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Palladium-Catalyzed Three Component Coupling on Solid Support

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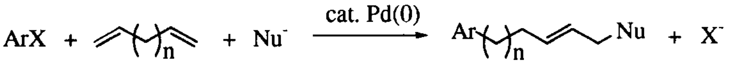
Abstract: Three component coupling of aryl halides, dienes and amines catalyzed by palladium, an efficient method of making aryl-substituted allylic amines, was successfully adapted to solid-phase synthesis. Amines were chosen to attach to a solid support, and reacted with a variety of aryl halides and dienes to give coupled products in good results.

Solid-phase synthesis of small molecules has been an important component of combinatorial chemistry in drug discovery.[2] The need of developing new synthetic methodologies on solid support (especially for C-C bond formation) has become urgent. Palladium-mediated reactions on solid support have attracted much attention recently. Several different types of reactions such as Heck,[3] Suzuki,[3b,4] and Stille reactions[5] have been reported. One of our interests is to investigate the methodology of more than one carbon-carbon or carbon-heteroatom bond formation in one step solid-phase synthesis. We have reported palladium-catalyzed solid-phase synthesis of heterocyclic compounds.[6] We herein describe our recent investigation on palladium-catalyzed three component coupling of aryl halides, dienes and resin-linked amines.

A palladium-catalyzed three component coupling reaction in solution phase has been reported (eq. 1).[7] It rapidly increases molecular complexity in a single step. It is an ideal type of reaction for making combinatorial libraries. The great potential of diversifying product structure is apparently due to the choices of each component.



(1)

In most reported palladium-catalyzed solid-phase reactions,[3-6] aryl halides if involved were immobilized. We chose amines as nucleophiles to attach to the solid support in the three component coupling process. The advantage over immobilizing aryl halides is that any possible by-products formed from aryl halides such as Heck products stay in solution and can simply be washed away. Therefore, the reaction conditions for the coupling of Rink resin attached amines with dienes and aryl halides (eq. 2) were thoroughly investigated.

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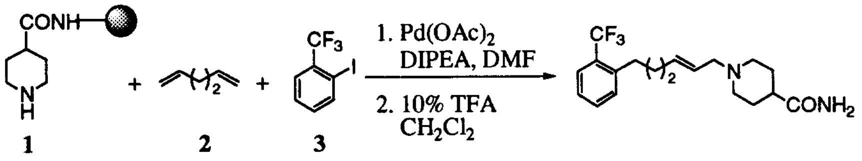
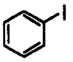
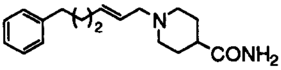
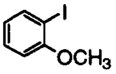
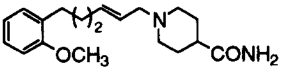
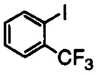
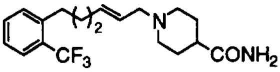
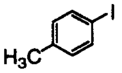
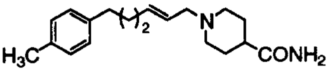
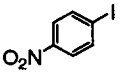
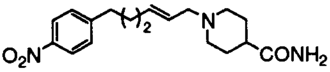
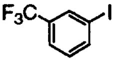
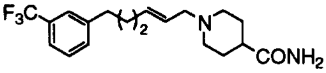
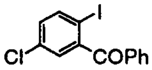
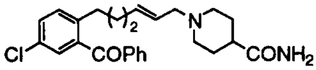
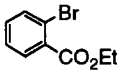
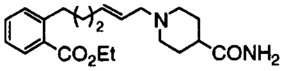
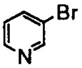
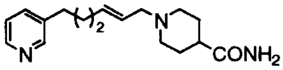
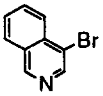
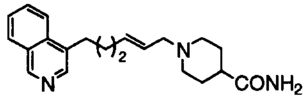
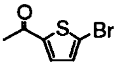
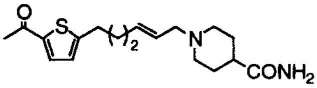


(2)

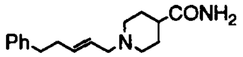
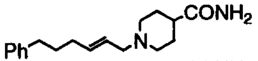
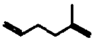
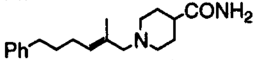
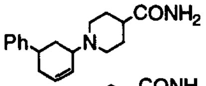
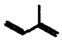
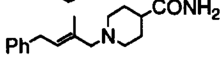
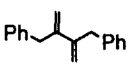
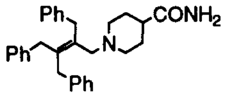
With optimized reaction conditions,[8] we demonstrated the diversity of structures formed by this three component coupling process. We first tested a variety of aryl halides. The results shown in Table 1 indicated that all the functionalized and unfunctionalized phenyl iodides or bromides provided good yields of the products regardless of the position of the functional group on the benzene ring; further, the electronic effect was not significant. We also examined several heterocyclic aromatic halides, which afforded good results.

Table 1. Palladium-Catalyzed Coupling of Solid Supported Piperidine, 1,5-Hexadiene and Aryl Halides[8]

entry	aryl halide	product	yield (%)	purity (%)
1			84	68
2			82	73
3			95	83
4			86	86
5			79	72
6			90	70
7			76	82
8			92	85
9			81	73
10			86	85
11			70	53

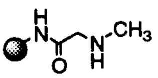
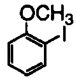
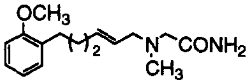
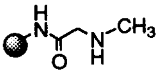
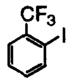
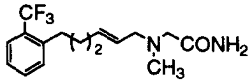
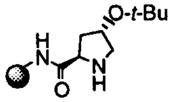
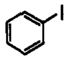
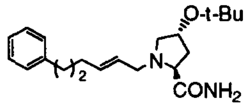
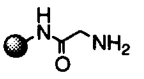
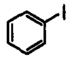
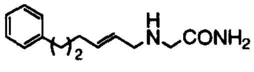
The dienes employed in the three component coupling could be nonconjugated or conjugated, acyclic or cyclic, and linear or substituted. Typical examples are shown in Table 2. Coupled with iodobenzene and solid supported piperidine **1**, the dienes tested here afforded very good results. For unsymmetrical dienes (entries 3 and 5), the phenyl group added to the less hindered C-C double bond of the diene.

Table 2. Palladium-Catalyzed Coupling of Solid Supported Piperidine, Iodobenzene and Dienes

entry	diene	product	yield (%)	purity (%)
1			75	75
2			78	68
3			85	77
4			91	85
5			78	76
6			90	92

Finally, we examined a few amino acids, which were attached to Rink resin as the nucleophiles. From these results and the observations summarized in Table 3, one can see that secondary amines as nucleophiles generally worked very well, while the one primary amine examined failed to provide the desired product (entry 4).

Table 3. Palladium-Catalyzed Coupling of Solid Supported Amines, 1,5-Hexadiene and Aryl Halides

entry	amine on resin	aryl iodide	product	yield (%)	purity (%)
1				87	69
2				84	68
3				75	52
4				–	–[a]

[a] HPLC analysis indicated that several products were formed.

In conclusion, we have shown that palladium-catalyzed three component coupling reaction proceeds quite well on solid support. It provided an efficient method for library syntheses of aryl-substituted allylic amines that may contain a variety of functional groups. Therefore, it has great potential to be used in the area of combinatorial chemistry and drug discovery.

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References and Notes

1. Current address: Shionogi BioResearch Corp., 45 Hartwell Ave., Lexington, MA 02173.
2. (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527. (c) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17.
3. (a) Berteina, S.; Wendeborn, S.; Brill, W. K.-D.; De Mesmaeker, A. *Synlett* **1998**, 676. (b) Ruhland, Beatrice; Bombrun, Agnes; Gallop, Mark A. *J. Org. Chem.* **1997**, *62*, 7820. (c) Hiroshige, M.; Hauske, J. R.; Zhou, P. *Tetrahedron Lett.* **1995**, *36*, 4567.
4. (a) Lorsbach, B. A.; Bagdanoff, J. T.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 2244. (b) Yoo, S.-E.; Seo, J.-S.; Yi, K.-Y.; Gong, Y.-D. *Tetrahedron Lett.* **1997**, *38*, 1203. (a) Han, Y.; Walker, S. D.; Young, R. N. *Tetrahedron Lett.* **1996**, *37*, 2703.
5. (a) Chamoin, S.; Houldsworth, S.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4175. (b) Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306. (c) Sucholeiki, I.; Forman, F. W. *J. Org. Chem.* **1995**, *60*, 523.
6. Wang, Y.; Huang, T.-N. *Tetrahedron Lett.* **1998**, *39*, 9605.
7. (a) Larock, R. C.; Wang, Y.; Lu, Y.; Russell, C. A. *J. Org. Chem.* **1994**, *59*, 8107. (b) Larock, R. C.; Lu, Y.; Bain, A. C.; Russell, C. A. *J. Org. Chem.* **1991**, *56*, 4589.
8. Typical Procedure: To a mixture of 206 mg of Rink resin bound piperidine **1** (0.73 mmol/g) and 2 mL of DMF in a pressure tube was added 3.4 mg (0.015 mmol) of $Pd(OAc)_2$, 13 mg (0.3 mmol) of LiCl, 0.28 mL (1.5 mmol) of DIPEA, 62 mg (0.3 mmol) of iodobenzene and 125 mg (1.5 mmol) of 1,5-hexadiene respectively. Sealed with a Teflon cap, the tube was shaken at 100 °C for 2 days. After cooling to rt, the resin was filtered and washed with DMF, CH_2Cl_2 and MeOH three times. The dried resin was treated with 2 mL of 10% TFA in CH_2Cl_2 for 1 hour, then filtered and washed with CH_2Cl_2. The filtrate was evaporated under reduced pressure to give the product in 84% yield with 68% purity (Table 1, entry 1). The molecular weight (M+H: 287) was confirmed by LC-MS spectroscopy. ^{1}H NMR (DMSO-d_6) δ 1.71 (quintet, J = 7.8 Hz, 2 H), 1.77 (br m, 2 H), 1.93 (br m, 2 H), 2.11 (q, J = 6.8 Hz, 2 H), 2.39 (br m, 1 H), 2.61 (t, J = 7.8 Hz, 2 H), 2.85 (br m, 2 H), 3.40 (br m, 2 H), 3.63 (d, J = 6.8 Hz, 2 H), 5.53 (dt, J = 15.6, 6.8 Hz, 1 H), 5.97 (dt, J = 15.6, 6.8 Hz, 1 H), 7.15-7.29 (m, 5 H).