Orthogonal Cross-Couplings

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Differentiating C–Br and C–Cl Bond Activation by Using Solvent Polarity: Applications to Orthogonal Alkyl–Alkyl Negishi Reactions**

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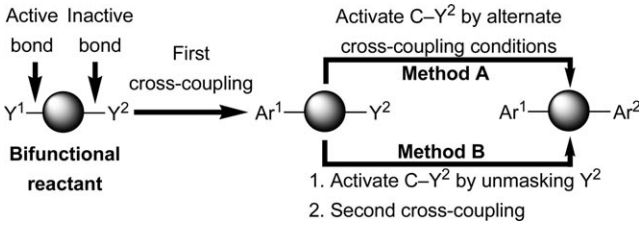
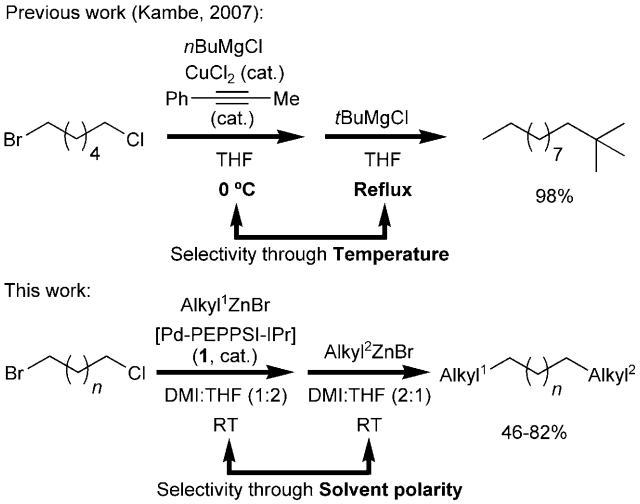
Orthogonal reactivity allows one to chemoselectively address one of two reactive centers—both of which are capable of undergoing the same chemical transformation, e.g., cross-couplings—within a bifunctional starting material or intermediate (Scheme 1). This is most commonly achieved by one



Scheme 1. General overview of orthogonal cross-coupling strategies.

of two methods: A) fine-tuning the reaction conditions (i.e., temperature, catalyst, additives, etc.) for each reactive center or B) protecting group chemistry. Method A is commonly achieved by taking advantage of the differences in bond enthalpies (C–I > C–Br ≫ C–Cl),[1] and more recently has come to include the C_{aryl}–O bonds (i.e., aryl carboxylates,[2] carbamates, carbonates, and sulfamates[3]) that can be efficiently coupled in the presence of a Ni (but not Pd) catalyst, lending itself to orthogonal reaction strategies.[4]

Method B has been applied in the form of masked boronic acids, including pinacol esters,[5] BF_3K salts,[6] *N*-methyliminodiacetic acid (MIDA),[7] and 1,8-diaminonaphthalene (dan)-borane[8] derivatives. Strategies based on method B generally discount the possibility of one-pot reaction sequences due to the need for deprotection chemistry. However, bifunctional organodiborane linchpins possessing two of these boronic acid derivatives have been applied successfully in various orthogonal cross-coupling strategies to form aryl–aryl or aryl–vinyl motifs.[9] Largely absent from the literature are examples of orthogonal alkyl–alkyl cross-couplings of two unactivated alkyl fragments; to our knowledge, only one



Scheme 2. An overview of known orthogonal alkyl–alkyl cross-couplings.

example[10] is known (Scheme 2, previous work).[11] Kambe and co-workers showed in a single example that 1-bromo-6-chlorohexane could undergo sequential Kumada–Tamao–Corriu cross-couplings using temperature as the orthogonal trigger in one-pot in the presence of a Cu^{II} catalyst. Examples of this type are rare as specially designed, highly active catalysts are typically required to couple unactivated alkyl fragments efficiently,[12] with the trade-off that discrimination between C_{alkyl}–Br and C_{alkyl}–Cl bonds is now less chemoselective. For example, we have shown that NHC–Pd catalysts (NHC = N-heterocyclic carbene), generated in situ from either an imidazolium salt[13] or a pre-catalyst,[14] namely [Pd-PEPPSI-IPr] (**1**),[15] can effectively couple both unactivated primary C_{alkyl}–Br and C_{alkyl}–Cl bonds in the Negishi reaction at room temperature.[16] During the course of these studies, however, we discovered a unique property that allowed us to chemoselectively couple C_{alkyl}–Br bonds in the presence of C_{alkyl}–Cl bonds with alkylzinc reagents: that is, solvent polarity. This is a valuable attribute of this reaction, as it provides an opportunity for one-pot orthogonal alkyl–alkyl cross-couplings of bifunctional bromochloroalkanes by a solvent polarity "trigger" (Scheme 2). At its core, the chemoselectivity of these alkyl–alkyl Negishi cross-couplings depend on the ratio of dimethylimidazolidinone (DMI, $\varepsilon = 37.6$) to tetrahydrofuran (THF, $\varepsilon = 7.5$).

Preliminarily, a competition experiment (Table 1) was designed to evaluate the chemoselectivity in the alkyl–alkyl Negishi reaction. The *n*BuZnBr for these studies was

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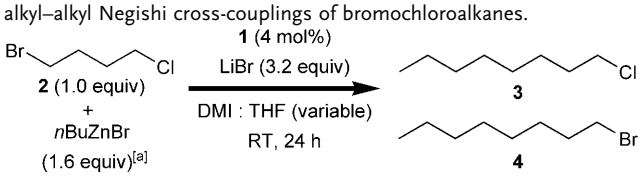
Table 1: Effect of the DMI:THF solvent ratio on the chemoselectivity in alkyl–alkyl Negishi cross-couplings of bromochloroalkanes.



Entry	DMI:THF	**2** [%][b]	**3** [%][b]	**4** [%][b]	Apparent selectivity[19] (**3**:**4**)
1	1:2	9	61	5	12.2:1
2	1:1	–	61	12	5.1:1
3	2:1	–	58	20	2.9:1
4	3:1	–	49	19	2.6:1
5	1:0	10	42	17	2.5:1

[a] *n*BuZnBr (1.0 M in DMI) was prepared according to Huo's method.[17] [b] Percent conversion was assessed by GCMS analysis using undecane as a calibrated internal standard.[20] Reactions were performed in duplicate and the average conversions are reported.

prepared as a solution in DMI by oxidative addition of activated Zn dust into *n*BuBr following a procedure reported by Huo;[17] this method of organozinc preparation is preferred as it requires relatively little synthetic effort, is efficient and produces no inorganic byproducts.[18] The optimal solvent ratio in the cross-coupling reaction involving 1-bromo-4-chlorobutane and *n*BuZnBr was found to be 1:2 DMI:THF, where a 12.2:1 apparent selectivity[19] (C_{alkyl}–Br:C_{alkyl}–Cl) was obtained (Table 1, entry 1); increasing the proportion of DMI relative to THF was detrimental to the apparent selectivity (entries 2–5).[20] Thus, while the same highly active catalyst that is required in the cross-coupling of alkyl halide electrophiles also leads to a reduction in the intrinsic reactivity differences in C_{alkyl}–X bonds, excellent chemoselectivity can still be achieved with these bifunctional precursors through a simple adjustment of the solvent polarity.

A more detailed study was conducted subsequently to further delineate the observed solvent polarity effect (Figure 1). 1-Bromo-3-phenylpropane was subjected to Negishi reaction conditions with *n*BuZnBr, catalyst **1**, and LiBr[18] at room temperature for 2 h in various ratios of DMI:THF (■ data points). Using pure THF, only a trace amount of product was detected by GCMS analysis, however, the conversions steadily increased as the proportion of DMI was increased relative to THF, and plateaus at near quantitative conversion at ca. 1:1 DMI:THF solvent ratio. The analogous reaction, using 1-chloro-3-phenylpropane and LiCl, remained mostly dormant at this solvent ratio, and useful conversions were not observed until the proportion of DMI was increased to establish ca. 2:1 DMI:THF solvent ratio (● data points). To verify that the solvent polarity dependence was not an artifact of a Finkelstein reaction with Br^- (that arises from the use of *n*BuZnBr), wherein substitution first takes place and is followed by efficient cross-coupling of the resultant alkyl bromide, *n*BuZnCl was prepared. The Grignard reagent *n*BuMgCl was first formed from *n*BuCl and Mg turnings, and subsequent transmetalation with $ZnCl_2$ provided *n*BuZnCl free from any Br^-. Cross-

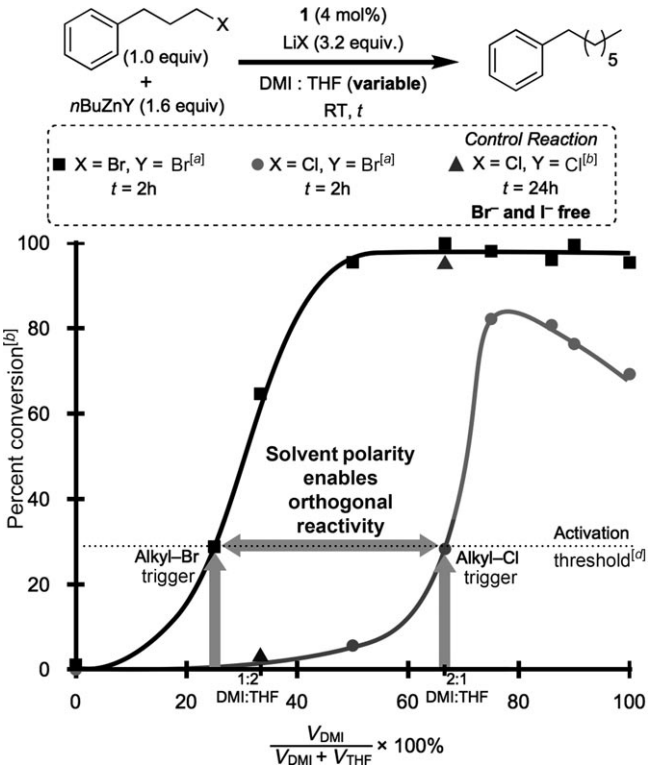
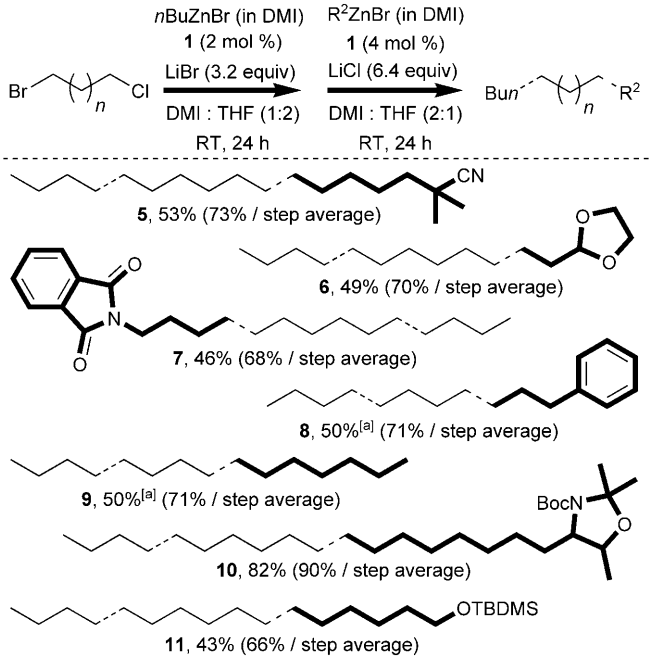


Figure 1. Alkyl–alkyl Negishi cross-couplings carried out at various ratios of DMI:THF. The plot reveals solvent polarity dependence for the coupling of alkyl bromides and chlorides. [a] For data points ranging from 0–59% DMI, *n*BuZnBr in THF was used (0.5 M, Rieke's method);[22] 60–100% DMI, *n*BuZnBr in DMI was used (1.0 M, Huo's mothod). [b] *n*BuZnCl (0.75 M in THF) was prepared by transmetalation of *n*BuMgCl with $ZnCl_2$. [c] Percent conversion was assessed by GCMS analysis using undecane as a calibrated internal standard. Reactions were performed in duplicate and the average conversions are reported. [d] The activation threshold refers to the point at which sufficient conversion is obtained; it is arbitrarily set at 30% for illustrative purposes.

coupling reactions carried out with 1-chloro-3-phenylpropane, LiCl and *n*BuZnCl in the presence of catalyst **1** (▲ data points) revealed a similar solvent polarity dependency, ruling out the Finkelstein mechanism. These control reactions also reveal that at a 1:2 DMI:THF solvent ratio, increasing the reaction time to 24 h had little effect on the percent conversion, indicating the reaction is truly switched off. At a 2:1 DMI:THF solvent ratio, a marked increase in percent conversion was obtained when increasing the reaction time from 2 to 24 h. Thus, the solvent polarity trigger is real and can be used as an on/off switch in the cross-coupling reaction of alkyl chlorides and bromides. These findings provide a unique, and to our knowledge, unexplored approach to orthogonal reactivity in bifunctional starting materials. A solvent polarity "trigger" permits the chemoselective cross-coupling of an C_{alkyl}–Br bond in the presence of a dormant C_{alkyl}–Cl bond, with the latter "activatable" simply by increasing the proportion of DMI in the reaction mixture.

Following this study, a general one-pot double alkyl–alkyl Negishi orthogonal reaction sequence (Scheme 3) was devised whereby a bifunctional bromochloroalkane was



Scheme 3. Substrate study for one-pot, orthogonal alkyl–alkyl Negishi cross-couplings that rely on a change in solvent polarity to achieve the orthogonality. Subsequent to the first cross-coupling, R^2ZnBr was added to the same pot as a solution in DMI (1.0 M) that effectively alters the DMI:THF solvent ratio that "activates" the C_{alkyl}–Cl bond to cross-coupling. Yields of isolated product are reported, unless indicated otherwise, along with the per-step average for the two cross-couplings. [a] Percent conversion was assessed by GCMS analysis using undecane as a calibrated internal standard.

dissolved in THF along with catalyst **1** and 3.2 equiv of LiBr. A solution of *n*BuZnBr (1.0 M in DMI) was added subsequently to achieve a final solvent ratio of 1:2 DMI:THF. After 24 h, the second alkylzinc reagent (1.0 M in DMI) was added to attain a final solvent ratio of 2:1 DMI:THF such that the dormant C–Cl bond was rendered active by the change in solvent polarity. For optimal results, the second cross-coupling required an additional 6.4 equiv of LiCl.[21] This one-pot orthogonal reaction sequence provided access to aliphatic derivatives **5**–**11** in good yields at room temperature.

In conclusion, orthogonal reactivity of bifunctional and unactivated bromochloroalkanes was possible in a double Negishi alkyl–alkyl cross-coupling strategy. The orthogonality was made possible by a relatively simple solvent polarity "trigger", lending itself to a one-pot approach. To our knowledge, this is the first general strategy for orthogonal alkyl–alkyl cross-couplings, and the first to use solvent polarity as the orthogonal trigger. We are currently investigating the rationale behind the solvent polarity-mediated chemoselectivity of the alkyl–alkyl Negishi reaction.

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[20] The mass balance of **2** for each entry in Table 1 is attributed primarily to quenched (4-chlorobutyl)zinc bromide (volatility of 1-chlorobutane hinders quantification, b.p. 77–78 °C), which is the product of disproportionation of *n*BuZnBr with **2**. Trace (< 5 %) quantities of 1,8-dichlorooctane are observable in the GCMS chromatograms of each entry, suggesting that the intermediate (4-chlorobutyl)zinc bromide couples with **2** to some extent. Trace quantities of 1,4-dibromobutane (Finkelstein) and dodecane (coupling each site on **2**) are observed in some entries. For the GCMS chromatograms of each entry, see Figure S2 in the Supporting Information.

[21] Whereas 3.2 equiv of LiBr or LiCl is sufficient for the first cross-coupling, the second cross-coupling requires 6.4 equiv to achieve optimal conversions. For optimization studies, see Table S1 in the Supporting Information.

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