[3] a) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; b) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975; c) for a recent review on asymmetric synthesis with organic catalysts see P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3841; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726.
[4] E. Emori, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 4043–4044.
[5] S. Colonna, A. Re, H. Wynberg, *J. Chem. Soc. Perkin Trans. 1* **1981**, 547.
[6] a) H. Wynberg, *Top. Stereochem.* **1986**, *16*, 87; b) H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417.
[7] K. Suzuki, A. Ikegawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277.
[8] M. Ostendorf, S. van der Neut, F. P. J. T. Rutges, H. Hiemstra, *Eur. J. Org. Chem.* **2000**, 105.
[9] a) F. Toda, K. Tanaka, J. Sato, *Tetrahedron: Asymmetry* **1993**, *4*, 1771; b) A. Ito, K. Konishi, T. Aida, *Tetrahdron Lett.* **1996**, *37*, 2585; c) K. Nishimura, M. Ono, Y. Nagaoka, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 12974.
[10] For a highly diastereoselective reduction of (*R*)-3-(*p*-*tert*-butylphenylsulfanyl)cyclohexan-1-one see: K. Suzuki, A. Ikegawa, T. Mukaiyama, *Chem. Lett.* **1982**, 899.
[11] For conversion of thioethers to ketones see: a) A. D. Lebsack, L. E. Overman, R. J. Valentekovich, *J. Am. Chem. Soc.* **2001**, *123*, 4851; b) R. D. Little, S. O. Myong, *Tetrahedron Lett.* **1980**, *21*, 3339.
[12] a) Y. Chen, S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2000**, *122*, 9542; b) C. Choi, S.-K. Tian, L. Deng, *Synthesis* **2001**, 1737; c) S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 6195; d) Y. Chen, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 11302; e) J. Hang, S.-K. Tian, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 12696.

Directed *ortho*-Metalation, a New Insight into Organosodium Chemistry[**]

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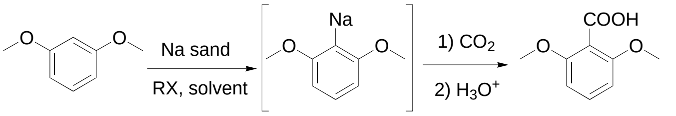
and Charles Mioskowski[*]

From laboratory to industrial scale, the use of strong organoalkali metal bases is almost exclusively restricted to alkyllithium derivatives.[1] They are commercially available as 1–2 M solutions, quite stable and easily generated from alkylhalides and lithium. In contrast, the synthesis of alkylsodium compounds is much more troublesome and requires high-speed mechanical stirring, low temperatures, and excess sodium.[2–6] Under classical conditions, organohalides react with sodium to give mainly Wurtz coupling products.[7, 8] Moreover, alkylsodium compounds show poor stability, especially in ethereal solvents.[9, 10] As a consequence, in spite of the low cost of metallic sodium and the sometimes demonstrated interesting reactivity,[11] alkylsodium compounds have not been considered so far as valuable organometallic reagents in organic synthesis.

Herein we report on a straightforward and efficient one-pot *ortho*-metalation procedure relying on the generation of sodiated organic bases from RCl and a stoichiometric amount of metallic sodium in the presence of aromatic substrates.[12] Under these conditions, handling and storage of alkylsodium compounds is avoided and *ortho*-metalation is favored over usual coupling and solvolysis side reactions.[13]

1,3-Dimethoxybenzene (1,3-DMB), known to undergo *ortho*-metalation with alkyllithium bases in good yields,[14] was selected as a model substrate to investigate the scope of the reaction with alkylsodium compounds [Eq. (1)]. Several parameters, including solvent, temperature, and the nature of the organohalide, were varied (Table 1). All reactions were quenched by addition of dry-ice, and the yield of acid [see Eq. (1)] was considered as indicative of the metalation efficiency.[15]



(1)

Table 1. Influence of some parameters on the directed *ortho*-sodiation of 1,3-DMB [Eq. (1)].[a]

Entry	RX	Solvent	T [°C]	Yield [%]
1	1-chlorooctane	toluene	20	70
2	2-chloropropane	toluene	20	8[b]
3	2-bromopropane	toluene	0	21
4	chlorobenzene	toluene	20	35[c]
5[d]	1-chlorooctane	Et_2O or THF	20	45 or 86
6	1-chlorooctane	THF or toluene	–15	30 or 28
7	1-chlorooctane	toluene	110	20

[a] The sodium sand was obtained by dispersing melted sodium under vigorous mechanical stirring; see Experimental Section. [b] T = room temperature or 0°C. [c] 2,6-dimethoxybiphenyl was also isolated in 35% yield.[16, 17] [d] Me_2SO_4 instead of CO_2 used as electrophile.

In the presence of 1-chlorooctane (or 1-chloropropane) 2,6-dimethoxybenzoic acid was obtained in 70% yield (entry 1), comparable to the yield of classical *n*BuLi metalations.[14] When the reaction was conducted in a two-step manner, that is, when the alkylsodium compound was synthesized prior to the addition of 1,3-DMB, only trace amounts (<1%) of carboxylic acid were detected. The sterically hindered neopentyl chloride did not give any metalation product, and secondary chloroalkanes gave poor results (entry 2).[3a] As expected, primary bromoalkanes were too reactive toward sodium, even at low temperature. Yet, secondary bromoalkanes, with a lower tendency to undergo Wurtz coupling, gave the desired acid in moderate yield (entry 3).

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Although alkylsodium compounds react with ethereal solvents much faster than alkyllithium compounds,[10] reaction (1) was efficiently conducted not only in toluene, but also in THF and to a lesser extent in diethyl ether (entries 1 and 5). The thermal instability of alkylsodium compounds[18] did not prevent the reaction using melted sodium to give the metalation product in 20 % yield (entry 7). This result emphasizes the exceptional thermal stability of 2,6-dimethoxyphenylsodium. At −15 °C, 2,6-dimethoxybenzoic acid was formed in modest yields (entry 6). In this case, part of the chlorooctane remained unreacted, and no improvement was achieved by increasing the reaction time.

Noteworthy, under optimized conditions, that is, slow addition of 1.2 equiv of pure 1-chlorooctane at room temperature to a mixture of the aromatic substrate and 2.6 equiv of sodium in toluene, the reaction was successfully carried out on a 1-kg scale.

Since only few reports exist on the reactivity of sodiated carbanions the *ortho*-sodiated anion was quenched with various electrophiles. The results proved to be comparable to those reported for conventional commercially available organolithium bases,[19–23] with yields ranging from 52 to 86 % (Table 2).

Table 2. Reaction of various electrophiles with 2,6-dimethoxyphenylsodium.

Entry	Electrophile	Yield [%][a]	Entry	Electrophile	Yield [%][a]
1	DMF	52 (–)	4	$PhCH_2Br$	75 (57[21])
2	$B(OMe)_3$	70[b] (57[19])	5	Me_2S_2	75 (85[22])
3	Me_3SiCl	76 (83[20])	6[c]	Me_2SO_4	86 (76[23])

[a] Yields from other publications in brackets. [b] 2,6-Dimethoxyphenylsodium was added dropwise to a trimethylborate solution in toluene. [c] With THF as solvent.

We then tried to extend the scope of our method to other aromatic ethers. 1,2-DMB failed to react under the optimized conditions given above (Table 3, entry 1). Only nonylbenzene arising from solvent metalation was obtained.[24] Changing the solvent from toluene to THF resulted in a complex reaction mixture. When 1-chlorooctane was added over a 3 h period to disfavor Wurtz coupling, the yield was brought to 20 % (entry 1). To further favor the heterogeneous reaction, hence the formation of the alkylsodium compound, finely divided micronized sodium was tested.[25] Under these conditions, 1,2-DMB underwent clean metalation affording the corresponding carboxylic acid in 80 % yield (entry 2).

Table 3. Sodiation of other substrates in the presence of 1-chlorooctane.

Entry	Aromatic compound	Sodium dispersion[a]	Solvent	Yield [%]
1	1,2-DMB	sand	toluene	0, 20[b]
2	1,2-DMB	micronized	toluene	80
3	1,4-DMB	micronized	toluene	88
4	anisole	micronized	toluene	25, 45[b]
5	thiophene	sand	toluene	90
6	benzofuran	sand	toluene	85

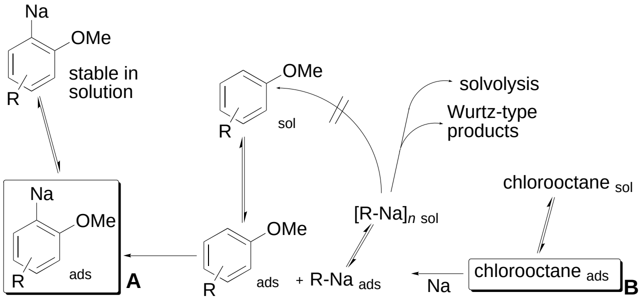
[a] The micronized dispersion in toluene is commercially available from Aldrich. [b] This yield was obtained when diluted 1-chlorooctane was added slowly.

Similar trends were observed with 1,4-DMB and anisole. No acid was formed in toluene or THF until micronized sodium dispersion was used (entries 3 and 4). The slow metalation of anisole might account for the modest 45 % yield obtained.[26]

Heterocyclic systems known to easily undergo α-metalation, such as thiophene and benzofuran, were successfully metalated using sodium sand dispersion (entries 5 and 6).[27] Not surprisingly,[28] other aromatic compounds bearing electron-withdrawing groups, like oxazolines, secondary and tertiary amides, invariably failed to undergo metalation.[12b, 29] In these cases, metallic sodium reacts with the aromatic ring to form complex mixtures even prior to the addition of the chlorooctane.

The three-component heterogeneous *ortho*-metalation presented here involves a complex set of equilibria. The desired path will be followed as soon as the aromatic derivative to be metalated will efficiently trap the in situ formed alkylsodium compound. In other words, the extent of side reactions indebted to the alkylsodium compound, that is homo-coupling and solvolysis, has to be minimized. This holds as long as the substrate bears a readily labile hydrogen as in the case of thiophene or benzofuran (see Table 3, entries 5 and 6). Nevertheless, the substrate acidity alone cannot account for our experimental results as studies by Schlosser and Maggi of the relative rates of the metalation of the DMB isomers with *s*-butyllithium in THF gave the order 1,4- > 1,3- ≫ 1,2-DMB.[30]

1,3-DMB is the only substrate that reacts with the sodium sand dispersion, although 1,4-DMB undergoes proton abstraction with ease. Hence, an additional parameter that influences the whole process has to be taken into account. We believe the *ortho*-metalation step takes place on the metallic surface within the coordination sphere of the alkylsodium molecules progressively formed (Scheme 1), whereby the substrate is driven onto the surface as a result of its affinity for Na^+. Literature and our experimental data strongly support this hypothesis. If the abilities of lithiated and of sodiated alkyl bases to coordinate to aromatic ethers are assumed to be similar, anisole binds weakly to an alkylsodium compound whereas 1,3-DMB and an alkylsodium compound form a strong complex.[31] 1,3-DMB bears a labile hydrogen and binds Na^+ tightly,[30, 32] *ortho*-metalation on the sodium surface will



Scheme 1. Proposed mechanism for the directed *ortho*-sodiation of aromatic ethers.

be highly favored, and the reaction will proceed even with sodium sand. Interestingly, 1,3-DMB forms a strong complex with Na^+ as the reaction can be successfully carried out in weakly coordinating solvents such as THF or diethylether (Table 1, entries 5 and 6).[33,34] In contrast, anisole binds Na^+ weakly and reacts very slowly with strong bases.[26] As a result, the amount of anisole on the sodium sand surface is low, and alkylsodium molecules will be slowly released in the solution. While Wurtz-type products (nonylbenzene and hexadecane) will form in toluene, alkylsodium compounds will decompose rapidly in THF and no *ortho*-metalation is observed.

Since both 1-chlorooctane and anisole compete for the occupation of the metallic surface, complex **A** will more likely form if the specific area of the metal is increased and/or if the chlorooctane concentration is kept negligible, that is, when the amount of **B** is made as low as possible (Scheme 1; Table 3, entry 4).[35]

The behavior of 1,2- and 1,4-DMB lies between these two extreme cases; they show intermediate reactivity toward the sodium/alkylchloride metalation system. 1,4-DMB is metalated very efficiently,[30] while its affinity for Na^+ is close to that of anisole. On the other hand, 1,2-DMB coordinates to Na^+ quite strongly[32b] but reacts very slowly with strong bases.[30] Low reactivity and low affinity prevent *ortho*-metalation in the presence of sodium sand (Table 3, entry 1). Nevertheless, the reaction proceeds with ease when the specific area of sodium is increased (Table 3, entries 2 and 3).

Besides, the low reactivity of secondary chloroalkanes and the failure of the reaction at low temperature can be ascribed to the fact that the disruption of the sodium particles into smaller aggregates caused by the heat released during the alkylsodium formation is inhibited.[36] The formation of secondary alkylsodium compounds is much less exothermic,[3a] so the metallic surface is more and more shielded as NaCl is progressively formed on it; the result of this is a poor metalation efficiency (Table 1, entries 2 and 6). This hypothesis is corroborated by the unaltered aspect of the sodium dispersion at the end of the reaction.

In conclusion, we have demonstrated that alkylsodium compounds are synthetically useful reagents. Our process requires only inexpensive and readily available reagents. Transportation, storage, and handling of sensitive and dangerous organolithium bases are also avoided. This sodium/chlorooctane-mediated metalation opens new prospects for the metalation of aromatic ethers and heterocycles in laboratories and in the industry.[37] Investigations are currently underway to extend the strategy to the metalation of aromatic derivatives containing electron-withdrawing groups.

Experimental Section

Preparation of the sodium dispersion: The quantity of sodium needed was cut off in small pieces from metal sticks, washed with hexane, and immediately added to dry toluene (35 mL per g Na) under inert atmosphere in a three-necked flask equipped with a condenser, a mechanical stirrer and a dropping funnel. The temperature was raised to 110 °C under gentle stirring until the metal fusion was complete (a uniformly bright metal was obtained). The mixture was then cooled to room temperature under vigorous stirring until a finely divided sodium dispersion was obtained. The dispersion usually consisted of small round gray particles of roughly 1 mm size.

Typical metalation procedure: The aromatic substrate (1 equiv) was added to the sodium dispersion (2.6 equiv) at room temperature. A small portion (roughly one tenth of 1.3 equiv) of the alkyl halide was added drop-wise to initiate the reaction. The reaction initiated within 2–5 min and was characterized by a slight increase of the temperature. The remaining alkyl halide was then added at constant temperature (if necessary, the reaction was cooled). Metalation was monitored by the slow disappearance of sodium and was usually complete within one to two hours. The electrophile was finally added to the mixture at room temperature and allowed to react for a period ranging from two to ten hours depending on the electrophile.

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[1] For general references on organoalkali metal reagents see a) M. Schlosser, *Organometallics in Synthesis*, Wiley, New York, **1996**, chap. 1 and 2; b) R. G. Jones, H. Gilman, *Chem. Rev.* **1954**, *54*, 835.

[2] For general reviews on alkylsodium compounds see a) M. Schlosser, *Angew. Chem.* **1964**, *76*, 258; *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 362; b) M. Schlosser, *Angew. Chem.* **1964**, *76*, 124; *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 287; c) R. A. Benkeser, D. J. Foster, D. M. Sauve, J. F. Nobis, *Chem. Rev.* **1957**, *57*, 867.

[3] For examples see a) A. A. Morton, J. B. Davidson, R. J. Best, *J. Am. Chem. Soc.* **1942**, *64*, 2239; b) P. G. Gassman, D. S. Patton, *J. Am. Chem. Soc.* **1968**, *90*, 7276; c) M. Schlosser, J. Hartmann, M. Stähle, J. Kramar, A. Walde, A. Mordini, *Chimia* **1986**, *40*, 306; d) M. Stähle, R. Lehmann, J. Kramar, M. Schlosser, *Chimia* **1985**, *39*, 229; e) J. Einhorn, J. L. Luche, *Tetrahedron Lett.* **1986**, *27*, 501; f) D. H. R. Barton, F. S. Guziec, I. Shahak, *J. Chem. Soc. Perkin Trans. 1* **1974**, 1794.

[4] a) Ref. [3a]; b) W. L. Carothers, D. D. Coffman, *J. Am. Chem. Soc.* **1929**, *51*, 588; c) A. A. Morton, J. B. Davidson, R. J. Best, *J. Am. Chem. Soc.* **1942**, *64*, 2240; d) A. A. Morton, G. M. Richardson, *J. Am. Chem. Soc.* **1940**, *62*, 123.

[5] a) H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109; b) H. Gilman, R. V. Young, *J. Am. Chem. Soc.* **1935**, *57*, 1121; c) W. Schlenk, J. Holtz, *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 269.

[6] Their reactivity was shown to depend on the method employed for their synthesis, see A. A. Morton, J. T. Massengale, *J. Am. Chem. Soc.* **1940**, *62*, 120.

[7] Historically, alkylsodium compounds were prepared from different sources, see a) J. A. Wanklyn, *Justus Liebigs Ann. Chem.* **1858**, *107*, 125; b) F. S. Acree, *Am. Chem. J.* **1903**, *29*, 588; c) W. Schlenk, J. Appendrodt, A. Michael, A. Thal, *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 473; d) W. Schlenk, E. Marcus, *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 1664; e) W. Schlenk, J. Holtz, *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 262; f) K. Hess, H. Munderloch, *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 377; g) H. Gilman, R. V. Young, *J. Am. Chem. Soc.* **1936**, *58*, 315; h) R. L. Letsinger, J. G. Traynham, *J. Am. Chem. Soc.* **1948**, *70*, 3342; i) L. Lochmann, J. Pospisil, D. Lim, *Tetrahedron Lett.* **1966**, 257; j) U. Azzeno, T. Denurra, G. Melloni, A. M. Piroddi, *J. Org. Chem.* **1990**, *55*, 5386; k) E. Weiss, *Angew. Chem.* **1993**, *105*, 1565; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1501.

[8] A. Wurtz, *Justus Liebigs Ann. Chem.* **1855**, *96*, 364.

[9] See ref. [4b,c].

[10] Alkylsodium compounds react very rapidly with ethereal solvents to afford sluggish reaction mixtures: a) P. Schorigin, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1938; b) P. Schorigin, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 2711.

[11] a) Ref. [5a]; b) H. Gilman, H. A. Pacevitz, O. Baine, *J. Am. Chem. Soc.* **1940**, *62*, 1514.

[12] Reviews on *ortho*-metalation: a) V. Snieckus, *Bull. Soc. Chim. Fr.* **1988**, 67; b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.

[13] Examples of *ortho*-metalations using essentially pure solutions of alkylsodium compounds can be found in ref. [2c] and references therein.

[14] R. Levine, J. R. Sommers, *J. Org. Chem.* **1974**, *39*, 3559.

[15] H. Gilman, H. A. Pacevitz, *J. Am. Chem. Soc.* **1940**, *62*, 1301.

[16] Under optimized conditions, the biphenyl derivative was obtained in 72 % yield.

[17] This reaction has already been observed: G. Ehrhart, *Chem. Ber.* **1963**, 96, 2042.
[18] a) Ref. [4b]; b) A. A. Morton, H. A. Newey, *J. Am. Chem. Soc.* **1942**, *64*, 2242.
[19] D. Q. Quan, *Bull. Soc. Chim. Fr.* **1973**, *2*, 767.
[20] G. P. Crowther, R. J. Sundberg, A. M. Sarpeshkar, *J. Org. Chem.* **1984**, *49*, 4657.
[21] F. J. Brown, P. E. Bernstein, L. A. Cronk, D. L. Dosset, K. C. Hebbel, *J. Med. Chem.* **1989**, *32*, 820.
[22] P. Jacob, A. T. Shulgin, *Synth. Commun.* **1981**, *11*, 957.
[23] J. P. Lambooy, *J. Am. Chem. Soc.* **1956**, *78*, 771.
[24] a) Ref. [3a]; b) Ref. [11b]; c) A. A. Morton, G. M. Richardson, *J. Am. Chem. Soc.* **1941**, *63*, 327.
[25] The micronized sodium dispersion refers to sodium dust <100 μm.
[26] a) Ref. [5a]; b) A. A. Morton, E. J. Lanpher, *J. Org. Chem.* **1958**, *23*, 1639.
[27] a) H. W. Gschwend, H. R. Rodriguez, *Org. React.* **1979**, *26*, 1; b) J. W. Schick, H. D. Hartough, *J. Am. Chem. Soc.* **1948**, *70*, 286.
[28] E. Alonso, D. J. Ramon, M. Yus, *Tetrahedron* **1998**, *54*, 13629.
[29] H. W. Gschwend, A. Hamdan, *J. Org. Chem.* **1975**, *40*, 2008.
[30] M. Schlosser, R. Maggi, *Tetrahedron Lett.* **1999**, *40*, 8797.
[31] 1,3-DMB and anisole disrupt butyllithium oligomers in C_8D_8. While 1,3-DMB forms a stable complex, free and complexed anisole coexist in solution: W. Bauer, P. von R. Schleyer, *J. Am. Chem. Soc.* **1989**, *111*, 7191.
[32] a) Ref. [31]; b) in addition, the binding energies for Na^+–1,2-dimethoxyethane and Na^+–dimethylether in the gas phase were measured and calculated; the affinity is stronger in the case of the cyclic bridged chelate (39.4 and 17.6 kcal mol^{-1}, respectively): T. B. McMahon, G. Ohanessian, *Chem. Eur. J.* **2000**, *6*, 2931.
[33] For examples see: a) M. Vos, F. J. J. de Kanter, M. Schakel, N. J. R. van Eikema Hommes, G. W. Klumpp, *J. Am. Chem. Soc.* **1987**, *109*, 2187; b) E. Wehman, J. T. B. H. Jastrzebski, J. M. Ernsting, D. M. Grove, G. van Koten, *J. Organomet. Chem.* **1988**, *353*, 145.
[34] a) H. J. Reich, B. O. Gudmundsson, *J. Am. Chem. Soc.* **1996**, *118*, 6074; b) H. J. Reich, W. S. Goldenberg, A. W. Sanders, C. C. Tzschucke, *Org. Lett.* **2001**, *3*, 33.
[35] The fact that very slow addition of the chlorooctane led to some product formation ruled out the hypothesis that the higher reactivity observed with the micronized dispersion is a consequence of a different origin of the sodium dispersions. For the preparation and reactivity of metals see: P. Cintas, *Activated Metals in Organic Chemistry*, CRC, Boca Raton, FL, USA, **1993**.
[36] The composition of these aggregates was analyzed: A. A. Morton, A. E. Brachman, *J. Am. Chem. Soc.* **1954**, *76*, 2980.
[37] a) A. Wagner, C. Mioskowski, A. Gissot, J. R. Desmurs, S. Jost (Rhodia Chimie), WO 0064905, **2000**; b) V. Pévère, J. R. Desmurs, C. Mioskowski, A. Wagner, A. Gissot (Rhodia Chimie), WO 9959941, **1999**.

Palladium-Catalyzed Regio- and Diastereoselective Tandem Silastannylation/Allyl Addition of Allene Aldehydes and Allene Ketones: Synthesis of *cis* Cyclopentanols and Cyclohexanols[**]

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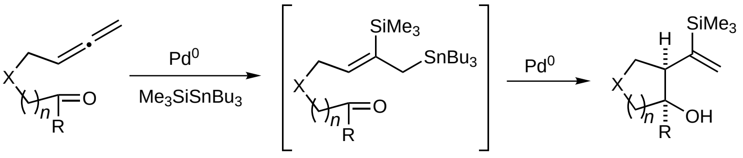
To achieve economically useful transformations in organic synthesis it would be desirable if multistep bond formations and/or bond cleavages could be facilitated with a single catalyst in one pot at a constant temperature. Such a process would minimize the amount of chemicals, the production of waste, and the processing time.[1, 2] In this regard, Jeong et al.[3] reported allylation/Pauson–Khand reactions with two artificial catalysts in a one-pot procedure. Subsequently, Evans et al.[4] developed the allylation/Pauson–Khand reaction in a tandem sequence with a Rh complex as the only catalyst. Recently, Shibasaki and co-workers[5] reported a one-pot synthesis of β-cyanohydrin from olefins mediated by a Zr catalyst.

The palladium-catalyzed addition of silylstannanes to allenes is known[6] and the palladium- or platinum-catalyzed addition of allylstannanes to aldehydes was reported by Yamamoto et al.[7, 8] However, to the best of our knowledge, the transition metal catalyzed addition of allylstannanes to ketones has not yet been successful. Our ongoing studies into the use of allene substrates in organic synthesis[9] led us to believe that allene aldehydes and allene ketones are good substrates for palladium-catalyzed silastannylations. In a tandem reaction, the resulting allylstannanes would be good candidates for carbonyl allyl addition with a single palladium catalyst at a constant temperature (Scheme 1).

The results of the tandem silastannylation/carbonyl allyl addition of allene aldehydes and allene ketones to form *cis* cyclopentanols[10] are summarized in Table 1. In finding



Scheme 1. Tandem silastannylation/allyl addition of allene aldehydes and allene ketones ($n = 1, 2$; R = H, CH_3; X = NTs, O, $C(CO_2Et)_2$, etc.).

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