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Exploring New Partners for the Domino α-Arylation/Michael Addition Reaction Leading to Tetrahydroisoquinolines

Daniel Solé,*[a] Ferran Pérez-Janer,[a] Yago García-Rodeja,[b] and Israel Fernández*[b]

Abstract: Sulfonates, sulfonamides and phosphonates are useful nucleophiles for palladium-catalyzed intramolecular α-arylation leading to tetrahydroisoquinolines. While the sulfonate α-arylation can be successfully combined in a domino process with a broad range of Michael acceptors, only vinyl sulfones can be used in Michael additions when starting from sulfonamides. No domino process was developed with the phosphonate derivative. Density functional theory (DFT) calculations were carried out to gain more insight into the experimental differences observed in the reactions involving these substrates.

Introduction

In the continuous search for more environmentally friendly reaction processes, domino reactions have emerged as a powerful tool for synthetic organic chemists.[1] Ideally, a multicomponent domino process would simply involve the mixing of all the reagents, which would then participate chemoselectively in a particular sequence of events leading to the final product without requiring any additional modification of the reaction conditions.[2] The advantages of domino strategies include lower costs, a more expeditious procedure, less purification, and often higher overall reaction yields.

In the last years, different domino processes combining palladium-catalyzed transformations with Michael addition reactions have been developed for the synthesis of a variety of aza-heterocycles.[3] In this context, we have recently reported efficient syntheses of highly functionalized tetrahydroisoquinolines[4] and indoles[5] by domino aza-Michael/Pd-catalyzed α-arylation/Michael addition processes based on the use of sulfones both as electrophiles and nucleophiles. To further generalize the application of these synthetic methodologies and access diversely functionalized

heterocycles, we were interested in exploring the feasibility of other electron-withdrawing groups in the domino α-arylation/Michael addition strategy.

In this paper, we expand our previous studies towards the use of sulfonates, sulfonamides[6] and phosphonates[7] as nucleophiles in the α-arylation[8] step of the domino process leading to tetrahydroisoquinolines[9] (Scheme 1). The combined experimental and computational study of these reactions establishes the scope and limitations of these electron-withdrawing groups as alternatives to sulfones.
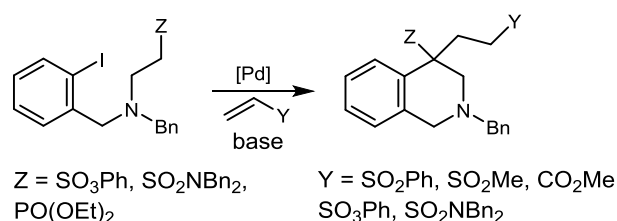
Scheme 1. Domino α-arylation/Michael addition process.

Results and Discussion

In our previous work on the α-arylation/Michael addition domino process, we realized that the Pd-catalyzed reaction constituted the most challenging step of the entire transformation. Thus, we first examined the α-arylation of sulfonate **1a**, sulfonamides **1b** and **1d**, and phosphonate **1c** (Table 1).

Treatment of **1a** with $Pd_2(dba)_3$/xantphos as the catalyst and K_3PO_4 as the base in THF, an effective combination for the intramolecular α-arylation of β-amino sulfones,[4] afforded tetrahydroisoquinoline **2a** in a modest 27% yield (entry 1). While exchanging the solvent for toluene increased the yield up to 45% (entry 2), changing the base to Cs_2CO_3 resulted in the complete decomposition of the material. In this context, it should be noted that **2a** was rather unstable and partially decomposed during the chromatographic purification, as evidenced by the isolation of significant amounts of phenol.

The reaction of sulfonamide **1b** using the couple $Pd_2(dba)_3$/xantphos and K_3PO_4 in THF led to the desired tetrahydroisoquinoline **2b** in 46% yield (entry 3). Interestingly, performing the α-arylation of **1b** using Cs_2CO_3 as the base afforded **2b** in 75% yield (entry 4). Treatment of phosphonate **1c** under the same reaction conditions gave **2c** in 61% yield (entry 5). The use of PPh_3 as the ligand instead of xantphos afforded a similar result (entry 6), while PCy_3 increased the yield considerably up to 80% (entry 7). The use of K_3PO_4 as the base,

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maintaining the same combination of Pd source and ligand, resulted in a slower reaction (entry 8).

Table 1. Pd-catalyzed α-arylation of **1a-c**.[a]

1a, Z = SO$_3$Ph
1b, Z = SO$_2$NBn$_2$
1c, Z = PO(OEt)$_2$
1d, Z = SO$_2$NHBn

2a
2b
2c

Entry	1	[Pd]/ligand (mol%)	Base	Solvent	Products (yield)[b]
1	1a	Pd$_2$(dba)$_3$ (7.5) xantphos (15)	K$_3$PO$_4$	THF	2a (27%)[c]
2	1a	Pd(PPh$_3$)$_4$ (10) xantphos (10)	K$_3$PO$_4$	toluene	2a (45%)[c,[d]
3	1b	Pd$_2$(dba)$_3$ (7.5) xantphos (15)	K$_3$PO$_4$	THF	2b (46%)[e]
4	1b	Pd$_2$(dba)$_3$ (7.5) xantphos (15)	Cs$_2$CO$_3$	THF	2b (75%)
5	1c	Pd$_2$(dba)$_3$ (7.5) xantphos (15)	Cs$_2$CO$_3$	THF	2c (61%)[e]
6	1c	Pd(PPh$_3$)$_4$ (10)	Cs$_2$CO$_3$	THF	2c (59%)[e]
7	1c	Pd$_2$(dba)$_3$ (7.5) PCy$_3$ (15)	Cs$_2$CO$_3$	THF	2c (80%)
8	1c	Pd$_2$(dba)$_3$ (7.5) PCy$_3$ (15)	K$_3$PO$_4$	THF	1c:2c (1:2.5)[f]

[a] Reaction conditions: [Pd]/ligand (see table), base (3 equiv.) in the indicated solvent at 120ºC for 72 h in a sealed tube. [b] Yield refers to products isolated by chromatography. [c] Significant amounts of phenol were observed in the reaction mixture. [d] A similar result was obtained when using Pd(PPh$_3$)$_4$ (15) and xantphos (15) as the catalyst; however, the higher amount of PPh$_3$ ligand hindered the isolation and purification of **2a**. [e] Significant amounts of the corresponding hydrodehalogenation product were observed in the reaction mixture. [f] ^{1}H NMR ratio, yields were not quantified.

Finally, sulfonamide **1d**, which has an acidic H atom at the nitrogen, failed to undergo a similar α-arylation, and was recovered unaltered under all explored reaction conditions.

The results in Table 1 show that sulfonates, sulfonamides as well as phosphonates can undergo α-arylation and, consequently, they are all potential candidates for the proposed domino cascades. We therefore decided to explore the α-arylation/Michael addition domino process using these substrates with a variety of Michael acceptors (Table 2).

Gratifyingly, treatment of sulfonate **1a** with a catalytic amount of Pd(PPh$_3$)$_4$/xantphos and K$_3$PO$_4$ in the presence of phenyl vinyl sulfone in THF afforded sulfonate **3aa** in 68% yield

(entry 1). A similar reaction was observed when using methyl vinyl sulfone as the Michael acceptor, which afforded **3ab** in 70% yield (entry 2). The α-arylation/conjugated addition tandem process was also possible when using methyl acrylate, phenyl ethenesulfonate and *N,N*-dibenzylethenesulfonamide, which allowed us to prepare **3ac**, **3ad**, and **3ae**, respectively, in moderate yields (entries 3-5). It should be noted that, except when using *N,N*-dibenzylethenesulfonamide as the Michael acceptor, the domino reactions from **1a** proceeded with higher yields than the α-arylation, confirming that the observed lower yield of the latter is partially due to the degradation of the arylated sulfonate **2a** under the reaction conditions.

Table 2. Tandem α-arylation/Michael addition reactions.[a]

1a-b

3aa-3bb

Entry	Z	Y	[Pd]/ligand	Base	Products (yield)[b]
1	SO$_3$Ph	SO$_2$Ph	Pd$_2$(dba)$_3$ xantphos	K$_3$PO$_4$	3aa (68%)
2	SO$_3$Ph	SO$_2$Me	Pd$_2$(dba)$_3$ xantphos	K$_3$PO$_4$	3ab (70%)[c]
3	SO$_3$Ph	CO$_2$Me	Pd$_2$(dba)$_3$ xantphos	K$_3$PO$_4$	3ac (43%)[c]
4	SO$_3$Ph	SO$_3$Ph	Pd$_2$(dba)$_3$ xantphos	K$_3$PO$_4$	3ad (50%)
5	SO$_3$Ph	SO$_2$NBn$_2$	Pd$_2$(dba)$_3$ xantphos	K$_3$PO$_4$	3ae (25%)
6	SO$_2$NBn$_2$	SO$_2$Ph	Pd(PPh$_3$)$_4$	Cs$_2$CO$_3$	3ba (74%)
7	SO$_2$NBn$_2$	SO$_2$Me	Pd(PPh$_3$)$_4$	Cs$_2$CO$_3$	3bb (67%)[c]

[a] Reaction conditions: [Pd] (10%), ligand (10%), base (3 equiv.), and Michael acceptor (1.5 equiv.) in THF at 120ºC in a sealed tube for 72 h. [b] Yield refers to products isolated by chromatography. [c] Michael acceptor (3 equiv.).

In the tandem reactions, sulfonamide **1b** afforded parallel results to sulfonate **1a** with phenyl vinyl sulfone and methyl vinyl sulfone (entries 6-7), but no product was formed when using methyl acrylate, phenyl ethenesulfonate and *N,N*-dibenzylethenesulfonamide as the Michael acceptor, and only the α-arylation product **2b** was isolated. Similarly, phosphonate **1c** also failed to undergo the α-arylation/conjugated addition tandem process with any of the Michael acceptors explored herein. Once again, the corresponding α-arylation compound **2c** was the only product isolated in the reaction mixtures.

It is noteworthy that in all domino reactions with **1a** and **1b**, the α-arylation took place without any interference from the competing Heck reaction, which agrees with the unfeasibility previously observed for this particular pathway when using sulfones in the domino process.[5]

According to our previous study involving 2-iodoanilines and sulfones,[5] two alternative reaction pathways for the above palladium-catalyzed α-arylation reactions leading to the observed tetrahydroisoquinolines **2** can be envisaged: the direct base-mediated α-arylation reaction and a concerted metalation-deprotonation (CMD) C–H activation process. The competition between the two pathways in the reactions involving the new nucleophiles was explored computationally by means of density functional theory calculations.[10] To this end, we computed the corresponding reaction profiles starting from **INT0**, the intermediate formed after a model benzylamine derivative (in which the benzyl group attached to the nitrogen atom was replaced by a methyl group) underwent oxidative addition to the model Pd(PMe$_3$)$_2$ catalyst, in the presence of carbonate as the base.
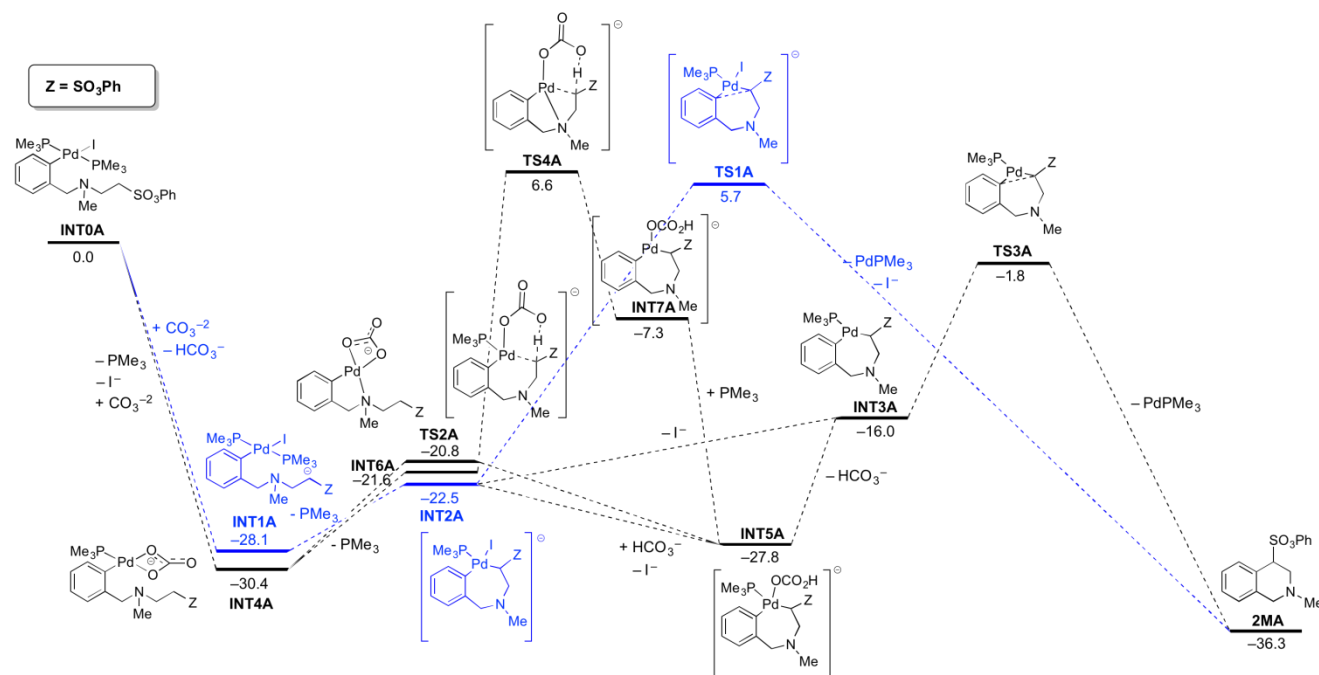

Figure 1. Computed reaction profiles for the palladium catalyzed α-arylation reaction of **INT0A**. Relative free energies (ΔG, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level.

Figure 1 shows the reaction profiles for the process involving **INT0A** (Z = SO$_3$Ph). The base-mediated α-arylation pathway (in blue) begins with the base-mediated deprotonation of the acidic hydrogen atom at the carbon atom linked to the sulfonate group, therefore leading to the carbanionic intermediate **INT1A** in a strongly exergonic process (ΔG$_R$ = −28.1 kcal/mol). This species would then evolve to complex **INT2A** by the slightly endergonic (ΔG$_R$ = 5.6 kcal/mol) coordination of the carbanion to the transition metal and concomitant release of a phosphine ligand. This step typically proceeds with the initial endergonic release of the phosphine ligand to produce a coordination vacant which is then saturated by the carbanionic ligand. The latter intramolecular coordination is typically associated with a low barrier (< 10 kcal/mol)[11] and therefore, it does not constitute the rate-limiting step of the transformation. The reductive elimination reaction would then

take place to produce the tetrahydroisoquinoline **2MA**. This exergonic step (ΔG$_R$ = −13.8 kcal/mol) proceeds via **TS1A**, a transition state associated with the direct formation of the new C–C bond, with a relatively high activation barrier of 28.2 kcal/mol. A similar activation barrier of 28.6 kcal/mol was computed for the strongly related direct α-arylation reaction involving 2-iodoaniline derivatives with Z = SO$_2$Me,[5] thus indicating that neither the substrate nor the Z group has a significant influence on this reaction step. Alternatively, **INT2A** can be transformed into the coordinatively unsaturated complex **INT3A** by releasing the iodide ligand in an endergonic process (ΔG$_R$ = 6.5 kcal/mol). This species would be then converted into the final reaction product **2MA** in a highly exergonic transformation (ΔG$_R$ = −20.3 kcal/mol) through **TS3A** with a much lower activation barrier of 14.2 kcal/mol.

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The alternative reaction pathway involving the C–H activation begins with the also highly exergonic (ΔG_R = −30.4 kcal/mol) replacement of the iodide and phosphine ligand in **INT0A** by the bidendate CO_3^{-2} ligand, thus forming the anionic complex **INT4A**. A concerted metalation deprotonation (CMD) C–H activation reaction assisted by the carbonate ligand then occurs to produce **INT5A** in a slightly endergonic transformation (ΔG_R = 2.6 kcal/mol). Strikingly, this reaction step proceeds with an activation barrier of only 9.6 kcal/mol (via **TS2A**), which is much lower than that computed not only for the direct α-arylation via **TS1A** (see above) but also for the analogous process involving 2-iodoaniline derivatives with Z = SO_2Me ($\Delta G^{\neq}$ = 26.1 kcal/mol).[5] Subsequent release of the HCO_3^- ligand would produce **INT3A** which, as mentioned above, readily evolves to the final reaction product via **TS3A**. Although, based on the computed relative activation barriers, our calculations suggest that the CMD pathway is strongly favored for the benzylamine derivative with Z = SO_3Ph, the alternative **INT1A→INT2A→INT5A** or **INT1A→INT2A→INT3A** pathways cannot be completely discarded.

We also explored the analogous C–H activation/reductive elimination sequence from **INT6A**, the intermediate formed upon coordination of the benzylic nitrogen atom to the transition metal in **INT4A**. However, the CMD reaction pathway from **INT6A** can be considered as non-competitive in view of the much higher activation barrier ($\Delta G^{\neq}$ = 28.2 kcal/mol) and endergonicity (ΔG_R = 14.3 kcal/mol, from **INT6A**) computed for the corresponding CMD reaction via **TS4A** (see Figure 1).

These calculations indicate that the α-arylation of sulfonate **1a** in the presence of Cs_2CO_3 could proceed through the two competing mechanisms sharing the common intermediate **INT3A**, from which the reductive elimination affords the tetrahydroisoquinoline. As no α-arylation product was isolated in the reactions of **1a** when using Cs_2CO_3 as the base, we can conclude that the failure of the transformation has to be due to the instability of the arylated sulfone under the reaction conditions. In contrast, the α-arylation of **1a** did take place when using K_3PO_4 as the base, and in this case, the reaction should follow the base-mediated pathway through **INT1A**.

Similar conclusions (i.e. preference of the C–H activation) can be drawn for the analogous system with the phosphonate substituent (Z = $PO(OMe)_2$ in the calculations, see Figure S1 in the Supporting Information). In this particular transformation, although the CMD step proceeds with a higher activation barrier of 16.5 kcal/mol, this pathway is still preferred over the direct α-arylation reaction. Indeed, the corresponding transition state for the latter process (**TS1C**) lies 17.8 kcal/mol above that associated with the CMD reaction (**TS2C**, see Figure S1).

Thus, starting from phosphonate **1c** and using Cs_2CO_3, the α-arylated product **2c** could be formed by both competing mechanisms, while in the presence of K_3PO_4, only the base-mediated α-arylation pathway would be operative.

The scenario involving the sulfonamide group (Z = SO_2NMe_2 in the calculations) is slightly different to that found for Z = SO_3Ph or $PO(OMe)_2$ (see Figure 2).
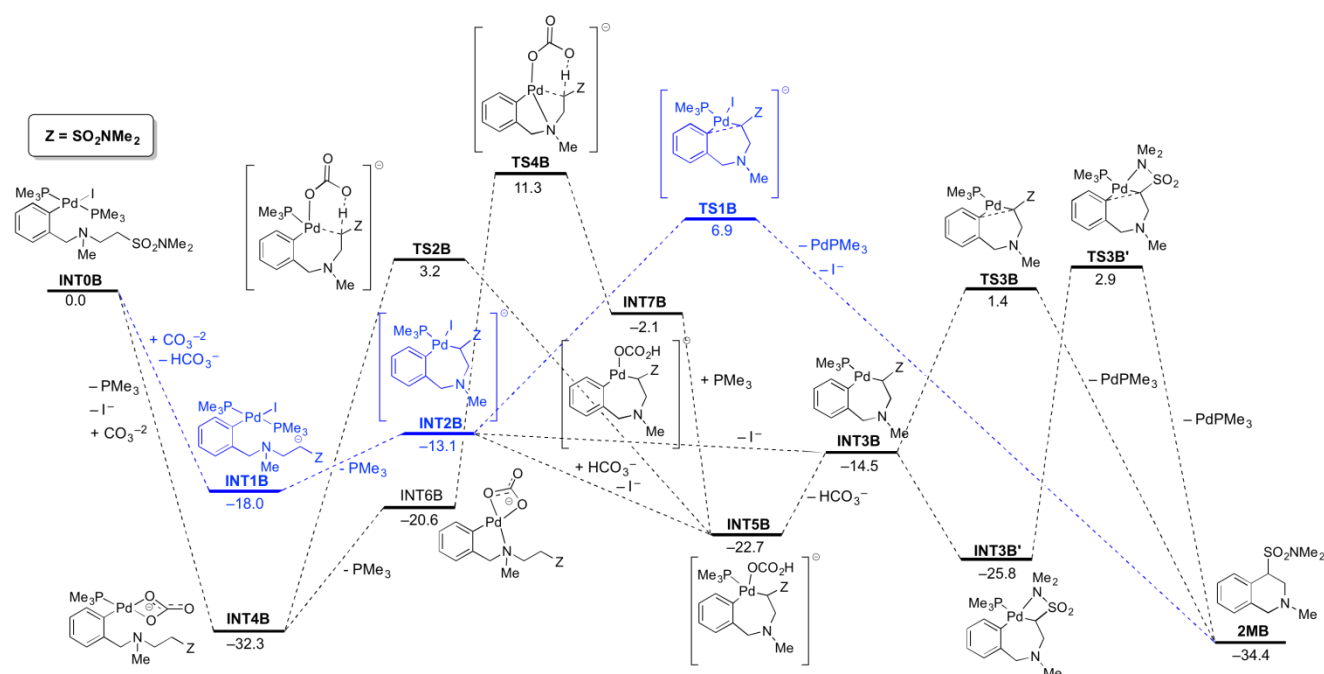

Figure 2. Computed reaction profiles for the palladium catalyzed α-arylation reaction of **INT0A**. Relative free energies (ΔG, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level.

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Indeed, in this case, the corresponding CMD reaction step proceeds with a much higher activation barrier ($\Delta G^{\neq}$ = 35.5 kcal/mol, via **TS2B**), which makes this process unlikely. This is in part due to the higher C–H bond strength in **INT4B** than in **INT4A**, as confirmed by the corresponding computed Wiberg bond indices (0.89 and 0.86 for **INT4B** and **INT4A**, respectively) and more likely due to higher pKa of the R–CH_2–SO$_2$NMe$_2$ species as compared to R–CH$_2$–SO$_3$Ph.[12] Therefore, the preferred α-arylation pathway when Z = SO$_2$NMe$_2$ seems to be **INT0B → INT1B → INT2B → INT3B → TS3B → 2MB**. In this particular case, it can also be suggested that the nitrogen atom of the sulfonamide can coordinate the transition metal in the coordinatively unsaturated complex **INT3B**. However, although such coordination is strongly exergonic (ΔG_R = −11.3 kcal/mol), the corresponding reductive elimination reaction via **TS3B'** proceeds with a much higher activation barrier ($\Delta G^{\neq}$ = 28.7 kcal/mol) than the analogous process involving **TS3B** ($\Delta G^{\neq}$ = 15.9 kcal/mol).

Finally, we investigated the reasons for the observed lower yields in the domino reactions involving methyl acrylate (43%) or *N,N*-dibenzylethenesulfonamide (25%) with respect to vinyl sulfones (ca. 70%) as Michael acceptors (see Table 2). As shown in Figure 3, the computed activation barriers involving Y = CO$_2$Me ($\Delta G^{\neq}$ = 19.7 kcal/mol) or Y = SO$_2$NMe$_2$ ($\Delta G^{\neq}$ = 21.6 kcal/mol) are clearly higher than that computed for the Michael addition reaction involving the vinyl sulfone (Y = SO$_2$Ph, $\Delta G^{\neq}$ = 15.8 kcal/mol). This can be ascribed to the relative electrophilicity of the Michael acceptor, which can be roughly estimated by the relative energy of the corresponding LUMO: −1.64 eV (Y = SO$_2$Ph) > −1.49 eV (Y = CO$_2$Me) > −1.11 eV (Y = SO$_2$NMe$_2$). Therefore, the experimentally observed reactivity trend is very likely related to the relative electrophililicity of the Michael acceptor used in the α-arylation/Michael addition domino process.
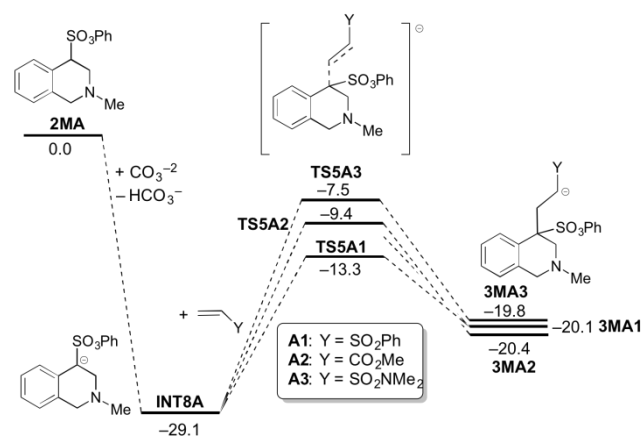

Figure 3. Computed reaction profiles for the Michael addition reaction involving **2MA** and the different Michael acceptors. Relative free energies (ΔG, at 298 K) are given in kcal/mol. All data were computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-TZVP//PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level.

Conclusions

In summary, this joint experimental-computational comparative study has established the feasibility of using different nucleophiles and Michael acceptors in the domino α-arylation/Michael addition process leading to tetrahydroisoquinolines. Our calculations indicate that two competing mechanisms, namely the direct base-mediated α-arylation reaction and a concerted metalation-deprotonation (CMD) C–H activation process, can be operative in the α-arylation step of sulfonates and phosphonates when using Cs$_2$CO$_3$ as the base. In contrast, in the sulfonamide reaction, the base-mediated process seems to be preferred over the concerted metalation-deprotonation pathway. Our study also indicates that the success of the two-step domino process is strongly related to the electrophilicity of the Michael acceptor.
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Experimental Section

General Remarks: All commercially available reagents were used without further purification. All nonaqueous reactions were carried out under an argon atmosphere. TLC was carried out on SiO$_2$ (silica gel 60 F$_{254}$, Merck), and the spots were located with UV light, 1% iodoplatinate reagent or 1% aqueous KMnO$_4$. Flash chromatography was carried out on SiO$_2$ (silica gel 60, SDS, 230-400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na$_2$SO$_4$. Solvents were evaporated with a rotatory evaporator. ^{1}H- and ^{13}C-NMR spectra were recorded using Me$_4$Si as the internal standard, with a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me$_4$Si for ^{1}H- and ^{13}C- NMR. HRMS were obtained using a LC/MSD TOF mass spectrometer.

Typical Method for the Pd(0)-Catalyzed α-Arylation Reaction (Table 1, Entry 4). A mixture of sulfonamide **1b** (75 mg, 0.123 mmol), Pd$_2$(dba)$_3$ (8 mg, 0.009 mmol), xantphos (11 mg, 0.018 mmol), and Cs$_2$CO$_3$ (120 mg, 0.37 mmol) in THF (8 mL) was stirred at 120 ºC in a sealed tube for 72 h. The reaction mixture was partitioned between saturated NaHCO$_3$ aqueous solution and Et$_2$O. The organic extracts were dried and concentrated. The residue was purified by chromatography (CH$_2$Cl$_2$) to give sulfonamide **2b** (45 mg, 75%).

Phenyl 2-benzyl-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (2a). Chromatography (SiO$_2$, from hexanes to CH$_2$Cl$_2$). Orange oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 3.03 (dd, *J* = 13.0 and 4.2 Hz, 1H), 3.50 (d, *J* = 15.2 Hz, 1H), 3.71 (d, *J* = 12.8 Hz, 1H), 3.73 (ddd, *J* = 13.0, 4.2 and 1.0 Hz, 1H), 3.79 (d, *J* = 12.8 Hz, 1H), 3.94 (d, *J* = 15.2 Hz, 1H), 4.72 (t, *J* = 4.2 Hz, 1H), 6.99-7.02 (m, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.19-7.34 (m, 8H), 7.40 (d, 2H), 7.65 (d, *J* = 7.4 Hz, 1H), ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ 51.4 (CH$_2$), 55.2 (CH$_2$), 62.3 (CH), 62.3 (CH$_2$), 122.2 (2 CH), 125.4 (C), 126.8 (CH), 126.9 (CH), 127.3 (CH), 127.5 (CH), 128.5 (2 CH), 129.0 (CH), 129.2 (2 CH), 129.7 (2 CH), 130.5 (CH), 137.1 (C), 137.4 (C), 149.3 (C). HRMS (ESI-TOF) calcd. for C$_{22}$H$_{22}$NO$_3$S: 380.1315 [M+H]$^+$; found: 380.1324.

N,N,2-Tribenzyl-1,2,3,4-tetrahydroisoquinoline-4-sulfonamide (2b). Chromatography (SiO$_2$, from CH$_2$Cl$_2$ to CH$_2$Cl$_2$-MeOH 1%). Brown oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.78 (dd, *J* = 12.8 and 4.4 Hz, 1H), 3.37 (d, *J* = 15.2 Hz, 1H), 3.57 (d, *J* = 12.8Hz, 1H), 3.69 (dd, *J* = 12.8 and 2.4 Hz, 1H), 3.78 (d, *J* = 12.8 Hz, 1H), 3.90 (d, *J* = 15.2 Hz, 1H), 4.12 (s, 4H), 4.50 (dd,

J = 4.4 and 2.4 Hz, 1H), 6.95-6.99 (m, 4H), 7.06-7.31 (m, 14H) 7.71 (d, J = 7.6 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ 52.1 (CH$_2$), 52.3 (CH$_2$), 55.2 (CH$_2$), 63.0 (CH$_2$), 64.9 (CH), 126.6 (C), 126.7 (CH), 127.1 (CH), 127.4 (CH), 127.6 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.7 (CH), 130.8 (CH), 136.4 (C), 136.6 (C), 136.7 (C). HRMS (ESI-TOF) calcd. for C$_{30}$H$_{31}$N$_2$O$_2$S: 483.2101 [M+H]$^+$: found: 483.2103.

Diethyl 2-benzyl-1,2,3,4-tetrahydroisoquinolin-4-ylphosphonate (2c). Chromatography (SiO$_2$, from CH$_2$Cl$_2$ to CH$_2$Cl$_2$/MeOH 4%). Yellow oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.16 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H), 2.86 (ddd, J = 25.2, 11.6 and 4.8 Hz, 1H), 3.29 (td, J = 11.6 and 4.8 Hz, 1H), 3.42-3.51 (m, 2H), 3.64 (d, J = 13.2 Hz, 1H), 3.73 (dd, J = 15.2 and 1.6 Hz, 1H), 3.76 (d, J = 13.2 Hz, 1H), 3.84-4.09 (m, 4H), 6.98 (m, 1H), 7.11-7.19 (m, 2H), 7.24-7.41 (m, 5H), 7.54 (m, 1H). ^{13}C NMR (CDCl$_3$, 100.5 MHz) δ 16.4 (d, J_{C-P} = 6.1 Hz, CH$_3$), 16.5 (d, J_{C-P} = 4.5 Hz, CH$_3$), 38.9 (d, J_{C-P} = 137.9 Hz, CH), 51.6 (d, J_{C-P} = 4.6 Hz, CH$_2$), 55.7 (d, J_{C-P} = 1.5 Hz, CH$_2$), 62.1 (d, J_{C-P} = 6.1 Hz, CH$_2$), 62.2 (d, J_{C-P} = 6.9 Hz, CH$_2$), 62.8 (CH$_2$), 126.3 (d, J_{C-P} = 3.0 Hz, CH), 126.7 (d, J_{C-P} = 3.0 Hz, CH$_2$), 126.9 (d, J_{C-P} = 2.3 Hz, CH$_2$), 127.3 (s, CH), 128.3 (s, 2 CH), 129.4 (s, 2 CH), 129.6 (s, C), 129.7 (d, J_{C-P} = 4.6 Hz, CH), 135.5 (d, J_{C-P} = 6.9 Hz, C), 138.0 (s, C). HRMS (ESI-TOF) calcd. for C$_{20}$H$_{27}$NO$_3$P: 360.1723 [M+H]$^+$: found: 360.1724.

Typical Method for the Domino Reactions (Table 2, Entry 1). A mixture of sulfonate **1a** (75 mg, 0.148 mmol), Pd(PPh$_3$)$_4$ (17 mg, 0.015 mmol), xantphos (8.5 mg, 0.015 mmol), phenyl vinyl sulfone (37 mg, 0.22 mmol), and K$_3$PO$_4$ (94 mg, 0.44 mmol) in THF (8 mL) was stirred at 120 ºC in a sealed tube for 72 h. The reaction mixture was poured into water and extracted with Et$_2$O. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO$_2$, from CH$_2$Cl$_2$ to CH$_2$Cl$_2$-MeOH 1%) to give sulfonate **3aa** (55 mg, 68%).

Phenyl   2-benzyl-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (3aa). Yellow foam. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.62 (td, J = 13.6 and 4.4 Hz, 1H), 2.80-2.91 (m, 2H), 3.13 (dd, J = 12.4 and 2.0 Hz, 1H), 3.26 (d, J = 12.4 Hz, 1H), 3.50 (ddd, J = 14.4, 13.2 and 4.4 Hz, 1H), 3.53 (d, J = 15.6 Hz, 1H), 3.60 (d, J = 12.8 Hz, 1H), 3.73 (d, J = 15.6 Hz, 1H), 3.74 (d, J = 7.6 Hz, 1H), 6.79 (m, 2H), 7.09 (d, J = 7.6 Hz, 1H), 7.13-7.38 (m, 10H), 7.51-7.59 (m, 3H), 7.66 (tt, J = 7.6 and 1.2 Hz, 1H), 7.79 (m, 2H). ^{13}C NMR (CDCl$_3$, 100.5 MHz) δ 31.2 (CH$_2$), 52.1 (CH$_2$), 56.6 (CH$_2$), 57.0 (CH$_2$), 62.7 (CH$_2$), 68.1 (C), 121.9 (2 CH), 127.0 (CH), 127.4 (CH), 127.6 (CH), 127.9 (CH), 128.0 (CH), 128.1 (C), 128.2 (2 CH), 128.8 (2 CH), 129.1 (CH), 129.4 (2 CH), 129.5 (2 CH), 129.7 (2 CH), 134.0 (CH), 136.9 (C), 137.3 (C), 138.6 (C), 149.1 (C). HRMS (ESI-TOF) cald for C$_{30}$H$_{30}$NO$_5$S$_2$: 548.1560 [M + H]$^+$; found: 548.1567.

Phenyl   2-benzyl-4-[2-(methylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (3ab). Yellow Oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.67-2.78 (m, 2H), 2.75 (s, 3H), 2.90-3.01 (m, 1H), 3.22 (dd, J = 12.4 and 1.6 Hz, 1H), 3.27 (d, J = 12.4 Hz, 1H), 3.37-3.47 (m, 1H), 3.60 (d, J = 12.8 Hz, 1H), 3.61 (d, J = 14.8 Hz, 1H), 3.82 (d, J = 12.8 Hz, 1H), 3.83 (d, J = 14.8 Hz, 1H), 6.85 (m, 2H), 7.14 (dd, J = 8.0 and 1.2 Hz, 1H), 7.18-7.40 (m, 10H), 7.79 (dd, J = 8.0 and 1.2 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100.5 MHz) δ 31.1 (CH$_2$), 40.5 (CH$_3$), 50.7 (CH$_2$), 56.5 (CH$_2$), 56.9 (CH$_2$), 62.6 (CH$_2$), 68.1 (C), 122.0 (2 CH), 127.1 (CH), 127.5 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 128.5 (C), 128.9 (2 CH), 129.2 (CH), 129.6 (2 CH), 129.8 (2 CH), 137.0 (C), 137.2 (C), 149.1 (C). HRMS (ESI-TOF) cald for C$_{25}$H$_{28}$NO$_5$S$_2$: 486.1403 [M + H]$^+$; found: 486.1403.

Phenyl   2-benzyl-4-[2-(methoxycarbonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (3ac). Pale yellow solid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.22 (ddd, J = 16.2, 11.2 and 5.2 Hz, 1H), 2.65 (ddd,

J = 11.2, 8.0 and 5.2 Hz, 1H), 2.69 (ddd, J = 11.2, 8.0 and 5.2 Hz, 1H), 2.84 (ddd, J = 16.2, 11.2 and 5.2 Hz, 1H), 3.18 (dd, J = 12.4 and 1.6 Hz, 1H), 3.38 (d, J = 12.4 Hz, 1H), 3.58 (d, J = 14.8 Hz, 1H), 3.63 (s, 3H), 3.69 (d, J = 13.2 Hz, 1H), 3.70 (d, J = 14.8 Hz, 0031H), 3.74 (d, J = 13.2 Hz, 1H), 6.84 (m, 2H), 7.08 (dd, J = 7.6 and 1.2 Hz, 1H), 7.16-7.38 (m, 10H), 7.77 (dd, J = 7.6 and 1.2 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100.5 MHz) δ 29.7 (CH$_2$), 32.5 (CH$_2$), 51.9 (CH$_3$), 56.3 (CH$_2$), 57.0 (CH$_2$), 62.6 (CH$_2$), 69.2 (C), 122.1 (2 CH), 126.8 (CH), 127.2 (CH), 127.3 (CH), 127.7 (CH), 128.4 (CH), 128.6 (2 CH), 128.7 (CH), 129.1 (C), 129.2 (2 CH), 129.6 (2 CH), 137.2 (C), 137.3 (C), 149.3 (C). 173.0 (C). HRMS (ESI-TOF) cald for C$_{26}$H$_{28}$NO$_5$S: 466.1683 [M + H]$^+$; found: 466.1683.

Phenyl   2-benzyl-4-[2-(phenoxysulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (3ad). Yellow foam. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.93 (td, J = 12.4 and 3.2 Hz, 1H), 2.99 (td, J = 12.4 and 3.2 Hz, 1H), 3.11 (td, J = 12.4 and 3.2 Hz, 1H), 3.27 (s, 2H), 3.56 (d, J = 15.2 Hz, 1H), 3.63 (d, J = 12.8 Hz, 1H), 3.72 (td, J = 12.4 and 3.2 Hz, 1H), 3.78 (d, J = 12.8 Hz, 1H), 3.82 (d, J = 15.2 Hz, 1H), 6.87 (m, 2H), 7.13 (dd, J = 7.6 and 0.8 Hz, 1H), 7.17-7.38 (m, 15H), 7.82 (dd, J = 8.0 and 1.2 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100.5 MHz) δ 32.3 (CH$_2$), 46.7 (CH$_2$), 56.6 (CH$_2$), 56.8 (CH$_2$), 62.6 (CH$_2$), 68.0 (C), 122.0 (2 CH), 122.1 (2 CH), 127.1 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 128.3 (C), 128.9 (2 CH), 129.2 (CH), 129.3 (2 CH), 129.8 (2 CH), 130.1 (2 CH), 136.7 (C), 137.1 (C), 149.0 (C), 149.1 (C). HRMS (ESI-TOF) cald for C$_{30}$H$_{30}$NO$_6$S$_2$: 564.1509 [M + H]$^+$; found: 564.1518.

Phenyl   2-benzyl-4-[2-(N,N-dibenzylaminosulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonate (3ae). Yellow oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.68-2.79 (m, 2H), 2.88-2.99 (m, 1H), 3.07 (dd, J = 12.4 and 1.2 Hz, 1H), 3.26 (d, J = 12.4 Hz, 1H), 3.20-3.33 (m, 1H), 3.54 (d, J = 14.8 Hz, 1H), 3.61 (d, J = 13.2 Hz, 1H), 3.69 (d, J = 14.8 Hz, 1H), 3.71 (d, J = 13.2 Hz, 1H), 4.22 (d, J = 15.2 Hz, 2H), 4.30 (d, J = 15.2 Hz, 2H), 6.85 (m, 2H), 7.09 (dd, J = 7.6 and 1.2 Hz, 1H), 7.17-7.35 (m, 20H), 7.71 (dd, J = 8.0 and 0.8 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100.5 MHz) δ 31.7 (CH$_2$), 49.7 (CH$_2$), 50.3 (2 CH$_2$), 56.5 (CH$_2$), 57.0 (CH$_2$), 62.6 (CH$_2$), 68.4 (C), 122.0 (2 CH), 127.0 (CH), 127.4 (CH), 127.5 (CH), 127.8 (CH), 128.1 (2 CH), 128.3 (CH), 128.4 (C), 128.7 (2 CH), 128.8 (4 CH), 128.9 (4 CH), 129.0 (CH), 129.2 (2 CH), 129.7 (2 CH), 135.7 (2 C), 137.0 (C), 137.2 (C), 149.2 (C). HRMS (ESI-TOF) cald for C$_{38}$H$_{39}$N$_2$O$_5$S$_2$: 667.2295 [M + H]$^+$; found: 667.2289.

2,N,N-Tribenzyl-4-[2-(phenylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonamide (3ba). Yellow oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.63 (ddd, J = 13.6, 12.8 and 4.8 Hz, 1H), 2.79 (ddd, J = 13.6, 12.8 and 3.6 Hz, 1H), 2.86 (d, J = 12.4 Hz, 1H), 2.89 (ddd, J = 13.6, 12.8 and 3.6 Hz, 1H), 3.16 (d, J = 12.4 Hz, 1H), 3.44 (d, J = 12.8 Hz, 1H), 3.49 (ddd, J = 13.6, 12.8 and 4.8 Hz, 1H), 3.49 (d, J = 14.8 Hz, 1H), 3.57 (d, J = 14.8 Hz, 1H), 3.70 (d, J = 12.8 Hz, 1H), 4.01 (broad s, 4H), 6.77 (d, J = 6.8 Hz, 4H), 7.06-7.35 (m, 14H), 7.55 (tt, J = 7.6 and 1.2 Hz, 2H), 7.65 (tt, J = 7.6 and 1.2 Hz, 1H), 7.76 (dd, J = 8.0 and 1.2 Hz, 1H), 7.83 (m, 2H). ^{13}C NMR (CDCl$_3$, 100.5 MHz) δ 31.6 (CH$_2$), 52.4 (CH$_2$), 52.5 (2 CH$_2$), 56.4 (CH$_2$), 57.1 (CH$_2$), 63.0 (CH$_2$), 69.7 (C), 127.4 (CH), 127.5 (CH), 127.6 (2 CH), 127.9 (CH), 128.2 (2 CH), 128.3 (4 CH), 128.5 (4 CH), 128.6 (CH), 128.8 (2 CH), 128.9 (CH), 129.5 (2 CH), 129.6 (C), 129.7 (2 CH), 133.9 (CH), 135.7 (2 C), 136.5 (C), 137.2 (C), 138.7 (C). HRMS (ESI-TOF) cald for C$_{38}$H$_{39}$N$_2$O$_4$S$_2$: 651.2346 [M + H]$^+$; found: 651.2349.

2,N,N-Tribenzyl-4-[2-(methylsulfonyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-sulfonamide (3bb). Yellow oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.73-2.91 (m, 3H), 2.81 (s, 3H), 2.94 (dd, J = 12.4 and 1.2 Hz, 1H), 3.18 (d, J = 12.4 Hz, 1H), 3.42-3.51 (m, 1H), 3.45 (d, J = 12.8 Hz, 1H), 3.55 (d, J = 14.8 Hz, 1H), 3.66 (d, J = 14.8 Hz, 1H), 3.77 (d, J = 12.8 Hz, 1H), 4.08 (broad s, 4H), 6.80 (d, J = 6.4 Hz, 4H), 7.09-7.17

(m, 7H), 7.24-7.36 (m, 7H), 7.99 (dd, *J* = 7.6 and 1.6 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100.5 MHz) δ 31.7 (CH$_2$), 40.4 (CH$_3$), 50.9 (CH$_2$), 52.4 (2 CH$_2$), 56.6 (2 CH$_2$), 62.9 (CH$_2$), 69.7 (C), 127.4 (CH), 127.5 (CH), 127.6 (2 CH), 127.9 (CH), 128.3 (4 CH), 128.5 (4 CH), 128.6 (CH), 128.8 (2 CH), 129.0 (CH), 129.7 (2 CH), 130.0 (C), 135.7 (2 C), 136.5 (C), 137.1 (C). HRMS (ESI-TOF) cald for C$_{33}$H$_{37}$N$_2$O$_4$S$_2$: 589.2189 [M + H]$^+$; found: 589.2199.

Computational Details

All the calculations reported in this paper were obtained with the GAUSSIAN 09 suite of programs.[13] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[14] in conjunction with the D3 dispersion correction suggested by Grimme and co-workers[15] using the double-ζ quality plus polarization def2-SVP basis set[16] for all atoms. Reactants and products were characterized by frequency calculations,[17] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[18] Solvents effects were taken into account using the Polarizable Continuum Model (PCM).[19] Single point calculations on the PCM(THF)-B3LYP-D3/def2-SVP geometries were performed to estimate the change in the Gibbs energies at the B3LYP-D3 level using the triple-ζ quality plus polarization def2-TZVP basis set[16] for all atoms. This level is denoted PCM(THF)-B3LYP-D3/def2-TZVP//PCM(THF)-B3LYP-D3/def2-SVP.

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Domino α-arylation/Michael addition reactions: Sulfonates, sulfonamides and phosphonates are useful partners for the α-arylation/Michael addition process leading to tetrahydroisoquinolines

Z = SO₃Ph, SO₂NBn₂
PO(OEt)₂

Y = SO₂Ph, SO₂Me, CO₂Me
SO₃Ph, SO₂NBn₂

Domino α-arylation/Michael addition
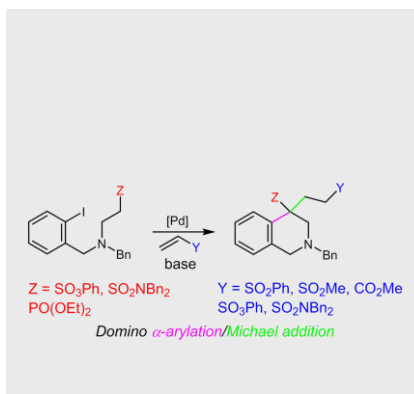
Domino α-arylation/Michael addition reactions

Daniel Solé,* Ferran Pérez-Janer, Yago García-Rodeja, and Israel Fernández*

Exploring New Partners for the Domino α-Arylation/Michael Addition Reaction Leading to Tetrahydroisoquinolines