Arylation

One-Pot Sequential N and C Arylations: An Efficient Methodology for the Synthesis of *trans* 4-*N*,*N*-Diaryl Aminostilbenes**

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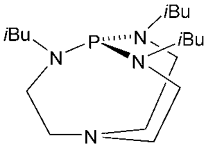
N,*N*-Diaryl aminostilbenes and *N*,*N*-diaryl aminostyrenes are versatile compounds that have found exciting applications in the field of photochemistry; most of these compounds are patented and they are widely used as electro-photographic photoconductors and photoreceptors.[1] Recent reports have demonstrated, for example, that these compounds can exhibit an amino-conjugation effect in their fluorescence enhancement spectra[2] and can act as ionophores for transition metals,[3] and have several other applications.[4] The synthetic routes to these compounds begin from aniline and the corresponding aryl halides through a three-step process involving an Ullmann/Vilsmeier/Wittig[5] reaction sequence or from triphenylamine through a Vilsmeir/Wittig/palladium-catalyzed arylation sequence.[6] Recently, the synthesis of *trans* 4-*N*,*N*-diaryl aminostilbenes from the corresponding halostilbenes or aminostilbenes by palladium-catalyzed amination reactions has also been reported.[2,3]

Palladium-catalyzed cross-coupling reactions, facilitated by a variety of ligands, are exceedingly powerful and reliable methods for C–C[7] and C–heteroatom[8] bond formations and have a vast number of applications in the pharmaceutical,[9] dye,[10] agriculture,[11] and polymer[12] industries. In recent years, our studies of commercially available proazaphosphatranes,[13] such as **1**, which were first synthesized by us, have shown them to be efficient ligands in palladium-catalyzed N arylations[14] and the Suzuki[15] and Stille[16] couplings. The substrates for these coupling reactions included aryl chlorides, which encompassed electron-poor, neutral, and electron-rich examples. Moreover, proazaphosphatranes can also function as strong non-ionic stoichiometric bases that facilitate a variety of useful organic transformations.[17]



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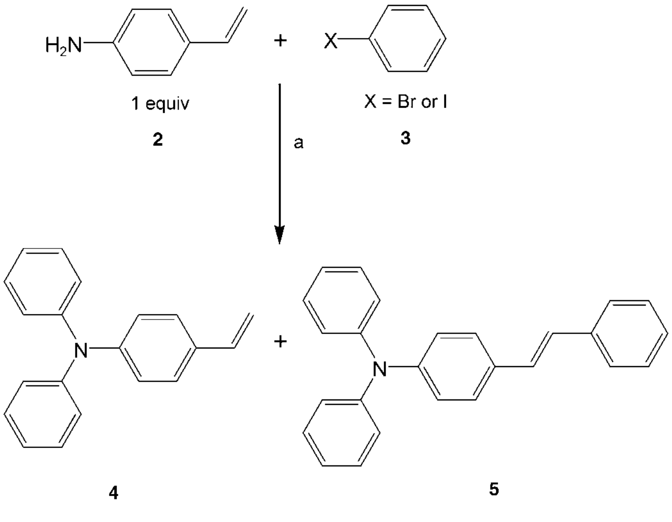
Herein, we report a one-pot synthesis of *trans* 4-*N*,*N*-diaryl aminostilbenes from commercially available starting materials using a double Buchwald–Hartwig amination/intermolecular Heck reaction sequence in the presence of [$Pd_2(dba)_3$]/**1** (dba = dibenzylideneacetone) as the catalytic system. Recently, transition-metal-catalyzed sequential C–C and C–heteroatom bond-forming reactions have attracted synthetic chemists because of their ability to facilitate the formation of more than one bond in a one-pot reaction. Reports of palladium-catalyzed amination/intramolecular cyclization reaction sequences for the synthesis of indole derivatives[18] illustrate the importance of such coupling reactions. A one-pot two-catalyst synthesis of 1,3-diphenylindazoles using a combination of copper-catalyzed N-arylation and palladium-catalyzed C-arylation reactions has also been reported.[19] To the best of our knowledge, a one-pot double amination/intermolecular Heck reaction sequence has not been described to date. Herein, we present the preliminary results of such a one-pot protocol.



Scheme 1. a) [$Pd_2(dba)_3$] (2 mol%), **1** (4 mol%), NaO*t*Bu (3.5 equiv), aryl halide (3.2 equiv), dry toluene (10 mL), under argon atmosphere.

Our studies commenced with the coupling of 4-aminostyrene with bromobenzene under the conditions given in Scheme 1. Optimization studies were carried out (Table 1), and it was initially found that when the reaction was carried out at 60 °C with ligand **1** over 3 h (entry 1), the only coupling observed was a double amination (product **4**); the Heck reaction required a minimum of 110 °C for the protocol to be efficient (entry 3). When iodobenzene was used instead, the Heck reaction occurred at 100 °C (entries 7 and 8) but faster conversion was realized at 110 °C (entry 9). In addition, other phosphines, such as davephos (2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl), *t*Bu_3P, and *rac*-binap (2,2′-

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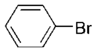
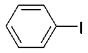
Table 1: Optimization of the one-pot double amination/intermolecular Heck reaction.

Entry	Aryl halide	Ligand	t [h]	T [°C]	Yield [%][a]		Total yield [%]
					4	**5**	**4**+**5**
1		**1**	3	60	90	0	90
2			12	100	92	2	94
3			16	110	9	83	92
4		davephos	3	60	53	0	53
5			16	110	69	14	83
6		*rac*-binap	16	110	56	34	90
7		**1**	12	100	32	66	98
8			24	100	0	94 (78)[b]	94
9			16	110	0	93	93
10		tBu$_3$P	16	110	74	11	85
11		*rac*-binap	16	110	0	56	56
12		davephos	16	110	27	61	88

[a] Yield of isolated product. [b] Reported yield for a two-step, two-pot synthesis.[2]

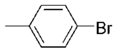
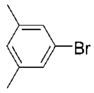
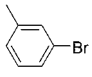
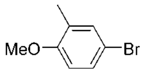
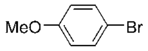
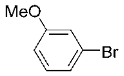
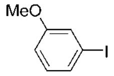
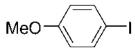
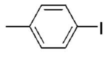
bis(diphenylphosphino)-1,1′-binapthyl), were found to be inefficient ligands (entries 4–6 and 10–12).

Next, we examined the coupling of a variety of aryl bromides and iodides with 4-aminostyrene to test the generality of this methodology (Table 2). The major products formed were *trans* *N*,*N*-diaryl aminostilbenes **5**, except when 4-bromoanisole and 3-bromoanisole were the substrates (entries 5 and 6, respectively). The yields of **5** from 4-bromotoluene and 4-iodotoluene as the substrates (entries 1 and 9, respectively) were similar to those reported previously,[20] whereas the yields of **5** from 4-bromoanisole and 4-iodoanisole were poor (entries 5 and 8). On the other hand, the yields of **5** from 4-bromotoluene and 4-iodotoluene (entries 1 and 9) were superior to the overall yield (55%) from a three-step procedure involving an Ullmann/Vilsmeier/Wittig reaction series.[20,21] All other products derived from this reaction series have not been previously reported (entries 2–4, 6 and 7).

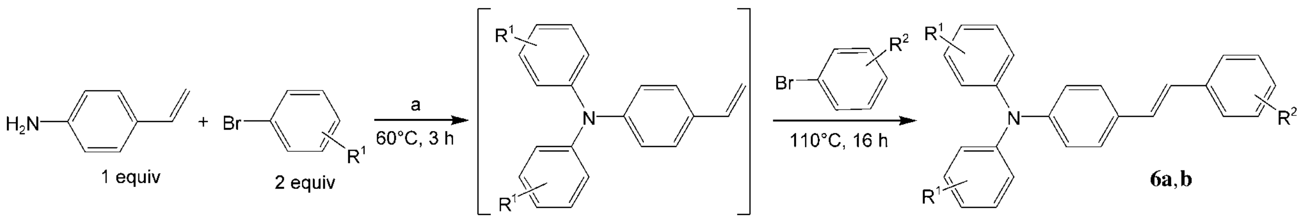
It is evident from the results of optimization experiments given in Table 1 that the reaction pathway to **5** is a double amination followed by an intermolecular Heck reaction. As the amination reactions were completed within 3 h at 60 °C and the Heck reactions required an elevated temperature and a longer reaction time, we were able to utilize this difference in coupling activity for the one-pot synthesis of **5** with two identical aryl groups at the nitrogen atom and a different one at the opposite terminus of **5** (Scheme 2). The first step of this one-pot procedure afforded the bisamination product in three hours, as monitored by TLC. The addition of 4-bromotoluene (1.2 equiv) in the second step afforded **6a** in very good yield. Reaction of 4-aminostyrene with 4-bromoanisole and bromobenzene under the same conditions gave the analogous product **6b** in moderate yield (Scheme 2). Our yield of **6a** (86%) is comparable to that reported in a patented procedure (89%) involving the single-step reaction of 4-methyldiethylbenzylphosphonate with 4-*N*,*N*-diphenylaminobenzaldehyde.[22a] However, our yield of **6a** is substantially better than the yield achieved through a Wittig reaction of 4-methylbenzyltriphenylphosphonium chloride with the aforementioned aldehyde (72%)[22a] and the overall yield (46%) of a previously reported three-step synthesis.[22bc] Although **6b** has been reported previously, no yield was given.[1]

In a similar manner, unsymmetrically *N*-substituted diaryl aminostilbenes **7a,b** were synthesized in very good yields by using aryl iodides instead of aryl bromides

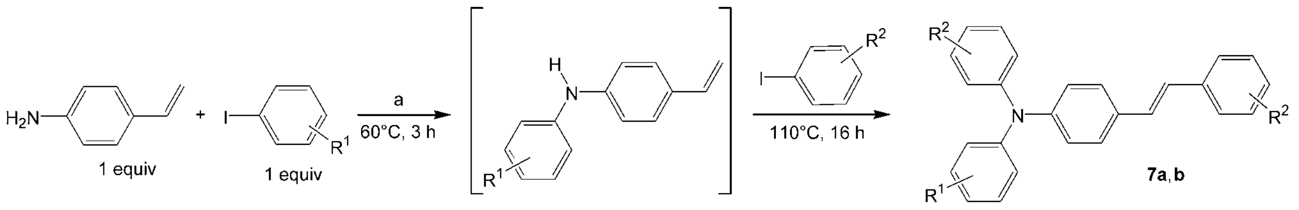
Table 2: One-pot double amination/intermolecular Heck reactions of 4-aminostyrene with aryl bromides and aryl iodides.

Entry	Aryl halide	Yield [%][a]		Total yield [%]
		4	**5**	**4**+**5**
1		11	84	95
2		37	61	98
3		28	60	88
4		27	59	86
5		47	34	81
6		60	34	94
7		32	63	95
8		0	41	41
9		0	87 (83%)[b]	87

[a] Yield of isolated product. Reaction conditions: [Pd$_2$(dba)$_3$] (2 mol%), **1** (4 mol%), NaOtBu (3.5 equiv), aryl halides (3.2 equiv), dry toluene (10 mL), 110 °C, 16 h, under argon atmosphere. [b] Reported yield.[20]



Scheme 2. a) [Pd$_2$(dba)$_3$] (2 mol%), **1** (4 mol%), NaOtBu (3.5 equiv), dry toluene (10 mL), in an argon atmosphere. **6a**, R^1 = H, R^2 = CH$_3$ (86%); **6b**, R^1 = 4-OMe, R^2 = H (60%).



Scheme 3. a) $[Pd_2(dba)_3]$ (2 mol%), **1** (4 mol%), NaO*t*Bu (3.5 equiv), dry toluene (10 mL), in an argon atmosphere. **7a**, $R^1 = CH_3$, $R^2 = H$ (78%); **7b**, $R^1 = 4\text{-OMe}$, $R^2 = H$ (79%).

(Scheme 3). Our yield of 78% for **7a** is lower than that of a previously reported synthesis involving the reaction of 4-(*N*-(4-methylphenyl)-*N*-phenylamino)benzaldehyde and diethylbenzylphosphonate (91%).[1] It should be noted that this higher yield was achieved in a single reaction involving two reactants, one of which required prior synthesis. When this requirement is taken into consideration, the overall yield is 50%[21] compared with our yield of 78% from a one-pot procedure. Although **7b** has been reported previously, no yield was given.[1]

In summary, we have developed a novel one-pot methodology for the synthesis of *trans* 4-*N*,*N*-diaryl aminostilbenes **5**, which hitherto have always been synthesized in multipot processes. It is also of note that: 1) the same catalyst system is used for both the amination and the intermolecular Heck coupling in a loading that is quite low (2 mol% of $[Pd_2(dba)_3]$ and 4 mol% of the ligand); 2) ligand **1** is superior to others in our protocol and is commercially available; 3) selective coupling of aryl halides with the nitrogen atom and the double bond of the styrenyl substrate can be achieved in a one-pot reaction by merely adding aryl halides sequentially at different temperatures. This strategy has significant potential for the design and synthesis of many complex molecules and for combinatorial libraries in which moieties with both C–N and C–C bonds are present; 4) higher overall yields than those reported previously have been achieved; 5) the reduction in the number of steps in such syntheses permit these types of transformations to be potentially more economical and environmentally friendly. Studies are under way with heteroaryl halides and additional aryl halides (including chlorides) as reagents in the methodology reported herein and will be reported in due course.

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