Radical and Palladium-Mediated Cyclizations of *Ortho*-Iodo Benzyl Enamines: Application to Solid Phase Synthesis.

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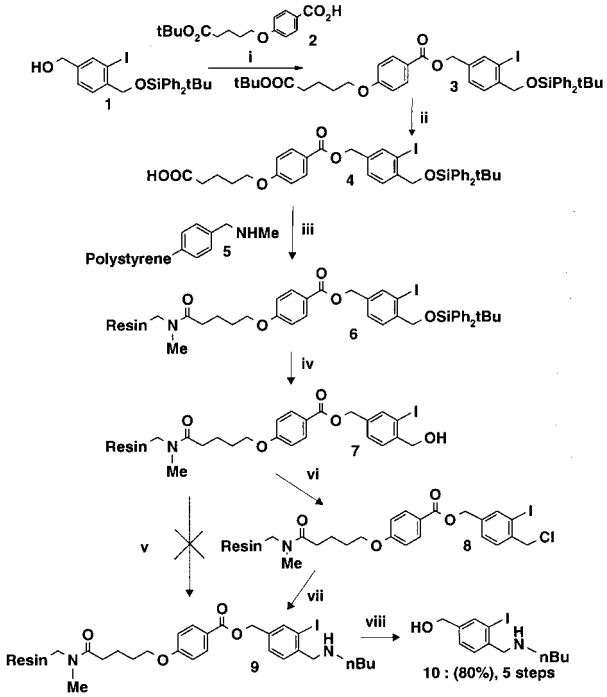
Abstract: *Ortho*-iodo benzyl enamines bound to polystyrene were efficiently cyclized under radical and Pd-mediated reaction conditions.

In the preceding paper,[1] we reported a scope and limitation study of radical and palladium-mediated cyclizations of *ortho*-iodo benzyl enamines and enol ethers performed in solution. Standard reaction conditions were identified, which could be translated to solid support synthesis. Palladium-mediated and radical cyclizations are complementary processes and would be very useful in combinatorial chemistry.[2,3] We describe here the successful application of these methods to aryl iodides bound to polystyrene.[4]

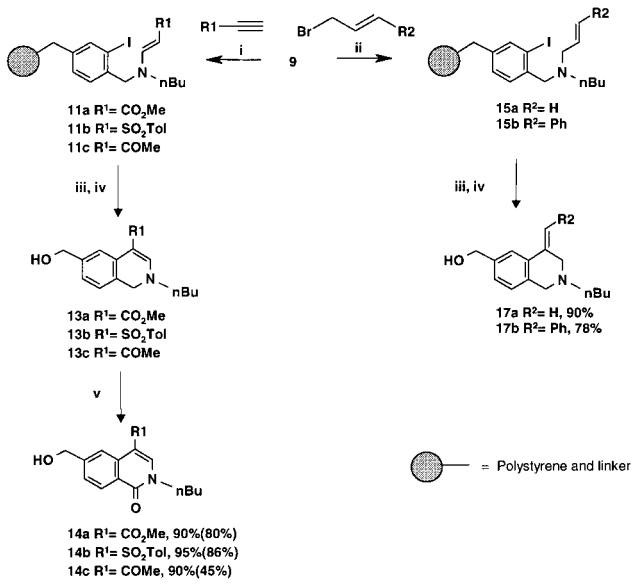
For the attachment of the aryliodide moiety to polystyrene we have used a base-labile linker **2**[1,3c] which was coupled with **1** (Scheme 1). After removal of the *tert*-butyl ester group, the carboxylic acid **4** was connected to the resin **5** using the corresponding N-hydroxybenzotriazole activated ester. For each chemical transformation, we investigated different reaction conditions on solid support. A cleavage by basic transesterification using MeONa in a mixture of MeOH/dioxane was realized after each step. The isolated yield of products cleaved from the resin were, in all cases, superior to 80%.



Scheme 1 i) 1 eq. **2**, 1.1 eq. $Me_2C=C(NMe_2)Cl$ (chlorenamine), CH_2Cl_2, RT, 3h; then 1 eq. **1**, 1.5 eq. NEt_3, 10 eq. pyridine, 0.2 eq. DMAP, CH_2Cl_2, RT, 21h, 89%; ii) CF_3CO_2H / CH_2Cl_2 (5/95), RT, 15h, 99%; iii) 4 eq. **4**, 4.4 eq. NEt_3, 4.4 eq. O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyl uronium tetrafluoroborate, 2 eq. N-hydroxybenzotriazole, dioxane, RT, 5h; then 1 eq. resin **5**, 10 eq. NEt_3, 1 eq. DMAP, dioxane, RT, 60h; iv) 8 eq. nBu_4NF, 8 eq. AcOH, dioxane, RT, 18h; v) 5 eq. CBr_4, 4.8 eq. Ph_3P, dioxane, RT, 3.5h; then 10 eq. $nBuNH_2$, RT, 42h; vi) 3 eq. $Me_2C=C(NMe_2)Cl$, CH_2Cl_2, RT, 5h; vii) 10 eq. $nBuNH_2$, 2 eq. nBu_4NBr, 3 eq. NEt_3, RT, 96h; viii) 6 eq. MeONa, MeOH/dioxane (1/4), RT, 24h.

The silyl protecting group was easily removed by use of tetrabutyl ammonium fluoride in the presence of acetic acid. The conversion of the benzylic alcohol **7** into the corresponding bromide using carbon tetrabromide and triphenyl phosphine was not efficient on solid support (**V**, Scheme 1), probably due to the insolubility of the phosphonium intermediate. On the contrary, the use of chlorenamine[5] followed by substitution with $nBuNH_2$ in the presence of nBu_4NBr, led to the desired core structure **9** in high yield.

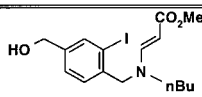
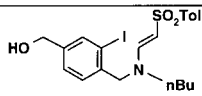
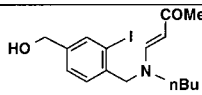
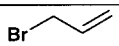
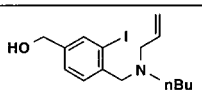
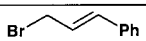
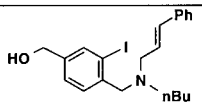
Different enamines or allyl amines were synthesized by reaction of the solid phase-bound amine **9** with Michael acceptors (C≡C) or allylbromide derivatives in good yields (Scheme 2). The intermediates before cyclization were cleaved from the resin by treatment with MeONa and isolated in very high overall yield (Table 1).



Scheme 2 i) 4 eq. R^1-≡-H, CH_2Cl_2, RT, 24h. ii) 4 eq. Br-CH_2-CH=CH-R^2, 2 eq. Schwesinger base[6], dioxane, RT, 70 h. iii) 0.2 eq. $Pd(OAc)_2$, 0.4 eq. Ph_3P, 2 eq. nBu_4NCl, 4 eq. K_2CO_3, DMA(0.05M), 100°C, 24h. iv) 6 eq. MeONa, MeOH/dioxane (1/4), RT, 24h. v) O_2, dichloroethane, RT, 24h.

Our optimized conditions[1] for palladium-mediated reactions[7] were successfully applied to resins **15a,b** (Scheme 2) to give the 6-*exo* cyclized products **17a,b,** and to substrates **11a-c** leading to the 6-*endo* cyclized products **13a-c**. The latter underwent slow air oxidation to isoquinolones **14a-c** (Scheme 2). The transformation of **13a-c** into **14a-c** was followed by ^1H NMR spectroscopy. Practically, a stream of oxygen was bubbled into a dichloroethane solution of the cyclized products **13a-c** for 24h at room temperature to perform a complete conversion into the corresponding isoquinolones. Almost pure samples of **13a-c**

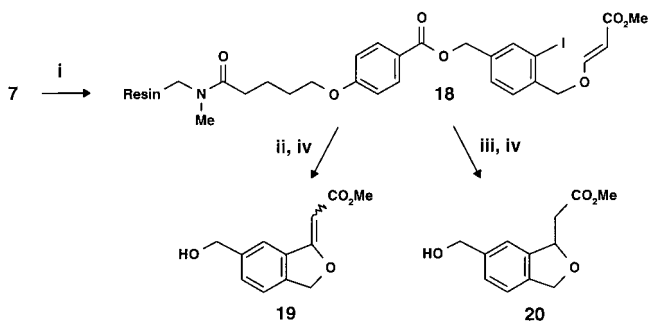
Table 1: Cyclization precursors isolated by cleavage from the resin

Entry	Reagents	Products	Yields [a] [%]
1	H-≡-CO_2Me		**12a**: 95 (71)
2	H-≡-SO_2PhMe_p		**12b**: 95 (86)
3	H-≡-COMe		**12c**:100 (92)
4			**16a**: 90 (64)
5			**16b**: 90 (56)

a) Yields were determined by ^{1}H NMR of the crude reaction mixture. In parentheses: yields obtained after purification by flash chromatography.

could be isolated and characterized by ^{1}H NMR immediately after cleavage from the resin.

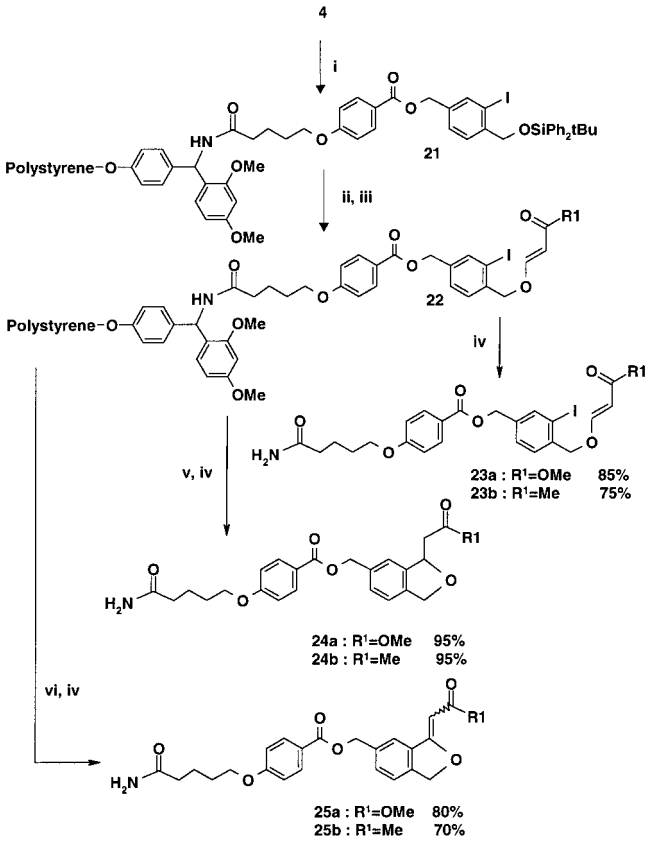
These conditions were applied to the corresponding vinyl ether **18** (Scheme 3). The cyclization precursor was synthesized on solid support from resin **7** by reaction with methyl propiolate activated by N-methylmorpholine[8] (Scheme 3). The conversion was complete for both processes, as demonstrated by cleavage from the resin. Nevertheless, the cyclized compounds **19** and **20** could not be isolated in satisfactory yield (30-40%). This resulted partially from a decomposition of the final product during the treatment of the resin with sodium methylate. This was confirmed by submitting purified **19** and **20** to standard cleavage conditions. Only 30-50% of **19** and **20** were recovered. Therefore, the cyclization of enol ethers was investigated with the acid labile Rink linker (Scheme 4).



Scheme 3 i) 6 eq. methyl propiolate, 6 eq. N-methylmorpholine, dioxane (0.1M), RT 48h. ii) 0.3 eq. $Pd(OAc)_2$, 0.6 eq. Ph_3P, 2 eq. nBu_4NCl, 4 eq. K_2CO_3, DMA (0.05M), 100°C, 27h, 30-40%. iii) 3 eq. nBu_3SnH, 0.6 eq. AIBN, benzene (0.05M), reflux, 48h, 30-40%. iv) 6 eq. MeONa, MeOH/dioxane (1/4) (0.25M), RT, 24h.

The iodide **4** was connected to the commercially available Rink resin, followed by cleavage of the *t*$BuPh_2Si$ group with nBu_4NF in the presence of AcOH. The reaction with electron-poor acetylenes and N-methylmorpholine led to the corresponding enol ethers **22** in high overall yield.

Radical[9] and Pd-mediated[7] cyclization reaction conditions were successfully applied to Rink resin **22a,b**. After acid cleavage with CF_3COOH, the desired products **24a**,**b** and **25a**,**b** were obtained in almost quantitative yield (Scheme 4).

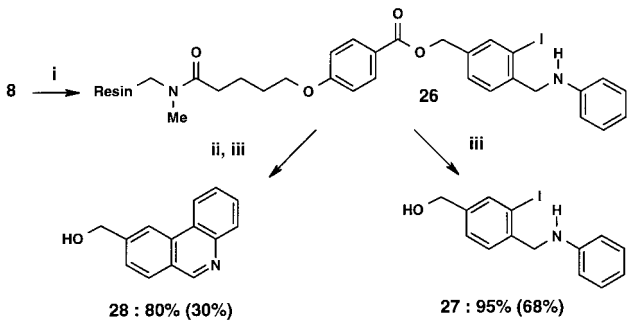


Scheme 4 i) 4 eq. **4**, 4.4 eq. NEt_3, 4.4 eq. O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uroniumtetrafluoroborate, 2 eq. N-hydroxy benzotriazole, dioxane, RT, 5h; then 1 eq. Rink resin, 10 eq. NEt_3, 1 eq. DMAP, dioxane, RT, 60h. ii) 8 eq. nBu_4NF, 8 eq. AcOH, dioxane, RT, 18h. iii) 6 eq. R^1CO-≡-H, 6 eq. N-methylmorpholine, dioxane (0.05M), RT 24h. iv) TFA/CH_2Cl_2 (1/4), RT. v) 3 eq. nBu_3SnH, 0.6 eq. AIBN, benzene (0.05M), reflux, 48h. vi) 0.3 eq. $Pd(OAc)_2$, 0.6 eq. PPh_3, 2 eq. nBu_4NCl, 4 eq. K_2CO_3, DMA (0.05M), 100°C, 27h.

Radical cyclizations can be extended to *ortho*-iodo benzyl anilides (Scheme 5). The substrate for cyclization was obtained in very high yield by substitution of the solid phase-bound benzyl chloride **8** with an excess of aniline in the presence of nBu_4NI and diisopropylethylamine. Complete conversion of the iodide into the cyclized product **28** was reached by sequential treatment with nBu_3SnH and a large excess of AIBN (Table 2). Isobutyronitrile radicals were required for the rearomatization of the cyclized radical intermediate by abstraction of the β hydrogen atom.[10]

It is noteworthy that efficient radical cyclization could be obtained, even on an aromatic ring, without interference of the polystyrene skeleton. Benzylic hydrogen atoms of polystyrene could have reduced the incipient phenyl radical prior to its cyclization on the N-phenyl ring which involves the disruption of aromaticity in the transition state.[10]

In conclusion, we have demonstrated that *ortho*-iodo benzyl alcohols bound to polystyrene can be converted in very high overall yield into the corresponding enol ethers and enamines. These intermediates can be efficiently cyclized by radical initiation and by palladium catalysis.



Scheme 5 i) 10 eq. aniline, 3 eq. diisopropylethylamine, 2 eq. nBu_4NI, dioxane (0.05M), 100°C, 36h; ii) nBu_3SnH, AIBN, benzene (0.05M), reflux; iii) 6 eq. MeONa, MeOH/dioxane (1/4) (0.25M), RT, 24h.

Table 2: Reaction conditions for radical cyclization of 26

Entry	Conditions **ii** (Scheme 5)	**27** [a)][%]	**28** [a)][%]
1	3.6 eq. nBu_3SnH (6 ×1.1 eq) 3 eq. AIBN (6×0.5 eq)	74	26
2	7.2 eq. nBu_3SnH (6 ×1.2 eq) 6 eq. AIBN (6×1 eq)	44	56
3	10.8 eq. nBu_3SnH (9 ×1.2 eq) 9 eq. AIBN (9×1 eq)	25	75
4	16.2 eq. nBu_3SnH (9 ×1.8 eq) 13.5 eq. AIBN (9×1.5 eq)	0	100

a) Yields were determined by ^1H NMR of the crude reaction mixture.

Using this methodology, highly diverse bicyclic and tricyclic structures could be produced on solid support.

References and Notes

1. Berteina, S.; De Mesmaeker, A. *Synlett* **1998**, 1227.
2. For intramolecular *Heck* reactions on solid phase, see: a) Goff, D.A.; Zuckermann, R.N. *J. Org. Chem.* **1995**, *60*, 5748. b) Yun, W.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 7189.
3. For radical cyclizations on solid support, see: a) Routledge, A.; Abell, C.; Balasubramanian, S. *Synlett*, **1997**, 61. b) Du, X.; Armstrong, R.W. *J. Org. Chem.*, **1997**, 62, 5678. c) Berteina, S.; De Mesmaeker, A. *Tetrahedron Lett.*, **1998**, *39*, 5759.
4. All reactions have been performed on scale 150-200 mg polystyrene beads (cross-linked with 1% divinyl benzene), (0.6 mmol/g), allowing the isolation of at least 20 mg crude product. The structure were determined by ^1H NMR and mass spectrometry and the yields refer to the weight of the crude product corrected by the purity evaluated by ^1H NMR (400MHz). The yields reported in parentheses are obtained after purification by flash chromatography or preparative t.l.c.
5. Devos, A.; Remion, J.; Frisque-Hesbain, A.; Colens, A.; Ghosez, L.; *J. Chem. Soc., Chem. Commun.* **1979**, 1180.
6. 2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine.
7. Experimental procedure: 150-200 mg of resin (0.1mmol of loading substrate) were suspended in DMA (2 ml); then Ph_3P, nBu_4NCl and K_2CO_3 were added. The mixture was degassed for 20 min then $Pd(OAc)_2$ was added. After 24h at 100°C, the resin was washed with DMA (6×3ml), CH_2Cl_2 (6×3ml), dioxane (6×3ml), H_2O (6×3ml), EtOH/H_2O (1/1) (3×3ml), EtOH (3×3ml), CH_2Cl_2 (6×3ml), MeOH (6×3ml), dioxane (6×3ml), CH_2Cl_2 (6×3ml), diethyl ether (3×3ml), and dried under vacuum.
8. Winterfeldt, E.; Preuss, H. *Chem. Ber.* **1966**, *99*, 450.
9. Experimental procedure: 150-200 mg of resin (0.1mmol of loading substrate) was suspended in degassed benzene; then 0.5 eq. nBu_3SnH and 0.1 eq. AIBN were added. The mixture was heated to reflux under an argon atmosphere. Every 5-8 h, 5 additional amounts of nBu_3SnH (0.5 eq.) and AIBN (0.1 eq.) were added. The resin was washed with benzene (6×4ml), toluene (6×4ml), hexane (6×4ml), CH_2Cl_2 (6×4ml), EtOH (6×4ml), EtOH/H_2O (1/1) (6×4ml), H_2O (6×4ml), dioxane (6×4ml), CH_2Cl_2 (6×4ml), MeOH (6×4ml), CH_2Cl_2 (6×4ml), diethyl ether (3×4ml) in order to eliminate the organotin compounds, and dried under vacuum.
10. Bachi, M.D.; Denenmark, D. *J. Am. Chem. Soc.* **1989**, *111*, 1886.