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A removable functional group strategy for regiodivergent Wittig rearrangement products†

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[1,2] and [2,3] Wittig rearrangements are competing reaction pathways, often leading to uncontrollable product distribution. We employ a single removable functional group to fulfill the dual role of attaining a reversible [2,3] and stabilizing radical intermediate for the [1,2] path to obtain both the Wittig products selectively for a broad range of substrates.

The base induced Wittig rearrangements of α-allyloxy carbanions ($\mathbf{1}^-$) are powerful carbon–carbon bond forming reactions but often suffer from the requirement of a strong base and competing [1,2] and [2,3] pathways.[1] Other side reactions such as β-elimination, [3,3] rearrangement, [1,4] shifts, and cyclization have also been reported.[2] The product distribution depends on the substrate nature, namely substitutions on alkene and carbanion carbons.[3] Only limited control over the [2,3] product distribution is realized *via* varying the reaction temperature.[2d,4] Despite the [1,2] product being thermodynamically stable and the [2,3] product being considered as kinetically stable, a classical switch *via* controlling reversible pericyclic [2,3] has not been achieved. The lack of generality and control over product formation restricts the widespread application of these useful classes of transformations (Fig. 1a). A selective product formation of choice would allow both the rearrangements to attain full synthetic utility.[5]

We hypothesized that choosing a suitable removable functional group (FG) on carbanion carbons could influence the energy of both the intermediates ($\mathbf{1}^-$ and **I1**/**I2**) appropriately, and thereby control the reaction course for stereodivergency (Fig. 1b). To achieve this, the FG effect on carbanions should make the [2,3] path kinetic for all substitution types. For the thermodynamic switch to [1,2], the FG influence on carbanion ($\mathbf{1}^-$) should make the previously unexplored reversible [2,3] attainable, and stabilize the radicals **I1**/**I2** for [1,2] products to be the next energetically achievable intermediates.

An electron withdrawing FG would stabilize the carbanion ($\mathbf{1}^-$) to make it less reactive for all possible side reaction paths including [1,2] to offer a better chance for [2,3] product formation selectivity under kinetic conditions. The stability could also make the reversible [2,3] attainable *via* reducing its energy gap with the oxo-anion product (**2**).[6] But the carbanion substitution influence on radical intermediates for the [1,2] path is largely unknown.[7] EWGs such as ester, amide, 2-oxindole, ketone, and diester with stable carbanions are known to produce only [2,3] products, even at a higher temperature (up to 60 °C).[2c,d,8] We suspect that the lack of [1,2] product formation might be due to the unattainable [1,2] path rather than the reversibility of [2,3]. A removable FG capable of dual anion and radical stabilization seems to be the requirement to achieve regiodivergency.

We started with 1,3-diheteroaromatic FGs (azoles), anticipating that they would stabilize both anions ($\mathbf{1}^-$) and radicals

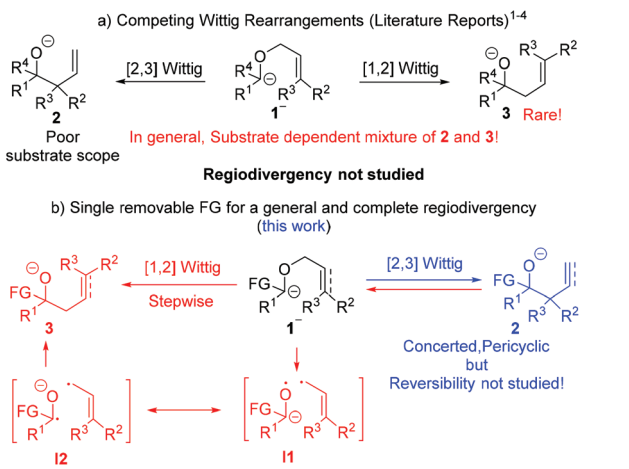

Fig. 1 (a) Poor product selectivity for Wittig rearrangements. (b) A single removable FG approach for regiodivergency.

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(**I1**/**I2**).[9] Additionally, azoles are easy to remove from alcohol products.[10] Substrate classes **1A** (R^1 = Ar, R^2 = H, R^3 = Alk) and **1B** (R^1 = Ar, R^2 = R^3 = Alk) were selected to test the feasibility of our hypothesis. KO^{t}Bu turned out to be an effective base in acetonitrile, and −40 °C reaction temperature led to fast and selective [2,3] product (**2A-1,2,3** and **2B-2,3**) formation (Scheme 1A).[11] The reaction temperature was slowly increased for **1A-1** having thiazole as the FG to obtain a possible regiodivergency *via* reversible [2,3] along with forward [1,2]. Unfortunately, no change occurred prior to slow decomposition at 50 °C. Changing the FG to benzoxazole (**1A-2**) led to reversible [2,3],[12] although no [1,2] product formed. But, to our delight, substrate class **1B** with benzoxazole (**1B-2**) results in a successful product switch to [1,2] by raising the reaction temperature to 0 °C (**3B-2**, 78%). Benzothiazole as the FG turned out to be the best FG with selective regiodivergent product formation for both substrate classes (Scheme 1B). A complete product switch for **1A-3** occurred at room temperature, compared to that at 0 °C for **1B-3**. The extra stabilization of the dialkyl allyl radical counterpart for the **1B** substrate class presumably lowers the overall activation energy requirement for [1,2]. It is worth noting that only the anion stabilizing ability of the FG is not enough and both anion and radical stabilization abilities enabled the regiodivergent reaction paths.[13]

With the discovery of benzothiazole as a suitable FG for regiodivergency, we set to study all possible substrate classes with varying substitution at every position. Other class **1A** substrates with different aryl groups (R^1) were tested successfully (Table 1A). The product switch for both electron rich and poor groups at the *para*-position is faster than that for the unsubstituted one, which indicates radical intermediacy for the [1,2] path.[14] The dr ratio of [2,3] products for **1A** is low to moderate (~1 : 1 to 3.5 : 1).

Substrate class **1B** with R^2 = Ar and both R^3 = R^4 = Me gave [2,3] at −40 °C, and completely switched to the [1,2] product at 0 °C in 4 h reaction time (Table 1B). The yields for both the regioisomeric products are good with unsubstituted phenyl and differently substituted aryl groups such as 3-Br and 2-F.

Substrate class **1C** with R^2 = Ar, R^3 = H, R^4 = Ar was tested next, where the reaction at −40 °C with KO^{t}Bu as a base in MeCN solvent led to the formation of mixtures of [2,3] and [1,2] products. Presuming that [2,3] is still the kinetic product, we cooled the reaction mixture to −78 °C with a temperature compatible solvent (THF) and base (*n*-BuLi). Gratifyingly, the lower temperature resulted in only the [2,3] product in 88% yield and ~1 : 1 dr (**2C-1**).[3a] The usual 0 °C reaction temperature with KO^{t}Bu as a base in MeCN solvent led to the selective product switch (**3C-1**) in good yield (Table 1C). A variety of substituents on either aryl groups were well tolerated, with *ortho*-Me substitution resulting in high dr (9 : 1) for [2,3] products.

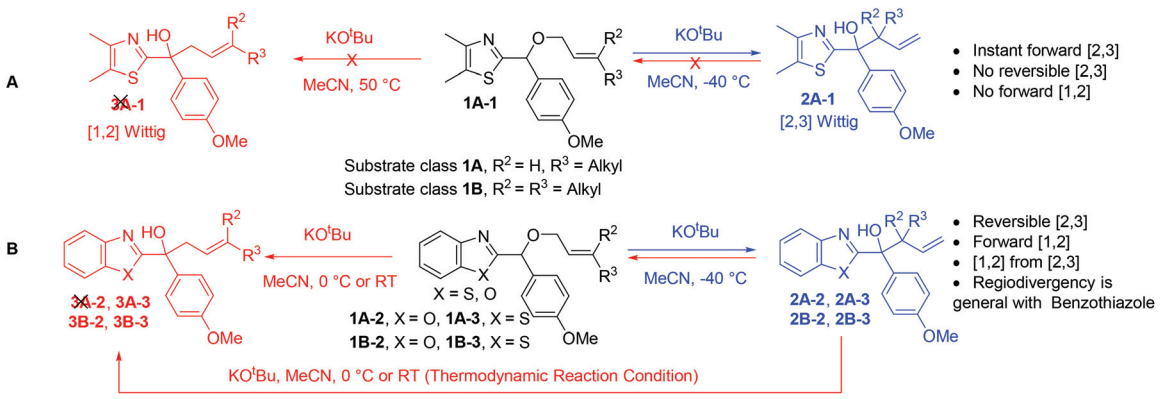
Substrate class **1D** with R^1 = Ar and highly substituted alkene (R^2 = Me, R^3 = Ph) is known to be troublesome and mostly avoided for Wittig rearrangements.[2d] Treatment of *n*-BuLi in THF or diethyl ether at low temperature, even up to −90 °C, resulted in only a [1,2] product (Table 1D & E). We replaced the removable FG with 2,3-dimethylthiazole (**1D-2**) which is the poorest for the [1,2] path with **1A-1**. Still, substrate **1D-2** failed to produce any kinetic [2,3] product. Since we did not obtain any [2,3] product, it is unclear if [2,3] is the kinetic product or [1,2] became both the kinetic and thermodynamic product for the **1D** substrate class.

Next, we repeated the entire alkene substitution pattern with an alkyl group at the carbanion carbon (R^1 = alkyl). KO^{t}Bu was found to be not strong enough, but KHMDS or *n*-BuLi successfully deprotonated to form the carbanion. A benzothiazole FG enabled direct alkyl carbanion generation is significant since it is not feasible otherwise, due to the lower acidity of carbanion C–H compared to those of allylic protons. As a result, rearrangements with carbanion carbon having alkyl or no substitution were generally realized *via* a Stille–Wittig transmetalation pathway.[15]

As with substrate class **1D**, the highly stable allyl radical in **1E-1** (R^2 = Me, R^3 = Ph) made the [1,2] path fast even at −90 °C, with no detection of the [2,3] product (Table 1D & E).

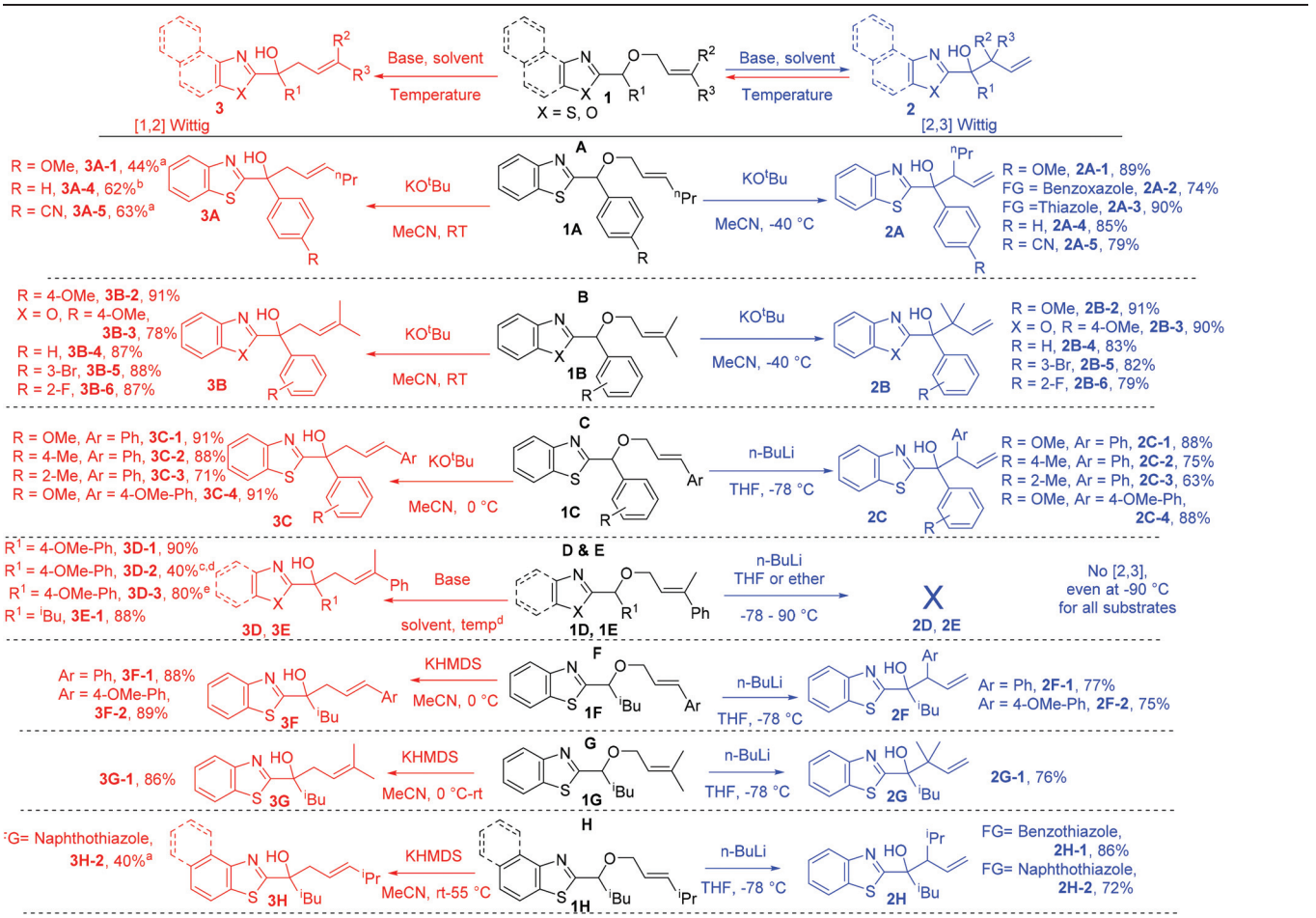
The complete product switch for mono-aryl (**1F-1**, **1F-2**) and dimethyl substituted alkene substrates (**1G-1**) were easily attainable, with good yields for all [2,3] and [1,2] products (Table 1F & G).

The mono-alkyl substituted alkene **1H-1** (R^2 = H, R^3 = Alkyl) resulted in 86% yield for [2,3], but no product switch occurred



Scheme 1 Single removable functional group (FG) at carbanion carbon and its effect on Wittig rearrangements.

Table 1 Regiodivergent Wittig products with differently substituted alkenes and carbanion carbons



Conditions: 0.1–0.3 mmol **1**, 2–3 equiv. base. [a] ~22% unidentified isomer. [b] ~15% [2,3] product remained along with ~20% unidentified isomer. [c] Side product formed in 60% yield. [d] FG = 4,5-dimethylthiazole. [e] FG = *N*-methylimidazole.

with slow decomposition at 50 °C (Table 1H). We expected the [1,2] activation to be the highest with the least stable radical pair combination. An extended naphthothiazole substrate (**1H-2**) was prepared next to enhance the radical stability. Still, no [1,2] product formed at room temperature but the reaction at 50 °C led to slow formation of the [1,2] product in (**3H-2**) poor yield (40%). The result with **1H-2** indicates a better radical stabilizing FG, which would enable an efficient product switch for this substrate class as well.

Overall, with benzothiazole as a removable FG, a large variety of substrate classes with different substitution patterns yielded [2,3] and [1,2] products regiodivergently, simply *via* controlling the reaction temperature. Substrate class **1H** resulted in poor yield for [1,2], while a highly substituted allyl group in **1D** and **1E** led to no [2,3] product formation.

To obtain the unattainable [2,3] with the substrate classes **1D** and **1E**, we tried to find an FG capable of anion stabilization but not radical stabilization. We planned to start with a traceless FG having those properties, which would leave the rearranged product quickly and irreversibly to trap the [2,3] product provided it is still the kinetic one.[16] Additionally, a traceless group would have the advantage of no extra chemical step requirement for its removal. We synthesized a traceless phosphonate FG version of **1D** and a cyano version of **1E** following literature procedures.[17] To our delight, both generated only a branched allyl ketone product[18] *via* [2,3] rearrangement followed by irreversible traceless group detachment (Scheme 2). The quaternary carbon in between the keto and alkene made these products stable under the basic reaction conditions. Overall, although the same FG did not produce

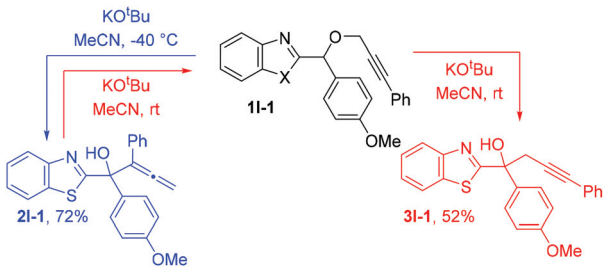
Scheme 2 A traceless FG to trap [2,3] rearrangement with a highly substituted alkene.

regiodivergency, the choice of two complementary FGs led to the regioisomeric products of choice with a highly substituted alkene.

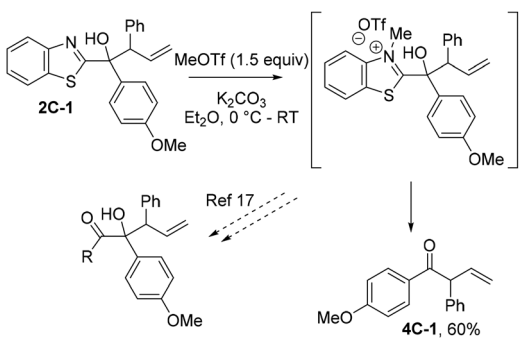
Intrigued by the success of different types of allylic rearrangements, we explored a possible regiodivergent route for a propargylic substrate as well. Propargyl substrates are known to generate only [1,2] products with a moderate yield, and an allene *via* [2,3] is rare with very poor yield.[19] We synthesized **1I-1** with a phenyl substituted alkyne, and upon treatment with KO^{t}Bu, it resulted in an allene *via* [2,3] at −40 °C. The starting ether completely transformed to a [1,2] product in 52% yield upon warming to room temperature (**3I-1**) (Scheme 3).

The emergence of benzothiazole as the common removable FG for all substrate classes allowed a single removal method to be sufficient. We chose **2C-1** as the model since [2,3] products are sterically more demanding, and the aryl, allyl ketone product (**4C-1**) would be the most challenging one due to its propensity for isomerization. Quaternization of benzothiazole with MeOTf in the presence of a weak and insoluble base K_2CO_3 in diethyl ether led to the formation of FG-detached allyl ketone product **4C-1**, with very little alkene isomerization (Scheme 4).[8,16] The α-hydroxy benzothiazole unit is also well utilized in the literature for one carbon homologated α-hydroxy carbonyl compounds.[20]

In conclusion, a single removable FG was successfully utilized for the synthesis of regiodivergent Wittig products. The attachment of benzo-thiazole allowed us to obtain a previously unattainable reversible [2,3] Wittig and favorable [1,2] *via* manipulation of intermediate stabilization for both reaction paths. The strategy was applied to a broad range of substituents at each position, and even with a propargylic system. Benzothiazole was removed in a single operation under mild conditions without isomerization of alkenes in a highly reactive allyl ketone. The challenging highly substituted alkene substrates were successfully used with a traceless FG strategy for selective [2,3] product formation. Currently, we are exploring the possibility of making these rearrangements catalytically enantioselective, using the coordination and anion stabilization power of the removable functional groups.



Scheme 3 Single removable FG mediated regiodivergent Wittig reaction with propargyl ether.



Scheme 4 FG removal for allyl ketones and one carbon added alcohols.

Conflicts of interest

There are no conflicts to declare.

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