Alkene Difunctionalization Hot Paper

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# Arylphosphonylation and Arylazidation of Activated Alkenes**

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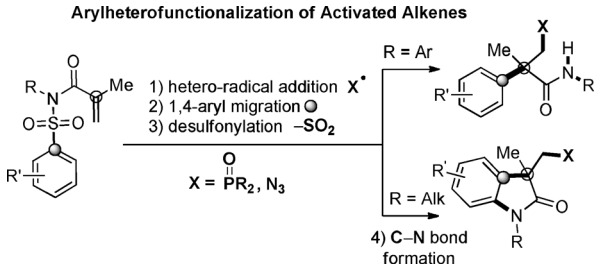
*Dedicated to Professor Max Malacria on the occasion of his 65th birthday*

***Abstract:*** *Two radical-mediated processes of activated alkenes, namely arylphosphonylation and arylazidation, are described. The difunctionalization of alkenes by a tandem process that involves radical addition, 1,4-aryl migration, and desulfonylation generates α-aryl-β-heterofunctionalized amides bearing a quaternary stereocenter when the substituent on the nitrogen atom is an aryl group. Alternatively, heterooxindoles or spirobicycles can be obtained with excellent regioselectivity in the presence of an alkyl substituent on the nitrogen atom.*

Alkenes represent privileged motifs in organic synthesis. Their accessibility, robust nature, and broad functionalization potential has triggered the development of novel methods to incorporate functional groups across the C=C π system. Following the pioneering work of Sharpless and co-workers,[1] alternative methods to enable the introduction of two functional groups across alkenes in a catalytic, regio- and stereocontrolled manner have been intensively studied.[2] Both metal-free as well as transition-metal-mediated dioxygenation,[3] aminooxygenation,[4] diamination,[5] aminohalogenation,[6] fluoroamination,[7] azidooxygenation,[8] and amino- and oxotrifluoromethylation[9] reactions of alkenes have been reported. In contrast, the carbo- and heterofunctionalization of alkenes involving the incorporation of arenes has been more limited and mostly restricted to the formation of oxindoles and related heterocycles.[10] In this context, phosphonyl[11] and azido[12] oxindoles have recently been described. Our group has reported the addition of a $CF_3$ radical to the double bond of tosyl acrylamides as a way to trigger an aryl migration/desulfonylation sequence.[13] We envisioned that, under the right set of conditions, diverse heteroatom-centered radicals could be engaged in such a cascade process, enabling the simultaneous formation of carbon–carbon and carbon–heteroatom bonds across alkenes beyond the well-established oxindole synthesis (Scheme 1). Herein, we report the successful realization of this concept with the introduction of azido and phosphonyl radicals for the flexible synthesis of unprecedented α-aryl-β-heterofunctionalized amides with a quaternary stereocenter. Furthermore, phosphorylated oxindoles and spirobicycles could also be obtained in a completely regioselective manner.




***Scheme 1.*** Arylheterofunctionalization of activated alkenes.

The optimization of the reaction conditions was performed with acryl sulfonamides **1** (Table 1).[14] It is well established that $Ph_2P(O)H$ reacts with silver salts to form the corresponding $[Ph_2P(O)Ag]$ complexes, which can subsequently add to alkenes.[11a,b,15] Different salts were explored in combination with substrate **1a**, with $AgNO_3$ showing the best performance (entries 1–3). The reaction seems not to be influenced by the presence of base and, in contrast to previous methods,[11a,b] the addition of other Lewis acids, such as $Mg(NO_3)\cdot 6H_2O$, leads to decomposition of the starting material (entries 4 and 5). The amount of silver could be reduced, and with 10 mol% of $AgNO_3$, the desired product **2a** could be isolated in 67% yield (entry 6). Next, we attempted the introduction of an azide group with iodine(III) reagent **4**.[8c] Its reaction with **1b** in toluene at 60°C furnished the desired product, but as part of a complex reaction mixture (entry 7). The reaction was found to be cleaner in dichloromethane, and **2b** could be isolated in 56% yield (entry 8). To increase the conversion of the starting material, different additives were used: Copper iodide (30 mol%) in the presence or absence of 2,2′-bipyridine as a ligand furnished complex mixtures (entry 9).[12] In contrast, the addition of $NaHCO_3$ (1 equiv) improved the conversion of the starting material (entry 10). After a small screening of bases,[14] the use of phenanthroline (phen) enabled us to isolate the desired α-aryl-β-azido amide **3b** in 71% yield (entry 11).

With the optimized reaction conditions for both processes in hand, we then set out to explore the scope of these transformations. Tosyl amide substrates that bear electron-donating or electron-withdrawing groups at the *para* position of the aromatic ring that is directly bound to the nitrogen atom ($R^1$; Table 2) produced the corresponding β-phosphonyl and β-azido amides **2b–e** and **3b–e** in good yields (entries 3–10). The presence of *ortho* substituents seemed to reduce the reaction efficiency (entries 11 and 12). The substitution

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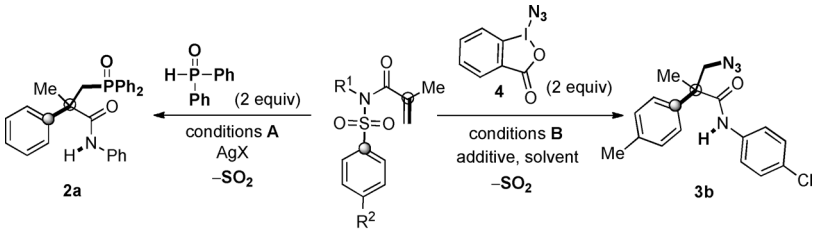
***Table 1:*** Optimization of the reaction conditions.[a]



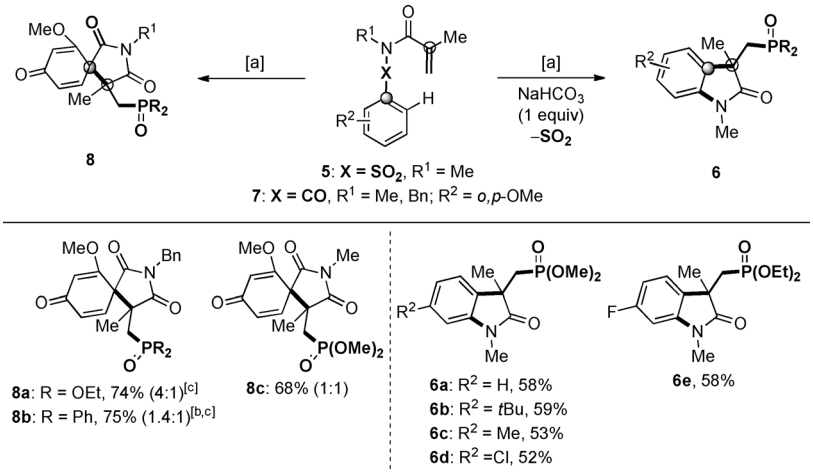

**1a**: $R^1$ = Ph, $R^2$ = H
**1b**: $R^1$ = *p*-$ClC_6H_4$, $R^2$ = Me

| Entry | Substrate | Solvent | Additives | Product | Yield[b] [%] |
|---|---|---|---|---|---|
| 1 | **1a** | MeCN | $AgBF_4$ (30%) | **2a** | 32 |
| 2 | **1a** | MeCN | AgOTf (30%) | **2a** | 19 |
| 3 | **1a** | MeCN | $AgNO_3$ (30%) | **2a** | 58 |
| 4 | **1a** | MeCN | $AgNO_3$ (30%), $NaHCO_3$ (1 equiv) | **2a** | 58 |
| 5 | **1a** | MeCN | $AgNO_3$ (30%), $Mg(NO_3)_2{\cdot}6H_2O$ (50%) | | –[c] |
| **6** | **1a** | **MeCN** | **$AgNO_3$ (10%)** | **2a** | **69 (67)** |
| 7 | **1b** | toluene | – | **3b** | 80[c] |
| 8 | **1b** | $CH_2Cl_2$ | – | **3b** | 59 (56) |
| 9 | **1b** | $CH_2Cl_2$ | CuI (30%), with or without bipy (30%) | | –[c] |
| 10 | **1b** | $CH_2Cl_2$ | $NaHCO_3$ (1 equiv) | **3b** | 75 |
| **11** | **1b** | **$CH_2Cl_2$** | **phen (1 equiv)** | **3b** | **78 (71)** |

[a] Reaction conditions A (used for substrate **1a**): $HPOPh_2$ (2 equiv), MeCN (0.05 M), 100 °C, 14 h. Reaction conditions B (used for substrate **1b**): **4** (1.5 equiv), solvent (0.05 M), 60 °C, 14 h. [b] Yield determined by $^1$H NMR spectroscopy using 1,2-dibromoethane as the internal standard. The value in brackets corresponds to the yield of isolated product after column chromatography on silica gel. [c] Complex reaction mixture.

pattern on the aromatic ring of the sulfonamide group was further explored ($R^2$; Table 2). *m*-Methyl, *p*-methoxy-, and *p*-phenyl benzosulfonamide substrates were efficiently transformed into the corresponding β-functionalized amides **2i**, **2j**, **3h**, and **3j** (entries 13–16). The reaction is completely regioselective so that the 1,4-migration of the aryl group takes place exclusively through the carbon atom that is bound to the $SO_2$ group in the substrate.

More elaborate arylsulfonyl substituents were also investigated. Substrates bearing 1,4-dioxolane, indane, or dibenzofurane sulfonyl moieties (**1k**–**m**) were transformed into the corresponding linear amides in good yields (entries 17–20). Finally, we also investigated different substituents on the alkene. Substrate **1n**, which bears a phenyl ring at the propene moiety, efficiently gave the corresponding amides **2n** and **3n** in 65 and 62% yield, respectively (entries 21–22). In contrast, trisubstituted olefin **1o** was found to be unreactive under reaction conditions A, but decomposed under reaction conditions B (entry 23).

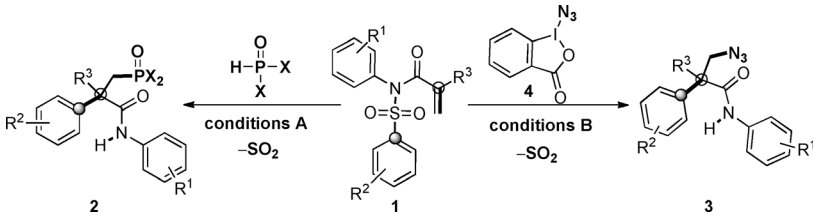


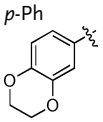
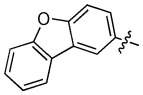
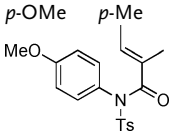

***Scheme 2.*** Scope of the silver-catalyzed arylphosphonylation reaction. Yields of isolated products after column chromatography on silica gel are given. [a] $HPOR_2$ (2 equiv), $AgNO_3$ (50 mol%), MeCN (0.05 M), 100 °C, 14 h. [b] Small quantities of $Ph_2P(O)OMe$ (**9**) were also detected in the reaction mixture. [c] Diastereoisomers could be separated by crystallization.

The influence of the nitrogen substitution pattern on the reaction was further evaluated. In contrast to the results that are summarized in Table 2, *N*-methyl-*N*-tosyl amide **5a** furnished phosphonyl oxindole **6a** in 58% yield in the presence of an increased amount of $AgNO_3$ (50 mol%; Scheme 2).[14] The presence of a more nucleophilic nitrogen atom in the molecule triggers, upon phosphonylation of the alkene, not only an 1,4-aryl migration/desulfonylation cascade, but also the formation of a new C($sp^2$)–N bond in the *ortho* position relative to the original sulfonyl group in a formal 1,3-N migration process. This method enables the synthesis of *meta*-substituted oxindoles **6b**–**d** in a completely regioselective fashion. Previously reported silver-catalyzed arylphosphonylations with acrylamide substrates only furnished an inseparable mixture of regioisomers of these products, as two possible sites for arylation of the double bond are present in the corresponding starting materials, thus highlighting the synthetic potential of this new method.[11a] Finally, when the arylsulfonyl moiety was replaced with an electron-rich benzoate group as in substrate **7**, phosphonylated spirobicyclic compounds **8a**–**c** were obtained in good yields and with moderate selectivities. The different reactivity of *N*-aryl- and *N*-alkyl-substituted substrates (**1** vs. **5**) was further explored: When an ester group was introduced at the *ortho* position of the arylsulfonamide moiety, the more nucleophilic alkyl-substituted nitrogen atom reacts with the ester furnishing the corresponding isoquinolinedione **6f** in 66% yield (Scheme 3a). In sharp contrast, the analogous *N*-aryl-sub-

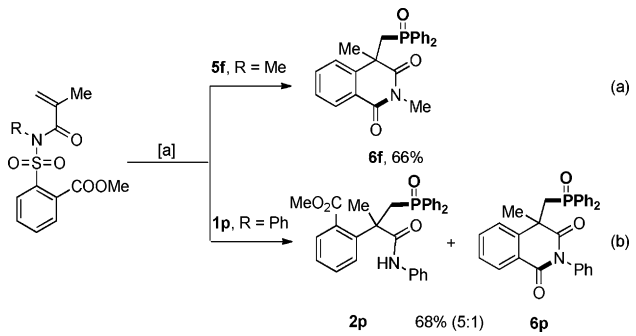
  

***Table 2:*** Scope of the arylphosphonylation and the arylazidation reaction.




| Entry | Cond.[a] | Substrate | $R^1$ | $R^2$ | Product[b] | Yield[c] [%] |
|---|---|---|---|---|---|---|
| 1 | A | **1a** | H | H | **2a** | 67 |
| 2 | B | **1a** | H | H | **3a** | 73 |
| 3 | A | **1b** | *p*-Cl | *p*-Me | **2b** | 61 |
| 4 | B | **1b** | *p*-Cl | *p*-Me | **3b** | 71 |
| 5 | A | **1c** | *p*-Me | *p*-Me | **2c** (X = OMe) | 68 |
| 6 | B | **1c** | *p*-Me | *p*-Me | **3c** | 75 |
| 7 | A | **1d** | *p*-Br | *p*-Me | **2d** (X = OMe) | 72 |
| 8 | B | **1d** | *p*-Br | *p*-Me | **3d** | 72 |
| 9 | A | **1e** | H | *p*-Me | **2e** | 68 |
| 10 | B | **1e** | H | *p*-Me | **3e** | 80 |
| 11 | A | **1f** | *o*-Cl | *p*-Me | **2f** (X = OMe, $R^3 = nC_6H_{13}$) | 60 |
| 12 | B | **1g** | *o*-F | *p*-Me | **3g** | 55 |
| 13 | B | **1h** | H | *m*-Me | **3h** | 84 |
| 14 | A | **1i** | H | *p*-OMe | **2i** (X = OMe) | 66 |
| 15 | A | **1j** | *p*-Cl | *p*-Ph | **2j** | 80 |
| 16 | B | **1j** | *p*-Cl | *p*-Ph | **3j** | 75 |
| 17 | A | **1k** | *p*-Cl |  | **2k** | 73 |
| 18 | B | **1k** | *p*-Cl | | **3k** | 80 |
| 19 | A | **1l** | *p*-Cl |  | **2l** (X = OEt) | 64 |
| 20 | B | **1m** | *p*-Cl |  | **3m** | 51 |
| 21 | A | **1n** | *p*-OMe | *p*-Me | **2n** ($R^3$ = Ph) | 65 |
| 22 | B | **1n** | *p*-OMe | *p*-Me | **3n** ($R^3$ = Ph) | 62 |
| 23 | A, B | **1o**: |  | | – | – |

[a] Reaction conditions A: $HPOPh_2$ (2 equiv), $AgNO_3$ (10%), MeCN (0.05 M), 100 °C, 14 h. Reaction conditions B (used for substrate **1b**): **4** (1.5 equiv), phen (1 equiv), $CH_2Cl_2$ (0.05 M), 60 °C, 14 h. [b] Unless otherwise stated, $R^3$ = Me and X = Ph. [c] The values correspond to the yield of isolated product after column chromatography on silica gel.



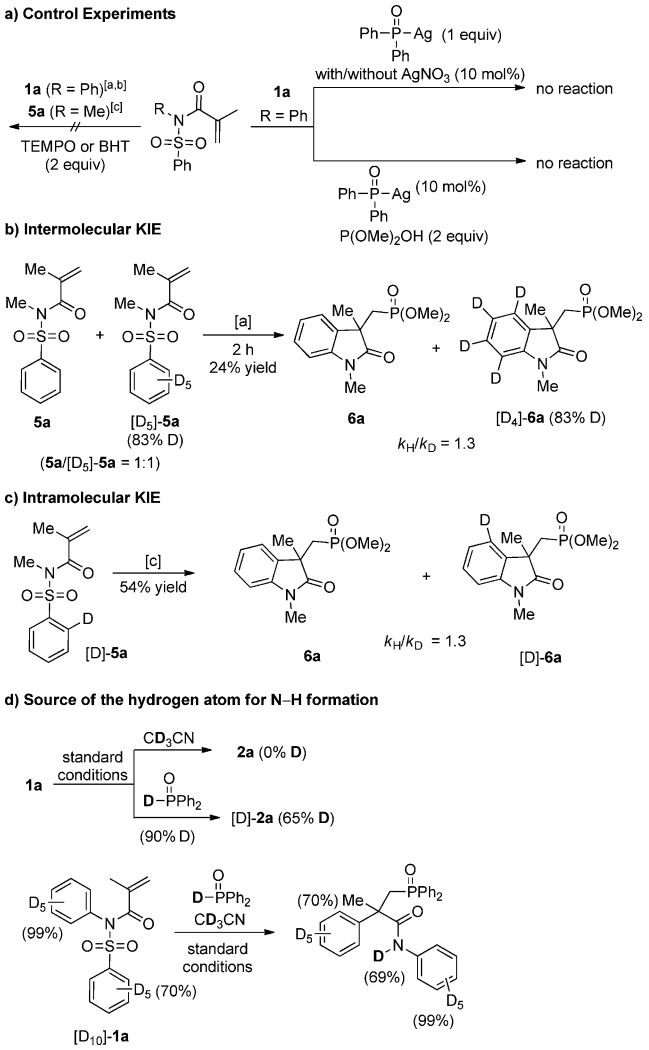

***Scheme 3.*** [a] Reaction conditions: $HPOPh_2$ (2 equiv), $AgNO_3$ (10 mol%), MeCN (0.05 M), 100 °C, 14 h.

stituted substrate **1p** provided a mixture of both amide **2p** and isoquinolinedione **6p** in a 5:1 ratio (Scheme 3b).

Control experiments were designed to investigate the mechanism of these transformations.[14] The efficiency of the reactions of **1a** and **5a** under the standard conditions was strongly affected by the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT), which points towards a radical mechanism (Scheme 4a, left).[14] When the $[Ph_2P(O)Ag]$ complex was used in a stoichiometric fashion,[15] in the presence or absence of $AgNO_3$, no conversion of **1a** was observed. The same result was obtained when $[Ph_2P(O)Ag]$ was used in a catalytic fashion in the presence of $P(OMe)_2OH$, thus suggesting that the silver additive is needed to generate the reactive phosphonyl radical from $Ph_2P(O)H$, but, in contrast to previously reported examples,[11a,b] that the $[Ph_2P(O)Ag]$ complex is not an active intermediate in our reaction (Scheme 4a, right).

Deuterium labelling experiments were also carried out. The lack of a primary intermolecular kinetic isotope effect (KIE) in the reaction of **5a** and $[D_5]$-**5a** confirmed that the rupture of the C–H bond on the arylsulfonyl group is not involved in the rate-determining step. A similar normal secondary KIE (KIE = 1.3) was measured in an intramolecular experiment with [D]-**5a** as the substrate (Scheme 4b,c).[16] We also aimed to determine the source of hydrogen that generates the amide moiety in the final products.[17] $Ph_2P(O)H$ seems to be the key hydrogen source in these reactions,[18] whereas in the reaction with azide-transfer reagent **4**, adventitious traces of water in the medium seem to be responsible for the formation of the N–H bond (Scheme 4d).[17] With these results in hand, the following mechanism can be proposed for these transformations (Scheme 5): In the first step, the phosphorus- or azide-centered radical interacts with the activated alkene to give a new $C(sp^3)$–P or $C(sp^3)$–N bond and an α-alkyl radical intermediate **I**. A 5-*ipso* cyclization then takes place on the aromatic ring generating aryl radical **II**, which leads to amidyl radical **III** upon rearomatization with concomitant desulfonylation. In the case of the arylphosphonylation reaction and

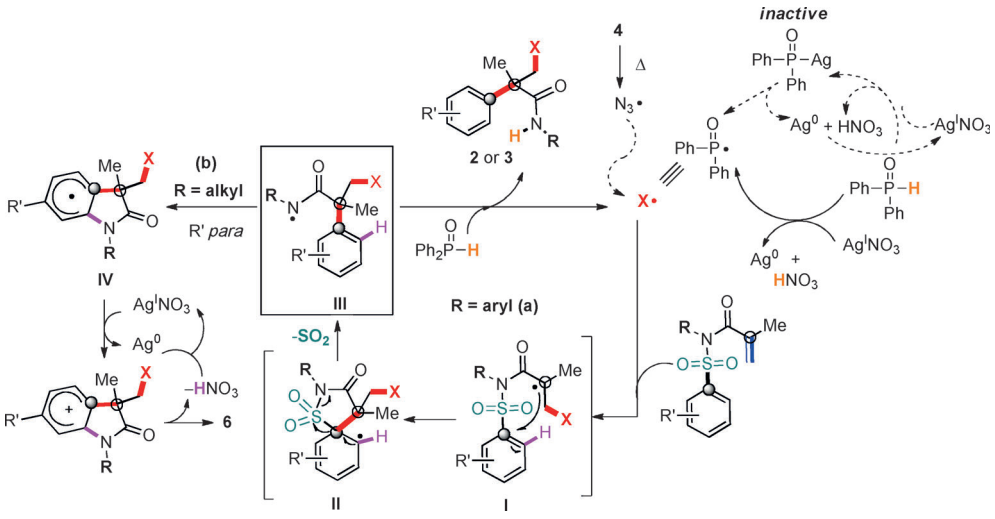



***Scheme 4.*** Mechanistic study. [a] Reaction conditions: $HPOPh_2$ (2 equiv), $AgNO_3$ (10 mol%), MeCN (0.05 M), 100 °C, 14 h. [b] Reaction conditions: **4** (1.5 equiv), phen (1 equiv), $CH_2Cl_2$ (0.05 M), 60 °C, 14 h. [c] Reaction conditions: $HPOPh_2$ (2 equiv), $AgNO_3$ (50 mol%), MeCN (0.05 M), 100 °C, 14 h.

according to the deuterium labelling experiments, the hydrogen is abstracted from $R_2P(O)H$, so that a self-propagating radical cycle operates without the need to further invoke a metal or a $[Ph_2POAg]$ complex, which is in contrast to previously described oxidative phosphonylation reactions.[11,19] The presence of an alkyl group on the nitrogen atom generates a more nucleophilic amidyl radical (see Scheme 2 and Scheme 3a), thus triggering a subsequent $C(sp^2)$–N bond formation. The intermediate aryl radical **IV** will be oxidized at the expense of $AgNO_3$, which, in this case, needs to be regenerated in the reaction mixture, thus explaining the need for a higher silver loading in these transformations. Functionalized oxindoles **6** were obtained in a completely regioselective fashion. The normal secondary kinetic isotope effect (sKIE) that is described in Scheme 4b,c could either indicate a $C(sp^3)$ to $C(sp^2)$ rehybridization in the transition state (α-sKIE) or an involvement of the C–H bond in hyperconjugation (β-sKIE). As no rehybridization of $C(sp^3)$–H/D to $C(sp^2)$–H/D can occur for the formation of products **6**, we rationalized that the observed effect in terms of a β-sKIE is due to a more efficient hyperconjugation by the C–H bond in intermediate **II**, which would point towards the *ipso*-cyclization/desulfonylation (**I** to **III**) being the rate-determining step of these transformations.[20]

Finally, the replacement of the sulfonyl group by a benzoate moiety with increased electron density furnished the corresponding spirobicycles **8** from an intermediate analogous to **II**.

In summary, two radical-mediated transformations of activated alkenes, namely arylphosphonylation and arylazidation, have been developed. α-Aryl-β-azido and α-aryl-β-phosphonyl amides could be obtained for the first time in excellent yields and also in a highly regioselective fashion. Control experiments suggest that a 5-*exo*-dig *ipso* cyclization of an α-alkyl-β-heterofunctionalized radical onto the aromatic ring for the formation of the new $C(sp^2)$–$C(sp^3)$ bond is followed by a desulfonylation process as the turnover-limiting step for these reactions. Further studies to introduce other radicals into these transformations are currently underway.




***Scheme 5.*** Mechanistic proposal.

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