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Palladium Catalyzed Stereoselective Cross-Couplings and Acylations of Chiral Secondary Diorganozincs

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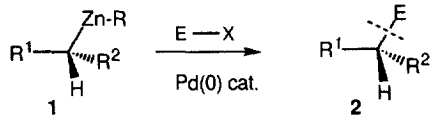
Abstract
Cyclic and open-chain trisubstituted olefins were hydroborated with (-)-IpcBH$_2$ and stereoselectively transmetalated to the corresponding chiral zinc reagents with excellent diastereoselectivity and good enantioselectivity. The palladium(0) catalyzed cross-coupling with alkenyl iodides or acyl chlorides proceeds with high retention of configuration in satisfactory overall yields.

Keywords: Stereoselective cross-coupling, palladium catalysis, alkenylation, acylation

Recently, we have developed a general preparation method for chiral cyclic[1] or open-chain[2] secondary organozincs type **1** by a hydroboration, boron-zinc exchange sequence. We have shown that these zinc organometallics react stereoselectively with allylic halides and alkynyl bromides in the presence of catalytic amounts of CuCN·2LiCl.[3] The allylation reaction proceeds with retention of configuration.[2] In order to extend the scope of the reaction we have examined the palladium catalyzed cross-coupling of the chiral organometallics **1** with alkenyl iodides[4,5] and acid chlorides[4,6] (Negishi reaction leading to products of type **2**, Scheme 1).



1 2

Scheme 1

The hydroboration of 1-methylindene **3a** with monoisopinocampheylborane **4** ((-)-IpcBH$_2$; 99% *ee*)[7] provides the chiral borane **5a** (ether, -35 °C, 2d). This organoborane was converted to the corresponding (alkyl)ethylborane by treatment with Et$_2$BH[8] (excess, 50 °C, 16 h) which readily undergoes a transmetalation with *i*-Pr$_2$Zn (3 equiv., rt, 5 h) furnishing the mixed zinc derivative **1a**. After much experimentation, we have found that in the presence of catalytic amounts of palladium bis(dibenzylideneacetone) (Pd(dba)$_2$, 2 mol%)[9] and tri(*o*-tolyl)phosphine (*o*-Tol$_3$P, 4 mol%),[10] the zinc reagent **1a** undergoes a highly stereoselective cross-coupling with *E*-1-iodohexene (**6a**) (3 equiv., THF, 0 °C to rt, 12 h) leading to the *trans*-1,2-disubstituted indane **2a** in 35% overall yield. The *cis-trans* ratio was 1:99 showing the excellent configurational stability of the chiral palladium(II) intermediate **7a**.[11] An enantiomeric excess of 56% was determined showing that the asymmetric hydroboration of **3a** with (-)-IpcBH$_2$ **4** is only moderately selective (Scheme 2). Similarly, the same sequence applied to 1-methyl-3,4-dihydronaphthalene (**3b**) furnishes a similar diastereoselectivity and enantioselectivity (see entry 2 of Table 1).

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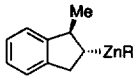
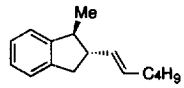
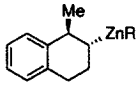
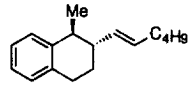
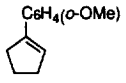
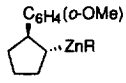
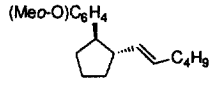
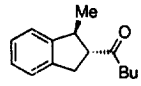
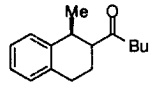
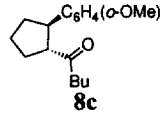
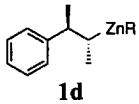
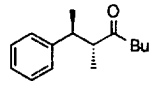
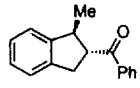
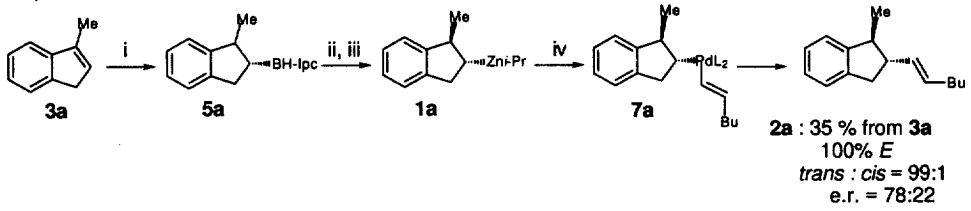
Table 1. Products obtained by the reaction of the configurationally stable zinc reagents **1** with electrophiles in the presence of Pd(0).

Entry	Starting Alkene **3**	Organozinc Reagent **1**[a]	EX **6**[b]	Product of Type	Yield[c] (%)	*anti*:*syn*	er[d]
1	 **3a**	 **1a**	A	 **2a**	35	99:1	78:22
2	 **3b**	 **1b**	A	 **2b**	41	99:1	76:24
3	 **3c**	 **1c**	A	 **2c**	40	98:2	91.5:8.5
4	**3a**	**1a**	B	 **8a**	39	92:8	82:18
5	**3b**	**1b**	B	 **8b**	43	92:8	80:20
6	**3c**	**1c**	B	 **8c**	58	99:1	90.5:9.5
7	 **3d**	 **1d**	B	 **8d**	45	90:10	94:6
8	**3a**	**1a**	C	 **8e**	41	95:5	80:20[e]

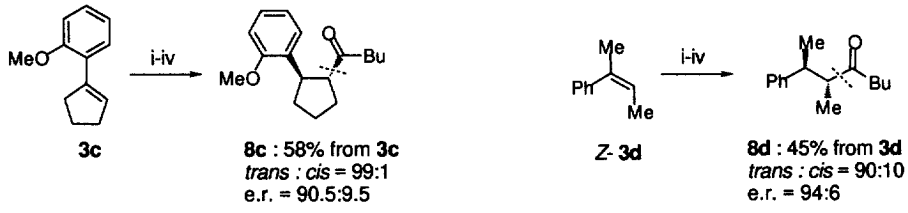
(a) R = *i*-Pr. (b) A = *E*-1-iodohexene; B = pentanoyl chloride; C = benzoyl chloride. (c) Yield of analytically pure product based on the starting alkene **3**. (d) Enantiomeric ratio of major diastereomer determined by GC analysis on a chiral cyclodextrin column. (e) No separation of the enantiomer signals could be obtained. Nevertheless by comparison with entries 1 and 4, a similar enantioselectivity close to 80:20 should be obtained.

Remarkably, the 1-(*o*-methoxyphenyl)cyclopentene (**3c**) can be hydroborated with $IpcBH_2$ with high enantioselectivity and in this case the alkenylated product (**2c**) is obtained with 83% *ee* (see entry 3 of Table 1).



Scheme 2: (i) (-)$IpcBH_2$ **4** (1 equiv.), ether, -35°C, 48h; (ii) Et_2BH (6 equiv.), 50°C, 16 h; (iii) *i*-Pr_2Zn (3equiv.), 25°C, 5 h; (iv) $Pd(dba)_2$ (2 mol%), P(*o*-tolyl)$_3$ (4 mol%), *E*-1-iodohexene **6a** (3 equiv.), THF, 0°C to 25°C, 16h

We have also examined the palladium catalyzed acylation[6] and have found that diastereoselectivities of up to 99:1 can be reached for cyclic secondary organozinc intermediates[12] (Scheme 3 and entries 4-6, 8 of Table 1). Generally, the observed diastereoselectivities of the resulting ketones of type **8** are better than 92:8. The palladium catalyzed acylation can be extended to open-chain secondary organozinc intermediates. Thus, the styrene derivative *Z*-**3d** affords after the standard asymmetric hydroboration and boron-zinc exchange sequence and palladium catalyzed acylation with BuCOCl, the desired ketone **8d** with a diastereomeric ratio of 90:10 and an enantiomeric excess of 88 % (e.r. = 94:6) (Scheme 3 and entry 7 of Table 1).



Scheme 3: (i) (-)$IpcBH_2$ **4** (1 equiv.), ether, -35°C, 48h; (ii) Et_2BH (6 equiv.), 50°C, 16 h; (iii) *i*-Pr_2Zn (3equiv.), 25°C, 5 h; (iv) $Pd(dba)_2$ (2 mol%), P(*o*-tolyl)$_3$ (4 mol%), pentanoyl chloride (3 equiv.), dioxane, 0°C to 25°C, 16h

In summary, we have shown that cyclic and open-chain chiral zinc reagents react stereoselectively with alkenyl iodides and acid chlorides in the presence of a palladium(0) catalyst given an access to various diastereomerically and enantiomerically enriched products. Extension of this methodology to other palladium catalyzed cross-couplings is currently underway in our laboratories.[13]

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References and Notes

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[10] Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955-958.
[11] The relative *trans*-stereochemistry of products **2** showing the ruring the cross-coupling has been proven in the case of **2b**. For this compound, a COSY-NMR experiment showed a NOE correlation between the benzylic methyl group and the neighbouring allylic proton as well as a NOE correlation between the benzylic proton and the vinylic proton.
[12] For the palladium catalyzed acylation of cyclic zinc homoenolates, see: (a) Sakami, S.; Houkawa, T.; Asaoka, M.; Takei, H. *J. Chem. Soc. Perkin Trans. 1*, **1995**, 285-6. (b) Houkawa, T.; Ueda, T.; Sakami, S.; Asaoka, M.; Takei, H. *Tetrahedron Lett.* **1996**, *37*, 1045-1048. (c) Asaoka, M.; Tanaka, M.; Houkawa, T.; Ueda, T.; Sakami, S.; Takei, H. *Tetrahedron* **1998**, *54*, 471-486.
[13] **Typical procedure: Preparation of (*1S*, *2R*)-1-(*o*-methoxyphenyl)-2-(hex-1-ene)cyclopentane (2c):** A Schlenk-flask was charged with $IpcBH_2$ **4** (2.5 mL, 2.5 mmol, 1.0 M) in ether, cooled to -35 °C and 1-(*o*-methoxyphenyl)cyclopentene (**3c**, 435 mg, 2.5 mmol) in ether (1 mL) was added. The reaction mixture was stirred at -35 °C for 48 h and the solvents were carefully evaporated under reduced pressure. Et_2BH (2.1 mL of a 7.3 M solution in Me_2S, 15 mmol) was added and the resulting solution was stirred at 50 °C for 16 h. The solvents were evaporated under reduced pressure (rt, 2 h). *i*-Pr_2Zn (2.5 mL of a 3 M solution in Et_2O, 7.5 mmol) was added over a 10 min period and the reaction mixture was stirred at rt for 5 h. The volatiles were evaporated under reduced pressure (0 °C to 25 °C, 30 min) and the resulting grey residue was dissolved in THF (5 mL). The mixture was filtered under inert gas and cooled to 0°C. A previously prepared mixture of $Pd(dba)_2$ (10 mg, 2 mol%) and P(*o*-tolyl)$_3$ (15 mg, 4 mol%) and *Z*-1-iodohexene **6a** (1.575 g, 7.5 mmol) in THF (3 mL) was added . The reaction mixture was allowed to warm slowly to 25°C. After 12 h the reaction mixture was quenched with aq. sat. NH_4Cl and extracted with Et_2O. After drying ($MgSO_4$) and evaporating the solvents, the crude residue obtained was purified by chromatography (SiO_2, hexanes) affording 258 mg (40% based on the starting alkene) of pure **2c**. The *syn*:*anti* ratio (d.r.: 2:98) and enantioselectivity (e.r.: 91.5:8.5) were determined by capillary GC analysis on a chiral cyclodextrin column (CP-Chirasil-Dex CB, Chrompack).
Typical procedure: Preparation of (*1 S*, *2 R*)-1-(*o*-methoxyphenyl)-2-(pentan-1-one)cyclopentane (8c): A Schlenk-flask was charged with $IpcBH_2$ **4** (3.1 mL, 2.5 mmol, 0.8 M) in ether, cooled to -35 °C and 1-(*o*-methoxyphenyl)cyclopentene (**3c**, 435 mg, 2.5 mmol) in ether (1 mL) was added. The reaction mixture was stirred at -35 °C for 48 h and the solvents were carefully evaporated under reduced pressure. Et_2BH (2.1 mL of a 7.3 M solution in Me_2S, 15 mmol) was added and the resulting solution was stirred at 50 °C for 16 h. The solvents were evaporated under reduced pressure (rt, 2 h). *i*-Pr_2Zn (2.5 mL of a 3 M solution in Et_2O, 7.5 mmol) was added over a 10 min period and the reaction mixture was stirred at rt for 5 h. The volatiles were evaporated under reduced pressure (0 °C to 25 °C, 30 min) and the resulting grey residue was dissolved in dioxane (5 mL). The mixture was filtered under inert gas and cooled to 0°C. A previously prepared mixture of $Pd(dba)_2$ (20 mg, 2 mol%) and P(*o*-tolyl)$_3$ (30 mg, 4 mol%) and pentanoyl chloride (905 mg, 7.5 mmol) in dioxane (3 mL) was added . The reaction mixture was allowed to warm slowly to 25 °C. After 12 h the reaction mixture was quenched with aq. NH_3 and stirred for 15 min. Then aq. 2M HCl was added and the mixture was extracted with Et_2O. After drying ($MgSO_4$) and evaporating the solvents, the crude residue obtained was purified by chromatography (SiO_2, hexanes:ether = 49:1) affording 375 mg (58% based on the starting alkene) of pure **8c**. The *syn*:*anti* ratio (d.r.: 1:99) and enantioselectivity (e.r.: 90.5:9.5) were determined by capillary GC analysis on a chiral cyclodextrin column (CP-Chirasil-Dex CB, Chrompack).