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Efficient Phosphine-Mediated Formal $C(sp^3)$ - $C(sp^3)$ Coupling Reactions of Alkyl Halides in Batch and Flow

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The construction of $C(sp^3)$ - $C(sp^3)$ bond is an essential chemical transformation in synthetic chemistry due to its abundance in organic scaffolds. Here we demonstrate a valuable adaptation of the Wittig-type chemical procedure to efficiently facilitate $C(sp^3)$ - $C(sp^3)$ bond formation utilizing a range of alkyl building blocks. Additionally the method is amenable with flow synthesis to afford coupled products in good to excellent yields without laborious purification process.

The $C(sp^3)$ - $C(sp^3)$ bond is the most abundant type of C-C bond in organic structures.¹ However, the construction of complex organic molecules generally does not involve retrosynthetic disconnections at $C(sp^3)$ - $C(sp^3)$ bonds² which is primarily due to a paucity of reliable methods to effect this transformation relative to analogous bond connections such as $C(sp^2)$ - $C(sp^2)$.³ At present, standard approaches for $C(sp^3)$ - $C(sp^3)$ bond formation entail palladium or nickel catalyzed coupling reactions of electrophilic alkyl halides/pseudo-halides with alkyl organometallic reagents,³⁻⁴ which can also be produced from alkyl halides (Scheme 1). Although there have been numerous seminal developments in this field,¹⁻⁵ the applicability of these processes remains limited by competing reactions as well as the inherent instability the organometallic coupling reagents and catalysts.^{5b} Therefore, the development of reliable methods for $C(sp^3)$ - $C(sp^3)$ coupling reaction remains a challenging issue in organic synthesis.

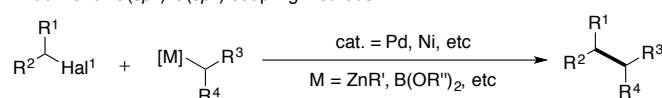
Phosphonium ylides have been commonly utilized as nucleophilic reagents for synthetically versatile Wittig and related olefination reactions.⁶ Apart from coupling with carbonyl compounds, their nucleophilicity also renders them reactive towards other types of chemical transformations, including the nucleophilic substitution reactions with alkyl

halides.⁷ Until now, however the latter type of reactions has been overshadowed by the more appealing reactivity of phosphonium ylides in Wittig reactions.⁸

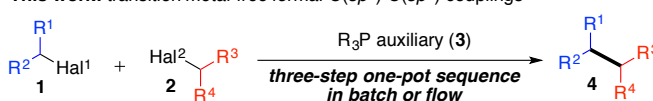
Hence, we envisaged that a phosphonium ylide, readily synthesized from an alkyl halide and a phosphine, could couple with another alkyl halide in a nucleophilic substitution reaction to form a secondary phosphonium salt. Subsequent cleavage of the resulting phosphorus moiety by hydrolysis⁹ could then afford the *formal* $C(sp^3)$ - $C(sp^3)$ cross coupling product of the two original alkyl halides. Prior to our work, this phosphine-mediated $C(sp^3)$ - $C(sp^3)$ bond formation has never been systematically studied or utilized in this sense. Thus, we herein report a valuable utilization of phosphines as synthetic auxiliaries to facilitate *formal* $C(sp^3)$ - $C(sp^3)$ coupling reactions on a broad range of alkyl building blocks (Scheme 1). The method can be efficiently implemented in batch or flow to afford coupled products in good to excellent yields. Most notably, the flow setup allowed access to the products without laborious purification process, which enable future practical applications of this alkyl-alkyl coupling protocol.

Initial investigation focused on the 'homo'-coupling reaction of benzylbromide (**1a**, Table 1). Upon initial screening of several trialkyl- and triarylphosphines (entries 1-10) as auxiliaries for the reaction, we observed the formation of the target dibenzyl product **4a** in moderate to good yields. The by-product **4a'**, that presumably formed from the base-assisted elimination side-reaction (see proposed mechanism^{9a} in Table 1), was also formed in these processes. Further studies revealed that trialkylphosphines with H-C-P moiety (entries 1, 3) were not

Traditional $C(sp^3)$ - $C(sp^3)$ coupling methods



This work: transition metal free *formal* $C(sp^3)$ - $C(sp^3)$ couplings


 Scheme 1. Phosphine mediated $C(sp^3)$ - $C(sp^3)$ coupling reactions

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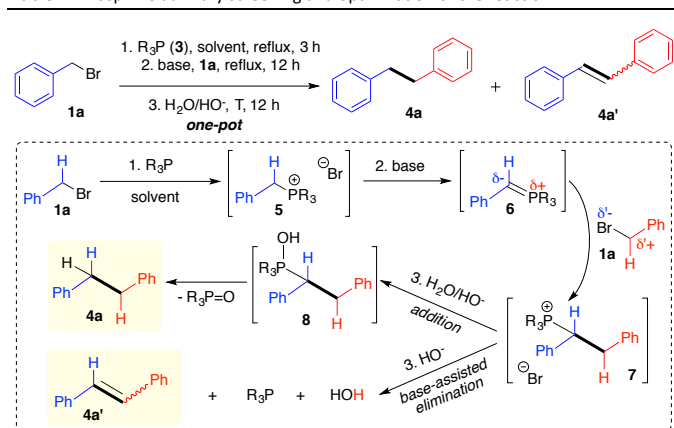
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Table 1: Phosphine auxiliary screening and optimization of the reaction^a

Entry	R ₃ P (3)	base/solvent ^b	temp.	4a/4a' (%) ^c
1	Cy ₃ P	KHMDS/THF	70 °C	21/trace
2	^t Bu ₃ P	KHMDS/THF	70 °C	58/11
3	ⁿ Bu ₃ P	KHMDS/THF	70 °C	15/trace
4	Ph ₃ P	KHMDS/THF	70 °C	60/12
5	<i>o</i> -ToI ₃ P	KHMDS/THF	70 °C	49/n.d.
6	<i>p</i> -ToI ₃ P	KHMDS/THF	70 °C	57/n.d.
7	(1-naphthyl) ₃ P	KHMDS/THF	70 °C	40/32
8	(2-furyl) ₃ P	KHMDS/THF	70 °C	64/15
9	(2,4,6-MeO ₃ Ph) ₃ P	KHMDS/THF	70 °C	51/n.d.
10	(C ₆ F ₅) ₃ P	KHMDS/THF	70 °C	trace/n.d.
11	Ph ₃ P	KHMDS/Tol	70 °C	49/trace
12	Ph ₃ P	KHMDS/MeCN	70 °C	66/trace
13 ^d	Ph ₃ P	KHMDS/MeCN	150 °C	94/trace
14 ^d	TPP-resin ^e	KHMDS/MeCN	150 °C	89/trace

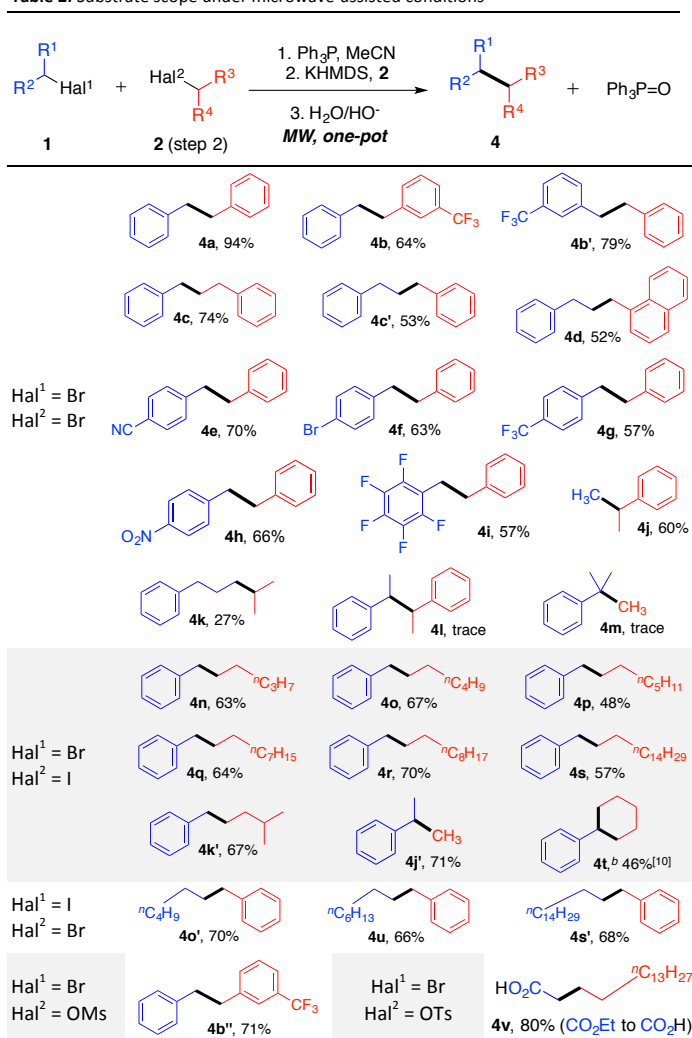
^a Reaction conditions: bromide **1a** (1.0 mmol) and phosphine **3** (1.0 mmol) in THF (3 mL), followed by the addition of **1a** (1.0 mmol) and base (1.0 mmol), finally aq. NaOH (1 mL) with conventional heating; ^b See Supporting Information for more details on base, solvent and concentration optimization; ^c Yield of isolated product; ^d All steps were carried out in MW reactor (step 1 = 2 h at 150 °C, step 2 = 3 h at 150 °C, step 3 = 1 h at 100 °C); ^e Ph₃P on polymer support (~3 mmol/g)

suitable for the reaction, which is unsurprising given that they are susceptible to side-reactions on unwanted positions. Among all triarylphosphines investigated (entries 4-10), triphenylphosphine and *tris*(2-furyl)phosphine gave most promising outcomes, presumably due to their optimal stereoelectronic properties for these chemical processes.

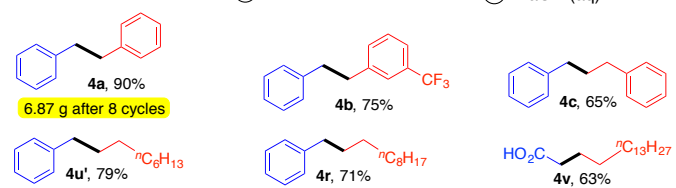
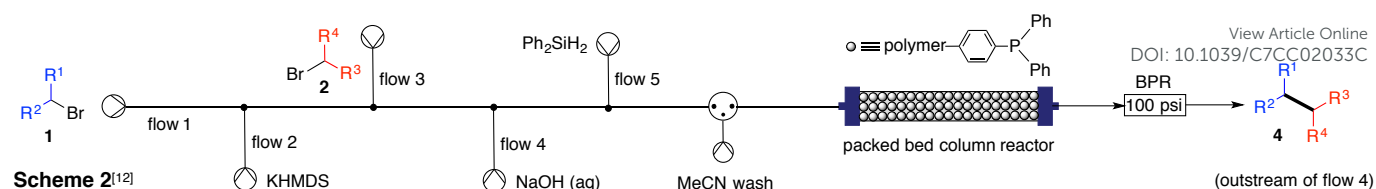
Optimization of reaction conditions on the more readily available triphenylphosphine concluded that this sequential one-pot alkyl-alkyl coupling process was best performed at 150 °C in acetonitrile under microwave irradiation.¹⁰ 2 M aqueous sodium hydroxide solution was optimal¹⁰ for the hydrolysis of phosphonium salt **7** (Table 1) to the target product **4a** via phosphonium hydroxide intermediate **8**.^{9a} Interestingly, polymer-supported triphenyl phosphine (TPP-resin, entry 14, Table 1) also gave comparable results, prompting our subsequent exploration of the scope of the protocol under flow chemistry¹¹ conditions (*vide infra*).¹⁰ Prior to flow chemistry investigation, the optimized microwave-assisted reaction conditions were applied to couple a wide range of alkyl halide substrates (Table 2). This triphenylphosphine-mediated protocol typically furnished the desired coupled products in good to excellent yields. Benzylic

bromides proved superior to other non-activated alkyl bromides in the role of alkyl halide **1** (e.g. Hal¹ = Hal² = Br, **4a-4i**, Table 2), most likely due to better formation of the first phosphonium salt (analogous to **5** in Table 1). Overall the method tolerated a range of functional groups (e.g. **4e-4i**, Table 2) however the efficiency decreased with utilization of secondary bromides (**4j-4l**, Table 2), which was attributed to steric hindrance of the alkyl moieties. Tertiary alkyl bromide (to **4m**) gave no product, apparently due to the fact that no ylide can be formed from its phosphonium derivative.

The replacement of bromides with iodides or other reactive *pseudo*-halides such as mesylates and tosylates afforded excellent outcomes (note superior yields of **4b''**, **4j'**, **4o'** and **4s'** when Hal¹ or Hal² changed from Br to I or OMs). Interestingly, double coupling reaction was possible to form cyclic product with moderate yield (**4t**, Table 2).¹⁰ Hence overall, an efficient three-step one-pot procedure¹⁰ to couple primary alkyl halides in a *formal* C(sp³)-C(sp³) bond formation was achieved using triphenylphosphine as synthetic auxiliary.

Table 2: Substrate scope under microwave-assisted conditions^a

^a Reaction conditions: halide **1** (1.0 mmol) and Ph₃P (1.0 mmol) in MeCN (3 mL), followed by the addition of halide **2** (1.0 mmol) and KHMDS (1.0 mmol), finally aq. NaOH (2 M, 1 mL). Step 1 = 2 h at 150 °C, step 2 = 3 h at 150 °C, step 3 = 1 h at 100 °C; ^b From benzyl bromide and 1,5-diiodopentane.¹⁰



Subsequent investigations focused on adapting the MW protocol to a total flow chemistry approach. As outlined in Scheme 2, the flow system utilized was comprised of five syringe pumps connected to an inline manual switching valve (Scheme 2) with the TPP-resin contained within a standard omnifit column.¹² The flow protocol mirrored the MW approach with alkyl bromide **1** initially flowed through the column followed by sequential flows of KHMDS, alkyl bromide **2** and NaOH solutions.¹² Gratifyingly, this rudimentary flow approach efficiently mediated the coupling reactions of a number of selected alkyl bromides to afford the desired products in good to excellent yields.

In terms of synthetic strategy, the generation of phosphine oxide waste in our earlier batch settings was unfavourable in comparison to other traditional catalytic methods for $C(sp^3)$ - $C(sp^3)$ coupling reactions. For the flow setup, this issue can be easily circumvented in light of current technological and methodological advances in recycling phosphine oxides.¹³ Preliminary studies on our TPP packed bed column reactor showed that after the NaOH hydrolysis step, the resulting phosphine oxide on the resin could be recycled to the reactive TPP-resin form with utilization of hydrosilanes.¹⁴ Indeed, Ph₂SiH₂ was pumped into the column reactor (flow 5, 120 °C)^{12,15} to reduce the TPP-oxide to TPP-resin, which could then be reused for another reaction cycle.

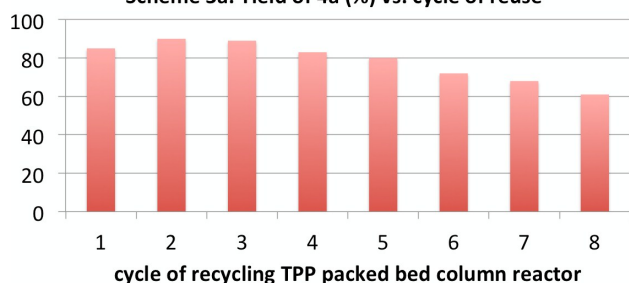
The efficiency of the process remained at > 60% even after the 8th cycle (Scheme 3a),¹⁰ which allowed access to multiple grams of the coupled product **4a**. The product yield of the second cycle was actually higher than that of the first cycle due to the fact that the TPP-resin from commercial suppliers contained some proportion of TPP-oxide. After reduction with Ph₂SiH₂, the performance of this packed bed column peaked at the second cycle before decreasing gradually over time. The presence of the phosphine, phosphine oxide and phosphonium salts intermediates in the reaction was confirmed by solid-state ³¹P NMR study of the TPP-resin in the homocoupling reaction of **1a** to form **4a** (Scheme 3b).¹⁶

This initial study demonstrated that the polymer-supported TPP mediated $C(sp^3)$ - $C(sp^3)$ coupling reaction is amenable to total flow synthesis and provides the advantage of removing physical handling requirements throughout the multi-step process. We also note that extensive scope for optimization of the flow protocol remains. Current investigations on adaptation of this to multiple-reactor system as well as further variations of solvent/temperature/flow-rate are on-going in our laboratories and will be reported in due course.

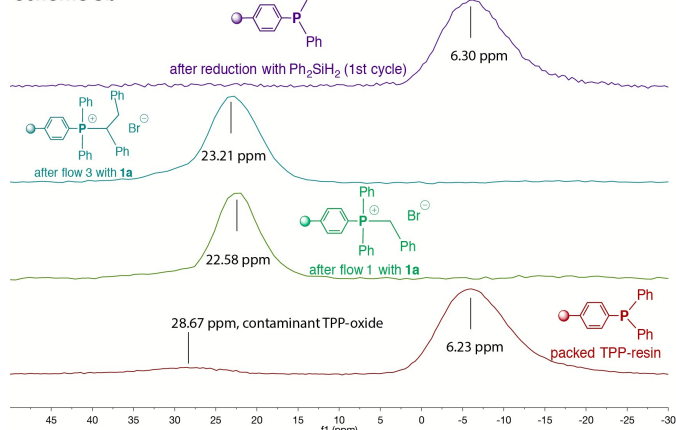
In conclusion, we have developed a new adaptation of the commonly known Wittig-type chemical procedure to efficiently enable $C(sp^3)$ - $C(sp^3)$ coupling reactions on a broad range of alkyl building blocks. This method can be implemented in batch or flow to afford coupled products in good to excellent yields. The flow setup allowed direct access to the products without laborious purification process, which paves ways for practical applications of this new alkyl-alkyl coupling protocol in the future.

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Scheme 3a. Yield of **4a** (%) vs. cycle of reuse



Scheme 3b



Scheme 3. (a) Recyclability of TPP packed bed column reactor; (b) Solid-state ³¹P NMR (121.4 MHz, 25 °C) of TPP-resin after selected flows (homocoupling of **1a** to **4a**).

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16. We could not obtain a solid state ³¹P NMR spectrum for the polymer-bound phosphonium ylide intermediate due to the unstable nature of this species.

1