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Enantioselective Synthesis of α-Ionone Derivatives Using an Anti S_N2' Substitution of Functionalized Zinc Organometallics

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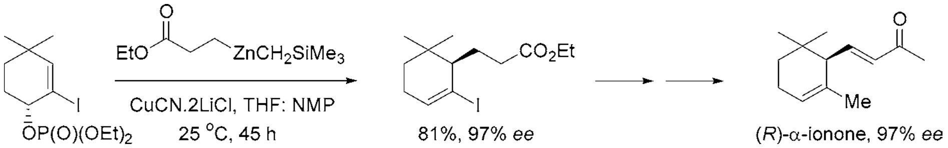
ABSTRACT



The allylic substitution of sterically hindered (2-iodocycloalkyl)phosphates proceeds with complete anti S_N2' stereoselectivity with mixed diorganozincs of the type $RZnCH_2SiMe_3$ in the presence of CuCN·2LiCl. Only the group R of the copper–zinc reagent is transferred in the allylic substitution. This method was used to prepare odoriferous substances such as (*R*)-α-ionone in 97% ee and (*R*)-dihydro-α-ionone in 98% ee.

The stereoselective formation of new carbon−carbon bonds is an important research field. Allylic substitutions are especially convenient for transferring the chirality of a C−X bond to a C−C bond. A range of copper-[1] and palladium-catalyzed[2] stereoselective allylic substitutions have been reported.[3] Recently, we have shown that various diorganozincs undergo highly stereoselective anti S_N2' allylic substitutions in the presence of CuCN·2LiCl[4] in cyclic[5] and acyclic[6] systems. Herein, we wish to demonstrate the remarkable ability of mixed zinc−copper organometallics prepared from mixed diorganozincs $RZnCH_2SiMe_3$ (**1**)[7] for undergoing S_N2' substitutions even with sterically hindered systems. As an application, we have prepared via this method (*R*)-α-ionone **2** in 97% ee and (*R*)-dihydro-α-ionone **3** in 98% ee starting from the readily available allylic phosphate **4**[8] (Scheme 1).

In a preliminary experiment, we have treated the allylic phosphate **4**[9] with dipentylzinc (2 equiv) and CuCN·2LiCl (1 equiv) in a 3:1 mixture of THF and *N*-methylpyrrolidinone

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[1] (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (b) *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH. (c) Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420. (d) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864. (e) Arai, M.; Kawasuji, T.; Nakamura, E. *J. Org. Chem.* **1993**, *58*, 5121. (f) Breit, B.; Demel, P. *Adv. Synth. Catal.* **2001**, *343*, 429. (g) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2001**, *66*, 5552. (h) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **2000**, *65*, 1601. (i) Spino, C.; Beaulieu, C. *J. Am. Chem. Soc.* **1998**, *120*, 11832. (j) Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984. (k) Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147. (l) Malda, H.; van Zijl, A. W.; Arnold, L. A.; Feringa, B. L. *Org. Lett.* **2001**, *3*, 1169. (m) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem.* **2001**, *113*, 1504; *Angew. Chem., Int. Ed.* **2001**, *40*, 1456. (n) Karlström, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J. E. *Synlett* **2001**, 923.

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[4] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

[5] Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059.

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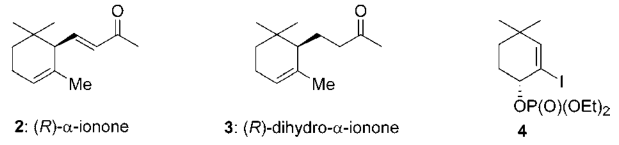
Scheme 1



(NMP) at temperatures from −30 to −10 °C for 14 h and have observed the formation of the anti substitution product **5a** in 80% yield and 97% ee. Despite the presence of a quaternary center bearing two methyl groups in the α-position, only the anti S_N2' product is obtained and no S_N2 substitution can be detected (Scheme 2). We have briefly examined the use of other leaving groups instead of a phosphate and have prepared the corresponding pentafluorobenzoate of **4**. However, in this case, the desired product was obtained only in 55% yield. Since we planned to perform the allylic substitution with a range of functionalized diorganozincs,[10,11] we have prepared the mixed diorganozincs $RZnCH_2SiMe_3$ (**1**), which transfer exclusively the R group to the electrophilic reagent[7,12] by the addition of commercially available solution of Me_3SiCH_2Li to the corresponding alkylzinc iodide RZnI (**6**) prepared by the direct insertion of zinc to the alkyl iodide (RI).

Scheme 2

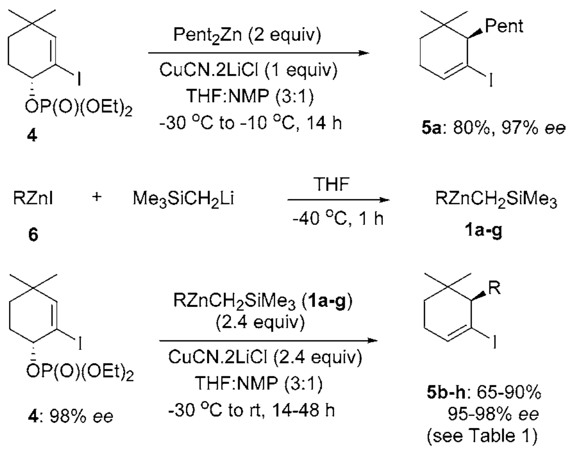
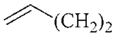
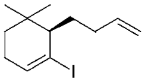
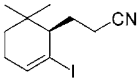
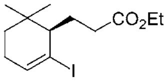
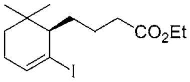
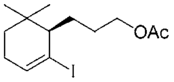
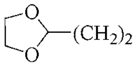
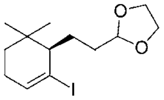
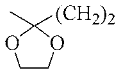
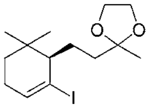


Table 1. Allylic Substitution Products **5b−h** Obtained by the Reaction of the Mixed Diorganozincs **1a−g** with the Allylic Phosphate **4** in the Presence of CuCN·2LiCl

entry	$RZnCH_2SiMe_3$ (R)	product of type **5**	yield (%)[a]	*ee* (%)[b]
1	 **1a**	 **5b**	85	98
2	$NC(CH_2)_2$ **1b**	 **5c**	73	95
3	$EtO_2C(CH_2)_2$ **1c**	 **5d**	81	97
4	$EtO_2C(CH_2)_3$ **1d**	 **5e**	82	98
5	$AcO(CH_2)_3$ **1e**	 **5f**	65	97
6	 **1f**	 **5g**	90	98
7	 **1g**	 **5h**	71	98

[a] Isolated yield of analytically pure product. [b] Enantiomeric excess was determined by chiral-GC. In each case, the racemic product was prepared for calibration.

The reaction of the mixed zinc reagents **1a−g** with the allylic phosphate **4** in the presence of CuCN·2LiCl in 3:1 mixtures of THF and NMP at temperatures between −30 °C and room temperature for 14−48 h produces the desired S_N2' substitution products **5b−h**, respectively. These are the only products obtained despite the steric hindrance of the two adjacent methyl groups in yields between 65 and 90% and enantioselectivities of 95−98% (Table 1 and Scheme 2). Excellent transfer of the chirality is observed, and the use of the mixed diorganozincs of type **1** avoids the waste of the polyfunctional zinc reagents **6**. Thus, the reaction of 3-butenyl(trimethylsilylmethyl)zinc (**1a**) with **4** furnishes under our standard conditions (14 h reaction time) the product **5b** in 85 and 98% ee. Remarkably, a range of functionalized zinc reagents (**1b−g**) can be used as well (entries 2−7). The somewhat unreactive 2-cyanoethyl(trimethylsilylmethyl)zinc (**1b**) requires a reaction time of 40 h but provides the expected nitrile in 73% yield with a slight erosion of the stereoisomeric purity (95% ee, entry 2). Ester-substituted

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(8) CBS reduction of 4,4-dimethyl-2-iodo-2-cyclohexen-1-one provides 4,4-dimethyl-2-iodo-2-cyclohexen-1-ol in 98% ee and 90% yield (see Supporting Information).

(9) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 251.

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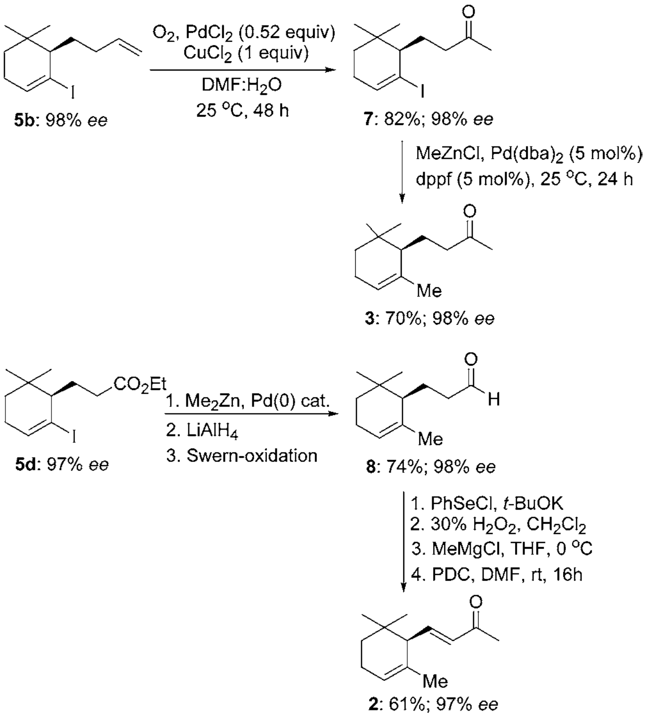
diorganozincs such as **1c**−**e** (entries 3−5) react perfectly affording the S_N2' substitution products (**5d**−**f**) in 97−98% ee (entries 3−5). Whereas aldehyde and ketone functionalities are not readily tolerated in this procedure, the use of the corresponding acetal or ketal is perfectly compatible with our mild reaction conditions, leading to the desired S_N2' substitution products (**5g** and **5h**) in 71−90% yield and 98% ee (entries 6 and 7).

Several of the products of type **5** can be used for the preparation of optically active α-ionone derivatives. This group of natural products having a violet-like odor are formed by the oxidative degradation of carotenes. They are widely distributed in vegetables and fruits, especially in tea and tobacco.[13] Thus, the palladium-catalyzed oxidation of the cyclohexenyl iodide **5b** ($PdCl_2$ (0.52 equiv), $CuCl_2$ (1 equiv), O_2, DMF:H_2O, 25 °C, 48 h) provides the ketone **7** in 82% yield (98% ee).[14] The reaction of the ketone **7** with MeZnCl (3 equiv) in the presence of $Pd(dba)_2$ (5 mol %) and bis-diphenylphosphinoferrocene (dppf)[15] (5 mol %) leads to (*R*)-dihydro-α-ionone **3** in 70% yield and 98% ee (Scheme 3).

(*R*)-α-Ionone (**2**) is best prepared from the iodoester **5d**. Negishi cross-coupling with Me_2Zn ($Pd(dba)_2$ (5 mol %, dppf (5 mol %), rt, 26 h) provides the desired methylated product in 81% yield. Reduction of this intermediate to the corresponding alcohol with $LiAlH_4$ (Et_2O, 0 °C, 10 min) followed by a reoxidation to the aldehyde **8** under Swern conditions proceeds with an overall yield of 74%. Phenylselenation with PhSeCl and *t*-BuOK (−78 °C, 5 h) followed by selenium oxidation and elimination (30% aq H_2O_2, CH_2Cl_2, rt) furnishes the expected unsaturated aldehyde. The synthesis of (*R*)-α-ionone is completed by the addition of MeMgCl in THF at 0 °C followed by PDC oxidation in DMF, affording (*R*)-α-ionone (**2**) in 61% yield and 97% ee.[16] Attempts to use the iodoacetal **5g** as a starting material for the synthesis of (*R*)-α-ionone (**2**) was complicated by acid-catalyzed cyclization side-reactions.

Scheme 3



In summary, we have shown that polyfunctional mixed diorganozinc compounds of the type FG-$RZnCH_2SiMe_3$ react with sterically very hindered allylic phosphates, providing anti S_N2' products with very high regio- and stereoselectivity.[17] We have demonstrated the utility of this procedure by preparing (*R*)-α-ionone (**2**) and (*R*)-dihydro-α-ionone (**3**).

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

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(17) **Typical Procedure: Preparation of 5d.** Freshly prepared 2-carboethoxyethyzinc iodide (1.64 M solution in THF, 0.8 mL, 1.2 mmol, 2.4 equiv) was treated with $TMSCH_2Li$ (1 M in pentane, 1.2 mL, 1.2 mmol, 2.4 equiv) at −40 °C for 1 h and then allowed to warm to −30 °C. To the resulting mixture was added successively a solution of CuCN·2LiCl (1 M solution in THF, 1.2 mL, 1.2 mmol, 2.4 equiv) and NMP (1 mL). The resulting mixture was stirred at −30 °C for 30 min. A THF solution of allylic phosphates (194 mg, 0.5 mmol, 1 equiv) was added, and the reaction mixture was stirred for 45 h while being warmed to 25 °C. The desired product **5d** was obtained after purification by column chromatography (SiO_2, 10% Et_2O/pentane) as a colorless oil (134 mg, 81% yield).