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LETTERS

Realization of High Regioselectivity in the Coupling Reaction of a Cyclopentadiene Monoepoxide Equivalent and Aryl Nucleophiles

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Abstract: Coupling reaction of monoacetate **2** and aryl hard nucleophiles is realized for the first time, which consists of the lithium arylborates as hard nucleophiles and $NiCl_2(PPh_3)_2$ as a catalyst. More importantly, the independent effects of *t*-BuCN and NaI and their synergistic function are discovered to increase regioselectivity furnishing *trans* 1,3-isomers **6** as the major products.

It is well recognized that the coupling reaction of cyclopentadiene monoepoxide (**1**) or its equivalent with hard nucleophiles under transition metal catalysis is a promising method for installation of a side chain onto the 5-membered ring system.[1-3] High regio- and stereoselectivities are attained in the palladium-catalyzed reaction with soft nucleophiles[2a,b] and thus its synthetic applications have been published.[2c-g] However, reports on reactions with hard nucleophiles are scarce[3] although there are many publications regarding acyclic diene monoepoxides or their synthetic equivalents.[3,4] The classical π-allylmetal intermediate (Figure 1: next page) is convincing to illustrate the difficulty in controlling the reaction site with hard nucleophiles: there is no steric interaction with the hydroxyl group nor coordination to it. In fact, the palladium-catalyzed reaction of **1** with aryl- and alkenylstannanes, the only example published so far, is highly stereoselective, but its regioselectivity is considerably low.[3] Recently, we reported that the 4-cyclopentene-1,3-diol monoacetate (**2**) as the synthetic equivalent of **1** in the nickel-catalyzed reaction with Li[B(2-furyl)$(OMe)_3$] furnished 1,3-isomer selectively.[5] Definite advantages in using **2** are its stability and the efficient methods that have been established for preparing both enantiomers of **2**.[6] Unfortunately, extension of the reaction to other borates was unsuccessful.[7] During these investigations more reactive borates **3**, which are prepared *in situ* from the cyclic boronate esters **5** and MeLi, have been developed.[8] Taking into consideration the importance of cyclopentanoids in the pharmaceutical


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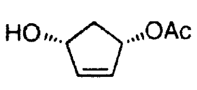
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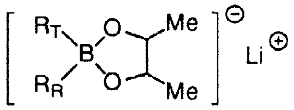
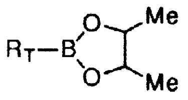

3: R_R = Me
4: R_R = Bu-*n*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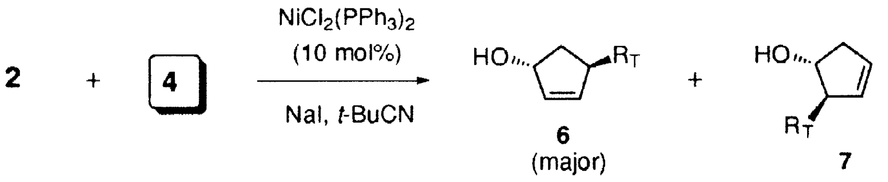

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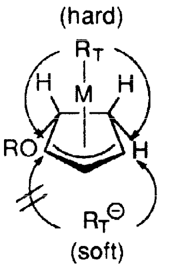
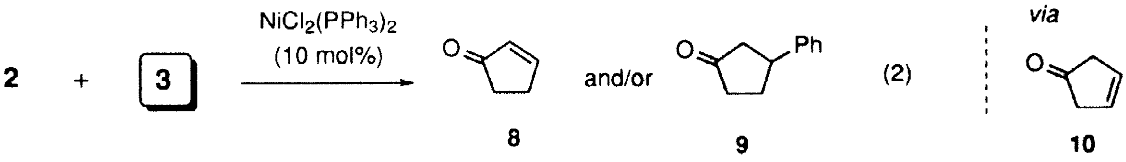


Figure 1. Transition states for soft and hard nucleophiles.

field and the advantages in using **2**, coupling of **2** with borates of type **3** seemed to be an attractive objective. Application of the reported protocol to phenylborate **3** (R_T = Ph) was again unsatisfactory. However, by using advanced borates **4** possessing a *n*-Bu ligand, the coupling was realized for the first time. More importantly, new additive effects securing high regioselectivity have been discovered. Herein we report the promising results summarized in eq 1.

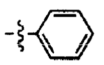
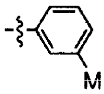
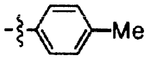
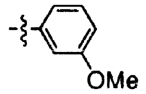
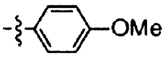
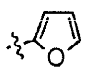
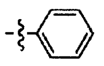
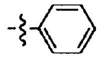
To elucidate the proper conditions under which the coupling takes place, phenylborate **3a** (R_T = Ph) was chosen because of its poor propensity to react with allylic carbonates, which had been observed during our earlier study.[9] First, the reaction was carried out using racemic **2**[10] under the reported conditions ($NiCl_2(PPh_3)_2$ (10 mol%), THF, room temp., overnight). Unfortunately, a mixture of **8** and **9** was produced (eq 2).[11] In other words, β-hydrogen elimination of the π-allylnickel to afford **10** was faster than transmetalation. This result recalls the same transformation strongly mediated by palladium catalysts.[12] To increase reactivity of the borate, more electron-releasing ligands were then examined. After several trials, borate **4a** (R_T = Ph) (1.5 equiv) prepared from **5a** (R_T = Ph) and *n*-BuLi was discovered to furnish *trans* products **6a** (R_T = Ph) and **7a** (R_T = Ph) in 82% yield.[13] No *cis* isomers nor the aforementioned side products **8-10** were detected in the crude ^1H NMR spectrum. However, regioselectivity was disappointingly low (**6a** : **7a** = 0.9 : 1). Other catalysts such as $NiCl_2(dppf)$, $NiCl_2(dppp)$, $NiCl_2(dppe)$, $NiCl_2(PBu_3)_2$, $NiCl_2(AsPh_3)_2$, and $PdCl_2(PPh_3)_2$ marginally improved the regioselectivity and the yield: complex mixtures containing **8** and/or **9** were obtained, while $Ni(PPh_3)_4$ and $Pd(PPh_3)_4$ gave **9** as the major product.[11]



Next, to seek better conditions for high regioselectivity, aprotic polar compounds and inorganic salts were surveyed. DMF, DMSO, NEt_3, pyridine, and *t*-BuCN were found to increase the selectivity for 1,3-isomer **6a** and among them, *t*-BuCN (2 equiv) showed the highest selectivity (**6a** : **7a** = 6.6 : 1). Other nitriles (MeCN, EtCN, PhCN, AIBN) were further checked, but the ratios were lower than that obtained with *t*-BuCN.[14] On the other hand, among the inorganic salts we tested, the best results were obtained when NaI (1 equiv) was added (**6a** : **7a** = 5 : 1). To the best of our knowledge, these effects are unprecedented for the nickel catalyst.[15] Since a deeper shade of brown was observed only in the NaI addition, the independent roles of *t*-BuCN and NaI were inferred. Consequently, *t*-BuCN and NaI were both added, and the *synergistic effect of 13 : 1 was indeed observed with 84% isolated yield!* (Table 1, entry 1).

The generality of the regio-enhancer [*t*-BuCN (2-5 equiv) + NaI (0.5-1 equiv)] was then checked. The arylborates **4b-f** were examined and their results are also shown in Table 1. All of the reactions were carried out using racemic **2** and 1.2-1.8 equiv of borates **4b-f** with the regio-enhancer. Arylborates **4b-f** gave 1,3-isomers as the major products. Although regioselectivities were dependent upon the borates, satisfactory levels for synthetic purposes were obtained for all of the borates. For comparison, inherent regioselectivities (obtained in

Table 1. Coupling of *rac*-2, 11, and 12 with the arylborates 4a-f[a]

					ratio of **6** : **7**[c,d]	
entry	substrate[b]	a–f	R_T of **4–7**	yield,%	with enhancer	no enhancer
1	**2**	**a**		84	13 : 1	0.9 : 1
2	**2**	**b**		80	7 : 1	1.2 : 1
3	**2**	**c**		81	12 : 1	1.5 : 1
4	**2**	**d**		84	6 : 1	0.7 : 1
5	**2**	**e**		81	9 : 1	
6	**2**	**f**		63	8 : 1	
7	**11**	**a**		81	16 : 1	
8	**12**	**a**		98	9 : 1	

[a] Reactions were carried out with $NiCl_2(PPh_3)_2$ (10 mol%) in the presence or absence of the regio-enhancer [*t*-BuCN (2-5 equiv) and NaI (0.5-1 equiv)]. [b] Racemic substrates were used. [c] Ratios were determined by ^1H NMR (300 MHz) spectroscopy. [d] Ratios given in entries 7 and 8 are for the MOM ethers of **6a/7a** and TBDMS ethers of **6a/7a**, respectively.

the absence of the enhancer) for some of the borates are also shown in Table 1.

Finally, the influence of the hydroxyl group present in **2** was studied briefly by using the MOM ether **11** and TBDMS ether **12** as substrates. Comparable ratios obtained with phenylborate **4a** (Table 1, entries 7 and 8) indicate that the hydroxyl (or alkoxy) group opposite the nickel on the transition state (Figure 1) does not affect the regioselectivity.

11 R = MOM
12 R = TBDMS

In summary, a new method for regioselective installation of hard nucleophiles onto a five-membered ring is described, which relies on discovery of the reactive borates **4** and the regio-enhancers as well as a finding of the synergistic effect of the enhancers. Use of 1.2-1.8 equiv of the borates **4** even in the presence of the free hydroxyl group on **2** is sufficient for reasonable yields. In addition, the large difference in R_f values between 1,3-isomers **6** and 1,2-isomers **7** allows easy separation of the isomers by column chromatography on silica gel. We are continuing our efforts to elucidate the π-allylnickel intermediate by spectroscopy.

General Procedure: To an ice-cold suspension of the boronate ester **5** (1.44 mmol) and $NiCl_2(PPh_3)_2$ (55 mg, 0.084 mmol), and NaI (120 mg, 0.80 mmol) in THF (2 mL) was added *n*-BuLi (1.2 mmol, ca 2 M in hexane).

After being stirred for 15 min at the same temperature, *t*-BuCN (0.18 mL, 1.6 mmol) and the monoacetate **2** (100 mg, 0.80 mmol) were added. The mixture was stirred at room temperature for several hours or overnight and then sat. NaHCO$_3$ solution was added. The resulting mixture was extracted as usual and purification by chromatography afforded the 1,2-isomer **7** first and then the 1,3-isomer **6**.

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REFERENCES AND NOTES

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11. (a) Plausible pathway to **8** and **9** is isomerization of **10** to **8** and the subsequent nickel catalyzed 1,4-addition[11b] of **3a** or **4a** to **8**. (b) Grisso, B. A.; Johnson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160-5165.
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14. Ratios of **6a**/**7a** obtained with the nitriles were 5.2 (MeCN), 3.9 (EtCN), 4.0 (PhCN), and 6.0 (AIBN), respectively.
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