with a

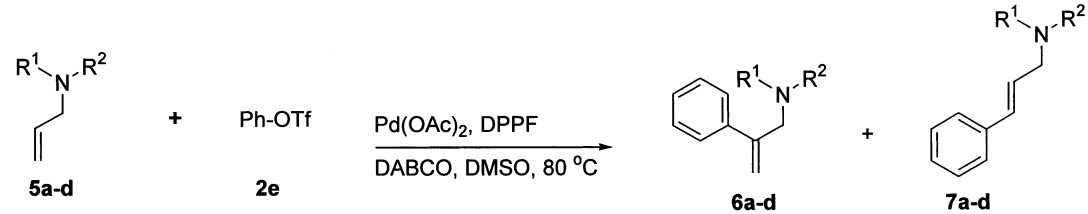
Table 2. Effect of ligand in the palladium-catalyzed arylation of *N*,*N*-dibenzylallylamine

Entry	Ligand	**3e**/**4e** branched/linear[a]	Assay yield[b] of **3** (%)
1	DPPF	11.5/1	56
2	DPPP	10.7/1	34
3	BINAP	1/2.1	12
4	Neocuproine	1/1.2	17
5	DPPE	–	0
6	PPh_3	1/1.7	9

[a] Based on HPLC assay and ^{1}H NMR.
[b] Based on HPLC assay determined from an analytically pure sample of the final product.

β/γ-selectivity of 11.4/1 and 1/1.8 and unoptimized yields of 56 and 28%, respectively (Scheme 2). Arylation using the silyl protected allylamines afforded a complex reaction mixture with little or no Heck product detected.

The scope and limitations of the regioselective Heck arylation of *N*,*N*-dibenzylallylamine was investigated with a variety of triflate partners under standard reaction conditions (Table 3). Sterically unhindered, stabilizing groups at the *ortho* position (entries 1–3) reacted to afford superior yields while sterically crowded *ortho*-substituted triflates (entries 7–9) gave poor yields. The electronic properties of the triflate has no apparent effect on the reaction since both electron-withdrawing (entries 2, 4, and 6) and donating (entry 3) groups at the *ortho* position reacted to afford β-substituted prod-

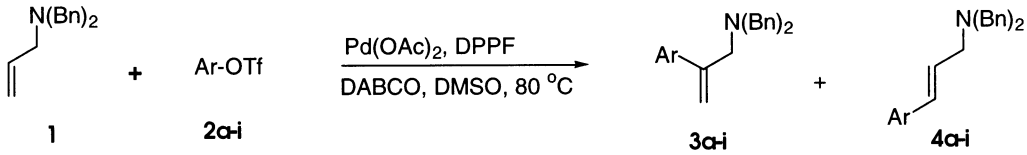


Scheme 2.

Table 3. Palladium-catalyzed arylation of olefin **1** with triflates **2a–i**

Entry	Ar-Triflate, Ar =	Assay yield[a] of **3** (%)	Isolated yield of **3**[12] (%)
1	1-Naphtyl (**a**)	80	74
2	2-Fluoro phenyl (**b**)	72	66
3	2-Methoxy phenyl (**c**)	70	68
4	4-Acetyl phenyl (**d**)	62	54
5	Phenyl (**e**)	56	51
6	4-Fluoro phenyl (**f**)	55	46
7	2-Cresol (**g**)	44	42
8	2-Trifluoromethyl phenyl (**h**)	27	–
9	2-Phenyl phenyl (**i**)	6	–

[a] Based on HPLC assay determined from an analytically pure sample of the final product.



Scheme 3.

ucts in good to excellent yields. Phenyl triflate (entry 5) gave 51% isolated yield of the β-substituted product. The γ-substituted product was not detected by ^{1}H NMR of the crude reaction mixture in any case except for entry 5 (Scheme 3).

Primary β-aryl allyl amines are known as biologically active enzyme inhibitors.[13] For example, 1-phenyl-1-(aminomethyl)ethene was reported to inhibit dopamine β-monooxygenase (DBM),[14] an enzyme which catalyzes the conversion of dopamine to norepinephrine in the central nervous system. Several syntheses of 1-phenyl-1-(aminomethyl)ethene have been reported previously, as well as several syntheses of aryl-substituted analogs.[15] However, almost all are cumbersome multi-step syntheses. β-Regioselective Heck arylation of *N*,*N*-dibenzylallylamine followed by cleavage[16] of the benzylic protecting group represents a straightforward approach for the efficient preparation of a variety of primary β-aryl allyl amines. In summary, we have identified conditions under which the palladium-catalyzed Heck arylation of *N*,*N*-disubstituted allylamines gives access to β-aryl allyl amines with excellent β-regioselectivity.

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12. **General procedure for arylation of *N*,*N*-dibenzylallylamine**: To a solution of $Pd(OAc)_2$ (16.9 mg, 0.075 mmol), DPPF (83.5 mg, 0.150 mmol), and DABCO (282 mg, 2.5 mmol) in DMSO (5 mL) purged with N_2, was sequentially charged with **2f** (612 mg, 2.5 mmol) and **1** (1.05 g, 4.43 mmol). The reaction mixture was aged at 80°C with stirring for 18 h and then water (50 mL) and EtOAc (50 mL) were added. The aqueous layer was separated and extracted with EtOAc (2×50 mL). The organic layers were combined, washed with brine (1×50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (2% EtOAc and 2% TEA in hexanes) of the resulting brown oil afforded **3f** (380 mg, 46%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.18 (12H, m), δ 6.99 (2H, t, $J=8.7$) δ 5.40 (1H, s), δ 5.35 (1H, s), δ 3.53 (4H, s), δ 3.42 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 145.3, 139.4, 136.1, 129.0, 128.5, 128.1, 127.0, 115.1, 114.7, 114.5, 58.4, 57.9. Anal. calcd: C, 82.95; H, 6.62, N, 4.15. $C_{23}H_{22}FN$ requires: C, 83.35; H, 6.69; N, 4.23.
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