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ROMPgel-supported biphenyl and naphthalene: reagents for lithiation reactions with minimal purification

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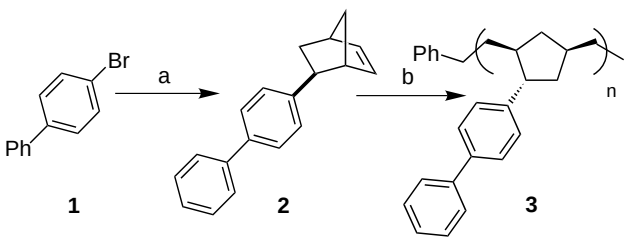
Abstract—The synthesis of ring opening metathesis, polymer (ROMPgel) supported naphthalene and biphenyl reagents was carried out. These reagents were utilized for catalytic lithiation reactions of aryl and alkyl chlorides and for the reductive deprotection of benzyl and allyl ethers.

Polymer-supported reagents are convenient for parallel solution phase synthesis with the removal of undesired by-products through simple phase separation.[1] For example, polystyrene supported toluene-4-sulfonyl azide has been used as a diazo transfer reagent to generate diethyl diazomalonate which was then purified by simple separation.[2] With the emergence of combinatorial chemistry in the pharmaceutical industry, polymer-supported reagents have been re-established as one of the most effective methodologies for the amalgamation of traditional solution phase chemistry with automation through the use of robotics.

The Barrett group has devised a novel approach to the synthesis of polymer supported reagents utilizing ring opening metathesis polymerization (ROMP) to support diverse reagents. This methodology has been successful in the synthesis of unsaturated esters and nitriles through Horner–Emmons reactions,[3] the synthesis of amides including Mosher amides utilizing ROMPgel[4] supported *N*-hydroxysuccinimide ester and for the synthesis of oxadiazoles[5] and oxazoles.[6] ROMPgel anhydride scavengers[7] have also been found to be effective for the removal of excess amine and hydrazine from solution phase reactions.

We now wish to report the application of ROMPgel supports to immobilize biphenyl and naphthalene to facilitate arene catalyzed lithiation reactions. ROMPgel supported arenes would allow for the facile purification of multifunctionalised compounds after an arene mediated lithiation through simple filtration. Arene catalyzed lithiation is a powerful method for the generation of unstable organolithium compounds in organic synthesis.[8] Halogen–lithium exchange can be achieved through reaction of an alkyl or aryl halide with an alkyllithium base or reduction of the halide species with lithium metal.[9] In the latter method, it is first necessary to activate the metal when performing the reaction at low temperature, which is achieved by using an arene electron carrier such as naphthalene and biphenyl.[10] Arene catalyzed lithiation has been utilized for diverse transformations, including reductive carbon–oxygen[11] and carbon–sulfur cleavages,[12] lithiation of functionalized alkyl and aryl chlorides,[13] reductive opening of saturated heterocycles,[14] and deprotection of a number of protecting groups.[15]



Scheme 1. *Reagents and conditions*: (a) $Pd(PPh_3)_2(OAc)_2$, norbornadiene, DMF, piperidine, HCO_2H, 60°C, 4 h, 75%; (b) i. **4** (1.5 mol%), CH_2Cl_2, 25°C, 12 h, 100%; ii. **5** (10 mol%), PhH, H_2, 150 psi, 120 h, 84%.

Synthesis of the ROMPgel supported biphenyl (ROMPgel biphenyl) was achieved via a Heck coupling[16] of 4-bromobiphenyl **1** to norbornadiene to afford **2** in 75% yield. Subsequent polymerization of norbornadiene **2** was then carried out with Grubbs' catalyst **4** (1.5 mol%) affording the insoluble ROMPgel

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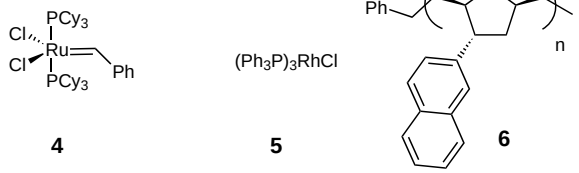
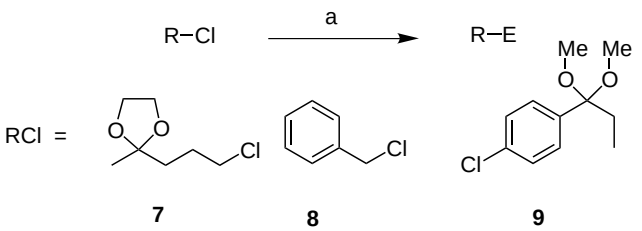
without using any cross-linker. The resulting polymer was suspended in benzene and hydrogenated in the presence of a homogenous catalyst **5** (10 mol%) to afford the reduced ROMPgel **3** in 84% yield[17] (Scheme 1). A similar strategy was utilized for the synthesis of the ROMPgel supported naphthalene **6** (ROMPgel naphthalene) in 66% yield. Arene lithiations of chlorinated compounds are traditionally conducted using a stoichiometric amount of naphthalene or biphenyl, either by the formation of the lithium species and subsequent addition of an electrophile or by the preparation of the lithium species in the presence of the electrophile.



4 **5** **6**

Recently, Yus and co-workers[15] have reported the preparation of organolithium species using only a catalytic amount of the arene (ca. 10 mol%), both in solution and using a polystyrene supported naphthalene and biphenyl.

To determine the utility of ROMP **3** and **6**, we examined a series of reductive lithiation reactions. Thus, a series of chlorinated compounds were allowed to react with an excess of lithium metal and the ROMPgel arene **3** or **6** (ca. 10 or 20 mol%) in THF at −78°C. Subsequent addition of an electrophile and hydrolysis gave rise to the expected products (Scheme 2 and Table 1).



7 **8** **9**

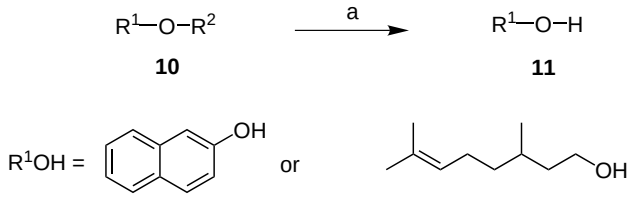
Scheme 2. *Reagents and conditions*: (a) Li, ROMPgel arene support **3** or **6** (10 mol% or 20 mol%), E^+ = PhAc, or PhCHO, or R_3SiCl, THF, −78 to 25°C, MeOH.

After hydrolysis, the polymer was simply removed by filtration through a short pad of silica (one fraction) and the solvent evaporated to afford the desired product in good yield and purity (Table 1). ROMPgel arenes **3** and **6** are easily prepared and inexpensive reagents which are convenient alternatives to the polystyrene arene resins utilized by Yus and co-workers.[18]

It is clear from Table 1 that ROMPgels **3** and **6** are useful for catalyzed lithiation reactions with minimal purification. Both chlorides **7** and **8** were smoothly converted into the corresponding alkyl and benzyl lithium reagents and trapped with several electrophiles.[19] Lithiation of the aryl chloride **9** and reaction with acetophenone and benzaldehyde gave adducts of lower purity. Finally, we examined the use of the ROMPgel arenes **3** and **6** for reductive cleavage of benzyl and allyl ether protecting groups, which are traditionally removed either by hydrogenation or using Lewis acids and oxidants.[20] We chose 1-naphthol and critronellol as the substrates, which were protected as benzyl, allyl and silyl ethers using traditional protocols.[21]

The results, which are summarized in Scheme 3 and Table 2 show that deprotection of allyl and benzyl ethers is possible using reduction in the presence ROMPgel **3** and **6**.

To conclude, we have successfully demonstrated the applicability of ROMPgel naphthalene **6** and biphenyl **3** for a series of arene catalyzed lithiation reactions. The two ROMPgel supported reagents are worthwhile alternatives to the use of naphthalene and biphenyl in



10 **11** **11a** **11b**

Scheme 3. *Reagents and conditions*: (a) Li, ROMPgel arene supports **3** and **6** (10 mol%), THF, −78°C, MeOH.

Table 1.

Chloride	Polymer	Electrophile	Time (h)	Yield[a] (%)	Purity[b] (%)
7	**3**	PhAc	20	87	91
7	**3**	PhCHO	20	88	96
7	**6**	^{t}BuPh$_2$SiCl	20	81	92
8	**3**	PhAc	20	85	91
8	**3**	PhCHO	20	78	93
8	**6**	^{t}BuMe$_2$SiCl	20	77	90
9	**3**	PhAc	30	71	81
9	**6**	PhCHO	30	65	80

[a] Isolated yields.
[b] Purity as determined by GC–MS and ^{1}H NMR.

Table 2.

R_1	R_2	Polymer	Time (h)	Yield (%)	Purity (%)
11a	$PhCH_2$	**3**	40	71	80
11a	Allyl	**3**	40	73	83
11a	$^tBuMe_2SiCl$	**6**	40	[a]	–
11b	$PhCH_2$	**6**	40	89	96
11b	Allyl	**6**	40	86	92
11b	$^tBuMe_2SiCl$	**3**	40	[a]	–

[a] No reduction observed.

solution phase chemistry and eliminate the need for laborious chromatography or vacuum sublimation to remove the naphthalene or biphenyl.

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References

1. (a) Cramps, F.; Castells, J.; Font, J.; Vela, F. *Tetrahedron Lett*. **1971**, 1715; (b) Weinshenker, N. M.; Shen, C.-M. *Tetrahedron Lett*. **1972**, 3281.
2. Roush, W. R.; Feitler, D.; Rebek, J. *Tetrahedron Lett*. **1974**, 1391.
3. Barrett, A. G. M.; Smith, M. L.; Zécri, F. J. *Org. Lett*. **2000**, *2*, 261.
4. Arnauld, T.; Barrett, A. G. M.; Hopkins, B. T.; Zécri, F. J. *Tetrahedron Lett*. **2001**, *42*, 8215.
5. Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zécri, F. J. *Comb. Chem. High Throughput Screen*. **2000**, *3*, 131.
6. Barrett, A. G. M.; Cramp, S. M.; Hennessy, A. J.; Procopiou, P. A.; Roberts, R. S. *Org. Lett*. **2001**, *3*, 271.
7. (a) Barrett, A. G. M.; Roberts, R. S.; Schröder, J. *Org. Lett*. **2000**, *2*, 2999; (b) Barrett, A. G. M.; Smith, M. L.; Zécri, F. J. *Chem. Commun*. **1998**, 2317.
8. Nájera, C.; Yus, M. *Trends Org. Chem*. **1991**, *2*, 155.
9. (a) Zieglar, K.; Colonius, H. *Annalen* **1928**, 463; (b) Gilman, H.; Langham, W.; Moore, F. W. *J. Am. Chem. Soc*. **1940**, *62*, 2327.
10. (a) Holy, N. L. *Chem. Rev*. **1974**, *74*, 243; (b) Cohen, T. *J. Am. Chem. Soc*. **1989**, *111*, 8976; (c) Dorigo, A. E.; Houk, K. N.; Cohen, T.; Joeng, I.-H.; Mudryk, D.; Bhupathy, M.; Award, M. M. *J. Org. Chem*. **1990**, *55*, 1528.
11. Alsono, E.; Guijarro, D.; Yus, M. *Tetrahedron* **1995**, *51*, 11457.
12. Alsono, E.; Guijarro, D.; Yus, M. *Tetrahedron* **1995**, *51*, 2699.
13. (a) Guijarro, A.; Yus, M. *Tetrahedron Lett*. **1993**, *34*, 3487; (b) Huerta, F. F.; Gómez, C.; Guijarro, A.; Yus, M. *Tetrahedron* **1995**, *51*, 3375.
14. (a) Bartmann, E. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 653; (b) Yus, M.; Soler, T.; Foubelo, F. *Tetrahedron* **2001**, *12*, 801.
15. Alonso, E.; Ramón, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 14355.
16. Arcadi, A.; Marinelli, F.; Bernocchi, E.; Cacchi, S.; Ortar, G. *J. Organomet. Chem*. **1989**, *368*, 249.
17. **Typical procedure for the preparation of ROMPgel**: Benzylidene bis(tricyclohexylphosphine)dichlororuthenium (12 mg, 10 μmol) in CH_2Cl_2 (2 mL) was slowly added to a stirred solution of 5-(4-phenylphenyl)bicyclo[2.2.1]hept-2-ene (250 mg, 1.00 mmol) in CH_2Cl_2 (1.5 mL). The solution was stirred at room temperature for 12 h. Ethyl vinyl ether (3 mL) was added, followed by the addition of CH_2Cl_2 (5 mL). The solution was filtered to afford a brown solid which was washed with MeOH (30 mL), CH_2Cl_2 (30 mL), Et_2O (30 mL) and dried in vacuo to afford the corresponding ROMP (250 mg, 100%) as a white solid. The solid was suspended in benzene and to the suspension was added tris(triphenylphosphine)rhodium(I) chloride (93 mg, 10 mol%) and hydrogenated at 150 psi for 120 h. The solid was filtered and washed with CH_2Cl_2 (2×30 mL) and MeOH (2×30 mL). The polymer was dried under vacuum to afford ROMPgel **3** as a yellow solid (208 mg, 84%).
18. (a) Yus, M.; Ramón, D. J. *Chem. Commun*. **1991**, 396; (b) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron* **1999**, *55*, 7017.
19. **Typical procedure**: A solution of lithium metal (12 mmol) and ROMPgel supported arene (0.2 mmol) in THF was cooled to −78°C under argon. To this suspension was added the chloride (2 mmol) and the electrophile (2 mmol). The solution was stirred at −78°C for 9 h and allowed to warm to 25°C. The solution was quenched with MeOH (5 mL) at 0°C and diluted with water (5 mL) and Et_2O (10 mL). The suspension was filtered through cotton wool and the organic phase was separated, dried (Na_2SO_4) and concentrated in vacuo. The residue was filtered through a short pad of silica gel to afford the desired products after evaporation of solvent.
20. (a) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem*. **1978**, *43*, 4194; (b) Kariyone, K.; Yazawa, H. *Tetrahedron Lett*. **1970**, 2885; (c) Garbers, C. F.; Steenkamp; Visagie, H. E. *Tetrahedron Lett*. **1975**, *16*, 3753; (d) Dufour, M.; Gramain, J.-C.; Husson, H.-P.; Sinibaldi, M.-E.; Troin, Y. *Tetrahdron Lett*. **1989**, *30*, 3429.
21. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.