JOC*Note*

Resin-Bound Triaryl Bismuthanes and Bismuth Diacetates: Novel Multidirectional Linkers and Novel Resin-Bound Arylation Reagents

L. Kyhn Rasmussen,† Mikael Begtrup,† and Thomas Ruhland*

Department of Medicinal Chemistry, H. Lundbeck A/S, 9 Ottiliavej, DK−2500 Valby, Denmark

tr@lundbeck.com

Received May 14, 2004

Abstract: A general synthesis of resin-bound triaryl bismuthanes and resin-bound triaryl bismuth diacetates starting from commercially available chloromethyl polystyrene is reported. For the first time resin-bound bismuth has been utilized as part of a multidirectional linker system for solid-phase organic synthesis and as a resin-bound arylation reagent.

In recent years intensive research efforts have been directed toward increasing the flexibility in solid-phase organic synthesis (SPOS) by means of new linker concepts such as traceless linkers and multidirectional linker systems.[1] Multidirectional linker strategies are particular attractive as they allow the synthesis of different scaffolds by the introduction of a wide range of diverse fragments in the final cleavage step.

The recent discovery of the chemical potential of triorganyl bismuth reagents in organic synthesis has significantly expanded the chemical toolbox, especially in the areas of mild and selective arylation reactions.[2−6] In particular, the pioneering work of Barton et al. has led to efficient methods for performing O-, N-, and C-arylations with a wide range of substrates under mild reaction conditions.[7−14] In comparison to palladium-catalyzed reactions, bismuth-assisted arylations have only played an "exotic" role and their application to the synthesis of bioactive compounds is scarce.[15−18] The synthesis of similar compounds by, for example, palladium-catalyzed cross-coupling reactions often requires tedious optimization of the catalytic systems for each individual case. We recognized that the combination of the versatile chemistry of triaryl bismuthanes coupled with the advantages of solid-phase chemistry would provide a powerful tool for solid-phase and solution-phase synthesis. In this paper we demonstrate that resin-bound bismuth represents a new and flexible alternative to the existing multidirectional linker methodologies.

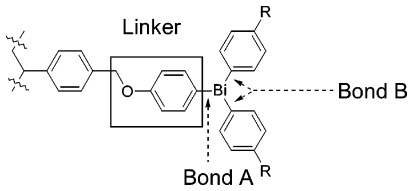
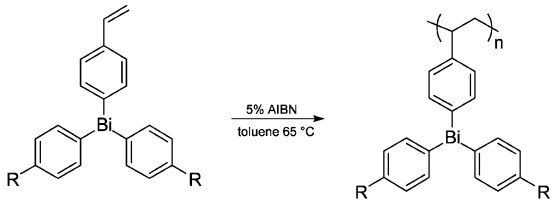


FIGURE 1. The linker system.

SCHEME 1. Suzuki's Synthesis of Resin-Bound Bismuthanes



R: Me, MeO

Resin-bound triaryl pnictogenes (group 15 elements) were first reported by Braun in 1962 while studying the polymerization process of pnictogene-substituted styrene monomers.[19] Almost 40 years later, Suzuki reported an improved synthesis of the monomers and their homopolymerization.[20]

Despite their early description and their obvious synthetic possibilities, resin-bound bismuthanes have, to the best of our knowledge, been used neither in SPOS nor as solid-phase reagents. The most likely explanations are the difficulties in making a diverse range of differently substituted resin-bound bismuthanes and the lack of selectivity by the cleavage of aryl groups from the bismuth.

In the following we describe a strategy that enables resin-bound bismuth to be used as a multidirectional linker in SPOS. Our method allows a simple attachment of bismuthanes without polymerization starting from commercially available chloromethyl polystyrene. Another key issue in our design strategy was to achieve sufficient discrimination between the two rather similar Bi-sp^{2}C bonds A and B shown in Figure 1. It is essential

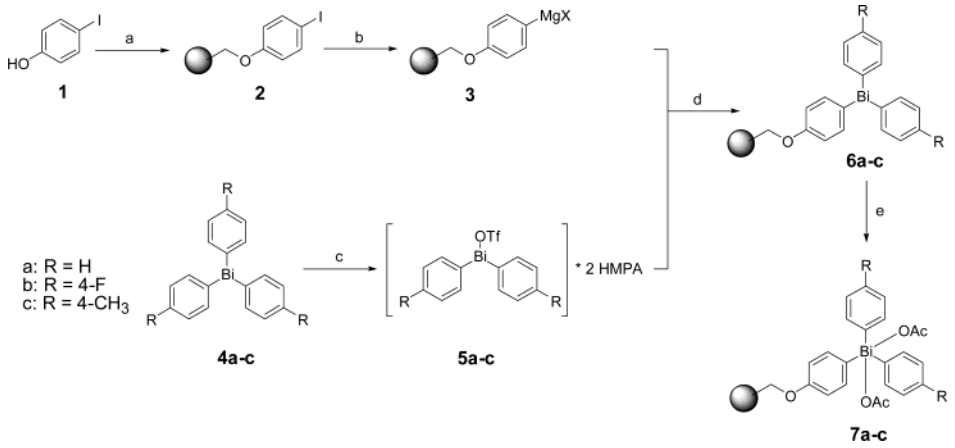
* To whom correspondence should be addressed. Phone: +45 3643 3304. Fax: +45 3643 8237.

† The Danish University of Pharmaceutical Sciences, 2 Universitetsparken, DK-2100 Copenhagen, Denmark.

(1) Brase, S.; Dahmen, S. *Chem. Eur. J.* **2000**, *6*, 1899−1905.
(2) Barton, D. H. R.; Finet, J.-P. *Pure Appl. Chem.* **1987**, *59*, 937−946.
(3) Abramovitch, R. A.; Barton, D. H. R.; Finet, J. P. *Tetrahedron* **1988**, *44*, 3039−3071.
(4) Finet, J. P. *Chem. Rev.* **1989**, *7*, 1487−1501.
(5) Suzuki, H.; Ikegami, T.; Matano, Y. *Synthesis* **1997**, *3*, 249−267.
(6) Elliott, G. I.; Konopelski, J. P. *Tetrahedron* **2001**, *57*, 5683−5705.
(7) Barton, D. H. R.; Ozbalik, N.; Ramesh, M. *Tetrahedron* **1988**, *44*, 5661−5668.
(8) Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1987**, *28*, 887−890.
(9) Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1988**, *29*, 1115−1118.
(10) Chan, D. M. T. *Tetrahedron Lett.* **1996**, *37*, 9013−9016.
(11) Arnauld, T.; Barton, D. H. R.; Doris, E. *Tetrahedron* **1997**, *53*, 4137−4144.
(12) Barton, D. H. R.; Finet, J.-P.; Khamsi, J.; Pichon, C. *Tetrahedron Lett.* **1986**, *27*, 3619−3622.
(13) Barton, D. H. R.; Bhatnagar, N. Y.; Finet, J.-P.; Khamsi, J.; Motherwell, W. B.;.Stanforth S. P. *Tetrahedron* **1987**, *43*, 323−332.
(14) Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1986**, *27*, 3615−3618.
(15) Sorenson, R. J. *J. Org. Chem.* **2000**, *65*, 7747−7749.
(16) Fan, P. C.; Ablordeppey, S. Y. *J. Heterocycl. Chem.* **1997**, *34*, 1789−1794.
(17) Banfi, A.; Bartoletti, M.; Bellora, E.; Bignotti, M.; Turconi, M. *Synthesis* **1994**, *8*, 775−776.
(18) Morel, S.; Chatel, F.; Boyer, G.; Galy, J. P. *J. Chem. Res., Synop.* **1998**, *1*, 4−5.
(19) Braun, B.; Diamon, H.; Becker, G. *Makromol. Chem.* **1963**, *62*, 183−195.
(20) Matano, Y.; Begum, S. A.; Suzuki, H. *Synthesis* **2001**, *7*, 1081−1085.

10.1021/jo049183o CCC: $27.50
Published on Web 09/02/2004

SCHEME 2. Synthesis of Resin-Bound Bismuthanes[a]



[a] Key: (a) (i) NaOH, DMSO, 90 °C, 1.5 h, (ii) chloromethyl polystyrene, rt overnight and 90 °C 3 h; (b) 5 equiv of *i*-PrMgBr, THF, −30 °C, 3 h; (c) 1 equiv of TMSOTf, 2 equiv of HMPA, MeOH/DCM, 0 °C to rt over 1 h, quantitative; (d) THF, 0 °C to rt over 1 h, then rt overnight; (e) $PhI(OAc)_2$, DCM, rt, 24 h.

to cleave bond B selectively because cleavage of bond A would lead to lower yield and contamination of the products.

From literature it is known that in unsymmetrically substituted triaryl bismuthanes the most electron-deficient aryl group is selectively transferred in arylations reactions. To improve the required discrimination in the cleavage step between the two different types of Bi-sp^2C bonds we have chosen a phenoxy group as spacer for the bismuth atom.[21]

The synthesis of the resin-bound triarylbismuthanes is shown in Scheme 2. Resin **2** was prepared by reaction of 4-iodophenol **1** with commercially available chloromethyl polystyrene (loading 2.38 mmol/g, cross-linked with 1−2% divinylbenzene, mesh 200).[22] The resin-bound aryl Grignard compound **3** was prepared from resin **2** by iodomagnesium exchange using isopropylmagnesium bromide.

To obtain resin-bound bismuthanes, a suitable bismuth electrophile was needed to be coupled to resin **3**. The choice of the electrophilic bismuth reagent is crucial, and $BiCl_3$, Ar_2BiCl, and Ar_2BiOTf were considered. The reaction with $BiCl_3$ would give an intermediate resin-bound dichloroarylbismuth, which in theory could react in a second step with 2 equiv of aryl Grignard reagent. However, as known from literature, scrambling of the aryl groups via ligand−ligand exchange may take place with the consequence that bismuth would be lost from the solid phase.[23] Ar_2BiCl has the disadvantage of undergoing dismutation reactions in solution.[24] Recently, Suzuki et al. used $Ar_2BiOTf \cdot 2HMPA$ complexes for the synthesis of unsymmetrically substituted triaryl bismuthanes, avoiding the disadvantages of $BiCl_3$ and Ar_2BiCl.[25] In addition, the complexes are readily accessible, air-stable, and soluble in most common organic solvents. The diaryl bismuth triflate HMPA complexes **5a**−**c** were prepared in quantitative yield from the bismuthanes **4a**−**c** as shown in Scheme 2. The bismuthanes **4a**−**c** were obtained by reaction of the aryl Grignard or lithium species with bismuth(III) chloride.[24,26]

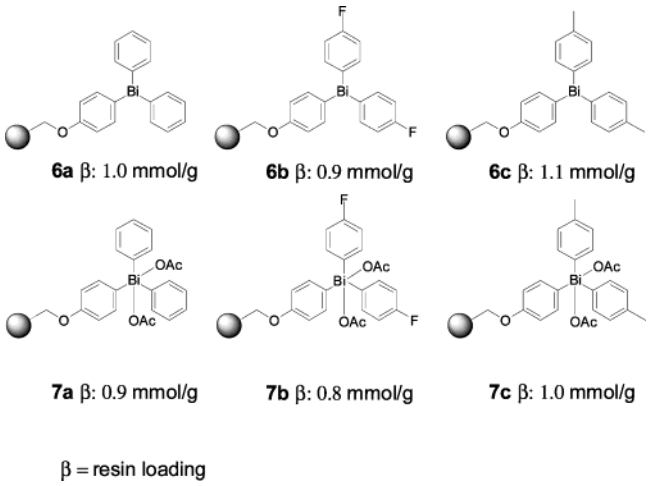


FIGURE 2. Prepared resin-bound triaryl bismuthanes **6a**−**c** and triaryl bismuth(V) diacetates **7a**−**c**.

Three different resin-bound triaryl bismuthanes **6a**−**c** were prepared from resin **3** with loadings from 0.9−1.1 mmol/g (Figure 2). The conversion of the attachment is in the range of 77−89%, the apparent reduction in resin loading being due to high mass of the attached bismuth construct. Resins **6a**−**c** were subsequently oxidized quantitatively with diacetoxy iodobenzene to the resin-bound triaryl bismuth(V) diacetates **7a**−**c** (Figure 2).[27]

Complete oxidation was verified by high-resolution magic angle spinning (HR MAS) ^{1}H NMR. The recorded HR MAS ^{1}H NMR spectra of resin **6c** and **7c** are shown in Figure 3. The change in chemical shifts of the aromatic protons ($\Delta\delta$ (H_A) = 0.34 ppm, $\Delta\delta$ (H_B) = 0.13 ppm) can be seen when comparing the two spectra; this is in

(21) Barton, D. H. R.; Bhatnagar, N. Y.; Finet, J.-P.; Motherwell, W. B. *Tetrahedron* **1986**, *42*, 3111−3122.
(22) Kobayashi, S.; Aoki, Y. *Tetrahedron Lett.* **1998**, *39*, 7345−7348.
(23) Challenger, F.; Allpress. *J. Chem. Soc., Perkin Trans. 1* **1921**, *119*, 913−926.
(24) Henry Gilman; H. L. Yablunky. *J. Am. Chem. Soc.* **1941**, *63*, 207−211.
(25) Matano, Y.; Miyamatsu, T.; Suzuki, H. *Organometallics* **1996**, *15*, 1951−1953.
(26) Henry Gilman; H. L.Yablunky; A. C. Svigoon. *J. Am. Chem. Soc.* **1939**, *61*, 1170−1172.
(27) Combes, S.; Finet, J. P. *Tetrahedron* **1998**, *54*, 4313−4318.

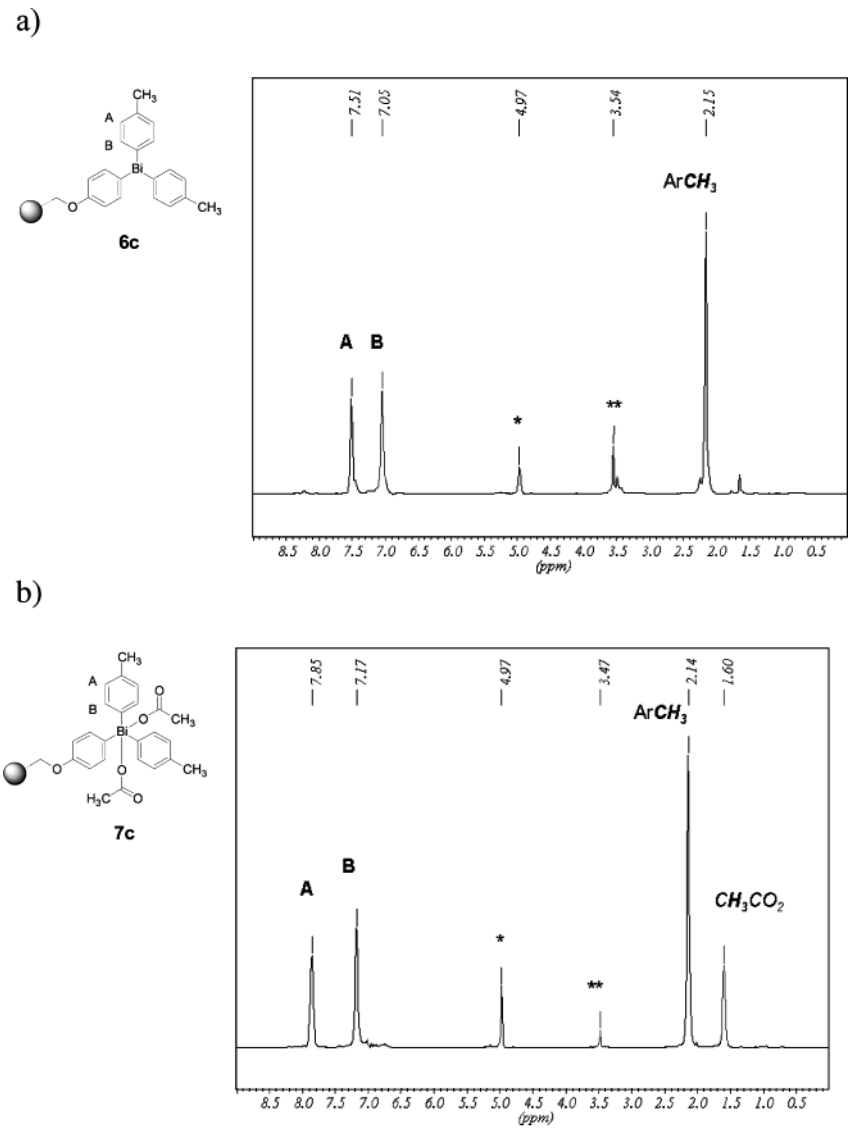
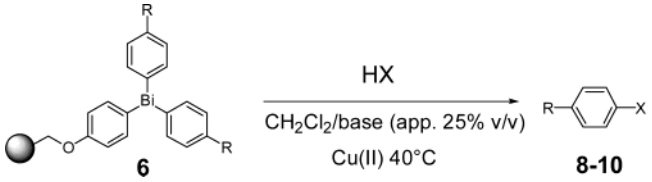


FIGURE 3. HR MAS ^{1}H NMR of (a) resin **6c** and (b) **7c**. The sample spinning speed was 5000 Hz, and 128 scans were acquired. A Carr−Purcell−Meiboom−Gill sequence consisting of 50 echoes were applied for backbone suppression. For **6c** the total echo time was 150 ms, whereas for **7c** the total echo time was 100 ms. (* DCM, ** H_2O)

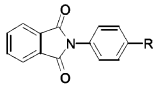
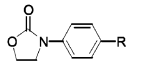
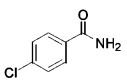
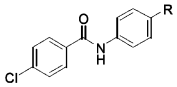
SCHEME 3. Cleavage from Resins 6a−c



accordance with studies of similar compounds in solution-phase chemistry.[11] Similar changes are observed when comparing the spectra from **6a/b** with **7a/b**.

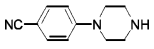
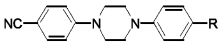
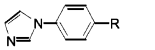
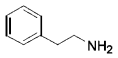
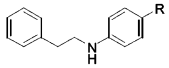
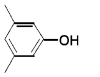
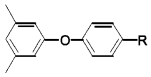
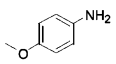
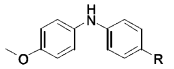
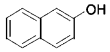
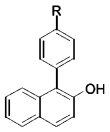
Cleavage from resin-bound bismuthanes **6a−c** (Scheme 3) was achieved using an imide, a carbamate, or an amide in the presence of a stoichiometric amount (1.5 equiv) of copper(II) acetate and a base in dichloromethane at 40 °C (Table 1). To avoid undesired protonation and thereby cleavage of the bismuth from the resin, a base (either pyridine or triethylamine) was used as cosolvent.[10] Nine different *N*-arylated products were obtained in yields from 57% to 83% after purification by column chromatography with NMR purities of >95%. The yields were approximately 30% lower than those reported for similar reactions in solution phase,[10] problably as a result of the

TABLE 1. N-Arylations by Use of Resins 6a−c

Substrate (HX): [a]	Resin:	Product:		R:	Yield: [b]
	**6a**		**8a**	H	57%[c]
	6b		**8b**	F	65%[c]
	6c		**8c**	Me	75%[c]
	**6a**		**9a**	H	65%[d]
	6b		**9b**	F	68%[d]
	6c		**9c**	Me	58%[d]
	**6a**		**10a**	H	59%[c]
	6b		**10b**	F	67%[c]
	6c		**10c**	Me	83%[c]

[a] Conditions: 2 equiv of substrate, 1.5 equiv of $Cu(OAc)_2$, CH_2Cl_2/base, 40 °C, 24 h. [b] Yield of product after flash chromatography, purities >95% by ^{1}H NMR. [c] Pyridine as base. [d] Triethylamine as base.

TABLE 2. N-, C-, and O-Arylations by Use of Resins 7a−c

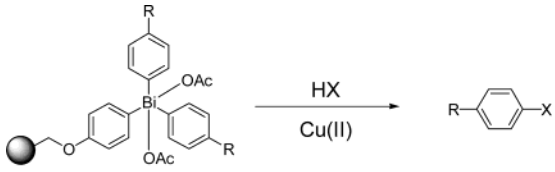
Substrate:	Resin:	Product:		R:	Yield:[a]
	**7a**		**11a**	H	87%[b]
	7b		**11b**	F	96%[b]
	7c		**11c**	Me	69%[b]
	**7a**		**12a**	H	83%[c]
	7b		**12b**	F	50%[c]
	7c		**12c**	Me	99%[c]
	**7a**		**13a**	H	81%[d]
	7b		**13b**	F	65%[d]
	7c		**13c**	Me	84%[d]
	**7a**		**14a**	H	43%[e]
	7b		**14b**	F	62%[e]
	7c		**14c**	Me	39%[e]
	**7a**		**15a**	H	90%[f]
	7b		**15b**	F	88%[f]
	7c		**15c**	Me	52%[f]
	**7a**		**16a**	H	68%[g]
	7b		**16b**	F	49%[g]
	7c		**16c**	Me	68%[g]

[a] Yield of product after flash chromatography, purity >95% by ^{1}H NMR. [b] 2 equiv of substrate, 10% $Cu(AcO)_2$, THF/triethylamine (25% v/v), rt 24 h. [c] 2 equiv of substrate, 10% $Cu(AcO)_2$, THF, 50 °C 24 h. [d] 1.5 equiv of substrate, 10% $Cu(AcO)_2$, THF, rt 24 h. [e] 1.5 equiv of substrate, 10% $Cu(PivO)_2$, DCM, rt 24 h. [f] 1.5 equiv of substrate, 10% $Cu(PivO)_2$, THF, rt 24 h. [g] 1.5 equiv of substrate, 1.2 equiv of TMG, THF, rt 24 h.

poor solubility of copper(II) acetate in the solvent used, with the consequence that the copper(II) acetate is not able to diffuse completely into the resins. Despite the better solubility, the use of Cu(II) triflate or Cu(II) pivaloate gave even lower yields, in accordance with similar studies from solution-phase chemistry. Another plausible explanation can be deducted from the fact that the resin-bound bismuthanes are unsymmetrical (i.e., two identical aryl groups available per Bi), whereas the reactions reported in solution phase have been carried out with symmetrical triaryl bismuthanes (i.e., three identical aryl groups available per Bi).

The resin-bound triaryl bismuth diacetates **7a−c** were treated with nucleophiles, resulting in formation of C−N, C−O, and C−C bonds under conditions similar to those reported for solution-phase synthesis (Table 2). Yields obtained from resins **7a−c** (Scheme 4) are comparable to analogous reactions in solution phase.[11,12,28−30] The O- and N-arylation reactions leading to products **11a−c**, **12a−c**, **13a−c**, **14a−c**, and **15a−c** were carried out using 10% copper(II) acetate for **11−14** and pivaloate for **15**. The use of a catalytic amount of copper(II) salts has the advantage of easier work up compared to cleavages from resin-bound triaryl bismuthanes using stoichiometric amounts of copper(II) acetate. Ortho-arylations of phenols takes place in the absence of copper additives. The cleavage with *β*-naphthol was performed using 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (TMG) as the base and furnished **16a−c** in moderate to good yields. In total, 18 N-, O-, and C-arylated derivatives **11−16** were obtained in moderate to excellent yields (39−99%) after purification by column chromatography, with NMR purities better than 95%.

SCHEME 4. Cleavage from Resins 7a−c



7 **11-16**

We have reported a general, convenient, and efficient synthesis of resin-bound triaryl bismuthanes and resin-bound triaryl bismuth diacetates that overcomes the disadvantages of previously reported methods. For the first time, resin-bound bismuth was used in SPOS as a multidirectional linker system and as a resin-bound arylation reagent. The utility was proven by O-, N- and C-arylations leading to products of high diversity. Thus *N*-arylimides, *N*-arylcarbamates, *N*-arylamides, *N*-arylpiperazines, *N*-arylimidazoles, *N*-arylamines, *N*,*N*-diarylamines, diaryl ethers, and biphenyls were obtained in moderate to good yields. Discrimination between the two different types of aryl groups was improved by the use of an electron-rich spacer between the linking bismuth atom and the polymer backbone. The oxidations of resins **6a−c** to the corresponding resin-bound triaryl bismuth diacetates **7a−c** were verified by HR MAS ^{1}H NMR. The resin-bound triaryl bismuth diacetates were superior as multidirectional linkers compared to resin-bound triaryl bismuthanes. Cleavage from resin-bound triaryl bismuth diacetates allows arylation of a wide range of substrates under mild conditions requiring only catalytic quantities of copper(II) salts and gives yields similar to those reported for analogous solution phase chemistry.

Acknowledgment. We thank Jens Christian Madsen for his expertise carrying out the HR MAS NMR experiments and Robert Dancer and Ejner K. Moltzen for proofreading the manuscript.

Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049183O

(28) Fedorov, A.; Combes, S.; Finet, J. P. *Tetrahedron* **1999**, *55*, 1341−1352.
(29) Combes, S.; Finet, J. P. *Tetrahedron* **1999**, *55*, 3377−3386.
(30) Fedorov, A. Y.; Finet, J. P. *Tetrahedron Lett.* **1999**, *40*, 2747−2748.